COURT FILE NUMBER	
COURT	COURT OF QUEEN'S BENCH OF ALBERTA
JUDICIAL CENTRE	WETASKIWIN
PLAINTIFFS	DR. BLAINE ACHEN, DR. GERT GROBLER, DR. NADR JOMHA and DR. TYLER MAY
DEFENDANT	ALBERTA HEALTH SERVICES
DOCUMENT	**CERTIFICATE**

ADDRESS FOR SERVICE AND CONTACT INFORMATION OF PARTY FILING THIS DOCUMENT

[redacted]

Certificate for Remote Commissioning of Affidavit

I, Eva Chipiuk, of the Justice Centre for Constitutional Freedoms, counsel for the Plaintiffs, am commissioning the Affidavit of Dr. Joel Kettner, sworn December 9, 2021, via the process as directed by the Court of Queen's Bench of Alberta for the remote commissioning of affidavits, as detailed in the Notice to the Profession and Public issued March 25th, 2020. I am satisfied that this process was necessary because it was impossible or unsafe, for medical reasons, for the deponent and the commissioner to be physically present together.

Dated at Calgary, Alberta, this 9th day of December 2021.

[redacted]

Justice Centre for Constitutional Freedoms
Counsel for the Plaintiffs

Clerk's Stamp:

COURT FILE NO.	
COURT	COURT OF QUEEN'S BENCH OF ALBERTA
JUDICIAL CENTRE	WETASKIWIN
PLAINTIFFS	DR. BLAINE ACHEN, DR. GERT GROBLER, DR. NADR JOMHA AND DR. TYLER MAY
DEFENDANT	ALBERTA HEALTH SERVICES
DOCUMENT	**AFFIDAVIT OF DR. JOEL KETTNER**

ADDRESS FOR SERVICE AND CONTACT INFORMATION OF PARTY FILING THIS DOCUMENT	Ackroyd LLP Barristers and Solicitors 1500, 10665 Jasper Avenue Edmonton, Alberta T5J 3S9 [redacted]	Justice Centre for Constitutional Freedoms #253, 7620 Elbow Drive SW Calgary, Alberta T2V 1K2 [redacted]

AFFIDAVIT OF DR. JOEL KETTNER
Sworn on December 9, 2021

I, Dr. Joel Kettner, of the City of Winnipeg, in the Province of Manitoba, SWEAR AND SAY THAT:

1. I am qualified to give expert opinion on public health matters. My qualifications are set out in the attached Curriculum Vitae ("CV") and marked as **Exhibit "A"** to this my Affidavit.

2. I have been asked, as a public health physician and former provincial chief medical officer of health, to give my professional opinion on the following questions.

    I. How does protection against COVID-19 infection by natural immunity compare with protection against COVID-19 from vaccine-induced immunity? Specifically, how do these compare with respect to levels of protection and duration of protection?

    II. Regarding question 1, what are current stated facts and opinions of official public health organizations?

III. In my opinion, what issues should be considered, what information should be obtained, and how should these considerations and information be used to set policies regarding the hindering of previously infected unvaccinated physicians and other health care workers to work in Alberta Health Services facilities?

3. I agreed to provide an expert report with my professional opinion on these matters.

4. Attached at **Exhibit "B"** to this my Affidavit is a copy of my report which sets out the information and assumptions on which my opinion is based.

5. In summary my opinion to the questions posed are as follows:

I. Current evidence and previous scientific observation of other anti-viral vaccines indicate that natural immunity from previous infection is at least as protective – and for at least as long – as vaccine-induced immunity.

II. There is a high level of consistency of observations and/or conclusions between the major public health organizations considered in this report – the World Health Organization, the European Centres for Disease Control, the USA Centers for Disease Control and Prevention and the Canadian Public Health Agency's National Advisory Committee on Immunization – with respect to the similarity of levels and duration of protection by natural immunity from previous infection and the levels and duration of protection by vaccine-induced immunity.

III. I have been unable to find relevant data or clear rationale for policies pertaining to the exclusion of health care workers because of their vaccination status, especially since there has been consistent evidence for equivalent – if not superior - protection by natural immunity resulting from previous infection, as described by the major public health organizations and the Public Health Agency's National Advisory Committee on Immunization.

6. Attached at **Exhibit "C**" to this my Affidavit are all sources referenced in my report.

7. I confirm that I was not physically present before Eva Chipiuk, a lawyer and Notary Public, at the time of swearing this Affidavit. I was, however, linked to zoom utilizing videoconferencing software.

8. I swear this Affidavit to provide expert evidence for the purpose of the within action and injunction application and for no improper purpose.

SWORN REMOTELY BEFORE ME by videoconferencing by Dr. Joel Kettner, in the City of Edmonton, in the Province of Alberta, this 9th day of December 2021.

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[redacted]

Exhibit "A"

This is **Exhibit "A"** referred to in the
Affidavit of Joel Kettner
sworn before me via videoconferencing
at Calgary, Alberta, this
9th day of December, 2021.

[redacted]

of Alberta

Eva Chipiuk
Barrister & Solicitor

CURRICULUM VITAE

Joel David Kettner
MSc MD FRCSC FRCPC

December 1, 2021

TABLE OF CONTENTS

PERSONAL AND PROFESSIONAL INFORMATION, CONTACT INFORMATION

Home Address: [redacted]

Home Telephone Numbers: [redacted]

Work Phone Number: [redacted]

Mobile Phone [redacted]

Work Emails: [redacted]

UM Address: University of Manitoba
[redacted]

Personal History

Date of Birth: [redacted]

Place of Birth: Minneapolis, Minnesota, U.S.A.
(Canadian citizen born abroad)

Citizenship: Canadian

Marital Status: Married, six children, seven grandchildren

Places of Residence

1951 – 1955	Minneapolis, Minnesota, U.S.A.
1955 – 1967	Winnipeg, Manitoba, Canada
1967 – 1968	London, England, United Kingdom
1968 – 1985	Winnipeg, Manitoba, Canada
1985 – 1988	London, England, United Kingdom
1988 – present	Winnipeg, Manitoba, Canada

PRESENT EMPLOYMENT

University of Manitoba	Associate Professor, Departments of Community Health Sciences and Surgery (since 1990); Associate Director, Public Health clerkship rotation, undergraduate medical education program; Postgraduate Medical Education CanMEDS intrinsic roles lead; Co-chair, Postgraduate Medical Education Truth and Reconciliation Action Plan Committee
University of Winnipeg	Adjunct professor, Dept of Indigenous Studies
Self-Employment	Independent consultant
	Consultant to several organizations with respect to COVID-19 (see court affidavits and expert reports, page 31.
	Lead and administrator, WhatsApp chat group for COVID-19 Open Minded Critical Thinkers (physicians from across Canada)
	Consultant, Advisory Circle, Health Transformation Project, Southern Chief's Organization, Manitoba.
	Vaccinator, First Nations Communities COVID-19 vaccine project.
	Chair, College of Physicians and Surgeons of Manitoba Inquiry Panel

EDUCATION and TRAINING

Pre-University

1968 – 1969	St. John's High School, Winnipeg, Canada
1967 – 1968	Woodhouse Grammar School, London, England
1964 – 1967	St. John's High School, Winnipeg, Canada

University – Undergraduate

1972 – 1976	Faculty of Medicine, University of Manitoba, Dean A. Naimark Winnipeg, Canada
1969 – 1971	"Pre-med" Arts & Science" University of Manitoba, Winnipeg, Canada

University – Graduate and Post – Graduate

2000	Medical Assistance in Dying Addictions medicine, opiate agonist therapy
1989 – 1990 (6 months)	Family Medicine Weekly clinics, Family Medicine Centre, University of Manitoba Winnipeg, Canada
1988 – 1990	Community Medicine (now Public Health and Preventive Medicine) Residency, Dept. of Community Health Sciences, Faculty of Medicine University of Manitoba Winnipeg, Canada
1987 – 1988	Clinical Research Fellow, Imperial Cancer Research Fund Colorectoral Cancer Unit, St. Mark's Hospital, London, England
1986 – 1987	Clinical Research Fellow, Hepato-biliary Surgical Unit, Dept. of Surgery, University of London Royal Postgraduate Medical School and Hammersmith Hospital, London, England

1985 – 1986	Master of Science, Epidemiology, Faculty of Medicine, University of London, England, London School of Hygiene and Tropical Medicine
1985	Post – fellowship, Gastrointestinal Endoscopy, Gastrointestinal Surgery and Gastroenterology (Health Sciences Centre and St. Boniface General Hospital, Winnipeg Canada
1979 – 1984	General Surgery Residency, Dept. Faculty of Medicine, University of Manitoba (Health Sciences Centre and St. Boniface General Hospital), Winnipeg, Canada
1977	Extended Internship, Intensive Care (voluntary), Health Sciences Centre and St. Boniface General Hospital, Winnipeg, Canada
1976 – 1977	Rotating Internship, University of Manitoba, Faculty of Medicine (Manitoba Affiliated Teaching Hospitals – Health Sciences Centre and St. Boniface General Hospital, Winnipeg, Canada)

UNIVERSITY DEGREES AND CERTIFICATES

1991	Specialist Certification, Community Medicine (now Public Health and Preventive Medicine), Royal College of Physicians of Canada (FRCPC)
1985	Master of Science in Epidemiology, London School of Hygiene and Tropical Medicine, Faculty of Medicine, University of London, England, (MSc) (MSc Thesis – Epidemiology for Surgeons)
1984	Specialist Certification, General Surgery, Royal College Surgeons of Canada (FRCSC)
1976	Doctor of Medicine (MD), University of Manitoba, Winnipeg, Canada
1976	Licentiate, Medical Council of Canada (LMCC)

FELLOWSHIPS, ACADEMIC PRIZES, DISTINCTIONS AND AWARDS

1991-2020	Nominated for best teacher of the year by undergraduate medical students in most years; most recently for small group teaching, inspiration, innovation, and mentorship by first and second year medical students.
2016	Long Service Award in Recognition and Appreciation of Twenty-five Years of Loyal Service, University of Manitoba.
2012-2014	McArthur Foundation Fellowship (two years), Masters Development Practice program, University of Winnipeg
2012	Nominated for Manitoba Civil Service Excellence Team Award – CPPHO Report on the Health of Manitobans report-team (leader).
2010	Winner of Manitoba Civil Service Excellence Team Award - Manitoba Health Pandemic H1N1 Influenza Incident Command Team (Medical lead)
1987 – 1988	University of Manitoba Faculty Fund Fellowship for studies in the clinical epidemiology of colorectal cancer.
1987 – 1988	Visiting Clinical Research Fellowship, Imperial Cancer Research Fund, UK, to study clinical epidemiology and Screening of colorectal cancer at the ICRF Colorectal Cancer Unit, St. Mark's Hospital, London, England
1985 – 1987	J.H.F. Knight Fellowship (University of London, England) to study epidemiology and screening for colorectal cancer
1985 – 1987	R.S. McLaughlin Foundation Fellowship (University of Manitoba) to study epidemiology and surgery at the University of London, England
1983	Davis and Geck Award for Best Surgical Resident of the Year
1982	Second Prize for paper presented at the American College of Surgeons (Manitoba Chapter), Manitoba
1969 – 1971	Dean's Honour List, both years of Pre-Medicine, Faculty of Science, University of Manitoba

MEDICAL WORK EXPERIENCE

Current	See "Present Employment"
2017	Consultant to Manitoba Keewatinowi Okimakanak, Inc. re northern health clinical transformation
2012-2017	Medical director, International Centre for Infectious Diseases
2012-2015	Director, Master of Public Health program, University of Manitoba
2012-2015	Scientific director, National Collaborating Centre for Infectious Diseases, International Centre for Infectious Diseases.
2012-2014	University of Winnipeg Visiting Professor and Senior Fellow Masters in Development Practice Program, Indigenous Faculty of Graduate Studies
2008-2012	Chief Provincial Public Health Officer of Manitoba
1999 – 2008	Chief Medical Officer of Health Province of Manitoba
1999	Medical Officer of Health Winnipeg Community Health Authority
1995 – 1999	Medical Officer of Health Winnipeg Region, Manitoba
1995 - 1999	Part-time general medical practice and travel clinics, Winnipeg City Clinic, 385 River Avenue, Winnipeg
1995 – 2010	Casual employment as emergency room physician, urgent care physician, and surgical assistant, Seven Oaks General Hospital Concordia General Hospital, Misericordia General Hospital, Grace Hospital, Victoria Hospital
1991 – 1995	Medical Officer of Health Thompson, Norman and Interlake Regions, Manitoba Health
1990	Attending surgeon, Surgical Intensive Care Unit, Health Sciences Centre

1986 – 1988	Locum tenens as senior registrar in Surgery, Hammersmith and St. Mark's Hospitals, London, England
1984 – 1985	Surgical Assistant, Cardiac, Surgery Unit, Health Sciences entre, Winnipeg, Canada
1977 – 1979	Full-time emergency room physician, St. Boniface General Hospital, Winnipeg, Canada

SELECTED CONTINUING PROFESSIONAL DEVELOPMENT

2020	Weekly Dept of Community Health Sciences Colloquia, on-line sessions, webinars, and conferences on topics including medical education and COVID-19.
2019	Many family medicine sessions and teaching development sessions at the University Office of Continuing Professional Development and the Office of Educational and Faculty Development. Annual Scientific Assembly, Manitoba College of Family Physicians, Canadian Conference of Medical Education, Niagara Falls. Canadian Public Health Association annual conference, Ottawa Public Health Physicians of Canada annual Continuing Professional Development Symposium, Ottawa.
2018	Canadian Conference Medical Education, Halifax. Canadian Public Health Association annual meeting, Montreal. Public Health Physicians of Canada annual meeting, Montreal. Weekly Colloquia, Department of Community Health Sciences. CPD sessions, Office of Educational and Faculty Development. Preparation for CAPE (clinical assessment and professional enhancement for re-entry to clinical practice.
2017	Canadian Conference Medical Education, Winnipeg. Canadian Public Health Association annual meeting. Public Health Physicians of Canada annual meeting. Weekly Colloquia, Department of Community Health Sciences.
2015-2016	Canadian Conference Medical Education, Montreal. Canadian Public Health Association Annual Meeting, Toronto. Choosing Wisely symposium, Public Health Physicians of Canada, Toronto. Association of Medical Microbiology and Infectious Diseases Annual Meeting, Vancouver. Annual BIO Conference, San Francisco. Weekly Colloquia, Department of Community Health Sciences and Weekly Medical Microbiology Case Presentations. Peer Mentoring session for instructors of Indigenous health course.
2014	Faculty Development Workshop - Community Health Sciences June 12, 2014
2012	Medical Education Workshops, University of Manitoba Learning Styles in the Classroom Feb 16/12 Teaching Clinical Reasoning April 10/12 Teaching Critical Thinking May 22/12

2007	Queen's University Executive Leadership Course
1994-1995	Observation and supervised experience in Emergency Medicine, Seven Oaks Hospital, Winnipeg Canada (organized by Dr. Kopelow, Department of Continuing Medical Education)
1993	Clinician's Assessment and Enhancement Program, Department of Continuing Medical Education, Faculty of Medicine, University of Manitoba, Winnipeg, Canada

PROFESSIONAL MEMBERSHIPS, ORGANIZATIONS AND LICENSES

2020	Lead, WhatsApp Chat Group, Open-Minded Critical Thinkers, COVID-19
2013 – 2016	President, Public Health Physicians of Canada.
2012 – present	Member, Board of Directors, Canadian Association of Medical Education Foundation, currently liaison member to the Canadian Medical Education Journal.
2012 – 2015	Executive member, Clinical Teachers Association of Manitoba
2012 – 2014	Member, Board of Directors, Canadian Public Health Association of Canada
1999 – present	Member, Public Health Physicians of Canada, previously National Specialty Society of Community Medicine
1993 - present	Member, College of Family Physicians of Canada
2000 – present	Member, Canadian Association of Medical Education
1991 – present	Fellow of the Royal College of Physicians of Canada (Community Medicine – now Public Health and Preventive Medicine)
1990 – 2012	Assistant Professor, Depts. of Community Medicines, Surgery and Family Medicine, Faculty of Medicine, University of Manitoba
2012 - present	Associate Professor, Depts. of Community Medicines, Surgery and Family Medicine, College of Medicine, Faculty of Health Sciences, University of Manitoba
1990 – present	Member of the Canadian Association of Teachers of Community Health
1988 – present	Member of the Canadian Public Health Association and the Manitoba Public Health Association
1984 – present	Fellow of the Royal College of Surgeons of Canada (General Surgery)
1976 – present	Licentiate of the College of Physicians and Surgeons of Manitoba, Current license, General Practice, with Specialty privileges in General Surgery and Community Medicine

1976 – present	Licentiate of the Medical Council of Canada
1976 – present	Member of the Canadian Medical Association (Manitoba Division)
1976 – present	Member of the Canadian Medical Protective Association

UNIVERSITY AND OTHER ACADEMIC ACTIVITIES

2020	Faculty appointee, Undergraduate Medical Education Financial Award Committee
2018 - 2020	Member, Postgraduate Medical Education Assessments Committee, Professional Curriculum Committee, Education Advisory Committee, Accreditation Working Group, and Competency-based Medical Education Committee.
2019 – present	Co-chair, Post-graduate Medical Education Truth and Reconciliation Action Plan Working Group
2017 - present	Post-graduate medical education CanMEDs intrinsic roles subject advisor
2015 - present	Associate director, Public Health part of Family Medicine/Public Health Clerkship.
2013- 2017	Member, Healthy Campus Advisory Committee, University of Winnipeg.
1991- present	Member (and previous chair), Dept of Community Health Sciences Undergraduate Committee
2012-2015	Director, Master of Public Health program, University of Manitoba
2012-2014	Visiting professor and senior fellow, University of Winnipeg, Masters in Development Practice program, Faculty of Graduate Studies
2012	Promoted to associate professor, University of Manitoba
2012-2015	Elected to University of Manitoba Senate by the Faculty Council of Medicine
2011-2012	Co-chair Curriculum Renewal Task Group on Health systems, Public Health, and Environmental and Occupational Health and member of the Curriculum Renewal Steering Committee, Faculty of Medicine, University of Manitoba

2007-2012	Founding member of the first national Public Health Educators Network, and participant author of its first national on-line learning resource for medical students (The Primer);
1995, 2006, 2010	Member, Search Committees for Head of the Department Community Health Sciences, Department of Community Health Sciences, Faculty of Medicine, University of Manitoba
1992-1994	MSc thesis advisor for Anita Kozyrskyj: Validation of an Electronic Prescription Database in Manitoba: An Opportunity to Evaluate Pharmacist Participation in Drug Utilization Review.
1994 – 1996	Member, Med I and II Curriculum Reform Committee –Core Concepts Block, Faculty of Medicine, University of Manitoba
1994 - 1995	Member, Search Committee for new tenure-track position, Department of Community Health Sciences, Faculty of Medicine, University of Manitoba
1991 – 2011	Member, Executive Committee, Department Community Health Sciences, Faculty of Medicine, University of Manitoba
1991 – 2015	Member, Committee of Evaluation, Faculty of Medicine, University of Manitoba
1991 – 2015	Member, Clerkship Curriculum Committee, Faculty of Medicine, University of Manitoba
1991 – 2011	Director, Undergraduate Program, Department of Community Health Sciences, Faculty of Medicine, University of Manitoba (special teaching responsibilities include Course Director, Line and major clerkship-Family Medicine Community Medicine, graduate course teaching, thesis supervision and teaching and supervision of community medicine residents).

Undergraduate courses taught at University of Manitoba

2015 - present	Small group teaching in the population and public health pre-clerkship and clerkship programs and the Indigenous health longitudinal course, totaling now more than 100 hours per year.
1991- 2014	Average of more than 50 hours per year in undergraduate teaching, including 2-5 lectures and 2-3 tutorials in Population Health and Medicine, including Introduction to Health and Medicine (first lecture to first year medical students), Natural History of Disease and Levels of Prevention, Measurements of Health and Disease, Determinants of Health, Social Responsibility of Physicians; Public Health part of the Family Medicine/Public Health clerkship rotation (8 rotations per year), including orientation, community health status assessment, a "hot" current topic, followed after the rotation by a debrief; Annual summary presentation of Population and public health (invited consistently by 4th year students) as part of the LMCC QE Part I exam review.

Graduate and Postgraduate courses taught at University of Manitoba

2004 – present	Graduate teaching (MPH, MSc and PhD level): Problem Solving in Public Health (formerly Current Topics in Community Medicine 93.7510)
2016 - present	Invited speaker on Population Health and Health Care Organization to surgical residents as part of their Principles of Surgery training program.
2019	Invited speaker, Clinical Investigators Program: Health advocacy and health advocacy research.
1991- 2015	Annual guest teaching of "Principles of Prevention" in Epidemiology I and "Risk Communication" in Epidemiology II

1995-2008	Designer, supervisor, and lecturer in a recurring series of learning sessions in Epidemiology, Statistics, and Critical Appraisal in the PGME Core curriculum for all residents at the Faculty of Medicine;

Graduate Student Supervision

2015-2016	Supervised practicum of MPH student at International Centre for Infectious Diseases and National Collaborating Centre for Infectious Diseases
1994 - 2015	Supervisor for PGME students in Public Health and Preventive Medicine (average one - two per year for one to four month rotations)
2012-2015	Advisor to 13 MPH students, including field placement supervision.
1992-1994	MSc thesis advisor for Anita Kozyrskyj: Validation of an Electronic Prescription Database in Manitoba: An Opportunity to Evaluate Pharmacist Participation in Drug Utilization Review.

Current Research Activities

2013 – present	Health mentor, Grand Challenges Phase 1 Grant (total $100,000) "Improving Maternal and Child Health at the Root through Village Level Biotechnologies" with International Institute of Sustainable Development (co-PI) and CTx Green (P.I.)

SELECTED SERVICES, PROVINCIAL COMMITTEES AND OTHER RELEVANT ACTIVITIES

2012 – present	Member, Manitoba Provincial Vaccine Advisory Committee
2015-2016	Member, planning committee, *Conference to develop a federal framework on Lyme disease, Ottawa, May 15-17, 2016*
1994 – 2018	Examiner, Medical Council of Canada Part II Qualifying Exam
2014 - 2016	Member, Winnipeg Harvest Health and Hunger Committee
2015 - 2016	Member, Advisory committee to the Public Interest Law Committee research study on guaranteed annual income.
2003 – 2015	Statistics Canada Canadian Health Measures Survey Expert Advisory Committee
2013-2015	Member, Public Health Infrastructure Task Group to develop a blueprint for a federated surveillance system in Canada
2006 – 2012	Member of the Advisory Committee, National Collaborating Centre for Infectious Disease
2003 – 2007	Healthy Living Issue Group of the Population Health Promotion Expert Group, Canadian Public Health Network responsible for leading the writing of the Pan-Canadian Healthy Living Strategy,
2006 – 2011	Federal Provincial Territorial Roles & Responsibilities in Pandemic Preparedness and Response Task Group, Public Health Network Council
2006	Member of the selection committee for scientific director, National Collaborating Centre for Infectious Disease
2006 – 2008	Medical Advisory Committee, Health Science Centre, Winnipeg, Manitoba, representing Department of Community Health Sciences
2002 – 2009	Emergency Preparedness Expert Group, Canadian Public Health Network
2002 – 2006	Manitoba member, Federal Provincial Territorial Deputy Ministers of Health Advisory Committee Population Health and Health Security
2004	Member of the Canadian delegation to the World Health Organization special meeting in Geneva November 1-12, 2004 to

	develop the fourth edition (2005) of the International Health Regulation introducing the concept, definition, and expectations of countries during a Public Health Emergency of International Concern (PHEIC).
2002 – 2003	Co-chair, Health Disparities Task Group, Federal Provincial Territorial Deputy Ministers of Health Advisory Committee Population Health and Health Security
2000-2001	Chair, Province of Manitoba Drinking Water Advisory Committee and sole accountable author of Report on Bacterial Safety of Drinking Water In Manitoba
1999 – 2002	Chair, Federal Provincial Territorial Deputy Ministers of Health Advisory Committee on Population Health
1999 – 2012	Council of Chief Medical Officers of Health of Canada (CCMOH)
1995 – 1999	Co-chair, Project Team, Community Health Status Assessments, Epidemiology Unit, Manitoba Health
1995	Participant, Federal-Provincial Working Group/Workshop for present the Prevention of Neural Tube Defects, Manitoba Health and Health Canada, Ottawa
1995	Member, Provincial Committee on Hepatitis A, B and C amongst Winnipeg street-evolved youth
1995 – 1999	Member, core committee to review the Public Health Act of Manitoba
1995	Member, Advisory Committee to the Baby Alert Program
1994 – 1995	Member, Steering Committee for Psychiatric Day Hospital and Community Services in Mental Health for Winnipeg, Manitoba Health
1994 – 1999	Member of the Manitoba Health Communicable Disease Control Surveillance Review Committee and Chairman, Subcommittee on Analysis and Dissemination of Results.
1994 – 1999	Member of the Winnipeg Air Quality Index Committee
1993 – 1995	Member, Provincial Cancer Control Committee and Chair of Subcommittee on Secondary Prevention of Cancer, Manitoba Health
1993-1994	Member, Working Group for Psychogeriatric Services in Winnipeg, Manitoba Health

1993-1994	Member, Committee to Define Core Services for Rural Health Associations, Manitoba Health
1993-1994	Member, Provincial Surgery Committee, Manitoba Health
1993	Participant, national workshop and consensus conference on the training of community medicine specialists, Toronto
1991 – 1995	Member, National Population Health Survey Provincial Advisory Committee, Manitoba Health
1989	Member, Provincial Task Force on Breast Cancer Screening in Manitoba, Manitoba Health
1986-1988	Member, Public Health Alliance of Britain
1985-1988	Member, International Physicians for the Prevention of Nuclear War
1977-1985	President, Progressive Medical Association, Winnipeg
1974-1976	Founding member of "The Community Medicine Group" medical students concerned about social and public health issues
1974-1976	Founding co-editor (with Dr. Brian Postl) of "The Meditoban", medical school student newspaper
1974-1976	Founding board member, NorWest Health Co-op, Winnipeg

PUBLISHED BOOKS

Northover, John M.A., Kettner, Joel D. and Mr. Barry Paraskeva PhD, FRCS. Your Guide to Bowel Cancer (Royal Society of Medicine). A Hodder Arnold Publication, 2007

Northover, John M.A. and Kettner, Joel D. Bowel Cancer: The Facts. New York, Oxford University Press, 1992

SIGNIFICANT REPORTS

Chief Provincial Public Health Officers' "Report on the Health Status of Manitobans 2010: Priorities for Prevention – Everyone, Every Place, Every Day" (published November, 2011)

PUBLISHED PAPERS

- SM Moghadas, M Haworth-Brockman, H Isfeld-Kiely, J Kettner. Improving public health policy through infection transmission modelling: Guidelines for creating a Community of Practice. Can J Infect Dis Med Microbiol 2015;26(X):1-5.

- Mahmud S, Hammond G, Elliott L, Hilderman T, Kurbis C, Caetano P, Van Caeseele P, Kettner J, Dawood M. Effectiveness of the pandemic H1N1 influenza vaccines against laboratory-confirmed H1N1 infections: population-based case-control study. **Vaccine**. 2011 Oct 19;29(45):7975-81. Epub 2011 Aug 30.

- Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza, Bautista E, Chotpitayasunondh T, Gao Z, Harper SA, Shaw M, Uyeki TM, Zaki SR, Hayden FG, Hui DS, Kettner JD, Kumar A, Lim M, Shindo N, Penn C, Nicholson KG. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. Review. **N Engl J Med**. 2010 May 6;362(18):1708-19.

- Zarychanski R, Stuart TL, Kumar A, Doucette S, Elliott L, Kettner J, Plummer F. Correlates of severe disease in patients with 2009 pandemic influenza (H1N1) virus infection. **CMAJ**. 2010 Feb 23; 182(3): 257-64. Epub 2010 Jan 21, 2010

- Verne J, Kettner J, Mant D *et al.* Self-administered faecal occult blood tests do not increase compliance with screening for colorectal cancer: results of a randomized controlled trial. **Eur J Cancer Prev** 1993; Jul: 301-305

- Yassi A, Kettner J, Hammond, G *et al.* Effectiveness and costs-benefit of an Influenza Vaccine Program for Healthcare Workers. **Can J In Dis** 1991: 101-108;

- Kettner, JD, Whatrup C, Verne JE *et al.* Is there a preference for different ways of performing faecal occult blood tests? **Int J. Colorectal Dis** 1990; May:82-86;

PUBLISHED ABSTRACTS

Kettner JD, Whatrup C, Miller K. A comparative study of three patient approach methods for faecal occult b1000 testing in a North London general practice. Coloproctology. 1988;10:129

Kettner JD, Whatrup C, Young K. A within-person comparison of efficacy and individual preference for two methods of faecal occult blood detection. Coloproctology 1988;10:123

Kettner JD, Whatrup C, Miller K *et al*. Evaluation of new faecal occult blood test-a comparison of individual preference and efficacy using Early Detector and Haemoccult. Theoretical Surgery 1987;2:82

Kettner JD, Whatrup C, Miller K *et al*. A randomized trail of invitation methods for occult blood screening. Theoretical Surgery 1987;2:81-82

Kettner J, Paetkau D, Slykerman L *et al*. Effect of treatment on cardiac performance when right ventricular afterload is gradually increased in dogs. Critical Care Medicine 1983; II;3:217

Paetkau D, Kettner J, Girling L, Slykerman L, Prewitt RM. What is the appropriate therapy to maintain cardiac output as pulmonary vascular resistance increases? Anacsthesiology, 57;3:A-56, September, 1982

PUBLISHED LETTERS

Kettner, J. Quebec's Public Health Cuts Canadian Journal of Public Health 2015:106:3 March/April.

Scholefield JH, Kettner, JD, Northover JMA. Papillomavirus infection and progress to abnormal cervical smears. Lancet, 1988:i:1405;

Scholefield JH, Kettner, JD, Northover JMA. Problems with anal cancer demographics. Diseases of the Colon and Rectum; 1988:31:10:831;

Kettner JD, Mant D, Northover JMA. Ethics of preventive medicine. Lancet; 1988;ii:44-45;

Kettner Joel and Northover, JM. Screening for colorectal cancer, Lancet 1986;i:562-563;

Kettner Joel and Northover, JM. Occult-blood screening, Lancet 1986;ii:110;

PRESENTATIONS, WEBINARS AND OTHER SCHOLARLY AND EDUCATIONAL ACTIVITIES

2016 Planning consultant and facilitator, NCCID-York University Workshop on Mathematical Modelling in Public Health Infectious Diseases, York University, Toronto, October 3-4, 2016

2016 Guest (as Infectious Diseases Public Health specialist) on This Hour Has 22 Minutes, CBC Television.

2016 Member of scientific planning committee, Lyme Disease symposium, May 15-17, 2016, Ottawa.

Public Health 2016 (annual conference of the Canadian Public Health Association)

- Member, Conference Scientific Planning Committee
- Welcoming remarks on behalf of the Public Health Physicians of Canada at the opening ceremony
- Organized and participated in a panel discussion on "Public Health Inspectors, Public Health Nurses, and Public Health Physicians As Leaders: A Candid Conversation about Collaboration and Change "

Moderator, and member of the scientific planning committee, International Centre for Infectious Diseases National Grand Rounds:

- February 18, 2016: *Zika virus - What to Know, What to Do*, University of Manitoba, in collaboration with the Dept of Community Health Sciences Bold Ideas Colloquium Series.

Moderator, and member of the scientific planning committee, International Centre for Infectious Diseases International Webinars:

- December 1, 2016: *Difficult-to-treat Gram Negative Pathogens*
- November 8, 2016: *The Burden and Preventability of Non-respiratory Complications of Influenza in Older Adults*
- October 27, 2016: *Antibacterial Resistance in Gram-Negatives: Prevalence, risk factors, and impact of inappropriate therapy*
- October 13, 2016: *Pneumococcal Immunization for Older Adults.*
- August 17, 2016: *Pneumococcal conjugate vaccines for infants: What have we learned since their introduction?*
- June 22, 2016: *HPV Immunization Programs: What is the advantage of including males?*
- February 25, 2016: *Vaccine Hesitancy: What is it, Why is it, What to do about it?*
- January 13, 2016: *Mind your T's and Q's - What do we know about today's influenza vaccine options?* (moderator) and speaker: *Today's Menu of Vaccine Choices – the Basics and the New Ingredients*

2017 Radio interview re: legal age of marijuana purchase and use in Manitoba.

2015-2016 Radio, Television, and Media interviews on subjects including Ebola, ZikaVirus, Malathion, Influenza.

2015-2016 Designer, moderator, and speaker of ICID National Grand Rounds (Influenza vaccine for under 2 year olds, Influenza vaccine choices for seniors, Zika virus) and webinars (e.g. HPV vaccine, new vaccine options including quadrivalent, pneumococcal disease)

2015-2016 Co-chair (International Centre for Infectious Diseases/National Foundation for Infectious Diseases) of scientific planning committee and chair of international advisory committee for an accredited on-line learning module produced by MDBriefcase on *Seasonal Influenza in Older Adults: Immunization Challenges and Options for Vaccination Strategies*

2015:

Moderator, and member of the scientific planning committee, International Centre for Infectious Diseases National Grand Rounds:

- December 17, 2015: *Influenza Vaccines for Adults Over 65: Evaluating the Evidence*, University of Manitoba Medical College
- October 27, 2015: *Flu Vaccines for Little Kids – What's New, What's True*, University of Toronto

Moderator, and member of the scientific planning committee, International Centre for Infectious Diseases International Webinars:

- May 6, 2015: *Males and HPV: Burden of Disease and Prevention through Immunization*

November 25, 2015: Invited speaker, Public Health Physicians of Canada Residents' national educational webinar series: *Life After Residency.*

Lyme Disease Best Brains Exchange in Ottawa, June, 2015.

Chaired panel discussion at annual meeting of CHVI RD Alliance Coordinating Office at Canadian Association of HIV Research annual meeting, Toronto, 2015.

DCHS Colloquium presentation on the NCCID program: with Ms. Margaret Haworth Brockman: Ebola Virus Disease and other Challenges and Opportunities for the NCCID

Activities at Public Health 2015 (annual conference of the Canadian Public Health Association)

- Welcoming remarks on behalf of the Public Health Physicians of Canada at the opening ceremony
- Organized and chaired a panel discussion on "The ebola outbreak: What have we learned that we didn't know before?"

- Facilitated a workshop on Burden of Illness in Infectious Diseases

Association of Medical Microbiology and Infectious Diseases annual conference, Charlottetown, May, 2015.

- Poster presentation: AMR, Public Health, and Knowledge Translation: A Forward Approach

2014	Reviewer of research proposals for CIHR SPOR projects, Institutes of Population and Public Health and Health Services Delivery.
2013-2014	Member, scientific planning committee, Consensus Conference on Antimicrobial Resistant Organisms, University of and Institute of Health Economics, June 18-20, 2014
2014	Invited speaker, Consensus Conference on Antimicrobial Resistant Organisms, University of Alberta Institute of Health Economics, June 18-20, 2014: "What is surveillance? What is screening? How are they related?"
2014	Series of four public lectures at the University of Winnipeg on Public Health in the 21st Century: - *Public Health Unpacked: What is it? Who needs it?* - *Priorities for Prevention in Manitoba: our Provincial Profile* - *Public Health ahead: What are the Possibilities? How can we prevent the threats that we do not see or know?* - *Power, Process, and Public Policy: The Peculiar Ethics and Politics of Public Health and its relationship to Sustainable Development.*
2013-2014	National webinars for Public Health and Preventive Medicine residents and public health physicians hosted by the National Collaborating Centres for Public Health. Topic: - "Treatment as Prevention" with Drs. A. Ronald and J. Montaner - " Knowledge Translation for Emerging Diseases"
2013	Options (VIII) for the Control of Influenza, September 5-9, Capetown, South Africa - Paper: Rapid Knowledge Translation during the 2009 influenza pandemic - Poster: A project to translate and exchange knowledge towards more effective, efficient and equitable public health and primary care strategies for influenza and influenza-like illness (ILI) in Canada. JD Kettner , E Cheuk
2013	Innovation in Medicine and Health Care, University of Piraeus, Piraeus, Greece - Paper: Knowledge Translation for Emerging Infectious Diseases: Challenges and Opportunities

2013	University of Winnipeg Summer Institute Course: Hosted a morning session and presented a lecture on "Principles of prevention of infectious and chronic diseases"
2014	Series of four public lectures on public health, University of Winnipeg.
2012	Surgery Grand Rounds: "A Surgeon's Career in Public Health – the Long and the Short of It"
2003-2011	Annual lecture (most years) at "Bug Day" including SARS, "Little Bugs in the Big Picture", H1N1, and tuberculosis.
2010	National Collaborating Centre for Public Health, Making Connections, Opening Ceremony and plenary, keynote speaker, and co-presenter with Dr. Pat Martens on partnerships between government and university in public health policy setting, Summer Institute of the National Collaborating Centres of Canada
2010	The Manitoba College of Family Physicians, 52 Annual Scientific Assembly, key note speaker: H1N1 De-Brief
2010	Doctors Manitoba, Western Conference of Provincial/Territorial Medical Association, "*How to Survive a Pandemic –What have we learned?*"
2010	International College of Dentists Annual meeting, Winnipeg. *Public Health and the H1N1 Pandemic Influenza*
2009	Continuing Medical Education, Mini Medical School, University of Manitoba 2009;
2009	Presented on H1N1 for disadvantaged populations and led a practice guidelines consensus session at the Pan-American Health Organization of the World Health Organization consultation conference in October 14-16, 2009 in Washington, D.C.,
2008	Mini-university lecture on what on public health and evidence for the news
2007-2013	Annual lecture on *Issues and Trends in Public Health* at Red River Community College Issues and Trends in Health course taught by Jim Hayes as part of the Health management course for employees in regional health authorities
2007	Plenary speaker and panel discussant: Ethical issues in the practice of public health. The First Canadian Roundtable on Public Health: Exploring the Foundations, Montreal, Quebec.

2000-2018 Department of Community Health Sciences Colloquia:

- 2020: COVID-19 – Is the Prevention Worse than the Disease?
- February 5, 2020: Organizer and moderator of Coronavirus – an Open Forum, livestreamed, University of Manitoba Faculty of Health Sciences.
- 2018: Seeking Bold Ideas to Strengthen Inter-College Collaboration in Primary Care and Public Health
- 2017: Trumpism: Another Global Public Health Threat Originating in the USA?
- 2015: Colloquium presentation on the status and future of the National Collaborating Centre for Infectious Diseases
- 2014: Hosted colloquium and joint learning session with students and staff of the University of Winnipeg MDP program and University of the North Midwifery program: Dr. Janet Smylie and Sara Wolfe: "Indigenous Knowledge Work as a tool for Community Driven Health Services Development"
- 2013: Co-presented with Dr. Julie Pelletier (University of Winnipeg) on "Two Masters Programs – Two Universities – One Vision?"
- CPPHO Report on the Health Status of Manitobans ... Priorities for Prevention: Everyone, Every Place, Every Day – 2011
- The New Public Health Act "Does it meet the Public's Needs of Today and Tomorrow?" – 2009
- Reorganization of Public Health in Manitoba: Challenges and Opportunities –2008
- Healthy Living Strategy: New-Old or Old-New? –2003
- Walkerton Water – Could it happen here? - 2000

1993 The role of the urban medical officer of health. Cadham Provincial Laboratory Seminar

1990 "Screeening" for an awful disease. Community Health Sciences, Colloquium, Faculty of Medicine, University of Manitoba

1990 Epidemiology in Orthopedic Surgery, Orthopedic Grand Rounds, Health Sciences Centre

1989 Surgical Epidemiology, Western Association of Clinical Surgeons

1989 Screening for colorectal cancer, Concordia General Hospital Medical Rounds

1989 Screening for colorectal cancer, Surgery Grand Rounds, Health Sciences Centre

1987 Epidemiology of hepatic metastases, Annual course in advance hepatobiliary and pancreatic surgery, Royal Postgraduate Medical School, Hammersmith Hospital, London, England

1987 Obstructive jaundice, Surgery for GPs annual course. Royal Postgraduate Medical School. Hammersmith Hospital, London England

1987 Epidemiological aspects of hepatobiliary malignancies. Workshop in Research Methods in Surgery, Royal Postgraduate in Medical School, Hammersmith Hospital, London, England

1987	The surgical epidemiology of cholangiocarcinomas. UK Chapter of the World Congress of Hepato-biliary Surgeons, Cardiff, Wales
1987	Community Screening – Early Diagnosis and Prevention of Colorectal Cancer – a meeting for general practitioners, St. Mark's Hospital, London, England
1987	Mass Screening for colorectal cancer. Common Gastrointestinal Problems – Course for general practitioners, St. Bartholomew's Hospital Medical College, London, England.
1986	Mass Population Screening for Colorectal Cancer. Symposium on Screening, Carmarthen General District Hospital Carmarthen, Wales

Prior to career as medical officer of health 1990-2012:

1990 "Community Health Status Assessment – A model for Aboriginal Communities". Poster presentation, circumpolar health Conference, Whitehorse, Yukon;

1987-1988 The following two papers were presented by me at the Surgical Efficiency and Economy World Conference, Lund, Sweden, August, 1987 and at the 2nd Beonnial Congress of the European Council of Coloproctology Advances in Coloproctology, Geneva, Switzerland, 1988:

" A randomized trail of invitation methods for occult blood screening"

"Evaluation of new faecal occult blood test- a comparison of individual preference and efficacy using Early Detector™ and Haemoccult™"

1982-1983 "Effect of treatment on cardiac performance when right ventricular afterload is gradually increased in dogs" (Authors: Kettner Joel, Paetkau Don, Slykerman M, Girling L and Prewitt R. Departments of Surgery, Anaesthesia and medicine, University of Manitoba.

This paper was presented by me at the following meetings:

- American College of Surgeons, Manitoba Chapter, Winnipeg, 1982 (awarded 2nd prize);
- Critical Care Society Meeting, New Orleans, USA, 1983;
- American Society of Anaesthesiologists, Las Vegas, USA 1982;
- Canada Anaesthetists Society Meeting, Vancouver, 1983

CONTRACTED AND OTHER REPORTS

Manitoba Health Provincial Health Indicators, member of Working Group. 1999.
https://www.gov.mb.ca/health/documents/ind-all.pdf

Kettner, Joel D. Community Health Status Assessment, Waterhen First nation; 1993 (for Waterhen First Nation, Manitoba)

Kettner, Joel D. and Postl, B Community Health Status Assessment: a tool to understand and improve the health of Aboriginal communities: 1991 (Northern Health Research Unit for Medical Services Branch, Health Canada)

Kettner, Joel D. Community Health Status Assessment, Cross Lake, Manitoba; 1989 (for Medical Services Branch, Health Canada)

INVITED REVIEWS

2017- 2021: Canadian Journal of Public Health

2018-2021: Canadian Journal of Medical Education

2021: Association of Medical Microbiologists and Infectious Disease Specialists of Canada

2021: University of Manitoba Medical Students Journal

SELECTED MEDIA, COVID 19

Winnipeg Free Press panel, Dec 10, 2020
https://www.youtube.com/watch?v=9l52CWsUGTE

Toronto Caribbean interview, November 26, 2020
https://www.youtube.com/watch?v=cpjk53umB_0&feature=emb_title

CBC West of Centre panel discussion
Circuit Breakers and Personal Freedom, November 12, 2020.
https://www.cbc.ca/listen/cbc-podcasts/407-west-of-centre/episode/15808413-circuit-breakers-and-personal-freedom

Open letter to first ministers, July 29, 2020
https://healthydebate.ca/opinions/an-open-letter-to-pm-covid19

Opinion piece CBC Manitoba, July 25, 2020
A new normal, or new abnormal? Change in direction needed on COVID-19 response
https://www.cbc.ca/news/canada/manitoba/joel-kettner-opinion-covid-19-response-1.5654062

Letter to the editor, Winnipeg Free Press, June, 27, 2020
https://www.winnipegfreepress.com/search/?keywords=clergy+kettner&searchSubmitted=y&sortBy=-startDate

Cross-country Check-up, March 15, 2020.
https://www.cbc.ca/listen/live-radio/1-13-cross-country-checkup/clip/15765826-march-15-2020-is-enough-done-slow-covid-19

Invited interviews and expert advice between March 15, 2020 till August 15, 2021:

- **CTV local news**
- **Global TV local news**
- **CBC TV local news**
- **CJOB local radio**
- **Winnipeg Free Press**
- **Shaw local television, Victoria, BC**

COURT AFFIDAVITS AND EXPERT REPORTS (available from courts or by request to [redacted]

Supreme Court of Yukon 20-AP002
Mercer vs Government of Yukon
Affidavit filed January 28, 2021

Supreme Court of British Columbia S 210209
Beaudoin vs Government of British Columbia and the Provincial Health Officer
Affidavit filed February 12, 2021

Supreme Court of Manitoba CI 20-01-29284
Gateway Bible Baptist Church et al vs Government of Manitoba
Affidavit filed April 1, 2021

Ontario Superior Court of Justice CV-20-00652216-000
Adamson Barbeque et al vs Ontario (Attorney General)
Affidavit filed April 14, 2021
Reply affidavit filed May 17, 2021

Ontario Superior Court of Justice CV-21-00013361-0000
Wellandport United Reformed Church vs Ontario (Attorney General)
Affidavit filed May 4, 2021.

Exhibit "B"

Table of Contents

INTRODUCTION

1. I have been asked, as a public health physician and former provincial chief medical officer of health, to give my professional opinion on the following questions:

    1. How does protection against COVID-19 infection by natural immunity compare with protection against COVID-19 from vaccine-induced immunity? Specifically, how do these compare with respect to levels of protection and duration of protection?

    2. Regarding question 1, what are current stated facts and opinions of official public health organizations?

    3. In my opinion, what issues should be considered, what information should be obtained, and how should these considerations and information be used to set policies regarding the hindering of previously infected unvaccinated physicians and other health care workers to work in Alberta Health Services facilities?

2. My opinions, along with my reasoning and supporting evidence are found below.

I. How does protection against COVID-19 infection by natural immunity compare with protection against COVID-19 from vaccine-induced immunity? Specifically, how do these compare with respect to levels of protection and duration of protection?

Conclusion summary: Current evidence and previous scientific observations of other anti-viral vaccines indicate that natural immunity from previous infection is at least as protective – and for at least as long – as vaccine-induced immunity.

a) UNDERSTANDING AND ASSESSING THE NATURAL HISTORY OF A DISEASE

3. When comparing protection by natural immunity following infection with vaccine-induced immunity following vaccination, there are many considerations. First, we must understand the natural history of infection of respiratory viruses. This is because there is more than one point at which immunity can influence the transmission and course of a disease. Typically, frameworks for this understanding can be used for all respiratory viruses, but the specifics vary between virus species and types.

4. The framework is relatively simple, but the application of the framework to decision-making is not. The following framework is called the "natural history" of a disease. These are the stages:

    Exposure -> transmission -> infection -> asymptomatic or pre-symptomatic infectious period -> symptomatic infectious period -> mild symptoms (recovery without need for hospitalization) or more severe symptoms -> hospitalization (+/- intensive care) -> death or recovery.

5. Not every step or outcome described above occurs with every case. For example, death may occur without hospitalization. Recovery may be complete or associated with ongoing illness.

6. For exposure to result in transmission of infection, an infected person ("case") must expose directly or indirectly another person ("contact") to the virus. An exposure is necessary, but not sufficient, to result in the transmission of infection. For transmission to occur, one person must be infectious and the other person must be susceptible, i.e. unprotected by a previous vaccination or previous infection.

7. Even without specific immunity to a specific virus, the innate, inherited, and generic immune system of humans can respond to previously undetected viruses. The innate ability of the human immune system is evident given that more than 80% of humans that were not previously infected or vaccinated have recovered from COVID-19 infections without any treatment.[1] Although often stated in categorical terms, one's biological immune state is more of a continuous variable, i.e. degrees of susceptibility or resilience. In other words, any one person's susceptibility is not 100% or 0%. Levels of protection can be estimated using epidemiological and laboratory evidence.

8. The definition or diagnosis of "infected" requires objective observation of pathological changes associated with direct impacts of the virus or the inflammatory response of the host (human). These phenomena may be obvious such as fever, cough, inflamed throat, or they may be inapparent such as microscopic signs of inflammation or the presence of new and specific antibodies in the blood. Without any of these phenomena, a more likely conclusion is that an *exposure* to the virus may have occurred, but *transmission of infection* did not.

9. There are several factors that determine whether exposure is likely to result in transmission of infection. The most important are: 1) the volume of virus (from the case) which contacts the surface of the mucous membranes of the respiratory tract of the exposed person (contact); and 2) the immune status of the exposed person (contact).

10. Note, I am using the term "case" as equivalent to being infected, regardless of whether that person has been tested and identified officially as a case. Similarly, I am using the term "contact" as equivalent to a person exposed to an infectious person (case), whether the infectious person has been officially determined to be a case, and whether the person that has been exposed has been identified officially as a contact.

11. Regardless of whether symptoms occur or not, cases are potentially infectious for a time that is defined as the "infectious period". For COVID-19, there is general agreement that the infectious period is, on average, about one week in the absence of symptoms (asymptomatic) or beginning one or two days prior to symptoms (pre-symptomatic).[2] If transmission occurs from an exposure during this period to one or more of their contacts, the chain of transmission continues. If no transmission occurs from a case, the propagation of that chain of transmitted infections comes to an end.

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[1] MyHealth.Alberta.ca: *Patient Care Handouts, Coronavirus disease (COVID-19): Care instructions.* https://myhealth.alberta.ca/health/AfterCareInformation/pages/conditions.aspx?hwid=custom.ack9673ahs.

[2] World Health Organization Scientific Brief, *Transmission of SARS-CoV-2: implications for infection prevention precautions,* 9 July 2020. https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions.

12. In addition to the modes of transmission of communicable diseases, the term "natural history" refers to the clinical course of one person's infection. As above, this begins with an exposure that results in transmission of infection. After infection has occurred, the person may or may not develop symptoms. It is estimated that about one-third of infections are asymptomatic, i.e. have no symptoms.[3] For the other two-thirds, symptoms may be mild or severe, on a continuum.

13. A usual way to think about severity is the degree of impact of the infection on the person's activities and their need for care. These include interference with activities of daily living, the need for medical care - especially hospitalization or intensive care -, duration of illness, or, in rare cases, death.

14. In other words, we need to know how infection is transmitted – the modes of transmission – and we need to know about the clinical course – the natural history - in persons that have been infected.

15. Transmission is the first stage of the natural history of an infection. We need to measure how frequently infection is transmitted. We need to measure the severity of the clinical course. These two measurements – frequency and severity - are the fundamental epidemiological descriptors of the burden of illness from COVID-19 and any other disease.

16. Understanding and measuring burden of illness, combined with understanding and measuring the benefits and harms of intervention options are the basis for proposing and implementing rational public health policies and actions. To justify any policy requires a transparent description of the quantitative measurements and estimates used as well as the rationale for how they have been used.

17. In communicable diseases, the transmission of infection and the course of the disease describes the impact of infection on individuals. In addition, it is important to understand the impact of one person's infection on others. This happens in two main ways: 1) transmission of their infection to another person; or 2) their utilization of health care services, potentially limiting access to care for others.

b) PUBLIC HEALTH CONSIDERATIONS WHEN ASSESSING DISEASES AND ASSOCIATED PUBLIC RISKS

18. Public health uses this framework to estimate and monitor harmful impacts associated with the disease. These include severity of illness and deaths, utilization of health services, and impacts on the health care, social, and economic determinants of health.

19. A major challenge of making and describing these estimates is distinguishing harmful impacts attributable to direct consequences for infected persons from the impacts of the policies and interventions of public health officials and their governments. For example, health care workers may be in reduced supply because of absenteeism from COVID infections or they may be in reduced

[3] Oran, D. P.; Topol, E. The Proportion of SARS-CoV-2 Infections That Are Asymptomatic, A Systematic Review. Annals of Internal Medicine. May 2021. https://www.acpjournals.org/doi/10.7326/M20-6976.

supply because of policies which hinder them from working, such as isolation, quarantine protocols or mandatory vaccination policies.

20. To compare the immune protection of two states – post-vaccination with post-infection – requires clarification of what we are comparing. As described in paragraph three, immunity can offer protection for the individual exposed to the virus at three stages of the natural history:

    1. It can enable the contact to interrupt transmission, thus preventing infection from occurring;
    2. It can reduce the severity of infection; and
    3. It can reduce the transmission of infection to others by reducing the volume of virus and symptoms (e.g. coughing, sneezing).

21. In other words, to compare levels of protection, the outcome of interest, each of these stages must be specified, measured, and compared. Good public health planning sets measurable objectives for relevant outcomes, identifies optimal strategies to address them, and monitors progress of achieving the outcomes.

22. Let's use the example of a policy to hinder from working unvaccinated healthcare workers.

    1. To estimate the transmission of infection to unvaccinated healthcare workers, case counts of new infections should be estimated in advance of formulating such a policy and should be used for monitoring. This should include similar measurements for comparison with healthcare workers that have been vaccinated. This makes it possible to estimate the size of any additional risk for unvaccinated healthcare workers to get infected in comparison to vaccinated healthcare workers.

    2. To assess severity of illness and need for hospitalization, indicators should be identified and estimated in advance of formulating such a policy and should be used for monitoring. This should include measurements of hospital admissions associated with exposure to unvaccinated healthcare workers in comparison with exposure to vaccinated healthcare workers. This comparison would make it possible to estimate the size of any additional risk of severe illness and hospitalizations associated with the provision of health care by unvaccinated healthcare workers.

    3. To compare unvaccinated healthcare workers with vaccinated healthcare workers with respect to transmission of infection to others in healthcare facilities , case counts of new infections associated with transmission from healthcare workers should be estimated in advance of formulating such a policy and should be used for monitoring. This makes it possible to estimate the size of any additional risk of unvaccinated healthcare workers transmitting infection in healthcare facilities.

       Policies which disrupt the work and personal lives of health care workers should be justified by estimates of the size of the risk attributable to unvaccinated status and the estimated

effect size of policy intervention. Both beneficial and harmful effects should be estimated.

There are many factors to consider. A fundamental consideration is the comparison of protection by natural immunity following infection with the protection by vaccine-induced immunity following vaccination. In other words, the comparisons described above in 1), 2), and 3) should also be analyzed in consideration of whether previous infection had occurred, both for vaccinated and unvaccinated workers.

23. These beneficial outcomes of immune protection can be estimated for the three stages in the natural history of transmission and the clinical course of the illness described above. They can be estimated generally, and they can be estimated for specific sub-groups of individuals, characterized and stratified by variations of biological (e.g. age, chronic conditions) and social factors, such as being disadvantaged by access to health care, income, discrimination, and in other ways.

24. In addition to estimating the beneficial outcomes of immune protection for individuals, public health undertakes assessments of protection at a population level. This is a more complicated assessment because of the dynamic processes of human interactions and the multiplicative impacts of exposure to infectious persons.

25. The higher the proportion of immune/protected individuals, the lower the probability of transmission in the population. This is true whether any one person has protection by natural immunity following previous infection, vaccine-induced immunity, and/or innate immunity prior to infection or vaccination. It is evident from Alberta's data that most people's innate immune systems have been able to prevent transmission and severity of illness related to Covid-19 infection.

26. Alberta's reported rate of death amongst cases for people under the age of 70 has been two per 1000 cases[4] and would be expected to be significantly lower amongst persons in good health. Even amongst the frailest –people over 80 years - more than 80% have survived an infection[5]. These rates are similar to those observed before vaccines were available. This is in part because of our innate immune systems, which have evolved to respond to new viruses that have not been "seen" before.

27. The actual infection fatality rates (proportion) are usually lower than the case fatality rates because of the higher number of actual infections – including asymptomatic infections – that have not been tested and identified as cases. The case fatality rate (proportion) is a simple calculation of the number of deaths from COVID-19 divided by the number of identified cases. If the actual number of infections is significantly greater than the number of identified cases, the true denominator is greater, and the infection fatality proportion is lower than that which only includes identified cases in the denominator.

28. To develop a rational policy regarding the provision of health care by people based on their innate immunity, natural immunity from previous infection, or vaccine-induced immunity requires many

[4] Government of Alberta, *COVID-19 Alberta statistics.* https://www.alberta.ca/stats/covid-19-alberta-statistics.htm#severe-outcomes.
[5] *Ibid.*

considerations. To estimate the frequency of transmission and the level of protection from exposure in health care facilities or other settings, requires surveillance and analysis of data from laboratories, contact tracing programs, medical care records in the community, and hospital and fatalities data.

29. Most provincial governments and public health officials, including Alberta, have not shown or explained information sufficiently for others to understand the trajectory of the pandemic or to understand the rationale for policy decisions. This may be because the data has not been collected and/or analyzed and/or summarized and/or made available in a transparent way. For example, data from the case and contact tracing program combined with laboratory data, hospital records, and mortality data should be used to estimate the number and rates of exposures, settings, and health, access to health care, and social circumstances associated with transmission, serious outcomes, and the need for hospitalization. Within such an analysis, one could estimate how much health care workers – vaccinated v unvaccinated – have contributed to the burden of illness and pressure on the health care system.

30. The estimates and information described above are only some of the ways to determine and estimate which inputs and which outputs are most important to compare in order to choose strategy options that will:

    a. achieve optimal benefit (e.g. reduction of serious infections and need for hospitalization);
    b. cause the least harm (e.g. adverse side-effects of vaccination, reduced capacity to care for all diseases),
    c. cause the least negative impact on everyday life (e.g. unemployment); and
    d. the least costly (e.g. costs for infection and control procedures and materials).

31. Despite efforts to find data, information, and rationale of the kind described in paragraphs 20-30, I have been unable to find evidence or rationale for Alberta Health Services' policies to prevent unvaccinated previously infected health care providers from working in health care facilities. Without such information, I have been unable to understand the rationale for such a policy and the estimated quantitative expectations of its benefits, harms, impacts on everyday life, and monetary costs.

c) PUBLIC HEALTH CONSIDERATIONS REGARDING PEOPLE PREVIOUSLY INFECTED

32. An important question, attracting worldwide attention, is to what degree vaccination increases the protection of people previously infected. There is increasing information in the literature, some of which has been summarized below by official national and international public health organizations.

33. As shown below in my answers to the second question, current evidence cited by official public health organizations has consistently shown that even the most effective vaccinations such as Pfizer's and Moderna's mRNA products produce, at best, similar levels of protection than that obtained by natural immunity in previously infected persons.

34. This observation is consistent with the overview of evidence in the Rapid Review Update of October 15, 2021, by the Public Health Agency of Canada National Collaborating Centre on Methods and Tools[6]. It stated that "Across immunogenicity studies, findings are consistent that those with a prior infection have a stronger response with follow-up periods closer to receipt of vaccination. The magnitude of the difference between groups appears to decrease over time, and in several studies was no longer statistically significant at the longest follow-up periods (5 - 7 months)".[7] In other words, natural immunity following infection provided better protection than immunization up until the longest period of follow-up of seven months. This difference appeared to decrease over time, but natural immunity remained stronger, albeit not statistically significant. It is not clear whether the lack of statistical significance is because of the small magnitude of the difference or the small size of the sample. Regardless, no evidence was found for inferiority of protection from natural infection in comparison to vaccination.

35. An updated USA Centers for Disease Control and Prevention Science Brief, found that "the immunity provided by vaccine and prior infection are both high but not complete (i.e. not 100%)"[8]. This is only one of many studies and summary statements of official public health organizations which are consistent in the opinion that natural immunity is at least as protective of vaccine-induced protection.

36. There are, however, differences of opinion about the degree, if any, of increased protection from vaccination in previously infected persons. Whereas there may be some increased protection, the estimated effect size is likely to be small given the high level of protection already conferred by natural immunity from a previous infection. Larger studies have observed that protection by natural immunity following infection is greater than 90%. A recent UK study quoted by the European Centre for Disease Control and Public Health England showed that for persons previously infected, the observed protection from re-infection with the Delta variant was greater than 99%[9]. Such observations reduce to negligible the potential of additional protection from vaccination in persons previously infected. Recent reports of waning immunity and the need for a third (booster) suggest that superiority of natural immunity may be increasing over time. This is discussed further later in this report.

37. Regarding the benefit and harm of vaccination in previously infected persons, the National Advisory Committee on Immunization (NACI) refers to an October 15, 2021 Rapid Review Update of the Public Health Agency of Canada National Collaborating Centre for Methods and Tools, McMaster University[10]. The most relevant finding was that "The evidence is very uncertain about the risk of

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[6] The National Collaborating Centre for Methods and Tools Prepared for: National Advisory Committee on Immunization (NACI), *Rapid Review Update 1: What is the ongoing effectiveness, immunogenicity, and safety of COVID-19 vaccines in persons who have had a prior, confirmed COVID-19 infection?* October 15, 2021. https://www.nccmt.ca/covid-19/covid-19-rapid-evidence-service/36 [NACI].

[7] *Ibid.* at page 3.

[8] Centre for Disease Control and Prevention, Science Brief: SARS-CoV-2 Infection-induced and Vaccine-induced Immunity, October 29, 2021. https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/vaccine-induced-immunity.html

[9] Public Health England, SARS-CoV-2 variants of concern and variants under investigation in England, Technical briefing 19, July 23, 2021. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1005517/Technical_Briefing_19.pdf at page 36. [Public Health England].

[10] NACI, *supra* note 6.

infection in individuals with previous COVID-19 infection who receive vaccination compared to those who remain unvaccinated."[11] In other words, Canada's National Collaborating Centre could not find sufficient evidence to confirm that vaccination for previously infected persons provided any additional protection.

38. Of equal concern is the occurrence of harmful adverse events from vaccination in persons previously infected. Policies mandating vaccination in people with evidence of previous infection should be able to demonstrate even more substantive evidence that vaccination will result in more benefit than harm. For healthcare workers and others previously infected, the benefit of vaccination appears to be of negligible value. Given current evidence for an equivalent if not higher level and duration of protection from previous infection, even a low rate of significant adverse events may well outweigh the small, if any, expected benefit.

39. In its Recommendations on the COVID-19 vaccines, NACI quotes a study entitled "Previous COVID-19 infection but not Long-COVID is associated with increased adverse events following BNT162b2/Pfizer vaccination"by Raw et al from the British Medical Journal.[12] This study estimated the risk of harmful adverse effects of COVID-19 vaccination in healthcare workers previously infected with COVID-19 and healthcare workers that were not previously infected. The authors concluded that prior COVID-19 infection was associated with a 50% higher rate of reported moderate/severe symptoms (e.g. fever, fatigue, muscle or joint pain, swollen lymph glands).[13]

40. Regarding booster doses in persons previously vaccinated with two doses, the NACI states in its Intermittent Guidance on booster COVID-19 vaccine doses in Canada, October 29, 2021, that its number one research question is "What is the efficacy, effectiveness, immunogenicity and safety of a booster dose in COVID-19 vaccine individuals who have had a previous laboratory-confirmed SARS-CoV-2 infection?"[14]

41. With regard to current knowledge on this question, NACI's Interim Guidance on Booster COVID-19 Vaccine Doses has one sentence. "The safety and effectiveness of a third dose in persons who had a previous SARS-CoV-2 infection is currently unknown."[15]

42. Given the current trends towards recommendations for routine administration of a booster (third) dose in all sub-populations, mandatory vaccination of healthcare workers may well soon include a third dose requirement. The frequency and severity of adverse events from a booster dose will become increasingly important to estimate, especially for previously infected persons, the incremental benefit and harms. As the incremental benefit from additional doses diminish and the incremental harm of adverse events increase, it can be anticipated that the benefit/harm ratio will

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[11] *Ibid.* at page 8.

[12] Raw. R.; Kelly, C.; *et. al*. *medRxiv*, Previous COVID-19 infection but not Long-COVID is associated with increased adverse events following BNT162b2/Pfizer vaccination, April 22, 2021. https://www.medrxiv.org/content/10.1101/2021.04.15.21252192v1.

[13] *Ibid.* at Abstract and page 6.

[14] Government of Canada, *Archived 21: National Advisory Committee on Immunization statement: Interim guidance on booster COVID-19 vaccine doses in Canada* [2021-10-29]. https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/recommendations-use-covid-19-vaccines/statement-guidance-booster-doses.html#a8. [NACI COVID-19 Booster Guidance]

[15] *Ibid.*

decrease. This should be estimated to explain and justify a policy to require booster doses, especially for previously infected persons.

II. Regarding question I, what are current stated facts and opinions of official public health organizations?

> **Conclusion summary.** There is a high level of consistency of observations and/or conclusions between the major public health organizations considered in this report – the World Health Organization, the European Centres for Disease Control, the USA Centers for Disease Control and Prevention, and the Canadian Public Health Agency's National Advisory Committee on Immunization – with respect to the similarity of levels and duration of protection by natural immunity from previous infection and the levels and duration of protection by vaccine-induced immunity.

a) USA CENTERS FOR DISEASE CONTROL AND PREVENTION (CDCP)

43. As of December 3, 2021, the USA Centers for Disease Control and Prevention (CDCP) has recommended COVID -19 vaccination for people that were previously infected.[16]

44. Without providing evidence that vaccination provides superior protection than previous infection, the public-oriented document claims that "emerging evidence "shows that getting a COVID-19 vaccine following previous infection provides added protection, referring only to one study to support this statement – a study of 246 cases and 492 controls.[17]

45. CDCP claims that Cavanaugh's study "showed" that previously infected unvaccinated persons had twice the odds of getting re-infected than previously infected vaccinated persons. However, the authors themselves did not claim that their study "showed" any conclusions. In fact, they clarified that their type of study could not be used to show a cause-and-effect connection, and instead use the word "suggested" rather than "showed", while pointing out that their study had "at least five limitations".[18]

46. This one and only study relied on by CDCP is inconsistent with the cited evidence and conclusions of the other major public health organizations included in this report.

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[16] Centre for Disease Control and Prevention*, COVID-19 Preparing for Your Vaccine*, December 3, 2021. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/prepare-for-vaccination.html.

[17] Centre for Disease Control and Prevention, *Morbidity and Mortality Weekly Report (MMWR)*, August 13, 2021. https://www.cdc.gov/mmwr/volumes/70/wr

[18] *Ibid*.

b) EUROPEAN CENTRE FOR DISEASE CONTROL (ECDC)

47. The following information was obtained from the *Rapid Risk Assessment 16th update* of September 30, 2021, found on the European Centre for Disease Control (ECDC) website on November 21, 2021.[19]

48. The section *Disease Background* beginning on page 12 addresses issues of protection against infection, comparing natural immunity with vaccination.[20] It also considers duration of protection and variants of concern.

49. Recognizing that there is a sparseness of longitudinal cohort comparisons, ECDC refers to a systematic review of 11 key studies by the Irish Health Information and Quality Authority[21]. This review estimated that the range of reinfection rates amongst previously infected persons was from 0% to 1.1%.[22] In other words, there was 99% or greater protection resulting from previous infection. This protection was observed to be maintained for up to 10 months after initial infection.

50. Of significance, ECDC, in its baseline modeling**,** assumed 100% protection by natural immunity in previously infected persons. It used in its model a 71% vaccine-induced protection against infection and an 82% vaccine-induced protection from hospitalization or death[23]. In modeling, the most important and impactful variables are selected for the mathematical formula and an estimate of their value is inserted into the model formula. The values selected should be realistic and based on best available evidence. The choice of these values indicate that the modelers considered the protection by natural immunity to be significantly higher than the protection from vaccination.

51. Regarding protection against reinfection by the Delta variant, ECDC refers to a Public Health England study[24] indicating that there was an adjusted odds ratio of 1.46 when comparing the odds of reinfection by the Delta variant to the odds of reinfection by the alpha variant. This indicates a 46% higher risk of reinfection with the Delta variant than the previously dominant Alpha strains. What is most important to understand is that in absolute terms and before adjustments were made for age and other variables, the protection by natural immunity against Alpha variant reinfection was 99.4% in comparison to protection of 98.7% for the Delta variant. Inversely, the probability of reinfection with the Delta virus was *100% - 99.4% = 0.6%* compared to the probably of re-infection with the Alpha variant of *100% - 98.7% = 1.3%*. After adjustments for relevant variables, this 0.7% difference (0.13% - 0.6% = 0.7%) shrinks to *0.9% - 0.6% = 0.3%*.

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[19] European Centre for Disease Prevention and Control, Assessing SARS-CoV-2 circulation, variants of concern, non-pharmaceutical interventions and vaccine rollout in the EU/EEA, 16th update, September 30, 2021. https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-rapid-risk-assessment-16th-update-september-2021.pdf [ECDC].

[20] *Ibid*. at page 12.

[21] Murchu, E.; Byrne. P. *et al*. *Medical Virology*, Quantifying the risk of SARS-CoV-2 reinfection over time, May 27, 2021. https://onlinelibrary.wiley.com/doi/10.1002/rmv.2260.

[22] *Ibid*. at Section 4.1.

[23] ECDC *supra*. note 19 at page 15.

[24] Public Health England *supra*. note 9 at page 36.

52. In other words, the probably of reinfection by a Delta variant in previously infected persons is 9 per 1000 compared with the probably of reinfection by the Alpha variant of 6 per 1000, an absolute rate difference of 3 per 1000. These rates are much lower than the rates of infection that have been observed post-vaccination in persons that did not have previous infection. Even if one uses the highest estimates of 95% protection by vaccines, the probability of infection by the Delta virus is 50 per 1000 for vaccinated persons compared to 10 per 1000 for previously infected persons.

53. Given the imprecision of observations of this study, one must be cautious in their interpretation of their results. This difference may be statistically significant because of the large numbers, but the magnitude of the difference and the relevance of this difference is of doubtful significance. A reasonable conclusion from these data, the prime evidence provided by ECDC for its assessment, is that natural immunity protects from reinfection with Delta variants in a similar way that it does for reinfection from an Alpha variant. None of the major public health organizations included in this report provided evidence or that natural immunity cannot be relied on as much as vaccine-induced immunity to protect against reinfection or infection, respectively, from the Delta virus or anticipated future variants of concern.

54. ECDC's section on "Reinfection with SARS-CoV-2" concludes with the statement "Taken together, the risk of reinfection with the Delta variant remains low, albeit with evidence of increased risk relative to the previously circulating Alpha variant."[25] Given the magnitude of the absolute risk difference of reinfection between two variants, the conclusion provided by the ECDC is reasonable and consistent with the very low risk of reinfection, with a negligible difference between the two variants.

c) WORLD HEALTH ORGANIZATION (WHO)

55. In May of 2021, WHO posted a technical guidance scientific brief on *COVID-19 Natural Immunity*[26]. WHO states that it monitors for changes that may affect the information in the brief, in which case further updates will be issued. The brief has yet to be updated, suggesting that there has been no new information of significance.

56. The brief concludes that "current evidence points to most individuals developing strong protective immune responses following natural infection" and that "recent evidence suggests that natural infection may provide similar protection against symptomatic disease as vaccination, at least for the available follow up period."

[25] ECDC *supra*. note 19 at page 15.

[26] World Health Organization, *COVID-19 natural immunity, Scientific brief,* May 10, 2021. https://apps.who.int/iris/bitstream/handle/10665/341241/WHO-2019-nCoV-Sci-Brief-Natural-immunity-2021.1-eng.pdf?sequence=3&isAllowed=y.

d) PUBLIC HEALTH AGENCY OF CANADA (PHAC) NATIONAL ADVISORY COMMITTEE ON IMMUNIZATION (NACI)

57. The Public Health Agency of Canada is the Government of Canada's official public health leading organization in Health Canada. The National Advisory Committee on Immunization (NACI) is the official advisory body to the Public Health Agency with respect to immunization policies for all types of infectious diseases and all types of vaccinations. It is not authorized to make decisions nor to set policy, but its advice (of credentialled experts and other members) is usually followed by federal and provincial jurisdictions, subject to feasibility, economic, and other considerations. In emerging events such as H1N1 (2009) or COVID-19, NACI produces rapid recommendations, updates, and interim guidance on the indications and contraindications of the use of vaccines. The approval of vaccines is the responsibility of the Health Products and Food Branch of Health Canada.

58. What has NACI recommended with respect to vaccination of persons previously infected with COVID-19? NACI's October 22, 2021, Recommendations on the Use of COVID-19 Vaccines classifies Recommendation 4 as a "*Discretionary Recommendation*". It states: "NACI recommends that a complete series with a COVID-19 vaccine *may be offered* to individuals in the authorized age group without contraindications to the vaccine who have had previously PCR-confirmed SARS-CoV-2 infection".[27] In other words, for those that have had a positive COVID-19 test and without contraindications to the vaccine, NACI is permissive, but does not actually recommend that they *should* get vaccinated.

59. NACI's recommendations are usually categorized as either "strong" or "discretionary". The rationale for a discretionary recommendation is "Known/anticipated advantages are closely balanced with known/anticipated disadvantages, or uncertainty in the evidence of advantages and disadvantages exists"[28].

60. The evidence provided in NACI's Recommendation 4 shows why NACI's recommendation is "discretionary" and why it has concluded that the advantages and disadvantages of vaccinating persons that were previously infected are "closely balanced" or that there is "uncertainty in the evidence".

61. For example, it is stated that "A number of large observational studies have found the incidence of reinfection in individuals with prior SARS-CoV-2 infection, with and without subsequent mRNA COVID-19 vaccination, to be comparable to individuals without prior infection who have received two doses of mRNA vaccine. In addition, a prospective observational study of the Israeli adult (≥16 years) population estimated that prior SARS-CoV-2 infection provided very high (94 to 96%) protection against subsequent infection, hospitalization, and severe illness, which were

[27] Public Health Agency of Canada, *Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI) Recommendations on the use of COVID-19 vaccines*, October 22, 2021, at page 56. https://www.canada.ca/content/dam/phac-aspc/documents/services/immunization/national-advisory-committee-on-immunization-naci/recommendations-use-covid-19-vaccines/recommendations-use-covid-19-vaccines-en.pdf. [Public Health Canada]

[28] *Ibid.* at page 61.

comparable to the estimates of protection provided by two doses of vaccine in the previously uninfected vaccinated cohort."[29]

62. NACI's Recommendations document refers to three "large observational studies", cited as 88, 89, 90 in NACI's endnotes, that compare natural immunity following infection with vaccine-induced immunity following vaccination.[30] The pertinent findings of each of these three studies by Shrestha, Hall, and Goldberg, respectively, are described in more detail in the following three paragraphs. Shrestha's study indicated that previously infected USA healthcare workers had the same protection from re-infection, whether vaccinated or not, as the protection from vaccination in previously uninfected persons.[31] Hall's study of UK healthcare workers indicated that vaccination was less protective than a previous infection.[32] Goldberg's population-based study in Israel showed that protection from previous infection was comparable to two doses of the Pfizer vaccine.[33] These three studies were the only large observational studies selected by NACI as evidence for comparing the protection from previous infection with protection from vaccination. The subjects in the studies in the USA and the UK were healthcare workers. The Israeli study was a whole population-based study, i.e. not a sample of subjects. The results are consistent in all three studies; natural immunity from previous infection provided equal or better protection than vaccination.

63. In the Shrestha study, 2,600 previously infected persons were followed up for 5 months. No cases of reinfection were observed. This group was part of a study of 52,000 health care system employees in the USA. *The cumulative incidence rate (total cases) of SARS-COV-2 infection amongst previously infected unvaccinated employees did not differ from that of previously infected fully vaccinated employees or from that of previously uninfected fully vaccinated employees.*[34] In other words, vaccination of previously infected healthcare workers did not reduce their risk of re-infection. The study concluded that "Individuals who have had SARS-CoV-2 infection are unlikely to benefit from COVID-19 vaccination, and vaccines can be safely prioritized to those who have not been infected before."[35]

64. Hall is cited for his study of 23,324 staff working for the National Health Service in UK hospitals. The protection for vaccinated (two-dose) persons without prior infection was 86% in comparison with 90% for unvaccinated persons with prior infections.[36]

65. Goldberg's paper is a prospective observational study capturing the entire adult (≥16 years) Israeli population. It provided estimates of protection against subsequent infection, hospitalization, and

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[29] Goldberg, Y.; Mandel M.; *et al*. medRxiv, Protection of previous SARS-CoV-2 infection is similar to that of BNT162b2 vaccine protection: A three-month nationwide experience from Israel, April 24. 2021. https://www.medrxiv.org/content/10.1101/2021.04.20.21255670v1.full.pdf. [Israel Study]

[30] Public Health Canada *supra* note 27 at page 39.

[31] Shrestha N.; Burke P.; *et al*. *medRxiv,* Necessity of COVID-19 vaccination in previously infected individuals. July 19, 2021. https://www.medrxiv.org/content/10.1101/2021.06.01.21258176v2. [Previous Infection Study]

[32] Hall V.; Foulkes S.; *et al*. Saei A, Andrews N, Oguti B, Charlett A, et al. *Lancet prepublication*, Effectiveness of BNT162b2 mRNA vaccine against infection and COVID-19 vaccine coverage in healthcare workers in England, multicentre prospective cohort study (the SIREN Study), February 22, 2021. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3790399. [Healthcare Workers in England]

[33] Isreal Study, *supra* note 29.

[34] https://www.Previous Infection Study *supra*. note 31 at Results: Cumulative Incidence of COVID-19.

[35] *Ibid*. at ABSTRACT: Conclusions.

[36] Healthcare Workers in England *supra*. note 32.

severe illness in previously infected unvaccinated individuals over 3 months of follow-up, when the B.1.1.7 (alpha) variant was the most prevalent variant. "In this unvaccinated population, the estimates of protection due to prior SARS-CoV-2 infection were 95% against subsequent infection, 94% against hospitalization, and 96% against severe illness compared to unvaccinated individuals without prior infection. *These estimates of protection from previous infection were comparable to the protection from two doses of Pfizer-BioNTech vaccine in the previously uninfected vaccinated cohort*" (emphasis mine).[37]

66. It is further stated by NACI that "These observational studies suggest previous infection with SARS-CoV-2 induces good protection against subsequent infection and that the protective effect may be comparable to complete mRNA COVID-19 vaccination in individuals without prior infection. However, whether the duration of protection generated from previous infection is similar to that elicited by mRNA COVID-19 vaccination remains unknown. The duration of protection provided by vaccination also remains unclear at this time."[38]

67. Research has not yet been able to answer other relevant questions such as duration of protection and cross-protection from variants of concern (VOCs). There is a lack of evidence comparing the immune responses against VOCs in unvaccinated, previously infected persons to immune responses against VOCs in vaccinated individuals.

68. Based on these studies and the recommendations of the Public Health Agency of Canada NACI, it is reasonable to conclude that there is a consensus or majority view amongst NACI's committee members that previous infection results in equivalent protection to that of vaccination. It is clear that NACI's Recommendation 4 does not say that vaccination of previously infected persons *should* be done, the wording that would be used for strong recommendations. It says, instead, that it *may* be done, but that there is insufficient evidence to support or reject this practice. This opinion is not qualified by the presence of predominance of a variant of concern. What this means to me is that NACI, as stated on October 22, 2021, has been of the opinion that there is insufficient evidence at this time to support a conclusion that vaccination of a previously infected person would improve the strength or duration of their protection from subsequent infection or infectiousness. NACI's opinion appears to apply to any variant of SARS-CoV-2. Furthermore, it appears NACI members share a concern that harmful adverse reactions to the vaccine by persons previously infected by COVID-19 could outweigh any benefits. I find these opinions and concerns of NACI to be reasonable and am not aware of any reasonable basis for policy makers to reject or ignore them.

69. With respect to the duration of protection, there is increasing evidence that immunity wanes within a few months after "full vaccination" of two doses of an mRNA vaccine. In a subsequent document prepared by NACI entitled: "Interim Guidance on Booster COVID-19 Vaccine Doses in Canada,

[37] Isreal Study, *supra* note 29.
[38] Public Health Canada *supra* note 27 at page 39.

October 29, 2021"[39] NACI recommends that a booster dose *should be offered* to key populations at *highest* risk of severe illness from COVID-19 and highest risk of waning protection[40]. It also recommends that booster doses *may* be offered to key populations of *increased* risk of severe illness from COVID-19 and *increased* risk of waning and/or lower protection. This recommendation of a third (booster) dose is based on several observations and opinions, including:

- Emerging evidence suggests a waning in COVID-19 vaccine immunogenicity and effectiveness against SARS-CoV-2 infection over time following completion of the primary series, although protection against severe COVID-19 outcomes appears to be more durable than protection against infection.[41]

- Increased incidence of breakthrough infections amongst those fully vaccinated is expected in the context of high community rates of SARS-CoV-2 (especially where vaccination coverage rates for the primary COVID-19 vaccine series are low) and the predominance of the Delta variant in Canada, given the somewhat lower vaccine effectiveness against infection with this VoC."[42]

70. Despite NACI's recognition in its October 22, 2021 Recommendations on the Use of COVID-19 Vaccines of the observed equivalence of immune protection from previous infection in unvaccinated persons and full vaccination of non-infected persons, there is no mention of any evidence regarding waning of natural immunity following previous infection. Neither is this question listed as a research priority. Given the importance of this question, it appears that NACI has accepted for now current observations and past empirical and scientific knowledge of the high levels and long duration of protection from natural immunity following infection from different types of viruses.

71. Policies which recommend or require persons previously infected by SARS-CoV-2 to be vaccinated are inconsistent with usual public health policies and practice for other vaccines. Vaccination is usually not recommended or contraindicated for persons with evidence of previous infection, such as measles, rubella, hepatitis A, hepatitis B, and rabies. This is because the harm from vaccination in these circumstances is considered to outweigh the benefit. In other words, when previous infection confers adequate levels and duration of protection, the benefit of vaccination is negligible. Any risk of harm, whether mild or severe, is likely to outweigh that benefit.

72. The *Alberta Health Services Standard on the Contraindications and Precautions Related to Immunization* defines contraindication as a "Situation in which a vaccine should not be given because the risk of an adverse event outweighs any potential therapeutic benefit of the vaccine"[43].

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[39] Public Health Agency of Canada, An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI) Interim guidance on booster COVID-19 vaccine doses in Canada, October 29, 2021. https://www.canada.ca/content/dam/phac-aspc/documents/services/immunization/national-advisory-committee-on-immunization-naci/recommendations-use-covid-19-vaccines/statement-guidance-booster-doses/statement-guidance-booster-doses.pdf.

[40] *Ibid.* at page 16.

[41] *Ibid.* At page 18.

[42] *Ibid.* at page 18.

[43] Alberta Health Services, *Standard on the Contraindications and Precautions Related to Immunization*, Revised: September 12, 2016. https://www.albertahealthservices.ca/assets/info/hp/cdc/if-hp-cdc-ipsm-standard-contraindications-precautions.pdf at page 2.

Alberta's immunization policy states that the vaccines for measles, mumps, and rubella are *indicated* for persons *without* previous recommended vaccination or *a history of laboratory-confirmed disease*.[44]

73. In NACI's Recommendations on the Use of COVID-19 Vaccines, referred to previously, several research priorities are listed regarding the use of vaccines in individuals who have had previous laboratory evidence of SARS-CoV-2 infection.[45]

74. For these questions to be in NACI's research priorities list shows that they are important questions for immunization policy-setting and that their answers are not yet known. NACI's questions include[46]:

> What is the efficacy, effectiveness, immunogenicity, and safety of COVID-19 vaccines in individuals who have had a previous laboratory evidence of SARS-CoV-2 infection?
>
> a. Is there a discernable difference between seronegative and seropositive people in any of the above parameters? (*Note, seronegative refers to persons whose blood does not have antibody evidence of previous infection; seropositive refers to persons whose blood has antibody evidence of previous infection.)
>
> b. Does previous exposure to SARS-COV-2 impact efficacy, effectiveness, immunogenicity, or safety of COVID-19 vaccines?
>
> c. Can a single-dose vaccine series be as effective and safe in individuals with previously proven COVID-19 disease?
>
> d. Are there any emerging safety signals with COVID-19 immunization that are not predicted by current understanding of the safety profile of similar vaccines?
>
> e. Does vaccination following prior SARS-CoV-2 infection or vaccination of SARS-CoV-2 naïve individuals elicit enhanced or altered disease upon subsequent infection by SARS-CoV-2 or other endemic coronaviruses?

75. It is significant that NACI considers these questions to be unanswered and to be relevant to COVID-19 policy-setting. Cautionary public health decision-making should take these uncertainties into account and explain transparently how they have been considered in the context of the evidence for and the expected outcomes of their policies.

76. In NACI's October 29, 2021 *Interim Guidance on Booster COVID-19 vaccine doses*[47], the first two of seven research priorities are: 1) "What is the efficacy, effectiveness, immunogenicity and safety of

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[44] Alberta Immunization Policy, *MMR Vaccine*, December 2021. https://open.alberta.ca/dataset/aip/resource/722329ea-4d90-42eb-8a7a-10c9fa0249d0/download/AIP-BP-MMR.pdf at pages 1-2.

[45] Public Health Canada *supra* note 27 at page 56.

[46] *Ibid.* at page 56.

[47] NACI COVID-19 Booster Guidance *supra*. note 14.

a booster dose COVID-19 vaccine in individuals who have had a previous laboratory-confirmed SARS-CoV-2 infection?"; and 2) "What is the effect of booster doses of COVID-19 vaccines on transmission of infection at a population level? How long do any beneficial effects on transmission last?"[48]

77. Of significance, these two research priorities for the COVID-19 vaccines reveal that there is insufficient evidence regarding the effectiveness and safety of a booster shot in individuals previously infected and the impact and duration at a population level of booster doses of COVID-19 vaccines.

78. In summary, regarding comparability of protection by natural immunity or vaccination, there is remarkable consistency between the documents of the official public health organizations most often referred to by Canada and the provinces, namely the United Nations World Health Organization, the European Centre for Disease Control, the USA Centers for Disease Control and Prevention, and the Public Health Agency's National Advisory Committee on Immunization. These reports and/or their referenced evidence indicate that natural immunity has been shown to be at least as protective as vaccine-induced immunity, while recognizing that the periods of follow-up have been of limited length of time to confirm the long-term strength and duration of protection.

III. In my opinion, what issues should be considered, what information should be obtained, and how should these considerations and information be used to set policies regarding the hindering of previously infected unvaccinated physicians and other health care workers to work in Alberta Health Services facilities?

Conclusion summary: I have been unable to find relevant data or clear rationale for policies pertaining to the exclusion of health care workers because of their vaccination status, especially since there has been consistent evidence for equivalent – if not superior - protection by natural immunity resulting from previous infection, as described by the major public health organizations and the Public Health Agency's National Advisory Committee on Immunization.

79. Alberta Health Services (AHS) has posted an "Ethics Decision-making Process"[49] on its website. It outlines five steps: 1) Clarify the key question, 2) Identify facts and stakeholders, 3) Identify values and prioritize, 4) Identify options, and 5) Make a decision and evaluate.

80. These steps are consistent with other public health decision-making frameworks. The question of importance is not whether the framework or process is good. The question is whether it has been used or not – and if so, how.

81. Consistent with the *Canadian Charter of Rights and Freedoms*, most public health acts and emergencies acts refer to the requirement of governments and public health authorities to use the least intrusive means necessary to respond to a public health threat. These decisions are matters

[48] *Ibid.*

[49] Alberta Health Services, *Values-Based Decision-Making Toolkit,* December 2019. if-hp-ethics-toolkit.docx (live.com)

of judgment. The standards and ethics of public health practice require that they be reasonable, fair, based on science and evidence, and be explained transparently. Like most ethical frameworks for public health, it is expected that respect for autonomy is listed along with beneficence, non-malevolence, and equity/fairness.

82. The Public Health Agency of Canada (PHAC) has posted the *Public Health Ethics Framework: A guide for use in response to the COVID-19 pandemic in Canada*[50]. One of the listed selected sources is *Alberta's Ethical Framework for Responding to a Pandemic Influenza (2016)*[51]. PHAC's framework includes the following.

> In order to promote well-being and minimise harm, the following must be considered when weighing options:
>
> **Effectiveness:** there should be a reasonable likelihood that the proposed decision or action will achieve its goals, and that its implementation is feasible. If scientific evidence is available, the proposed action or decision should be supported by the evidence;
>
> **Proportionality:** potential benefits should be balanced against risks of harm. Measures should be proportionate to the relevant threat and risks, and the benefits that can be gained. If a limitation of rights, liberties or freedoms is deemed essential to achieve an intended goal, the least restrictive measures possible should be selected, and imposed only to the extent necessary to prevent foreseeable harm;
>
> **Reciprocity:** those who are asked to take increased risks or face greater or disproportionate burdens in order to protect the public good should be supported by society in doing so, and the burdens they face should be minimised to the greatest extent possible;
>
> **Precaution:** scientific uncertainty should not prevent decision makers from taking action to reduce risks associated with COVID-19. The continued search for scientific evidence should nonetheless be a goal.

83. *Alberta's Ethical Framework for Responding to a Pandemic Influenza (2016)* includes all of the above considerations in "weighing options" in decision-making. How well does the Alberta Health Services Policy *"Immunization of Workers for COVID-19"*[52] conform to the expectations of Alberta's and Canada's frameworks for ethical decision-making?

84. Regarding *"effectiveness"*, I have been unable to find in the policy or its listed references any measurable goals (i.e. objectives) for disease transmission rates in health facilities, an assessment of causes and risk factors of outcomes (e.g. severe illness), or how this policy will achieve such

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[50] Government of Canada, *Public health ethics framework: A guide for use in response to the COVID-19 pandemic in Canada* https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/canadas-reponse/ethics-framework-guide-use-response-covid-19-pandemic.html#a2. [Canada Public Health Ethics Framework]

[51] Alberta Government Publications, Alberta's ethical framework for responding to pandemic influenza, January 1, 2016. Alberta's Ethical Framework for Responding to Pandemic Influenza

[52] Alberta Health Services, Policy 1189 – Immunization of Workers for COVID-10, Revised: November 29, 2021. https://extranet.ahsnet.ca/teams/policydocuments/1/clp-ahs-immunization-workers-1189.pdf.

objectives. There are no references to persons previously infected and how their immune protection compares with immunized workers. There is no explanation of why testing is not required for immunized workers whose protection has been shown to be similar, if not less than, previously infected workers.

85. Regarding "*proportionality",* there is no explanation of how other less restrictive options were considered in comparison. "If a limitation of rights, liberties or freedoms is deemed essential to achieve an intended goal, the least restrictive measures possible should be selected, and imposed only to the extent necessary to prevent foreseeable harm."[53]

86. Regarding "*reciprocity*", it is unclear why previously infected healthcare workers are expected to pay for testing and do the tests on their own time despite being equally or more protected from infection than their immunized co-workers.

87. Regarding "*precaution*", for example, I have not found references to precautions with respect to the impact that restrictions on unvaccinated healthcare workers will have on the number of healthcare workers available for staffing the health care facilities.

88. The Government of Canada has posted a document *Federal/Provincial/Territorial Public Health Response Plan for Ongoing Management of COVID-19*[54] wherein the broad goal of the plan is "*to minimize serious illness and overall deaths while minimizing societal disruption as a result of the COVID-19 pandemic*."[55] More specifically, there are 10 objectives, including "taking public health action to reduce the incidence, morbidity and mortality of COVID-19 to a locally manageable level (including operationalizing the vaccine strategy)" and "ensuring access to health care services (both COVID-19 and non-COVID-19 related services), supplies and treatment options."[56]

89. As expressed by the *Federal/Provincial/Territorial Public Health Response Plan for Ongoing Management of COVID-19*, to justify the use of any one specific restrictive public health measure, *governments and public health officials are expected to demonstrate transparently a risk, benefit, and harm analysis*.

A. PUBLIC HEALTH ASSESSMENT REQUIREMENTS

90. To be consistent with these expectations, decisions should consider several factors, including the severity of the public health threat, the goals and objectives of the strategy, and the pros and cons of intervention options. In public health plans or strategies, goals are usually broad and unmeasured (e.g., reduced burden of COVID-19 on hospitals), whereas objectives are specific and measurable (e.g., to maintain health care worker absence because of illness or quarantine (self-isolation) to one percent at any one time). Without specific objectives, there is no rational basis for choosing and implementing specific policies or interventions. Measurable and time-defined

[53] Canada Public Health Ethics Framework *supra*. note 50.
[54] Government of Canada, *Federal/Provincial/Territorial Public Health Response Plan for Ongoing Management of COVID-19*, April 19, 2021. https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/guidance-documents/federal-provincial-territorial-public-health-response-plan-ongoing-management-covid-19.html#a4.1.
[55] *Ibid.* at *COVID-19 response goal, objectives and response to date.*
[56] *Ibid.*

objectives require making decisions based on evidence and reason – and explaining how the specified outcomes would be achieved and how the intervention can be evaluated and modified.

91. I have not been able to find in any of the public health orders or on an Alberta government website a description or explanation of specific objectives of the COVID-19 strategy in general, or specifically the mandating of vaccination in health care workers. A Google word search for "Alberta COVID strategies goals objectives" failed to find a website with a description of a strategy with goals and measurable objectives.

92. On Alberta's website for 'COVID-19 Info for Albertans'[57], the tag line is "taking action to protect the health care system, increase vaccination rates, and reduce the transmission of COVID-19". In the overview of its public health actions, it is stated that "Alberta has declared a state of public health emergency. Measures to protect the health care system, stop the spread, and increase vaccination rates are in effect."[58] No other details are provided to describe the data analysis, information, evidence, or rationale for these strategies or specific actions. Nor are there any "SMART" objectives (specific, measurable, achievable, reasonable, time-defined).

93. There is a table of vaccination phases, describing targeted age groups, but no measurable targets or objectives (e.g., a defined percentage of eligible persons to be vaccinated) were found.

94. Alberta Health Service's vision, mission, values, and strategies include broad and inspirational goals for Covid-19 but not specific, measurable, or time-defined objectives.[59] The "main objectives" are more like goals with a broad direction, but lacking in specifics. There are some specified and quantifiable measures such as "total Alberta residents who received a COVID-19 vaccination (at least the first dose)", but there are no objectives such as the percentage target or the time to achieve it. This is important because without such specific targets, any health policies (e.g. restrictions, incentives, and other public health measures) cannot be rationally determined or justified; nor can their progress or end-points be measured or evaluated.

95. The pros and cons of interventions should consider net effectiveness (benefit minus harm), efficiency (e.g., cost-effectiveness), and equity (fairness of the different impacts the intervention might have on people and communities, especially those that were already disadvantaged with respect to the determinants of health). I have not been able to find a description of the method or estimates used to consider effectiveness, cost-effectiveness, or equity of the orders for mandatory vaccination. Nor have I been able to find a description or comparative analysis of effectiveness, cost-effectiveness, and equity of other options.

96. Decisions and judgments should be made using available data and evidence, including scientific principles and previous relevant empirical experience. Because of the complex and changing nature

[57] Alberta, *COVID-19 info for Albertans, Taking action to protect the health care system, increase vaccination rates, and reduce the transmission of COVID-19.* https://www.alberta.ca/coronavirus-info-for-albertans.aspx.
[58] Alberta, *COVID-19 public health actions, Public health restrictions are in place to reduce the impacts of COVID-19 on the health care system. Some businesses can participate in the Restrictions Exemption Program*. https://www.alberta.ca/covid-19-public-health-actions.aspx
[59] Alberta Health Services, *AHS' Four Foundational Strategies*. https://www.albertahealthservices.ca/about/Page12951.aspx

of biology and human society, the available evidence is always incomplete.

97. This lack of complete data is often truer in a public health threat that has new and unforeseen elements, especially when the reactions of governments, public health leaders, and members of the public may be more difficult to predict or influence than the biological interactions between the virus and its human host organism.

98. The expected approach of decision-makers when data is incomplete is to make the best estimates possible of the most relevant and consequential parameters. It is incumbent on decision-makers to explain why they have chosen such parameters, their best estimates of each parameter, the evidence that has been used for making these estimates, and how they have used these estimates in their decision-making. Other considerations, some of which may be more qualitative than quantitative, should also be explained. These include values, norms, beliefs and other ethical principles. For further clarity, considerations and outcomes of various strategy options should include personal, psychological, spiritual, health and social care, social relationships, and networks, educational, environmental, economic (including employment and income), and recreational determinants of health.

99. For quantitative estimates, such as the effectiveness of certain interventions, it is not enough to say that "something works" or that something "may happen". In public health, like clinical medicine, effect size (measured benefits and harms) and probabilities should be estimated even in the absence of strong evidence. Assertions that mandatory vaccination will "work" without an estimate of the infection transmission reduction and other benefits and harms are just as unacceptable as asserting that a vaccine "works" without providing a numerical estimation of its efficacy or effectiveness such as the reduction of infections, hospitalizations, and deaths as well as the rate and severity of side effects.

100. For further clarity, public health strategies such as mandatory vaccination or restriction of activities for people without full vaccination, the beneficial effects and harms of such an intervention should be estimated, measured, and monitored. The choice of measurements should be determined by the objectives of the strategy, whether they are to incentivize and increase vaccination rates and/or to reduce infection transmission.

101. Interventions in public health should be explained and justified transparently, including admissions of uncertainty. Options should be described. Reasons for their acceptance or rejection should be explained. Without these, the ability of those most affected, experts, the media, and politicians to engage in meaningful discussion and debate is limited. Active engagement based on these principles should be expected to improve government decision-making and should be expected to gain the trust and willingness of those who are asked or mandated to make personal and family sacrifices in the interest of the public good.

B. PUBLIC HEALTH MEASURES REGARDING HEALTH CARE WORKERS

102. In my opinion, with respect to mandatory vaccination of health care workers, the following questions must be answered – as best as can be reasonably estimated – to rationally develop, implement, and monitor an effective, efficient, and equitable public health intervention of this

type. This is especially important when a policy could decrease the number of available healthcare workers, resulting in less patient care and more stress for those at work.

a. What are the specific targets for the number/rate of patients admitted to hospital and number/rate of patients currently in hospital and/or ICU's in which the reason for admission is attributable to COVID-19?

b. What is the estimated proportion of health care workers that have been vaccinated and/or previously infected (nasal swab/PCR or blood/antibodies)?

c. What is the estimated occurrence of transmission of infection from health care workers to other health care workers or to patients in health care facilities?

d. What is the estimated occurrence of new infections/cases of health care workers?

e. Of new infections/cases of health care workers, what proportion have been transmitted in health care facilities?

f. What has been the impact of transmission from health care workers with respect to the average number of cases of transmission, contribution to outbreaks (dependent on definition), need for hospitalizations, need for ICU, or deaths?

g. What is the estimated impact of anticipated missed work because of mandatory vaccination of healthcare workers and their families, other healthcare workers that they work with, all other health care workers because of less staff, and on the health care of patients, the families of patients and the length of patient wait lists?

h. What are the anticipated adverse events and what is the estimated frequency of side effects from vaccines given to persons that already have natural immunity from previous infection?

i. What is the estimated impact of mandatory vaccination for health care workers on the rates of hospitalizations and deaths attributable to COVID-19?

j. What is the estimated comparison of a policy of exclusion of unvaccinated health care workers previously infected with a policy of non-exclusion of unvaccinated health care workers previously infected with respect to absenteeism of healthcare workers, transmission of infections, and severe outcomes – direct and indirect – associated with transmission of infection in healthcare facilities?

103. Public health strategies should be based on specific and measurable objectives or targets that are appropriate to the public health threat and are reasonable and achievable in a way that optimizes overall population benefit and minimize harmful consequences. Without the information enumerated above, it is my opinion there is insufficient evidence and rationale to reasonably

demonstrate the appropriateness of implementing a public health policy to prohibit or otherwise hinder previously infected healthcare workers from doing their jobs.

104. For further clarity, I have been unable to find relevant and clear data or rationale for policies pertaining to the exclusion of health care workers because of their vaccination status, especially when there has been consistent evidence for equivalent – if not superior - protection from the natural immunity resulting from previous infection, as described by the major public health organizations and the Public Health Agency's National Advisory Committee on Immunization.

SUMMARY AND CONCLUSIONS

105. I have been asked, as a public health physician and former provincial chief medical officer of health, to give my professional opinion on the following questions.

I. How does protection against COVID-19 infection by natural immunity compare with protection against COVID-19 from vaccine-induced immunity? Specifically, how do these compare with respect to levels of protection and duration of protection?

106. *Current evidence and previous scientific observation of other anti-viral vaccines indicate that natural immunity from previous infection is at least as protective – and for at least as long – as vaccine-induced immunity.*

II. Regarding question I, what are current stated facts and opinions of official public health organizations?

107. *There is a high level of consistency of observations and/or conclusions between the major public health organizations – the World Health Organization, the European Centres for Disease Control, the USA Centers for Disease Control and Prevention and the Canadian Public Health Agency's National Advisory Committee on Immunization – with respect to the similarity of levels and duration of protection by natural immunity from previous infection and the levels and duration of protection by vaccine-induced immunity.*

III. In my opinion, what issues should be considered, what information should be obtained, and how should these considerations and information be used to set policies regarding the hindering of previously infected unvaccinated physicians and other health care workers to work in Alberta Health Services facilities?

108. *In summary, public health strategies should be based on specific and measurable objectives or targets that are appropriate to the public health threat and are reasonable and achievable in a way that optimize overall population benefit and minimize harmful consequences. This approach should apply to interventions in specific settings.*

In conclusion, I have been unable to find relevant data or clear rationale for policies pertaining to the exclusion of health care workers because of their vaccination status, especially since there has

been consistent evidence for equivalent – if not superior - protection by natural immunity resulting from previous infection, as described by the major public health organizations and the Public Health Agency's National Advisory Committee on Immunization.

Exhibit "C"

This is **Exhibit "C"** referred to in the
Affidavit of Joel Kettner
sworn before me via videoconferencing at
Calgary, Alberta, this
9th day of December, 2021.

_____
A Notary Public in and for the Province
of Alberta

Eva Chipiuk
Barrister & Solicitor

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TAB 1

MyHealth.Alberta.ca

Coronavirus disease (COVID-19): Care instructions

This information has been translated into other languages – see the links at the bottom of this page.

Overview

The coronavirus disease (COVID-19) is caused by a virus. COVID-19 symptoms are a lot like symptoms of the flu (influenza) or other illnesses that affect the lungs and airways (called respiratory illnesses). COVID-19 can cause:

- fever
- cough
- shortness of breath
- trouble breathing
- sore throat
- runny nose

If you're an adult and have any of these symptoms, you **must** self-isolate for at least 10 days after your symptoms started or until your symptoms are gone, whichever is longer.
For children and anyone over 18 years of age attending high school, use the daily screening checklist every day before they go to school, child care, or other activities. If your child has symptoms, follow the advice on the checklist.
If you are tested, follow instructions at ahs.ca/results based on your test results.
Other symptoms can include:

- stuffy nose
- painful swallowing
- headache
- chills
- muscle or joint aches
- feeling unwell in general
- feeling more tired than usual or having no energy at all
- feeling sick to your stomach (nausea), throwing up, diarrhea (watery stool), or not feeling hungry
- loss of sense of smell or taste
- pink eye (conjunctivitis)

If you have any of the other symptoms, stay home and limit your contact with others until your symptoms go away.
Most people (about 80%) have only mild symptoms or no symptoms at all. But people who are very sick may need care in a hospital. In severe cases, COVID-19 can cause pneumonia, make it hard to breathe without help, and can even lead to death.

How does it spread?

This virus spreads person-to-person through droplets from coughing and sneezing. It may also spread by touching something that has the virus on it, such as a doorknob or a tabletop, and then touching your face.

How is it diagnosed?

The virus is diagnosed with a test that uses a swab of fluid from your nose or throat, or sometimes uses sputum (phlegm) from the lungs. You may have other tests, such as blood tests and a computed tomography (CT) scans of the lungs. But even if you don't have a test, you may be told you probably have the virus based on your symptoms and history.
If you think you've been exposed to COVID-19 and have symptoms, take the COVID-19 Self-Assessment.

Is there medicine for COVID-19?

There is no medicine to fight the virus. If you have mild symptoms, you can care for yourself at home. You can take acetaminophen (Tylenol) for a fever or pain, if it's safe for you. Check with your doctor or pharmacist if you're not sure. Treatment in the hospital for more serious cases includes support, such as oxygen and help with breathing.

What should I do if I have COVID-19 or have symptoms of COVID-19?

If you've been diagnosed with COVID-19 or have symptoms of COVID-19, you **must** self-isolate for 10 days after your symptoms started or until your symptoms are gone (whichever is longer). This means you need to stay home and away from other people. To learn more visit www.alberta.ca/isolation.aspx.
Take the COVID-19 Self-Assessment to know if you need to be tested for COVID-19.
Call **Health Link** at **811** as soon as you have symptoms. Call ahead from home before going to a healthcare facility, such as a doctor's office or walk-in clinic.
Call **911** if you're seriously ill and need medical help right away. Tell them that you may have COVID-19.
Follow-up care is a key part of your treatment and safety. Be sure to make and keep all your healthcare appointments, and call your doctor or Health Link at 811 if you're having problems. It's also a good idea to know your test results and keep a list of the medicines you take.

Where can I learn more?

You can find the latest information about COVID-19 from these sources:

- Alberta Health
- Alberta Health Services
- Government of Canada

I have been diagnosed with COVID-19 or am self-isolating because I might have COVID-19. How can I care for myself at home?

- Be safe with medicines. Take your medicines exactly as prescribed. Call your doctor or Health Link at 811 if you think you're having a problem with your medicine.
- Stay home. Don't go to school, work, or public places. Don't use public transportation (such as the bus or train). Leave your home only if you need to get medical care. Call ahead from home before you go to a doctor's office. They can decide if in-person care or virtual care (such as a phone call or video call) is best for you. If you don't have a family doctor, go to AlbertaFindADoctor.ca.
- Wear a face mask if you have symptoms of COVID-19 and can't stay away from other people, such as in your own home or when you're going to get medical help. Wearing a mask can help stop the virus from spreading when you cough or sneeze.
- Limit contact with people in your home. Only one healthy person should care for you. If possible, stay in a separate bedroom and use a separate washroom from everyone else in your home.
- Cover your mouth and nose with a tissue when you cough or sneeze. Throw it in the trash right away.
- Wash your hands often, especially after you cough or sneeze. Use soap and water, and scrub for at least 20 seconds. If you don't have soap and water at the time, use an alcohol-based hand sanitizer.
- Don't share personal household items. These include bedding, towels, cups, eating utensils, and electronic devices (such as tablets and phones).
- Clean and disinfect your home every day. Use household cleaners and disinfectant wipes or sprays. Take special care to clean things that you grab with your hands. These include doorknobs, remote controls, phones, and handles on your refrigerator and microwave. And don't forget to clean countertops, tabletops, washrooms, and computer keyboards.
- Follow the advice you've been given about when it's safe to leave isolation. If you're not sure, call Health Link at 811.

When should I call for help?


Call **911** anytime you think you may need emergency care. Tell them you have COVID-19 symptoms.
For example, call if:

- You have severe trouble breathing or severe chest pain.
- You are very confused and not thinking clearly.
- You pass out (lose consciousness).

Call your doctor or Health Link at 811 now or get medical care right away if:

- You have new or worse trouble breathing.
- Your symptoms are getting worse.
- You start getting better than you get worse.
- You have severe dehydration. Symptoms of dehydration include:
  - having a very dry mouth
  - passing only a little urine
  - feeling very light-headed

Whether you have symptoms or not, call your doctor's office **before** you go. If you have symptoms, make sure you wear a face mask when you go to the doctor to stop the virus from spreading.

Related to Coronavirus Disease (COVID-19): Care Instructions

- COVID-19: Alberta Health Services
- COVID-19 information for Albertans: Alberta Health
- COVID-19 Self-Assessment

Other languages

Coronavirus Disease (COVID-19): Care instructions

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For 24/7 nurse advice and general health information call Health Link at 811.

Current as of: Nov 2, 2020
Author: Adapted from Healthwise

TAB 2

Transmission of SARS-CoV-2: implications for infection prevention precautions

Scientific Brief

9 July 2020

This scientific brief (text below) is outdated. For the latest information on COVID-19 transmission, please see:

Mask use in the context of COVID-19 (1 December 2020)

Roadmap to improve and ensure good indoor ventilation in COVID-19 context (1 March 2021).

This document is an update to the scientific brief published on 29 March 2020 entitled “Modes of transmission of virus causing COVID-19: implications for infection prevention and control (IPC) precaution recommendations” and includes new scientific evidence available on transmission of SARS-CoV-2, the virus that causes COVID-19.

Overview

This scientific brief provides an overview of the modes of transmission of SARS-CoV-2, what is known about when infected people transmit the virus, and the implications for infection prevention and control precautions within and outside health facilities. This scientific brief is not a systematic

review. Rather, it reflects the consolidation of rapid reviews of publications in peer-reviewed journals and of non-peer-reviewed manuscripts on pre-print servers, undertaken by WHO and partners. Preprint findings should be interpreted with caution in the absence of peer review. This brief is also informed by several discussions via teleconferences with the WHO Health Emergencies Programme ad hoc Experts Advisory Panel for IPC Preparedness, Readiness and Response to COVID-19, the WHO ad hoc COVID-19 IPC Guidance Development Group (COVID-19 IPC GDG), and by review of external experts with relevant technical backgrounds.

The overarching aim of the global Strategic Preparedness and Response Plan for COVID-19*(1)* is to control COVID-19 by suppressing transmission of the virus and preventing associated illness and death. Current evidence suggests that SARS-CoV-2, the virus that causes COVID-19, is predominantly spread from person-to-person. Understanding how, when and in what types of settings SARS-CoV-2 spreads is critical to develop effective public health and infection prevention and control measures to break chains of transmission.

Modes of transmission

This section briefly describes possible modes of transmission for SARS-CoV-2, including contact, droplet, airborne, fomite, fecal-oral, bloodborne, mother-to-child, and animal-to-human transmission. Infection with SARS-CoV-2 primarily causes respiratory illness ranging from mild disease to severe disease and death, and some people infected with the virus never develop symptoms.

Contact and droplet transmission

Transmission of SARS-CoV-2 can occur through direct, indirect, or close contact with infected people through infected secretions such as saliva and respiratory secretions or their respiratory droplets, which are expelled when an infected person coughs, sneezes, talks or sings.(2-10*)* Respiratory droplets are >5-10 μm in diameter whereas droplets ≤5μm in diameter are referred to as droplet nuclei or aerosols.*(*11*)* Respiratory droplet transmission can occur when a person is in close contact (within 1 metre) with an infected person who has respiratory symptoms (e.g. coughing or sneezing) or who is talking or singing; in these circumstances, respiratory droplets that include virus can reach the mouth, nose or eyes of a susceptible person and can result in infection. Indirect contact transmission involving contact of a susceptible host with a contaminated object or surface (fomite transmission) may also be possible (see below).

Airborne transmission

Airborne transmission is defined as the spread of an infectious agent caused by the dissemination of droplet nuclei (aerosols) that remain infectious when suspended in air over long distances and time. *(11)* Airborne transmission of SARS-CoV-2 can occur during medical procedures that generate aerosols ("aerosol generating procedures").*(12)* WHO, together with the scientific community, has been actively discussing and evaluating whether SARS-CoV-2 may also spread through aerosols in the absence of aerosol generating procedures, particularly in indoor settings with poor ventilation.

The physics of exhaled air and flow physics have generated hypotheses about possible mechanisms of SARS-CoV-2 transmission through aerosols.*(13-16)* These theories suggest that 1) a number of respiratory droplets generate microscopic aerosols (<5 μm) by evaporating, and 2) normal breathing and talking results in exhaled aerosols. Thus, a susceptible person could inhale aerosols, and could become infected if the aerosols contain the virus in sufficient quantity to cause infection within the recipient. However, the proportion of exhaled droplet nuclei or of respiratory droplets that evaporate to generate aerosols, and the infectious dose of viable SARS-CoV-2 required to cause infection in another person are not known, but it has been studied for other respiratory viruses.*(17)*

One experimental study quantified the amount of droplets of various sizes that remain airborne during normal speech. However, the authors acknowledge that this relies on the independent action hypothesis, which has not been validated for humans and SARS-CoV-2.*(18)* Another recent experimental model found that healthy individuals can produce aerosols through coughing and talking *(19)*, and another model suggested high variability between individuals in terms of particle emission rates during speech, with increased rates correlated with increased amplitude of vocalization.*(20)* To date, transmission of SARS-CoV-2 by this type of aerosol route has not been demonstrated; much more research is needed given the possible implications of such route of transmission.

Experimental studies have generated aerosols of infectious samples using high-powered jet nebulizers under controlled laboratory conditions. These studies found SARS-CoV-2 virus RNA in air samples within aerosols for up to 3 hours in one study *(21)* and 16 hours in another, which also found viable replication-competent virus.*(22)* These findings were from experimentally induced aerosols that do not reflect normal human cough conditions.

Some studies conducted in health care settings where symptomatic COVID-19 patients were cared for, but where aerosol generating procedures were not performed, reported the presence of SARS-CoV-2 RNA in air samples *(23-28)*, while other similar investigations in both health care and non-health care settings found no presence of SARS-CoV-2 RNA; no studies have found viable virus in air samples.*(29-36)* Within samples where SARS-CoV-2 RNA was found, the quantity of RNA detected was in extremely low numbers in large volumes of air and one study that found SARS-CoV-

2 RNA in air samples reported inability to identify viable virus. *(25)* The detection of RNA using reverse transcription polymerase chain reaction (RT-PCR)-based assays is not necessarily indicative of replication- and infection-competent (viable) virus that could be transmissible and capable of causing infection.*(37)*

Recent clinical reports of health workers exposed to COVID-19 index cases, not in the presence of aerosol-generating procedures, found no nosocomial transmission when contact and droplet precautions were appropriately used, including the wearing of medical masks as a component of the personal protective equipment (PPE). *(38, 39)* These observations suggest that aerosol transmission did not occur in this context. Further studies are needed to determine whether it is possible to detect viable SARS-CoV-2 in air samples from settings where no procedures that generate aerosols are performed and what role aerosols might play in transmission.

Outside of medical facilities, some outbreak reports related to indoor crowded spaces *(40)* have suggested the possibility of aerosol transmission, combined with droplet transmission, for example, during choir practice *(7)*, in restaurants *(41)* or in fitness classes.*(42)* In these events, short-range aerosol transmission, particularly in specific indoor locations, such as crowded and inadequately ventilated spaces over a prolonged period of time with infected persons cannot be ruled out. However, the detailed investigations of these clusters suggest that droplet and fomite transmission could also explain human-to-human transmission within these clusters. Further, the close contact environments of these clusters may have facilitated transmission from a small number of cases to many other people (e.g., superspreading event), especially if hand hygiene was not performed and masks were not used when physical distancing was not maintained.*(43)*

Fomite transmission

Respiratory secretions or droplets expelled by infected individuals can contaminate surfaces and objects, creating fomites (contaminated surfaces). Viable SARS-CoV-2 virus and/or RNA detected by RT-PCR can be found on those surfaces for periods ranging from hours to days, depending on the ambient environment (including temperature and humidity) and the type of surface, in particular at high concentration in health care facilities where COVID-19 patients were being treated.*(21, 23, 24, 26, 28, 31-33, 36, 44, 45)* Therefore, transmission may also occur indirectly through touching surfaces in the immediate environment or objects contaminated with virus from an infected person (e.g. stethoscope or thermometer), followed by touching the mouth, nose, or eyes.

Despite consistent evidence as to SARS-CoV-2 contamination of surfaces and the survival of the virus on certain surfaces, there are no specific reports which have directly demonstrated fomite transmission. People who come into contact with potentially infectious surfaces often also have

close contact with the infectious person, making the distinction between respiratory droplet and fomite transmission difficult to discern. However, fomite transmission is considered a likely mode of transmission for SARS-CoV-2, given consistent findings about environmental contamination in the vicinity of infected cases and the fact that other coronaviruses and respiratory viruses can transmit this way.

Other modes of transmission

SARS-CoV-2 RNA has also been detected in other biological samples, including the urine and feces of some patients.*(*46-50*)*One study found viable SARS-CoV-2 in the urine of one patient.*(*51*)*Three studies have cultured SARS-CoV-2 from stool specimens. *(*48*,* 52*,* 53*)* To date, however, there have been no published reports of transmission of SARS-CoV-2 through feces or urine.

Some studies have reported detection of SARS-CoV-2 RNA, in either plasma or serum, and the virus can replicate in blood cells. However, the role of bloodborne transmission remains uncertain; and low viral titers in plasma and serum suggest that the risk of transmission through this route may be low.*(*48*,* 54*)* Currently, there is no evidence for intrauterine transmission of SARS-CoV-2 from infected pregnant women to their fetuses, although data remain limited. WHO has recently published a scientific brief on breastfeeding and COVID-19.*(*55*)* This brief explains that viral RNA fragments have been found by RT-PCR testing in a few breast milk samples of mothers infected with SARS-CoV-2, but studies investigating whether the virus could be isolated, have found no viable virus. Transmission of SARS-CoV-2 from mother to child would necessitate replicative and infectious virus in breast milk being able to reach target sites in the infant and also to overcome infant defense systems. WHO recommends that mothers with suspected or confirmed COVID-19 should be encouraged to initiate or continue to breastfeed.*(*55*)*

Evidence to date shows that SARS-CoV-2 is most closely related to known betacoronaviruses in bats; the role of an intermediate host in facilitating transmission in the earliest known human cases remains unclear.*(*56*,* 57*)* In addition to investigations on the possible intermediate host(s) of SARS-CoV-2, there are also a number of studies underway to better understand susceptibility of SARS-CoV-2 in different animal species. Current evidence suggests that humans infected with SARS-CoV-2 can infect other mammals, including dogs*(*58*)*, cats*(*59*)*, and farmed mink.*(*60*)* However, it remains unclear if these infected mammals pose a significant risk for transmission to humans.

When do people infected with SARS-CoV-2 infect others?

Knowing when an infected person can spread SARS-CoV-2 is just as important as how the virus spreads (described above). WHO has recently published a scientific brief outlining what is known about when a person may be able to spread, based on the severity of their illness.*(61)*

In brief, evidence suggests that SARS-CoV-2 RNA can be detected in people 1-3 days before their symptom onset, with the highest viral loads, as measured by RT-PCR, observed around the day of symptom onset, followed by a gradual decline over time.*(47, 62-65)* The duration of RT-PCR positivity generally appears to be 1-2 weeks for asymptomatic persons, and up to 3 weeks or more for patients with mild to moderate disease.*(62, 65-68)* In patients with severe COVID-19 disease, it can be much longer.*(47)*

Detection of viral RNA does not necessarily mean that a person is infectious and able to transmit the virus to another person. Studies using viral culture of patient samples to assess the presence of infectious SARS-CoV-2 are currently limited. *(61)* Briefly, viable virus has been isolated from an asymptomatic case,*(69)* from patients with mild to moderate disease up to 8-9 days after symptom onset, and for longer from severely ill patients.*(61)* Full details about the duration of viral shedding can be found in the WHO guidance document on “Criteria for releasing COVID-19 patients from isolation”. *(61)* Additional studies are needed to determine the duration of viable virus shedding among infected patients.

SARS-CoV-2 infected persons who have symptoms can infect others primarily through droplets and close contact

SARS-CoV-2 transmission appears to mainly be spread via droplets and close contact with infected symptomatic cases. In an analysis of 75,465 COVID-19 cases in China, 78-85% of clusters occurred within household settings, suggesting that transmission occurs during close and prolonged contact.*(6)* A study of the first patients in the Republic of Korea showed that 9 of 13 secondary cases occurred among household contacts.*(70)* Outside of the household setting, those who had close physical contact, shared meals, or were in enclosed spaces for approximately one hour or more with symptomatic cases, such as in places of worship, gyms, or the workplace, were also at increased risk of infection.*(7, 42, 71, 72)* Other reports have supported this with similar findings of secondary transmission within families in other countries.*(73, 74)*

SARS-CoV-2 infected persons without symptoms can also infect others

Early data from China suggested that people without symptoms could infect others.(6) To better understand the role of transmission from infected people without symptoms, it is important to distinguish between transmission from people who are infected who never develop symptoms(75) (asymptomatic transmission) and transmission from people who are infected but have not developed symptoms yet (pre-symptomatic transmission). This distinction is important when developing public health strategies to control transmission.

The extent of truly asymptomatic infection in the community remains unknown. The proportion of people whose infection is asymptomatic likely varies with age due to the increasing prevalence of underlying conditions in older age groups (and thus increasing risk of developing severe disease with increasing age), and studies that show that children are less likely to show clinical symptoms compared to adults.(76) Early studies from the United States (77) and China (78) reported that many cases were asymptomatic, based on the lack of symptoms at the time of testing; however, 75-100% of these people later developed symptoms. A recent systematic review estimated that the proportion of truly asymptomatic cases ranges from 6% to 41%, with a pooled estimate of 16% (12%–20%). (79) However, all studies included in this systematic review have important limitations.(79) For example, some studies did not clearly describe how they followed up with persons who were asymptomatic at the time of testing to ascertain if they ever developed symptoms, and others defined “asymptomatic” very narrowly as persons who never developed fever or respiratory symptoms, rather than as those who did not develop any symptoms at all.(76, 80) A recent study from China that clearly and appropriately defined asymptomatic infections suggests that the proportion of infected people who never developed symptoms was 23%.(81)

Multiple studies have shown that people infect others before they themselves became ill, (10, 42, 69, 82, 83) which is supported by available viral shedding data (see above). One study of transmission in Singapore reported that 6.4% of secondary cases resulted from pre-symptomatic transmission. (73) One modelling study, that inferred the date of transmission based on the estimated serial interval and incubation period, estimated that up to 44% (25-69%) of transmission may have occurred just before symptoms appeared.(62) It remains unclear why the magnitude of estimates from modelling studies differs from available empirical data.

Transmission from infected people without symptoms is difficult to study. However, information can be gathered from detailed contact tracing efforts, as well as epidemiologic investigations among cases and contacts. Information from contact tracing efforts reported to WHO by Member States, available transmission studies and a recent pre-print systematic reviews suggests that individuals without symptoms are less likely to transmit the virus than those who develop symptoms.(10, 81, 84,

85*)* Four individual studies from Brunei, Guangzhou China, Taiwan China and the Republic of Korea found that between 0% and 2.2% of people with asymptomatic infection infected anyone else, compared to 0.8%-15.4% of people with symptoms.*(10, 72, 86, 87)*

Remaining questions related to transmission

Many unanswered questions about transmission of SARS-CoV-2 remain, and research seeking to answer those questions is ongoing and is encouraged. Current evidence suggests that SARS-CoV-2 is primarily transmitted between people via respiratory droplets and contact routes – although aerosolization in medical settings where aerosol generating procedures are used is also another possible mode of transmission - and that transmission of COVID-19 is occurring from people who are pre-symptomatic or symptomatic to others in close contact (direct physical or face-to-face contact with a probable or confirmed case within one meter and for prolonged periods of time), when not wearing appropriate PPE. Transmission can also occur from people who are infected and remain asymptomatic, but the extent to which this occurs is not fully understood and requires further research as an urgent priority. The role and extent of airborne transmission outside of health care facilities, and in particular in close settings with poor ventilation, also requires further study.

As research continues, we expect to gain a better understanding about the relative importance of different transmission routes, including through droplets, physical contact and fomites; the role of airborne transmission in the absence of aerosol generating procedures; the dose of virus required for transmission to occur, the characteristics of people and situations that facilitate superspreading events such as those observed in various closed settings, the proportion of infected people who remain asymptomatic throughout the course of their infection; the proportion of truly asymptomatic persons who transmit the virus to others; the specific factors that drive asymptomatic and pre-symptomatic transmission; and the proportion of all infections that are transmitted from asymptomatic and pre-symptomatic individuals.

Implications for preventing transmission

Understanding how, when and in which settings infected people transmit the virus is important for developing and implementing control measures to break chains of transmission. While there is a great deal of scientific studies becoming available, all studies that investigate transmission should be interpreted bearing in mind the context and settings in which they took place, including the infection prevention interventions in place, the rigor of the methods used in the investigation and the limitations and biases of the study designs.

It is clear from available evidence and experience, that limiting close contact between infected people and others is central to breaking chains of transmission of the virus causing COVID-19. The prevention of transmission is best achieved by identifying suspect cases as quickly as possible, testing, and isolating infectious cases. *(88, 89)* In addition, it is critical to identify all close contacts of infected people *(88)* so that they can be quarantined *(90)* to limit onward spread and break chains of transmission. By quarantining close contacts, potential secondary cases will already be separated from others before they develop symptoms or they start shedding virus if they are infected, thus preventing the opportunity for further onward spread. The incubation period of COVID-19, which is the time between exposure to the virus and symptom onset, is on average 5-6 days, but can be as long as 14 days. *(82, 91)* Thus, quarantine should be in place for 14 days from the last exposure to a confirmed case. If it is not possible for a contact to quarantine in a separate living space, self-quarantine for 14 days at home is required; those in self-quarantine may require support during the use of physical distancing measures to prevent the spread of the virus.

Given that infected people without symptoms can transmit the virus, it is also prudent to encourage the use of fabric face masks in public places where there is community transmission[1] and where other prevention measures, such as physical distancing, are not possible.*(12)* Fabric masks, if made and worn properly, can serve as a barrier to droplets expelled from the wearer into the air and environment.*(12)* However, masks must be used as part of a comprehensive package of preventive measures, which includes frequent hand hygiene, physical distancing when possible, respiratory etiquette, environmental cleaning and disinfection. Recommended precautions also include avoiding indoor crowded gatherings as much as possible, in particular when physical distancing is not feasible, and ensuring good environmental ventilation in any closed setting. *(92, 93)*

Within health care facilities, including long term care facilities, based on the evidence and the advice by the COVID-19 IPC GDG, WHO continues to recommend droplet and contact precautions when caring for COVID-19 patients and airborne precautions when and where aerosol generating procedures are performed. WHO also recommends standard or transmission-based precautions for other patients using an approach guided by risk assessment.*(94)* These recommendations are consistent with other national and international guidelines, including those developed by the European Society of Intensive Care Medicine and Society of Critical Care Medicine *(95)* and by the Infectious Diseases Society of America. *(96)*

Furthermore, in areas with COVID-19 community transmission, WHO advises that health workers and caregivers working in clinical areas should continuously wear a medical mask during all routine activities throughout the entire shift.*(12)* In settings where aerosol-generating procedures are performed, they should wear an N95, FFP2 or FFP3 respirator. Other countries and organizations, including the United States Centers for Diseases Control and Prevention *(97)* and the European

Centre for Disease Prevention and Control *(98)* recommend airborne precautions for any situation involving the care of COVID-19 patients. However, they also consider the use of medical masks as an acceptable option in case of shortages of respirators.

WHO guidance also emphasizes the importance of administrative and engineering controls in health care settings, as well as rational and appropriate use of all PPE *(99)* and training for staff on these recommendations (IPC for Novel Coronavirus [COVID-19] Course. Geneva; World Health Organization 2020, available at (https://openwho.org/courses/COVID-19-IPC-EN). WHO has also provided guidance on safe workplaces. *(92)*

Key points of the brief

Main findings

- **Understanding how, when and in what types of settings SARS-CoV-2 spreads between people is critical to develop effective public health and infection prevention measures to break chains of transmission.**
- **Current evidence suggests that transmission of SARS-CoV-2 occurs primarily between people through direct, indirect, or close contact with infected people through infected secretions such as saliva and respiratory secretions, or through their respiratory droplets, which are expelled when an infected person coughs, sneezes, talks or sings.**
- **Airborne transmission of the virus can occur in health care settings where specific medical procedures, called aerosol generating procedures, generate very small droplets called aerosols. Some outbreak reports related to indoor crowded spaces have suggested the possibility of aerosol transmission, combined with droplet transmission, for example, during choir practice, in restaurants or in fitness classes.**
- **Respiratory droplets from infected individuals can also land on objects, creating fomites (contaminated surfaces). As environmental contamination has been documented by many reports, it is likely that people can also be infected by touching these surfaces and touching their eyes, nose or mouth before cleaning their hands.**
- **Based on what we currently know, transmission of COVID-19 is primarily occurring from people when they have symptoms, and can also occur just before they develop symptoms, when they are in close proximity to others for prolonged periods of time. While someone who never develops symptoms can also pass the virus to others, it is still not clear to what extent this occurs and more research is needed in this area.**
- **Urgent high-quality research is needed to elucidate the relative importance of different transmission routes; the role of airborne transmission in the absence of aerosol generating procedures; the dose of virus required for transmission to occur; the settings and risk factors for superspreading events; and the extent of asymptomatic and pre-symptomatic transmission.**

How to prevent transmission

The overarching aim of the Strategic Preparedness and Response Plan for COVID-19*(1)* is to control COVID-19 by suppressing transmission of the virus and preventing associated illness and death. To the best of our understanding, the virus is primarily spread through contact and respiratory droplets. Under some circumstances airborne transmission may occur (such as when aerosol generating procedures are conducted in health care settings or potentially, in indoor crowded poorly ventilated settings elsewhere). More studies are urgently needed to investigate such instances and assess their actual significance for transmission of COVID-19.

To prevent transmission, WHO recommends a comprehensive set of measures including:

- **Identify suspect cases as quickly as possible, test, and isolate all cases (infected people) in appropriate facilities;**
- **Identify and quarantine all close contacts of infected people and test those who develop symptoms so that they can be isolated if they are infected and require care;**
- **Use fabric masks in specific situations, for example, in public places where there is community transmission and where other prevention measures, such as physical distancing, are not possible;**
- **Use of contact and droplet precautions by health workers caring for suspected and confirmed COVID-19 patients, and use of airborne precautions when aerosol generating procedures are performed;**
- **Continuous use of a medical mask by health workers and caregivers working in all clinical areas, during all routine activities throughout the entire shift;**
- **At all times, practice frequent hand hygiene, physical distancing from others when possible, and respiratory etiquette; avoid crowded places, close-contact settings and confined and enclosed spaces with poor ventilation; wear fabric masks when in closed, overcrowded spaces to protect others; and ensure good environmental ventilation in all closed settings and appropriate environmental cleaning and disinfection.**

WHO carefully monitors the emerging evidence about this critical topic and will update this scientific brief as more information becomes available.

[1]Defined by WHO as “experiencing larger outbreaks of local transmission defined through an assessment of factors including, but not limited to: large numbers of cases not linkable to transmission chains; large numbers of cases from sentinel surveillance; and/or multiple unrelated clusters in several areas of the country/territory/area” (https://www.who.int/publications-detail/global-surveillance-for-covid-19-caused-by-human-infection-with-covid-19-virus-interim-guidance)

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WHO continues to monitor the situation closely for any changes that may affect this scientific brief. Should any factors change, WHO will issue a further update. Otherwise, this scientific brief document will expire 2 years after the date of publication.

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TAB 3

Reviews | May 2021

Annals of Internal Medicine

The Proportion of SARS-CoV-2 Infections That Are Asymptomatic

FREE

A Systematic Review

Daniel P. Oran, AM, Eric J. Topol, MD

Author, Article and Disclosure Information

https://doi.org/10.7326/M20-6976

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Annals Author Insight Video - Eric Topol, MD, and Daniel Oran, AM

In this video, Eric Topol, MD, and Daniel Oran, AM, offer additional insight into the article, "The Proportion of SARS-CoV-2 Infections That Are Asymptomatic: A Systematic Review." (Duration 3:28)

Abstract

Background:

Asymptomatic infection seems to be a notable feature of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogen that causes coronavirus disease 2019 (COVID-19), but the prevalence is uncertain.

Purpose:

To estimate the proportion of persons infected with SARS-CoV-2 who never develop symptoms.

Data Sources:

Searches of Google News, Google Scholar, medRxiv, and PubMed using the keywords *antibodies*, *asymptomatic*, *coronavirus*, *COVID-19*, *PCR*, *seroprevalence*, and *SARS-CoV-2*.

Study Selection:

Observational, descriptive studies and reports of mass screening for S[illegible] CoV-2 that were either cross-sectional or longitudinal in design; were published through 17 November 2020; and involved SARS-CoV-2 nucleic acid or antibody testing of a target population, regardless of current symptomatic status, over a defined period.

Data Extraction:

The authors collaboratively extracted data on the study design, type of testing performed, number of participants, criteria for determining symptomatic status, testing results, and setting.

Data Synthesis:

Sixty-one eligible studies and reports were identified, of which 43 used polymerase chain reaction (PCR) testing of nasopharyngeal swabs to detect current SARS-CoV-2 infection and 18 used antibody testing to detect current or prior infection. In the 14 studies with longitudinal data that reported information on the evolution of symptomatic status, nearly three quarters of persons who tested positive but had no symptoms at the time of testing remained asymptomatic. The highest-quality evidence comes from nationwide, representative serosurveys of England (n = 365 104) and Spain (n = 61 075), which suggest that at least one third of SARS-CoV-2 infections are asymptomatic.

Limitation:

For PCR-based studies, data are limited to distinguish presymptomatic from asymptomatic infection. Heterogeneity precluded formal quantitative syntheses.

Conclusion:

Available data suggest that at least one third of SARS-CoV-2 infections are asymptomatic. Longitudinal studies suggest that nearly three quarters of persons who receive a positive PCR test result but have no symptoms at the time of testing will remain asymptomatic. Control strategies for COVID-19

should be altered, taking into account the prevalence and transmission risk of asymptomatic SARS-CoV-2 infection.

Primary Funding Source:

National Institutes of Health.

The asymptomatic fraction of infection is the proportion of infected persons who never develop, perceive, and report symptoms (1). Among common pathogens, the asymptomatic fraction varies widely. For example, an asymptomatic carrier state has not been documented for measles virus infection (2), whereas a significant proportion of persons with cytomegalovirus or poliovirus infection have no symptoms and are unaware of infection (3, 4). The asymptomatic fraction of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection seems to be sizable (5). The range of severity of illness associated with SARS-CoV-2 infection is noteworthy because it spans asymptomatic infection; mild illness; and severe, life-threatening illness.

Perhaps because of this broad spectrum of presentation, the topic of asymptomatic SARS-CoV-2 infection has generated some controversy (6). Imprecise use of the term "asymptomatic" is partly to blame. "Asymptomatic" should be reserved for persons who never develop symptoms, whereas "presymptomatic" is a better description of those who have no symptoms when they receive a positive test result but who eventually develop symptoms. We know for certain who is asymptomatic only in retrospect. On the basis of our current knowledge of the natural

history of coronavirus disease 2019 (COVID-19), after a person is infected with SARS-CoV-2, we must wait approximately 14 days to determine whether symptoms have developed (7). Infection without symptoms, whether presymptomatic or asymptomatic, is important because infected persons can transmit the virus to others even if they have no symptoms (8, 9).

In June 2020, we published a review of the limited data then available on the prevalence of asymptomatic SARS-CoV-2 infection (5). Since then, considerable new data have become available. The present review summarizes currently available data that might allow us to estimate the proportion of persons infected with SARS-CoV-2 who are asymptomatic.

Methods

Data Sources, Search Terms, and Study Selection

Using the keywords *antibodies*, *asymptomatic*, *coronavirus*, *COVID-19*, *PCR*, *seroprevalence*, and *SARS-CoV-2*, we periodically searched Google News, Google Scholar, medRxiv, and PubMed for observational, descriptive s... and reports of mass screening for SARS-CoV-2 that were either cross-sectional or longitudinal in design; were published through 17 November 2020; and involved SARS-CoV-2 nucleic acid or antibody testing of a target population, regardless of current symptomatic status, over a defined period.

Data Extraction and Quality Assessment

We recorded the total number of persons tested, the number that tested positive, the number of positive cases without symptoms, the criteria for determining symptomatic status, whether the data were cross-sectional or longitudinal in nature, whether random selection techniques were used to achieve a representative sample of a target population, and whether the testing involved polymerase chain reaction (PCR) analysis of a nasopharyngeal swab or serologic analysis of antibodies in a blood sample. For longitudinal studies that provided information on the evolution of symptomatic status, we recorded the proportion of persons who tested positive but had no symptoms at the time of testing and who then remained asymptomatic during a follow-up period. In addition, we flagged studies that required clarification of ambiguous details.

Studies or reports that are based on PCR results and include only cross-sectional data do not make it possible to distinguish between presymptomatic and asymptomatic SARS-CoV-2 infection because symptomatic status is observed on only 1 occasion, which may occur before the development of symptoms, if any. In contrast, we can distinguish between presymptomatic and asymptomatic infection with either antibody-based studies, in which an interview or questionnaire gathers information about symptoms reported at the time a blood sample is taken and during a prior period, or PCR-based studies that include longitudinal data.

In assessing quality, we put the greatest emphasis on random selection of participants to achieve a representative sample of a regional or national population, a large number of study participants ($n > 10\,000$), and study

designs that make it possible to distinguish between presymptomatic and asymptomatic infection. Evaluated in this manner, the highest-quality evidence comes from large-scale, national studies with representative samples that include data from either antibody or longitudinal PCR testing. In Tables 1 and 2, we show in boldface the details that increase a study's likelihood of providing higher-quality evidence.

Table 1. Nucleic Acid PCR Testing

Table 2. Antibody Testing

Data Synthesis and Analysis

We synthesized evidence qualitatively by evaluating study design, including whether data were collected longitudinally; testing methods; number of participants; and setting. We compared the range and consistency of estimates of the proportion of persons who tested positive but had no symptoms at the time of testing.

Role of the Funding Source

The National Institutes of Health played no role in the design, conduct, or analysis of this review or in the decision to submit the manuscript for publication.

Results

We identified 61 studies or reports that met eligibility criteria. Table 1 (10–54) summarizes data from the 43 that used PCR testing, and Table 2 (55–72) summarizes data from the 18 that used antibody testing. The heterogeneity of the studies—in particular, disparate settings and populations—precluded quantitative summaries using meta-analysis. We summarize the evidence in terms of the number of studies and the range, median, and interquartile range (IQR) for persons who tested positive but had no symptoms at the time of PCR testing or who reported having had no symptoms before or at the time of antibody testing. Thirty of the studies included a list of specific symptoms, independent of signs, used to determine symptomatic status (10–14, 17, 18, 22–28, 35, 36, 38, 42, 49, 51, 55–57, 60–62, 64). Many of the remaining studies used some variation of the catch-all phrase "symptoms compatible with COVID-19."

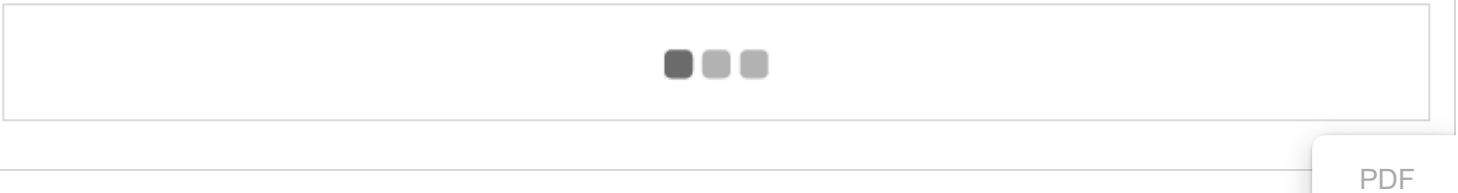
Nucleic Acid PCR Testing

Among the 43 studies using PCR testing (10–54), the proportion of persons who tested positive but had no symptoms at the time of testing ranged from 6.3% to 100%, with a median of 65.9% (IQR, 42.8% to 87.0%).

Nineteen of the PCR-based studies collected data on symptoms longitudinally after testing, making it possible to distinguish between presymptomatic and asymptomatic infection (15, 17, 18, 20, 22, 25, 26, 27, 32, 37–40, 45, 47, 48, 51, 53, 54). The follow-up period in these studies ranged from 2 to 70 days, with a median of 14 days (IQR, 14.0 to 15.8 days). The proportion of persons who tested positive and remained asymptomatic ranged from 6.3% to 91.7%, with a median of 42.5% (IQR, 29.6% to 77.8%).

Of the 19 longitudinal studies, 14 provided information on the evolution of symptomatic status (Table 3) (15, 17, 18, 20, 22, 32, 37–40, 47, 51, 53, 54). Among persons who tested positive but had no symptoms at the time of testing, the proportion who remained asymptomatic during a follow-up period ranged from 11.1% to 100%, with a median of 72.3% (IQR, 56.7% to 89.7%).

Table 3. Evolution of Symptomatic Status



Of the 43 studies that used PCR testing, 24 collected cross-sectional data and reported only the symptomatic status at the time of testing, so we could not distinguish between presymptomatic and asymptomatic cases (10–14, 16, 19, 21, 23, 24, 28–31, 33–36, 41–44, 46, 49, 50, 52). In these studies, the proportion of persons who tested positive but had no symptoms at the time of testing ranged from 40.7% to 100%, with a median of 75.5% (IQR, 50.3% to 86.2%).

Of the 43 studies that used PCR testing, 4 used random selection of participants to achieve a representative sample of their target population: residents of England (10–12, 14), Iceland (16), or Indiana (23). Proportions of persons who tested positive but had no symptoms at the time of testing ranged from 43.0% to 76.5%, with a median of 45.6% (IQR, 43.6% to 61.8%). None of the PCR testing studies that used random selection of participants collected longitudinal data on symptoms, so we could not distinguish between presymptomatic and asymptomatic cases.

The largest of the representative data sets, and the largest study identified in our search, was from the REACT (Real-time Assessment of Community Transmission) program. REACT has implemented nationwide nucleic acid and antibody testing (discussed later) for SARS-CoV-2 of persons in England aged 5 years and older in multiple phases since May 2020 (10–12). In Table 1, we have combined the results of 6 phases of nucleic acid testing from REACT, yielding data for 932 072 persons (England residents 1). At the time of testing, 1425 of 3029 persons (47.0%) who tested positive had no symptoms. The study did not collect longitudinal data on symptoms, so we could not distinguish between presymptomatic and asymptomatic cases.

The second largest of the representative studies was also from England; it included 36 061 persons tested between 26 April and 27 June 2020 (14). The proportion of persons who tested positive was 0.3%, identical to that reported by REACT, but the proportion of persons who tested positive but had no symptoms at the time of testing was 74.8%, much larger than in the

REACT study. The study did not collect longitudinal data on symptoms, so we could not distinguish between presymptomatic and asymptomatic cases.

In the cross-sectional study of Belgian long-term care facilities (n = 280 427), age did not seem to affect the proportion of persons who tested positive but had no symptoms at the time of testing (13). The study tested 138 327 staff and 142 100 residents. Median age was 42 years for staff and 85 years for residents; despite this considerable difference, the proportion of those who tested positive without symptoms was 74.0% for staff and 75.3% for residents. This finding is consonant with the finding of a longitudinal study from Vo', Italy, in which more than 85% of the town's 3275 residents were tested: "Among confirmed SARS-CoV-2 infections, we did not observe significant differences in the frequency of asymptomatic infection between age groups" (17).

Of the 43 studies that used PCR testing, 21 involved high-density living or working environments, such as nursing homes and factories (13, 15, 18, 19, 21, 22, 24–28, 30, 38, 40, 42, 46, 50, 51, 53, 54). The settings with the highest proportion of persons who tested positive without symptoms included prisons (19) and poultry processing plants (21). Yet, the data seem to be insufficient to conclude that setting was a causative factor. In the 21 studies of high-density environments, the proportion of persons who tested positive but had no symptoms at the time of testing ranged from 6.3% to 96.0%, with a median of 62.8% (IQR, 40.6% to 87.0%). In the remaining 22 studies that did not involve such high-density environments, the proportion ranged from 27.3% to 100%, with a median of 67.2% (IQR, 43.5% to 84.7%).

Antibody Testing

In the 18 studies based on antibody testing (Table 2) (55–72), the proportion of persons who tested positive but did not report having had symptoms ranged from 21.7% to 85.0%, with a median of 41.2% (IQR, 32.6% to 48.1%).

Among the 18 antibody testing studies, 6 used random selection of participants to achieve a representative sample of their target population: residents of England (55); Spain (56); Bavaria, Germany (59); Louisiana (60); Maranhão, Brazil (64); or Connecticut (68). In these antibody studies with representative samples, the proportion of persons who tested positive but did not report having had symptoms ranged from 21.7% to 47.3%, with a median of 32.7% (IQR, 28.7% to 43.4%).

The 2 largest studies based on antibody testing were nationwide serosurveys from England (55) and Spain (56), both designed to achieve representative samples of community-dwelling persons. The English data, from the REACT program described earlier, were collected during 3 rounds of testing from June through September 2020 and include 365 104 persons. The Spanish data were collected 27 April to 11 May 2020 and include 61 075 persons. The proportion of persons who tested positive but did not report having had symptoms was 32.4% in England and 33.0% in Spain.

Discussion

Symptom detection relies on the subjective reports of patients (73). For example, anosmia has turned out to be a distinctive symptom of COVID-19

(74), and we depend on patients to perceive and report a diminution, however slight, of their normal olfactory abilities. But such self-reports are influenced by many factors, including variability in the ability to recall symptoms and idiosyncratic awareness of bodily sensations.

Current data suggest that infected persons without symptoms—including both presymptomatic and asymptomatic persons—account for more than 40% of all SARS-CoV-2 transmission (75–77). The proportion of new infections caused by asymptomatic persons alone is uncertain, but when researchers in Wanzhou, China, analyzed epidemiologic data for "183 confirmed COVID-19 cases and their close contacts from five generations of transmission," they determined that the asymptomatic cases, which made up 32.8% of infected persons, caused 19.3% of infections (78).

The 61 studies and reports that we have collected provide compelling evidence that the asymptomatic fraction of SARS-CoV-2 infection is sizable. These data enable us to make reasonable inferences about the proportion of SARS-CoV-2 infections that are asymptomatic.

Studies designed to achieve representative samples of large populatio provide useful data because they may accurately reflect human populations in general. Four of the PCR-based studies are in this category, with target populations of England (10–12, 14), Iceland (16), and Indiana (23). The proportion of persons who tested positive but had no symptoms at the time of testing ranged from 43.0% to 76.5%, with a median of 45.6% (IQR, 43.6% to 61.8%). However, these studies fall short of providing the highest-quality

evidence because they collected only cross-sectional data. As a result, we cannot distinguish between presymptomatic and asymptomatic cases.

In 14 longitudinal studies that reported information on the evolution of symptomatic status, a median of 72.3% of persons who tested positive but had no symptoms at the time of testing remained asymptomatic during a follow-up period (15, 17, 18, 20, 22, 32, 37–40, 47, 51, 53, 54). If a similar proportion remained asymptomatic in the 4 large, representative, PCR-based studies, in which the median was 45.6%, the asymptomatic fraction of SARS-CoV-2 infection would be 33.0%.

Among the data that we have assembled here, the highest-quality evidence comes from the large-scale studies using antibody testing that were designed to achieve representative samples of nationwide populations in England (n = 365 104) (55) and Spain (n = 61 075) (56). It is remarkable that these independently conducted serosurveys yielded nearly identical proportions of asymptomatic SARS-CoV-2 infections: 32.4% in England and 33.0% in Spain.

We may infer that persons who receive positive antibody test results can be classified accurately as asymptomatic because such results are likely t occur only after the onset of symptoms, if any. In a study of 222 hospitalized patients in Wuhan, China, IgM and IgG antibodies to SARS-CoV-2 were first detected 3 and 4 days, respectively, after symptomatic onset of COVID-19 (79). In a study of 109 health care workers and 64 hospitalized patients in Zurich, Switzerland, the severity of illness seemed to affect how quickly SARS-CoV-2 antibodies appeared (80). Patients with severe COVID-19 had detectable SARS-CoV-2 antibody titers after symptom onset, but those with

mild cases “remained negative or became positive [for SARS-CoV-2 antibodies] 12 to 14 days after symptom onset” (80). These data suggest that positive antibody test results are unlikely to occur during the period when it is uncertain whether an infected person is presymptomatic or asymptomatic.

However, serosurveys do have significant limitations for the purpose of estimating the asymptomatic fraction. Not all persons who are believed to have been infected with SARS-CoV-2 later have a positive result for SARS-CoV-2 antibodies (81). The reasons may include a false-positive result on the initial PCR test; a false-negative result on the antibody test; or the absence of detectable antibodies, perhaps because the infection was cleared without requiring adaptive immunity. In addition, the role of mucosal immunity in clearing SARS-CoV-2 infection has not yet been fully elucidated (82), and a nasal wash to detect the IgA antibodies active in mucosal immunity is not part of standard testing practice. Persons who clear SARS-CoV-2 infection through innate or mucosal immunity might be more likely to be asymptomatic but would not be categorized as such in a serosurvey, possibly contributing to an underestimate of the asymptomatic fraction.

Another limitation of serosurveys is the requirement that an interview or questionnaire about symptomatic status accompany the blood sample. The onus is on the study participant to accurately recall symptoms, if any, from weeks or even months earlier. In the midst of a pandemic that has transformed everyday life around the globe, it seems reasonable to hypothesize that awareness of and memory for symptoms possibly related to

COVID-19 are heightened. This might result in a greater likelihood of noticing and reporting symptoms that would otherwise be missed or ignored, thereby leading to a lower estimate of the asymptomatic fraction. For these reasons, we have evaluated serosurveys in the context of other results and found them to be concordant.

When estimates from large-scale, cross-sectional, PCR-based studies with representative samples; longitudinal PCR-based studies; and nationwide serosurveys with representative samples are combined, it seems that the asymptomatic fraction of SARS-CoV-2 infection is at least one third. To confirm this estimate, large-scale longitudinal studies using PCR testing with representative samples of national populations would be useful. As SARS-CoV-2 vaccination campaigns are implemented worldwide, though, the window for such research may be closing.

In light of the data presented here, we believe that COVID-19 control strategies must be altered, taking into account the prevalence and transmission risk of asymptomatic SARS-CoV-2 infection. Frequent, inexpensive, rapid home tests (83) to identify and contain presympton asymptomatic cases—along with government programs that provide financial assistance and, if necessary, housing to enable infected persons to isolate themselves (84)—may be a viable option. And as the first generation of SARS-CoV-2 vaccines is deployed, more research will be needed to determine their efficacy in preventing asymptomatic infection (85).

Comments

Eric Topol, Daniel Oran • Scripps Translational Science Institute • 8 June 2021

Authors' Response to Berman

Personal observations are often the starting point of scientific inquiry, so we appreciate that Dr. Berman has shared his experience in advising camps, schools, and others. But he makes no mention of involvement in mass SARS-CoV-2 screening programs that test all persons in a group or locale without regard to symptomatic status. It is only through the study of data from such mass screening that the actual asymptomatic fraction can be ascertained. In our review, we assembled 61 data sets in this category, including more than 1.8 million persons worldwide. Regarding Dr. Berman's concern about ambiguity in defining the asymptomatic condition, we note in our review that "thirty of the studies included a list of specific symptoms, independent of signs, used to determine symptomatic status." In preparing our review, we relied on the competence and veracity of researchers in applying these criteria and assessing the symptomatic status of study participants.

Daniel S. Berman, M.D. • Montefiore Medical Center, Bronx, New York • 2 June 2021

Are "asymptomatic" infections truly "asymptomatic?"

In their recent review article on the incidence of asymptomatic SARS-Co-V-2 infection, Drs. Oran and Topol conclude that at least one third of SARS-Co-V-2 infections are "asymptomatic." The conclusion is based upon a summary of 61 studies and reports.

To arrive at this conclusion, one has to have a clear definition of "asymptomatic" versus “asymptomatic” cases. The understanding of symptoms related to SARS-Co-V-2 infection has evolved since we began to identify SARS-Co-V-2 infections in March 2020. I have been involved personally, in advising camps, schools and many individuals in managing outbreak situations. Early on in the course of the pandemic, we focused on the symptoms of cough and fever. Later on, we observed that many individuals, especially children and adults, presented with more subtle symptoms such as nasal stuffiness, headaches, G.I. symptoms or fatigue. We would sometimes ask individuals who tested positive about their symptoms and were told that they had none. Upon more persistent questioning, we would learn that they had a runny nose or some of the other mentioned symptoms for several days, but did not relate these symptoms to their positive test result.

In addition, it is difficult to define "asymptomatic" among the elderly or debilitated patients. Such patients often lack awareness of symptoms. Frequently, they are unable able to report subjective symptoms. These patients would not be defined as being "symptomatic," unless they developed fever, cough or shortness of breath.

In order to properly report on the incidence of "asymptomatic" infection, one must know that the individuals were carefully questioned about any symptoms, some of which would be subtle. In addition, it would be reasonable to place elderly debilitated patients in a separate category, as their symptoms can be easily missed.

In this way, I believe strongly that the actual incidence of "asymptomatic" infection is much lower than what Oran and Topol estimate. Summarizing studies without a clear understanding of how a history of symptoms was obtained can lead to false conclusions, which tends to increase the level of anxiety concerning asymptomatic infections. Such anxiety might not be warranted

Eric Topol, Daniel Oran • Scripps Translational Science Institute • 1 April 2021

Authors' Response to Yang and Ma

As noted in our review, we included data published as of 17 November 2020. It is inevitable, then, because of typically long lead times in journal publishing, that the data were collected before the widespread circulation of the SARS-CoV-2 variants of concern mentioned by Drs. Yang and Ma. In addition, all of the studies that they cite were published after our review appeared.

As new SARS-CoV-2 variants of concern emerge and the mix of variants in widespread circulation changes, we agree that it will be important to reassess the prevalence of asymptomatic infection.

Fan Yang, M.D.1,2* Dan Ma, M.D.2* *Author Fan Yang and Dan Ma contributed equally to this work. • 1.People's Hospital of Leshan 2.Department of Gastroenterology, Changhai Hospital, Second Military Medical University/Naval Medical University, • 28 March 2021

New Variants, Vaccines and The Proportion of Asymptomatic SARS-CoV-2 Infections

TO THE EDITOR:

A recent systematic review by Oran and Topol concluded that at least one third of SARS-CoV-2 infections are completely asymptomatic (1). As included large-scale representative data, the conclusion seemed more convincing than the initial narrative review.

Notably, evidence gap was still significant. Except the nationwide program in England, all the other studies included participants prior to September, 2020. Moreover, the vast majority of studies were not as long as 3 months. Therefore, the review was less likely to disclose whether the proportion of asymptomatic SARS-COV-2 infections would keep stable for a long period.

Since the SARS-COV-2 genome has thrown up numerous variants over one year evolution, it is reasonable to suspect the coronavirus might undergo phenotypic "drift". Circumstantial evidence came from almost 20 million international entrants to China. Between mid-April and mid-October 2020, the proportion of asymptomatic infections among all positive individuals increased significantly over time from 27.8% to 59.4% (2). This finding may signal an increase in asymptomatic infection globally, in which D614-to-G614 transition might have a place.

The viral variant problem became prominent at the end of 2020. Take fast-spreading B.1.1.7 as an example. The tendencies of spike gene dropout transition in the Pillar 2 sample (community testing of people with symptoms) closely matched the trends of a random sampling of the community (3). This might suggest that the proportion of asymptomatic infection in B.1.1.7 variant remained relatively stable, whereas hazard of death was estimated higher compared with previously circulating variants (3).

Further to this, the efficacy of first-generation vaccines on reduction in asymptomatic infections will soon face the imminent challenges of new variants (4), especially more worrisome lineages such as B.1.351 and P.1.

It is vital to keep track of mutations in the genome of SARS-CoV-2. An interactive mutation tracker system based on SARS-CoV-2 isolate genomes deposited to GISAID might provide an option to accrue the clinical metadata. However, with sizable missing data and lack of longitudinal follow-up on symptoms, the tool can only give a patchy understanding of disease severity (5).

Global coordination in productive expansion of sequencing efforts and robust collection of outcome data can allow us to really building the capacity to comprehend new variants and asymptomatic infections. The insight will support meaningful public health actions to choose the highest-efficacy vaccines and to make timely alterations in the existing vaccines, which could reduce selective pressure for emergence of more variants.

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Disclosures: No conflicts of interest.

Eric Topal, Daniel Oran • Scripps Research • 2 February 2021

Author Response to Bangash

We are in the midst of a profound transformation in how scientific knowledge is disseminated. As recently as 30 years ago, the gating factors in scientific publishing were the speed of postal mail and the high costs of printing. Today, ubiquitous access to the Internet allows for nearly instantaneous transmission at an infinitesimal price. The logical and welcome result has been the rise of preprints.

Peer review certainly serves a valuable role in scientific publishing, usually boosting the quality of the output. But in the current publishing environment, it would be a mistake to rely exclusively on peer-reviewed articles as the definitive source of scientific knowledge. Instead, we must become more discriminating consumers of scientific publications -- from both peer-reviewed journals and preprint servers -- and learn to assess for ourselves the quality and merit of the knowledge that is being shared.

In preparing our systematic review, we carefully evaluated the preprints that met our criteria for inclusion. In our opinion, they were of sufficiently high quality to include in our analysis, particularly because they provided knowledge that was not available from peer-reviewed sources. In the midst of a pandemic, in which our findings might be useful to both clinicians and policymakers, we decided that this was the most prudent course of action.

Jyotin Chandarana • ARH Hazard KY 41701 • 25 January 2021

Asymtomatic and presymptomatic cases

Concludng remarks should be added.

Ali Haider Bangash • STMU Shifa College of Medicine, Islamabad, Pakistan • 24 January 2021

Should conclusions be based on preprints that have not been peer-reviewed yet?

With great interest, the manuscript of the research article 'The Proportion of SARS-CoV-2 Infections That Are Asymptomatic: A Systematic Review' was critically evaluated. After expressing commendation for the effort by authors to explore the prevalence of asymptomatic SARS-CoV-2 infections, the commenter direct the attention of the Editor towards the fact that data from preprints which have not yet been peer-reviewed have been included in the synthesis of conclusions.

It is true that the COVID-19 pandemic has lead to an immense rise in the amount of literature getting published & preprint servers provide the optimal platform for accelerated dissemination of scientific research around this global health emergency[1], one can not deny that no peer-review process whatsoever is adopted while screening submitted manuscripts for publication at a preprint server which has lead to studies with flawed methodologies & biased conclusions getting published by the same preprint servers.[2] Thus, when conclusions are synthesized by evaluating data from a preprint alongside that taken from research articles published in peer-reviewed journals which have gone rigorous evaluation reviewers and editors, that significant status which peer-review process maintains in the scientific research publishing global standards

gets unintentionally blemished. This may translate into a prediction of the scientific community to disregard the findings of such research studies that take in data from preprints to synthesize conclusions. Consequently, the authors of such studies may not achieve their sincerest objective of positively contributing to the scientific discourse.

The commenter, therefore, suggests revising the methodology of the systematic review under consideration such that only peer-reviewed research articles are included for data extraction & subsequent qualitative systematic review. Including only peer-reviewed studies shall translate into a higher quality of synthesized conclusions which shall be better received by the scientific community. The suggested alternative is to revise the systematic review once all of the included preprints have either been published in peer-reviewed journals or have been retracted secondary to any reason.

Regards.

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[1]Majumder MS, Mandl KD. Early in the epidemic: the impact of preprints on global discourse about COVID-19 transmissibility. Lancet Glob Health. 2020 May;8(5):e627-e630. doi: 10.1016/S2214-109X(20)30113-3. Epub 2020 Mar 24. PMID: 32220289; PMCID: PMC7159059.

[2]Silva JATD. Silently withdrawn or retracted preprints related to Covid-19 are a scholarly threat and a potential public health risk: theoretical arguments and suggested recommendations. Online Information Review. 2020;ahead-of-print(ahead-of-print).

Disclosures:

I'm a moderator at PsyArXiv Preprints and a student member of the American College of Physicians.

PREVIOUS ARTICLE
NEXT ARTICLE

TAB 4

Notifications

COVID-19 Updates: State of public health emergency declared.

- Public health restrictions to reduce transmission are now in effect.
- Book your vaccine: All Albertans 5+ can get vaccinated.
- Get the facts: Vaccines are safe and save lives.

Alberta.ca

Cases in Alberta

COVID-19 Alberta statistics

Interactive aggregate data on COVID-19 cases in Alberta

COVID-19 in Alberta

COVID-19 data included in the interactive data application are up-to-date as of end of day December 06, 2021, unless stated otherwise.

View Alberta seasonal influenza statistics

- Highlights
- New Cases
- Total Cases
- Characteristics
- Vaccinations
- Vaccine Outcomes
- Severe Outcomes
- Pre-existing Conditions
- Healthcare Capacity
- Geospatial
- Laboratory Testing
- Variants of Concern
- Data Export
- Data Notes

373
current hospitalizations

76
current ICU

3,268
total deaths

4,105
active cases

3.9%
percent positivity, 7-day average

78 years
average age at death

7,028,981
total doses administered

89%
12+ population who received at least one dose

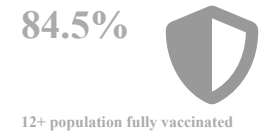


Figure 1: COVID-19 cases in Alberta by zone. First and second panels display new (from November 30-December 06, 2021) and active cases, respectively. Cases without a postal code or incorrect postal codes are labelled as unknown. Cases are under investigation and numbers may fluctuate as cases are resolved.

Figure 2: COVID-19 cases in Alberta by age group. First and second panels display new (from November 30-December 06, 2021) and active cases, respectively. Cases are under investigation and numbers may fluctuate as cases are resolved.

Figure 3: COVID-19 cases in Alberta by route of suspected acquisition. First and second panels display new (from November 30-December 06, 2021) and active cases, respectively. Cases are under investigation and numbers may fluctuate as cases are resolved.

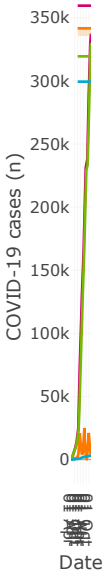


Figure 4: COVID-19 cases in Alberta by day and case status. Recovered is based on the assumption that a person is recovered 14 days after a particular date (see data notes tab), if they did not experience severe outcomes (hospitalized or deceased). Cases are under investigation and numbers may fluctuate as cases are resolved. Data included up to end of day December 06, 2021.

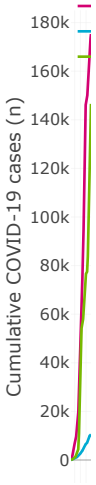


Figure 5: Cumulative COVID-19 cases in Alberta by route of suspected acquisition. Only includes COVID-19 cases where case report forms have been received. Data included up to end of day December 06, 2021.

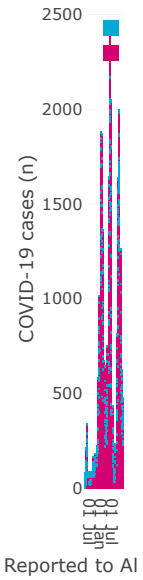


Figure 6: COVID-19 cases in Alberta by day and case status. Probable cases include cases where the lab confirmation is pending. Data included up to end of day December 06, 2021.

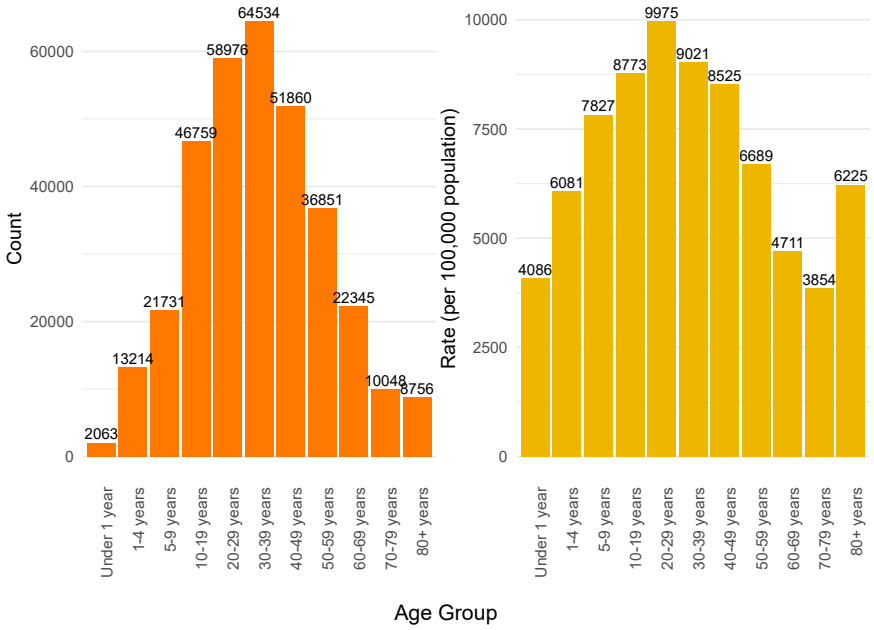


Figure 7: Number and rate of COVID-19 cases in Alberta by age group

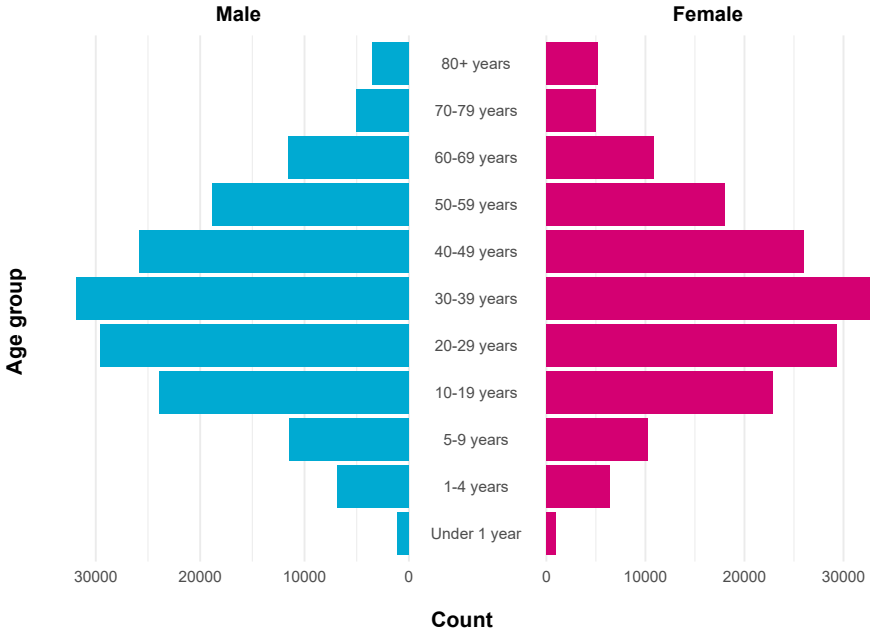
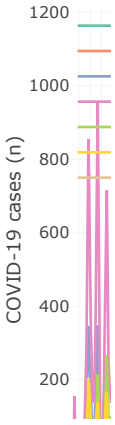


Figure 8: COVID-19 cases in Alberta by age group and gender

Table 1. COVID-19 cases in Alberta by age group and gender

	Gender							
	Female		Male		Unknown		All	
Age	Count	Percent	Count	Percent	Count	Percent	Count	Percent
Under 1 year	964	0	1,097	0	2	0	2,063	1
1-4 years	6,366	2	6,842	2	6	0	13,214	4
5-9 years	10,295	3	11,433	3	3	0	21,731	6
10-19 years	22,851	7	23,876	7	32	0	46,759	14
20-29 years	29,352	9	29,577	9	47	0	58,976	17
30-39 years	32,650	10	31,871	9	13	0	64,534	19
40-49 years	26,011	8	25,839	8	10	0	51,860	15
50-59 years	18,048	5	18,796	6	7	0	36,851	11
60-69 years	10,825	3	11,517	3	3	0	22,345	7
70-79 years	5,043	1	5,004	1	1	0	10,048	3
80+ years	5,224	2	3,530	1	2	0	8,756	3
Unknown	139	0	132	0	12	0	283	0
All	167,768	50	169,514	50	138	0	337,420	100



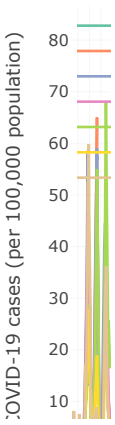


Figure 9: COVID-19 cases in Alberta by age group. First and second panels display counts (7-day rolling average) and rate per 100,000 (7-day rolling average), respectively.

Healthcare Workers

Table 2. Healthcare workers among COVID-19 cases

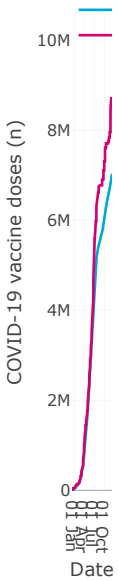
	Total	Active	Recovered	Died
Calgary Zone	5950	70	5876	4
Central Zone	2102	38	2064	0
Edmonton Zone	6606	55	6548	3
North Zone	1651	25	1625	1
South Zone	1345	12	1331	2
Alberta	17654	200	17444	10

Note:

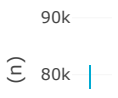
Status of Healthcare workers is self-reported and might be different from other sources. Please note these are not necessarily healthcare workers who were infected at work.

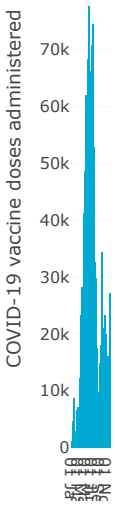
Vaccination data are up-to-date as of end of day December 06, 2021

- **7,028,981** doses of COVID-19 vaccine have been administered in Alberta
- **89** percent of 12+ population has received at least one dose (**77.3**% total population)
- **84.5** percent of 12+ population fully vaccinated (**71.9**% total population)



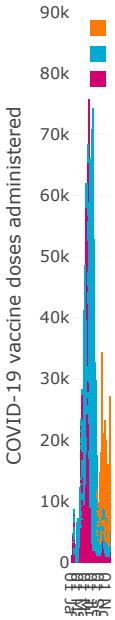
Cumulative COVID-19 vaccine doses received and administered by day in Alberta





Number of COVID-19 vaccine doses administered by day in Alberta

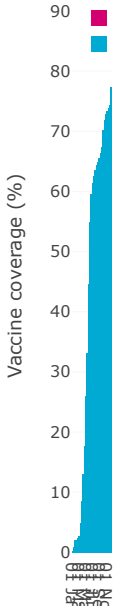
Note: Excludes aggregate doses reported by First Nations Inuit and Health Branch, Indigenous Services Canada



Number of COVID-19 vaccine doses administered by dose and day

Note: Excludes aggregate doses reported by First Nations Inuit and Health Branch, Indigenous Services Canada

Cumulative COVID-19 vaccine doses administered in Alberta



Cumulative percent of individuals who received at least one dose or are fully vaccinated by day in Alberta

Table 1. Breakdown of COVID-19 vaccine doses administered by provider.

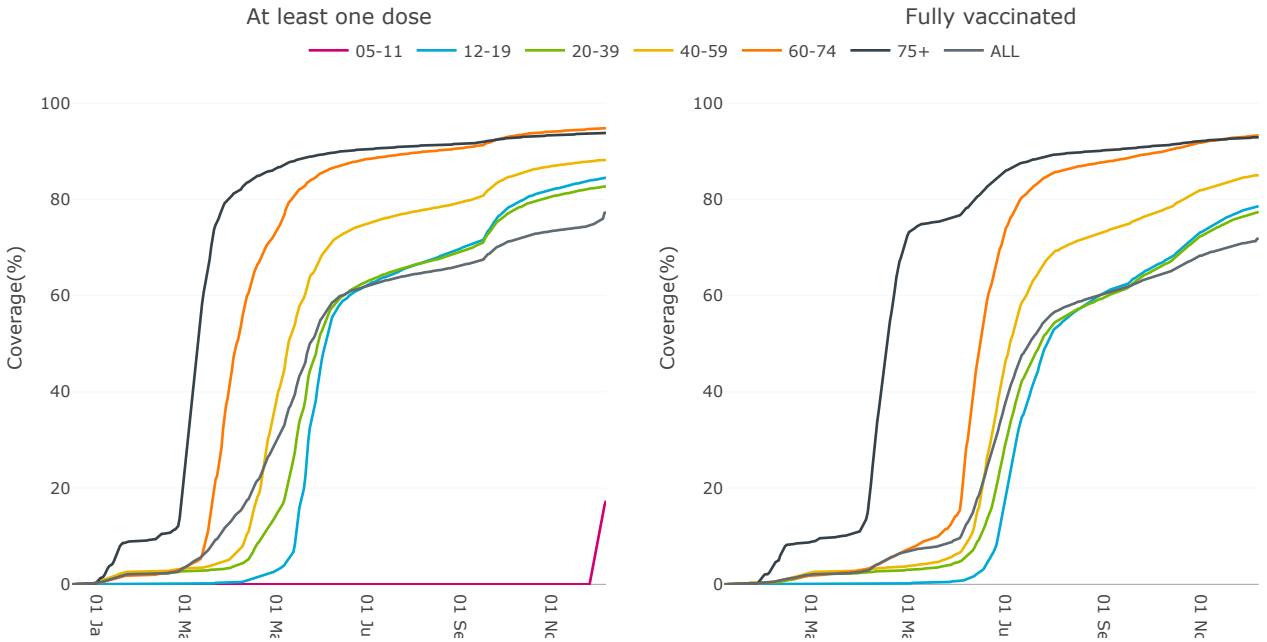
	Dose 1	Dose 2	Additional dose	Total administered
Alberta Health Services	1,741,419	1,488,596	103,006	3,333,021
Pharmacies	1,550,393	1,577,455	320,749	3,448,597
Other	125,537	107,001	14,825	247,363
Total	3,417,349	3,173,052	438,580	7,028,981

Note: Other includes submissions from First Nations communities and online submissions from other providers (e.g. physician clinics).

Table 2. Summary of COVID-19 vaccine doses administered and vaccine coverage by age group

Age group	Population	At least 1 dose	% of population with at least 1 dose	Fully vaccinated	% of population fully vaccinated	Additional dose	Total administered
00-04	267,791	0	0.0	0	0.0	0	0
05-11	391,430	68,282	17.4	0	0.0	0	68,282
12-14	162,518	136,757	84.1	126,714	78.0	203	263,674
15-19	256,700	217,314	84.7	203,000	79.1	780	421,012
20-24	276,916	231,043	83.4	212,826	76.9	2,927	446,529
25-29	314,340	252,434	80.3	234,108	74.5	6,542	492,735
30-34	356,224	291,183	81.7	273,649	76.8	8,760	573,067
35-39	359,135	305,511	85.1	290,226	80.8	11,073	606,236
40-44	319,735	278,664	87.2	268,280	83.9	25,407	571,825
45-49	288,613	253,304	87.8	244,128	84.6	26,628	523,619
50-54	266,607	239,117	89.7	231,116	86.7	25,773	495,624
55-59	284,313	251,481	88.5	242,305	85.2	34,472	527,931
60-64	264,324	245,349	92.8	238,626	90.3	55,820	539,568
65-69	209,995	201,114	95.8	198,209	94.4	32,629	431,785

Age group	Population	At least 1 dose	% of population with at least 1 dose	Fully vaccinated	% of population fully vaccinated	Additional dose	Total administered
70-74	157,696	152,471	96.7	152,575	96.8	42,351	347,300
75-79	103,045	97,525	94.6	96,794	93.9	68,921	263,181
80-84	68,661	64,233	93.6	63,638	92.7	46,119	173,985
85-89	44,188	40,880	92.5	40,414	91.5	30,037	111,320
90+	27,809	25,902	93.1	25,556	91.9	20,127	71,583
Unknown	NA	64,785	NA	34,929	NA	11	99,725
12+	3,760,818	3,349,067	89.1	3,177,093	84.5	438,580	6,960,699
5+	4,152,248	3,417,349	82.3	3,177,093	76.5	438,580	7,028,981
ALL	4,420,039	3,417,349	77.3	3,177,093	71.9	438,580	7,028,981



Cumulative percent of individuals who received at least one dose or are fully vaccinated by day in Alberta by age group

+−
Leaflet

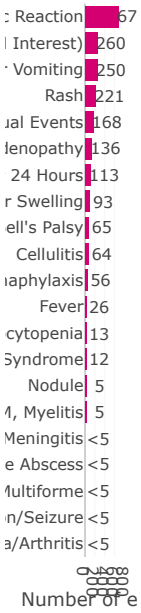
Coverage rate by local geographic area

Note: COVID-19 vaccine doses for all First Nations are included in the overall provincial totals. However, these totals do not necessarily appear in the LGA

map. First Nations with data sharing agreements with Alberta Health are included in LGA totals. First Nations without data sharing agreements are not reflected in individual LGAs.

> Geographies can be displayed by Alberta local geographic area (LGA). Individuals without a postal code or incorrect postal codes are not included. The colour categories for each LGA are based on the percent of the population (all ages) vaccinated. Vaccine uptake rates for the Vermilion River County LGA are underestimated as the Saskatchewan Health Authority provides public health services to all residents of Lloydminster.

- **2,089** adverse events following immunization (AEFI) have been reported to Alberta Health. This represents **2,038** people, and **2,176** symptoms.
  - **1,336** related to Pfizer
  - **537** related to Moderna
  - **210** related to AstraZeneca
- There have been **4,925** vaccine refusals and **4,487** contraindications to receiving the vaccine



Number of adverse events following immunization (AEFI) by condition reported in Alberta

Note: Information is collected on individuals and reported to Alberta Health when an AEFI is confirmed. One AEFI report can have multiple events associated with it. For AEFI definitions, please refer to this link.

- Since Jan 1, 2021, **0.3**% of people with one dose (11,779/3,395,472) were diagnosed with COVID-19 14 days after the first immunization date
- Since Jan 1, 2021, **0.9**% of people with two doses (27,870/3,170,483) were diagnosed with COVID-19 14 days after the second immunization date
- **78**% of cases (182,609/234,157) since Jan 1, 2021 were unvaccinated or diagnosed within two weeks from the first dose immunization date
- **77.9**% of hospitalized cases (9,096/11,675) since Jan 1, 2021 were unvaccinated or diagnosed within two weeks from the first dose immunization date
- **67.3**% of COVID-19 deaths (1,169/1,737) since Jan 1, 2021 were unvaccinated or diagnosed within two weeks from the first dose immunization date

Table 3. COVID-19 case outcomes in Alberta by vaccine status. Counts are provided for new, active cases, and those currently identified as being hospitalized.

Outcome	Vaccine status	Count (n)	Percent (%)
New cases	Complete	94	38.52
New cases	Partial	9	3.69
New cases	Unvaccinated	141	57.79
Active cases	Complete	1,739	42.36
Active cases	Partial	133	3.24
Active cases	Unvaccinated	2,233	54.40

Note:

Vaccine status category is based on protection. Doses administered within 14 days prior to a person's COVID-19 diagnosis are not considered protective; as a result, partial or complete vaccination categories only include those identified as cases over 14 days past their first or second immunization date.

Outcome	Vaccine status	Count (n)	Percent (%)
Currently hospitalized	Complete	121	32.44
Currently hospitalized	Partial	16	4.29
Currently hospitalized	Unvaccinated	236	63.27

Note:

Vaccine status category is based on protection. Doses administered within 14 days prior to a person's COVID-19 diagnosis are not considered protective; as a result, partial or complete vaccination categories only include those identified as cases over 14 days past their first or second immunization date.

Table 4. COVID-19 cases in the past 120 days in Alberta by vaccine status and pre-existing condition

		Complete		Partial		Unvaccinated	
		with condition	no condition	with condition	no condition	with condition	no condition
Age group	**Total**	**n %**	**n %**	**n %**	**n %**	**n %**	**n %**
Under 12 years	18,977	0 –	0 –	0 –	0 –	1,988 10.5%	16,989 89.5%
12-29 years	25,375	991 3.9%	3,805 15.0%	504 2.0%	2,088 8.2%	3,601 14.2%	14,386 56.7%
30-39 years	19,306	1,387 7.2%	4,502 23.3%	427 2.2%	1,459 7.6%	2,594 13.4%	8,937 46.3%
40-49 years	14,858	1,539 10.4%	4,077 27.4%	362 2.4%	902 6.1%	2,075 14.0%	5,903 39.7%
50-59 years	9,469	1,537 16.2%	2,065 21.8%	278 2.9%	423 4.5%	1,850 19.5%	3,316 35.0%
60-69 years	6,588	1,722 26.1%	1,378 20.9%	202 3.1%	146 2.2%	1,582 24.0%	1,558 23.6%
70-79 years	3,322	1,438 43.3%	439 13.2%	83 2.5%	27 0.8%	905 27.2%	430 12.9%
80+ years	2,444	1,525 62.4%	174 7.1%	77 3.2%	7 0.3%	533 21.8%	128 5.2%
Unknown	138	0 –	26 18.8%	0 –	11 8.0%	0 –	101 73.2%

Note:

Vaccine status category is based on protection as Table 3. Pre-existing conditions include respiratory diseases, diabetes, stroke, dementia, cardiovascular disease, liver diseases, renal diseases, cancer and immuno-deficiency diseases.

Table 5. Active COVID-19 cases in Alberta by vaccine status and pre-existing condition

		Complete		Partial		Unvaccinated	
		with condition	no condition	with condition	no condition	with condition	no condition
Age group	**Total**	**n %**	**n %**	**n %**	**n %**	**n %**	**n %**
Under 12 years	1,096	0 –	0 –	0 –	0 –	138 12.6%	958 87.4%
12-29 years	630	55 8.7%	224 35.6%	12 1.9%	29 4.6%	67 10.6%	243 38.6%
30-39 years	724	115 15.9%	334 46.1%	5 0.7%	25 3.5%	55 7.6%	190 26.2%
40-49 years	721	124 17.2%	330 45.8%	12 1.7%	21 2.9%	56 7.8%	178 24.7%
50-59 years	373	91 24.4%	130 34.9%	3 0.8%	11 2.9%	51 13.7%	87 23.3%
60-69 years	322	106 32.9%	86 26.7%	4 1.2%	6 1.9%	61 18.9%	59 18.3%
70-79 years	160	68 42.5%	25 15.6%	3 1.9%	1 0.6%	45 28.1%	18 11.2%
80+ years	78	46 59.0%	5 6.4%	1 1.3%	0 –	25 32.1%	1 1.3%
Unknown	1	0 –	0 –	0 –	0 –	0 –	1 100.0%

Note:

Vaccine status category is based on protection as Table 3. Pre-existing conditions include respiratory diseases, diabetes, stroke, dementia, cardiovascular disease, liver diseases, renal diseases, cancer and immuno-deficiency diseases.

Table 6. COVID-19 hospitalization, count and rate (per 100,000 population) in the past 120 days in Alberta by vaccine status Vaccine status category is based on protection as Table 3.

Age group	Fully vaccinated & hospitalized (n)	Fully vaccinated & hospitalized (rate per 100K)	Partially vaccinated & hospitalized (n)	Partially vaccinated & hospitalized (rate per 100K)	Unvaccinated & hospitalized (n)	Unvaccinated & hospitalized (rate per 100K)
Under 12 years	0	0.00	0	0.00	130	19.67

Age group	Fully vaccinated & hospitalized (n)	Fully vaccinated & hospitalized (rate per 100K)	Partially vaccinated & hospitalized (n)	Partially vaccinated & hospitalized (rate per 100K)	Unvaccinated & hospitalized (n)	Unvaccinated & hospitalized (rate per 100K)
12-29 years	39	5.07	22	33.61	444	255.74
30-39 years	66	11.85	42	117.10	630	514.06
40-49 years	58	11.46	45	191.51	595	754.24
50-59 years	106	22.50	57	320.49	773	1246.71
60-69 years	216	49.88	41	331.13	833	2881.90
70-79 years	303	123.99	37	715.81	642	5731.63
80+ years	440	345.30	44	1292.22	402	4090.58
12+ years	1228	39.50	288	176.08	4319	886.87

Table 7. Hospitalized COVID-19 cases in the past 120 days in Alberta by vaccine status and pre-existing condition

		Complete		Partial		Unvaccinated	
		with condition	no condition	with condition	no condition	with condition	no condition
Age group	**Total**	**n %**	**n %**	**n %**	**n %**	**n %**	**n %**
Under 12 years	130	0 –	0 –	0 –	0 –	28 21.5%	102 78.5%
12-29 years	505	13 2.6%	26 5.1%	10 2.0%	12 2.4%	137 27.1%	307 60.8%
30-39 years	738	27 3.7%	39 5.3%	17 2.3%	25 3.4%	248 33.6%	382 51.8%
40-49 years	698	39 5.6%	19 2.7%	23 3.3%	22 3.2%	290 41.5%	305 43.7%
50-59 years	936	90 9.6%	16 1.7%	45 4.8%	12 1.3%	464 49.6%	309 33.0%
60-69 years	1,090	193 17.7%	23 2.1%	37 3.4%	4 0.4%	565 51.8%	268 24.6%
70-79 years	982	281 28.6%	22 2.2%	37 3.8%	0 –	526 53.6%	116 11.8%
80+ years	886	419 47.3%	21 2.4%	42 4.7%	2 0.2%	333 37.6%	69 7.8%
Unknown	2	0 –	0 –	0 –	1 50.0%	0 –	1 50.0%

Note:

Vaccine status category is based on protection as Table 3. Pre-existing conditions include respiratory diseases, diabetes, stroke, dementia, cardiovascular disease, liver diseases, renal diseases, cancer and immuno-deficiency diseases.

Table 8. COVID-19 ICU admission, count and rate (per 100,000 population), in the past 120 days in Alberta by vaccine status. Vaccine status category is based on protection as Table 3.

Age group	Fully vaccinated & admitted in ICU (n)	Fully vaccinated & admitted in ICU (rate per 100K)	Partially vaccinated & admitted in ICU (n)	Partially vaccinated & admitted in ICU (rate per 100K)	Unvaccinated & admitted in ICU (n)	Unvaccinated & admitted in ICU (rate per 100K)
Under 12 years	0	0.00	0	0.00	18	2.72
12-29 years	5	0.65	1	1.53	75	43.20
30-39 years	7	1.26	4	11.15	117	95.47
40-49 years	15	2.96	7	29.79	161	204.09
50-59 years	15	3.18	5	28.11	256	412.88

Age group	Fully vaccinated & admitted in ICU (n)	Fully vaccinated & admitted in ICU (rate per 100K)	Partially vaccinated & admitted in ICU (n)	Partially vaccinated & admitted in ICU (rate per 100K)	Unvaccinated & admitted in ICU (n)	Unvaccinated & admitted in ICU (rate per 100K)
60-69 years	48	11.08	13	104.99	262	906.43
70-79 years	48	19.64	8	154.77	163	1455.23
80+ years	21	16.48	1	29.37	33	335.79
12+ years	159	5.11	39	23.84	1067	219.10

Table 9. Hospitalized COVID-19 cases in ICU in the past 120 days in Alberta by vaccine status

		Complete	Partial	Unvaccinated
Age group	**Total**	**n %**	**n %**	**n %**
Under 12 years	18	0 –	0 –	18 100.0%
12-29 years	81	5 6.2%	1 1.2%	75 92.6%
30-39 years	128	7 5.5%	4 3.1%	117 91.4%
40-49 years	183	15 8.2%	7 3.8%	161 88.0%
50-59 years	276	15 5.4%	5 1.8%	256 92.8%
60-69 years	323	48 14.9%	13 4.0%	262 81.1%
70-79 years	219	48 21.9%	8 3.7%	163 74.4%
80+ years	55	21 38.2%	1 1.8%	33 60.0%
Unknown	1	0 –	0 –	1 100.0%

Note:

Vaccine status category is based on protection as Table 3. Pre-existing conditions include respiratory diseases, diabetes, stroke, dementia, cardiovascular disease, liver diseases, renal diseases, cancer and immuno-deficiency diseases.

Table 10. Hospitalized COVID-19 cases in ICU in the past 120 days in Alberta by vaccine status and pre-existing condition

		Complete		Partial		Unvaccinated	
		with condition	**no condition**	**with condition**	**no condition**	**with condition**	**no condition**
Age group	**Total**	**n %**	**n %**	**n %**	**n %**	**n %**	**n %**
All ages	1,284	144 11.2%	15 1.2%	32 2.5%	7 0.5%	695 54.1%	391 30.5%

Note:

Vaccine status category is based on protection as Table 3. Pre-existing conditions include respiratory diseases, diabetes, stroke, dementia, cardiovascular disease, liver diseases, renal diseases, cancer and immuno-deficiency diseases.

Table 11. COVID-19 deaths, count and rate (per 100,000 population), in the past 120 days in Alberta by vaccine status. Vaccine status category is based on protection as Table 3.

Age group	Fully vaccinated & died (n)	Fully vaccinated & died (rate per 100K)	Partially vaccinated & died (n)	Partially vaccinated & died (rate per 100K)	Unvaccinated & died (n)	Unvaccinated & died (rate per 100K)
Under 12 years	0	0.00	0	0.00	1	0.15
12-29 years	1	0.13	0	0.00	7	4.03
30-39 years	1	0.18	1	2.79	18	14.69
40-49 years	8	1.58	1	4.26	25	31.69
50-59 years	8	1.70	2	11.25	80	129.03

Age group	Fully vaccinated & died (n)	Fully vaccinated & died (rate per 100K)	Partially vaccinated & died (n)	Partially vaccinated & died (rate per 100K)	Unvaccinated & died (n)	Unvaccinated & died (rate per 100K)
60-69 years	27	6.24	8	64.61	116	401.32
70-79 years	67	27.42	7	135.42	190	1696.28
80+ years	165	129.49	16	469.90	188	1913.01
12+ years	277	8.91	35	21.40	624	128.13

Table 12. COVID-19 deaths in the past 120 days in Alberta by vaccine status

		Complete	Partial	Unvaccinated
Age group	**Total**	**n %**	**n %**	**n %**
Under 12 years	1	0 –	0 –	1 100.0%
12-29 years	8	1 12.5%	0 –	7 87.5%
30-39 years	20	1 5.0%	1 5.0%	18 90.0%
40-49 years	34	8 23.5%	1 2.9%	25 73.5%
50-59 years	90	8 8.9%	2 2.2%	80 88.9%
60-69 years	151	27 17.9%	8 5.3%	116 76.8%
70-79 years	264	67 25.4%	7 2.7%	190 72.0%
80+ years	369	165 44.7%	16 4.3%	188 50.9%
Unknown	2	1 50.0%	0 –	1 50.0%

Note:

Vaccine status category is based on protection as Table 3. Pre-existing conditions include respiratory diseases, diabetes, stroke, dementia, cardiovascular disease, liver diseases, renal diseases, cancer and immuno-deficiency diseases.

Table 13. COVID-19 deaths in the past 120 days in Alberta by vaccine status and pre-existing condition

		Complete		Partial		Unvaccinated	
		with condition	**no condition**	**with condition**	**no condition**	**with condition**	**no condition**
Age group	**Total**	**n %**	**n %**	**n %**	**n %**	**n %**	**n %**
All ages	939	270 28.8%	8 0.9%	31 3.3%	4 0.4%	508 54.1%	118 12.6%

Note:

Vaccine status category is based on protection as Table 3. Pre-existing conditions include respiratory diseases, diabetes, stroke, dementia, cardiovascular disease, liver diseases, renal diseases, cancer and immuno-deficiency diseases.

Table 14. COVID-19 vaccine effectiveness in Alberta by vaccine manufacturer

Vaccine	Vaccine Effectiveness: Partial (95% CI)	Vaccine Effectiveness: Complete (95% CI)
AstraZeneca	61% (58 to 63%)	89% (89 to 90%)
Moderna	81% (80 to 82%)	91% (90 to 91%)
Pfizer	75% (74 to 76%)	90% (90 to 90%)

Table 15. COVID-19 vaccine effectiveness against variants of concern in Alberta

Variant of Concern	Vaccine Effectiveness: Partial (95% CI)	Vaccine Effectiveness: Complete (95% CI)
Alpha	76% (75 to 77%)	90% (88 to 91%)
Delta	57% (51 to 63%)	89% (89 to 90%)
Gamma	72% (67 to 76%)	88% (80 to 93%)

Note:

(a) Vaccine effectiveness estimates include 95% confidence intervals (CI) and describes the protection against infection. Vaccine effectiveness for hospitalization and death could have different estimates.

(b) Vaccine effectiveness estimates for some variants are not provided due to limited sample sizes, which make estimates unstable and difficult to interpret. Information on other variants will be provided when estimates become stable.
(c) Partial vaccination: people are considered partially vaccinated 14 days after their first dose of a two dose series (for vaccines that require two doses)
(d) Effectiveness: how well a vaccine prevents the outcome of interest in the real world

Figure 10: Case rate per 100,000 population by vaccination status in Alberta, 12+ population only. Note: Vaccine status category is based on protection as Table 3.

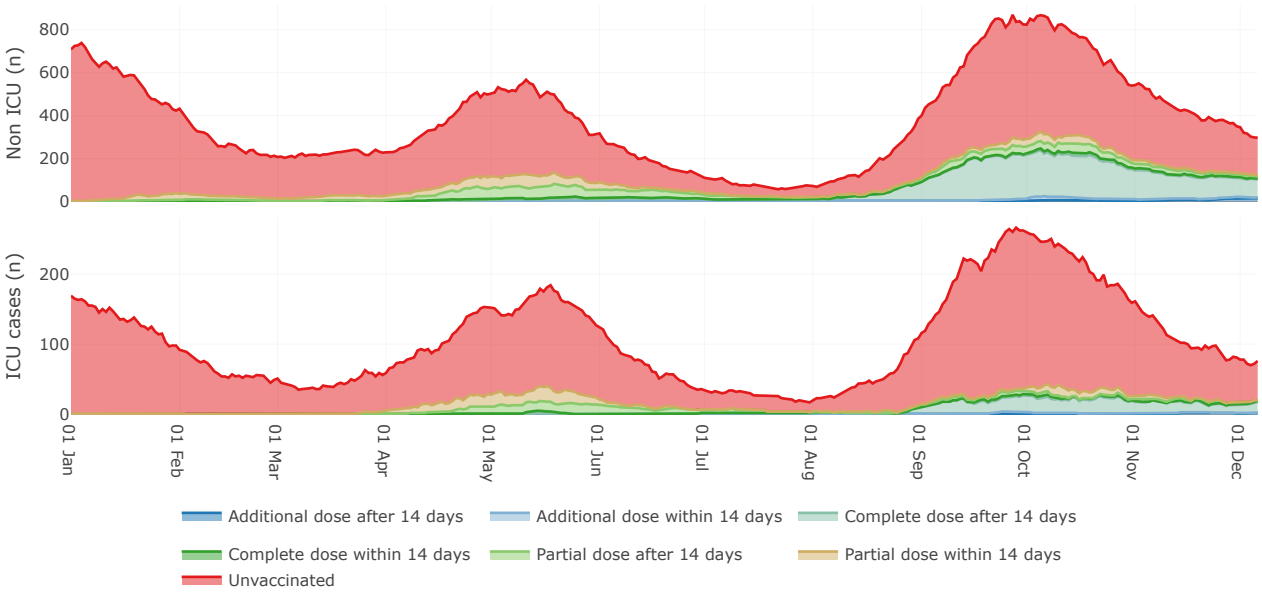


Figure 11: Current non-ICU (top) and ICU(bottom) by vaccine status.

Note:

Time from immunization date to COVID-19 diagnosis date (or Date reported to Alberta Health). COVID-19 hospitalizations reported are not due to immunization events.

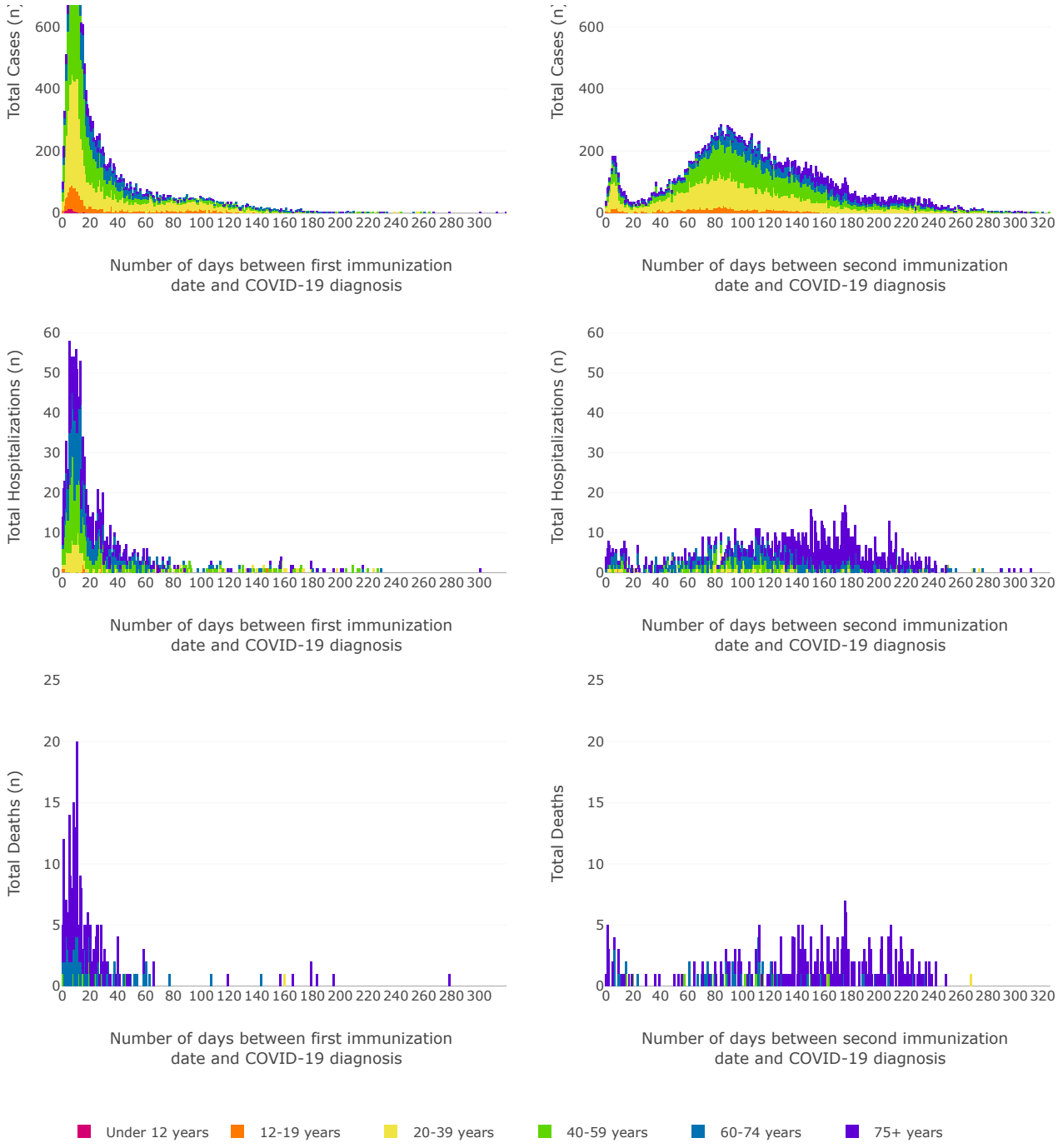


Figure 12: Time from first dose (left) and second dose immunization (right) to COVID-19 diagnosis by age group:
TOP: cases
MIDDLE: of those who became hospitalized
BOTTOM: of those who died from COVID-19
Note: First dose immunization also includes people who became a case prior to their second dose immunization date. COVID-19 hospitalizations reported are not due to immunization events.

Summary

- Average age for COVID cases that died is 78 years (range: 1-107)
- Average age for COVID cases hospitalized with an ICU stay is 56 years (range: 0-99)
- Average age for COVID cases hospitalized is 59 years (range: 0-104)
- Average age for COVID cases not hospitalized is 34 years (range: 0-121)

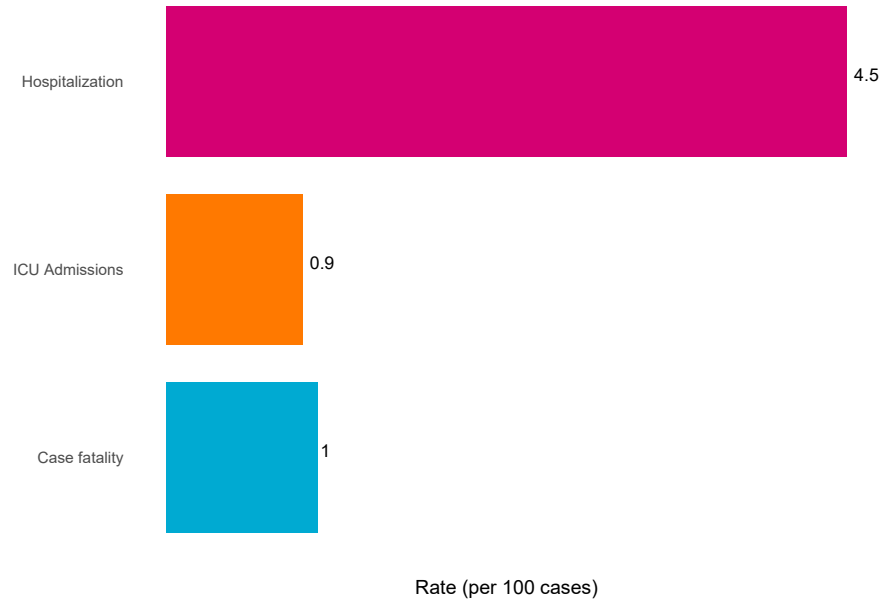


Figure 13: Rate of total hospitalizations, ICU admissions, and deaths among COVID-19 cases in Alberta

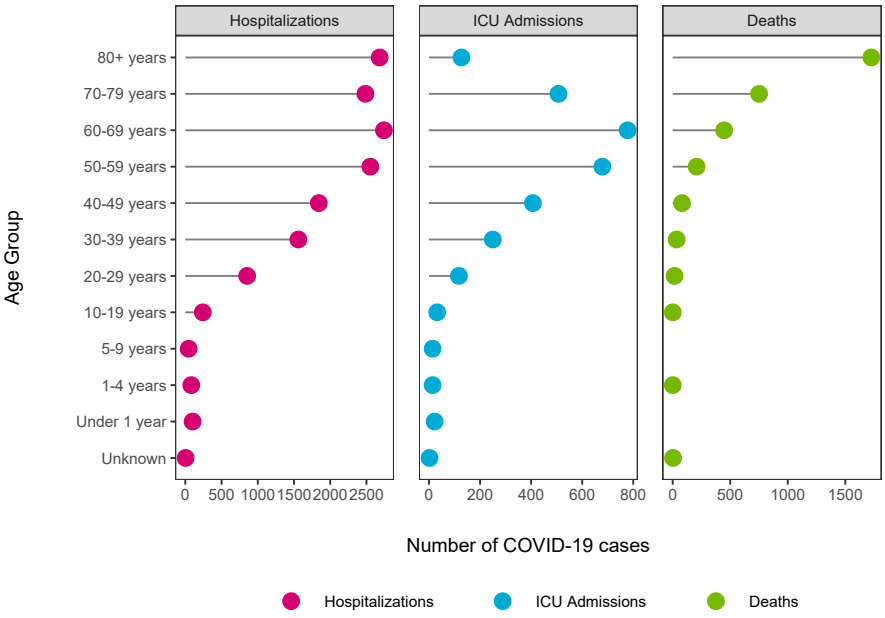


Figure 14: Total hospitalizations, ICU admissions and deaths (ever) among COVID-19 cases in Alberta by age group. Each ICU admission is also included in the total number of hospitalizations.This is based on totals rather than current hospitalizations and ICU admissions.

Table 16. Total Hospitalizations, ICU admissions and deaths (ever) among COVID-19 cases in Alberta by age group

Age Group	Cases	Hospitalized			ICU			Deaths		
	Count	Count	Case rate	Pop. rate	Count	Case rate	Pop. rate	Count	Case rate	Pop. rate

Note:

Based on total hospitalizations and ICU admissions ever.

Row percent is out of the number of cases in each age group.

Each ICU admission is also included in the total number of hospitalization

Case rate (per 100 cases)

Population rate (per 100,000 population)

Age Group	Cases	Hospitalized			ICU			Deaths		
	Count	Count	Case rate	Pop. rate	Count	Case rate	Pop. rate	Count	Case rate	Pop. rate
Total	337420	15190	4.5	343.7	2949	0.9	66.7	3268	1.0	73.9
Under 1 year	2063	100	4.8	198.1	22	1.1	43.6	0	0.0	0.0
1-4 years	13214	82	0.6	37.7	14	0.1	6.4	1	0.0	0.5
5-9 years	21731	46	0.2	16.6	14	0.1	5.0	0	0.0	0.0
10-19 years	46759	241	0.5	45.2	32	0.1	6.0	1	0.0	0.2
20-29 years	58976	853	1.4	144.3	117	0.2	19.8	16	0.0	2.7
30-39 years	64534	1560	2.4	218.1	250	0.4	34.9	34	0.1	4.8
40-49 years	51860	1842	3.6	302.8	407	0.8	66.9	81	0.2	13.3
50-59 years	36851	2553	6.9	463.4	679	1.8	123.2	208	0.6	37.8
60-69 years	22345	2741	12.3	577.9	778	3.5	164.0	447	2.0	94.2
70-79 years	10048	2486	24.7	953.4	507	5.0	194.4	751	7.5	288.0
80+ years	8756	2682	30.6	1906.8	127	1.5	90.3	1726	19.7	1227.1
Unknown	283	4	1.4	NA	2	0.7	NA	3	1.1	NA

Note:

Based on total hospitalizations and ICU admissions ever.

Row percent is out of the number of cases in each age group.

Each ICU admission is also included in the total number of hospitalization

Case rate (per 100 cases)

Population rate (per 100,000 population)

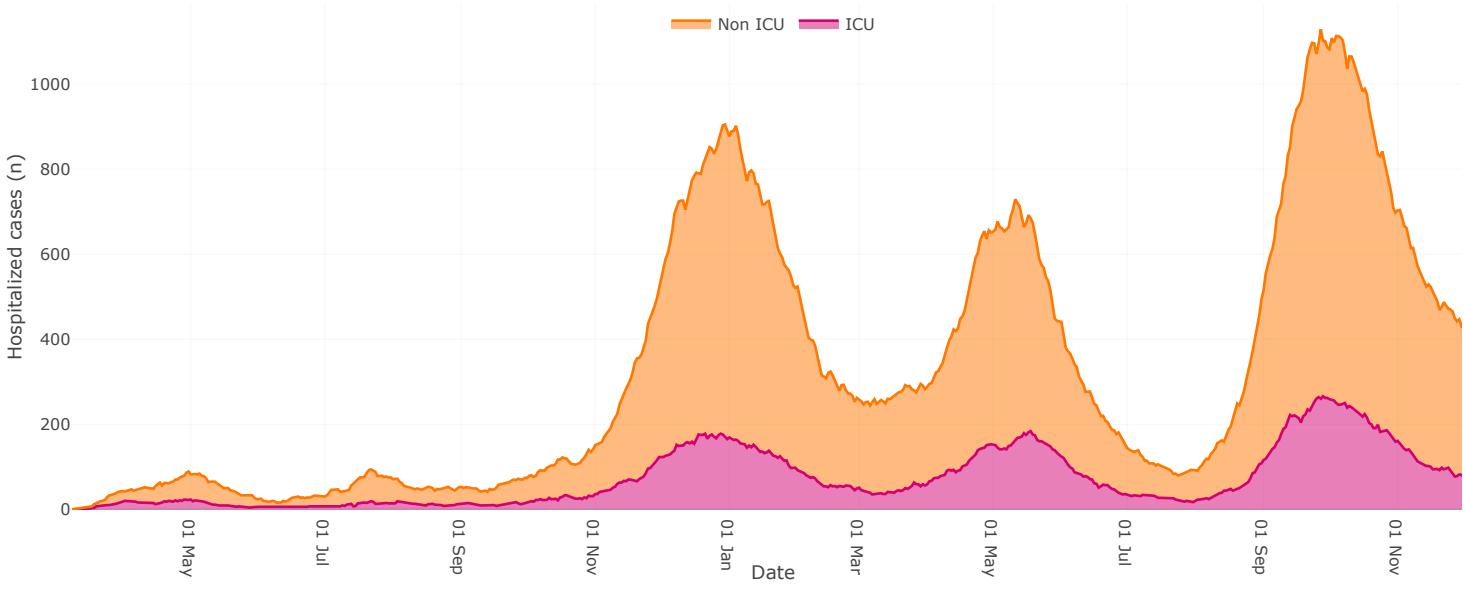
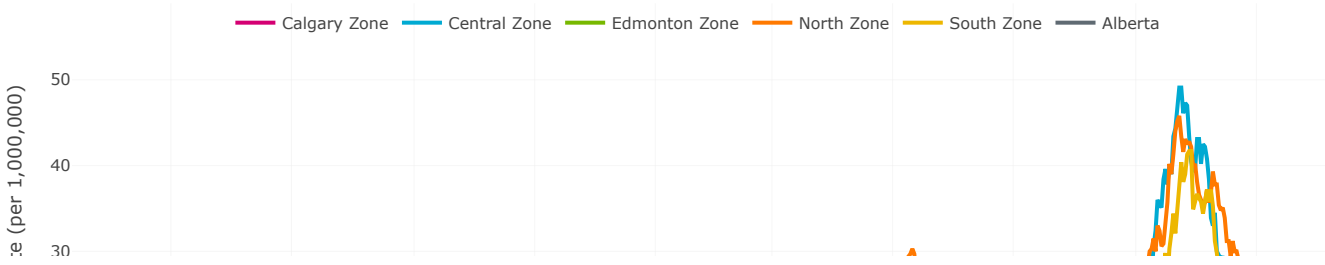


Figure 15: Number of current COVID-19 patients in hospital, ICU and non-ICU



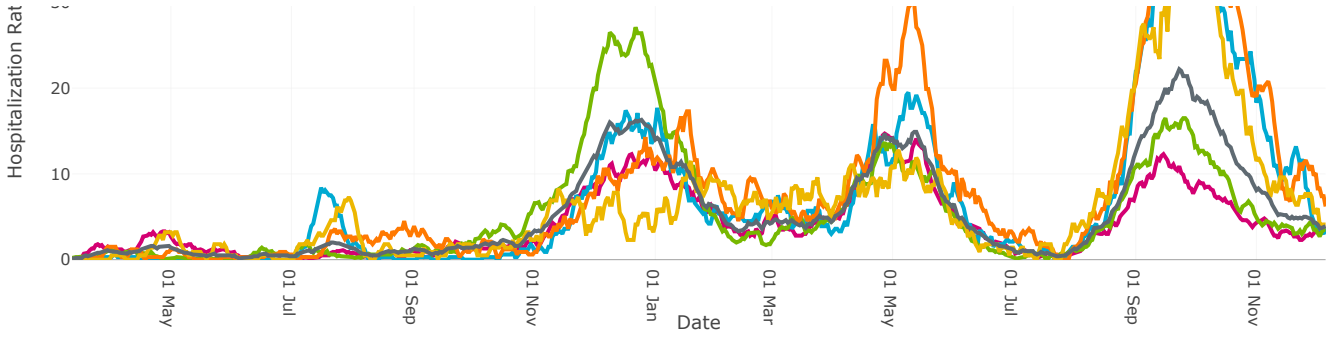


Figure 16: Rate of new hospitalizations (7-day rolling average, average of current day and previous 6 days) by admission date in Alberta and by zone

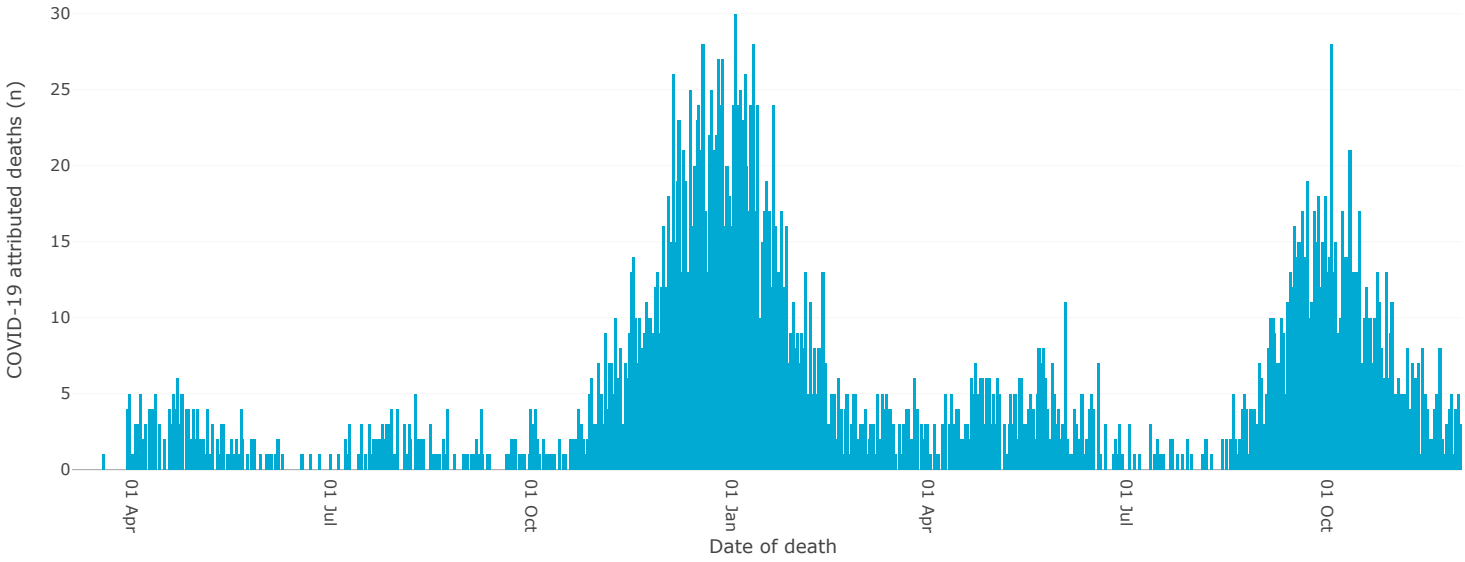


Figure 17: Daily COVID-19 attributed deaths. Data are subject to change; when death date is unavailable the date reported to Alberta Health is used until a death date is known.

Table 17. Number and percent of health conditions among COVID-19 deaths. Data updated on 2021-12-06.

Condition	Count	Percent
Hypertension	2690	82.3%
Cardio-Vascular Diseases	1693	51.8%
Renal Diseases	1653	50.6%
Diabetes	1445	44.2%
Respiratory Diseases	1297	39.7%
Dementia	1222	37.4%
Cancer	752	23.0%
Stroke	592	18.1%
Liver Diseases	145	4.4%
Immuno-Deficiency Diseases	119	3.6%

Note:

One individual can have multiple conditions.

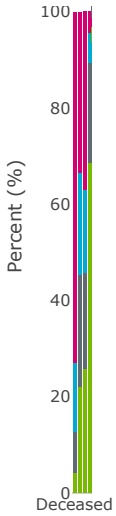


Figure 18: Percent of COVID-19 cases with no pre-existing conditions, one condition, two conditions, or three or more conditions by case severity (non-severe, hospitalized but non-ICU, ICU but not deceased, and deceased), all age groups and both sexes combined, all Alberta. Pre-existing conditions included are: Diabetes, Hypertension, COPD, Cancer, Dementia, Stroke, Liver cirrhosis, Cardiovascular diseases (including IHD and Congestive heart failure), Chronic kidney disease, and Immuno-deficiency. Data updated on 2021-12-06.

Table 18. Number and percent of COVID-19 cases with no pre-existing conditions, one condition, two conditions, or three or more conditions by case severity (non-severe, hospitalized but non-ICU, ICU but not deceased, and deceased), all age groups and both sexes combined, Alberta. Pre-existing conditions included are: Diabetes, Hypertension, COPD, Cancer, Dementia, Stroke, Liver cirrhosis, Cardiovascular diseases (including IHD and Congestive heart failure), Chronic kidney disease, and Immuno-deficiency. Data updated on 2021-12-06.

	Non-Severe		Non-ICU		ICU		Deaths	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent
No condition	220579	68.7%	2786	25.8%	480	22.1%	141	4.3%
With 1 condition	66397	20.7%	2161	20.0%	507	23.3%	274	8.4%
With 2 conditions	19919	6.2%	1861	17.2%	459	21.1%	472	14.4%
With 3 or more conditions	14272	4.4%	4005	37.0%	726	33.4%	2381	72.9%

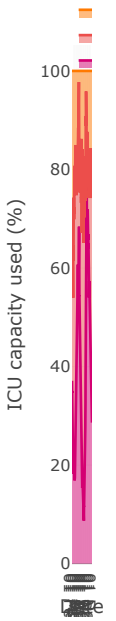


Figure 19: Intensive Care Unit (ICU) bed capacity. Data included may only be available at a lagged interval. As a result, the number of COVID occupied ICU beds on a particular day may not match the number reported elsewhere on the dashboard.

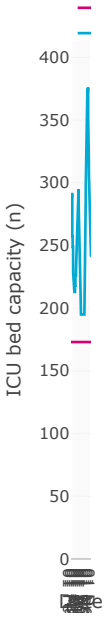


Figure 20: Total ICU bed capacity over time. Data included may only be available at a lagged interval. As a result, the number of COVID occupied ICU beds on a particular day may not match the number reported elsewhere on the dashboard.

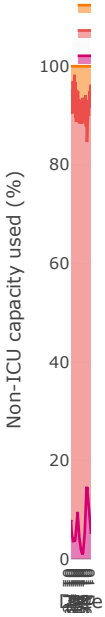
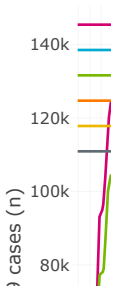


Figure 21: Non-ICU bed capacity. Data included may only be available at a lagged interval. As a result, the number of COVID occupied inpatient beds on a particular day may not match the number reported elsewhere on the dashboard. Data reflects the non-ICU hospital occupancy at the 14 largest hospitals, excluding pediatrics.



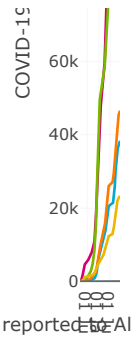


Figure 22: Cumulative COVID-19 cases in Alberta by zone and date reported to Alberta Health. Cases without a postal code or incorrect postal codes are labelled as unknown.

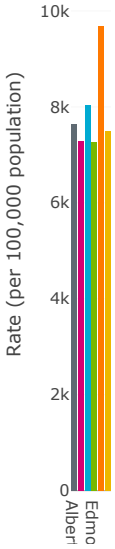


Figure 23: Rate of COVID-19 cases (per 100,000 population) in Alberta and by zone

Table 19. COVID-19 cases in Alberta by zone

Zone	Count	Percent
Calgary Zone	124,538	37
Central Zone	38,341	11
Edmonton Zone	104,623	31
North Zone	46,553	14
South Zone	23,324	7
Unknown	41	0
All	337,420	100

Geographies can be displayed by municipality or local geographic area (LGA). When viewing by municipality, regions are defined by metropolitan areas, cities, urban service areas, rural areas, and towns with approximately 10,000 or more people; smaller regions (i.e. villages, and reserves) are incorporated into the corresponding rural area. Cases without a postal code or incorrect postal codes are not included. Location information missing/invalid for: 922 case(s).

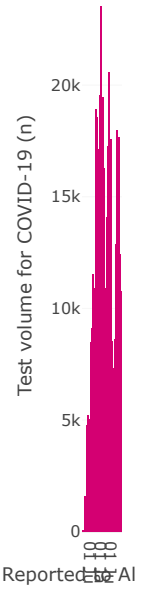


Figure 24: Tests performed for COVID-19 in Alberta by day. Tests can be performed for the same person multiple times.

Table 20. COVID-19 testing in Alberta

	Number (n)
Test volume	6,181,640
People tested	2,597,485

Table 21. Number of people tested for COVID-19 in Alberta by zone

Zone	Count	Percent
Calgary Zone	1,029,115	40
Central Zone	235,896	9
Edmonton Zone	817,510	31
North Zone	251,343	10
South Zone	164,933	6
Unknown	98,688	4
All	2,597,485	100

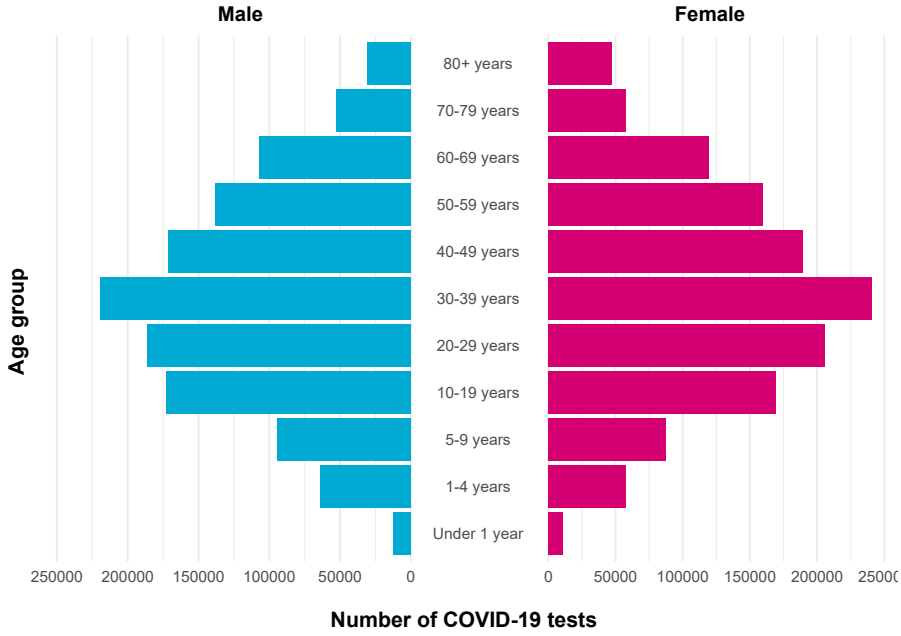


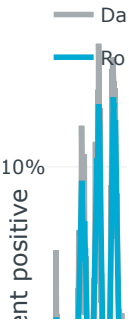
Figure 25: People tested for COVID-19 in Alberta by age group and gender.

Table 22. People tested for COVID-19 in Alberta by age group and gender

	Gender							
	Female		Male		Unknown		All	
Age	Count	Percent	Count	Percent	Count	Percent	Count	Percent
Under 1 year	10,843	0	12,460	0	30	0	23,333	1
1-4 years	57,850	2	63,722	2	82	0	121,654	5
5-9 years	87,408	3	94,413	4	127	0	181,948	7
10-19 years	169,225	7	172,411	7	455	0	342,091	13
20-29 years	205,848	8	186,093	7	722	0	392,663	15
30-39 years	240,651	9	219,098	8	718	0	460,467	18
40-49 years	189,294	7	171,467	7	544	0	361,305	14
50-59 years	159,597	6	137,952	5	446	0	297,996	11
60-69 years	119,264	5	106,903	4	259	0	226,426	9
70-79 years	57,578	2	52,830	2	86	0	110,494	4
80+ years	46,935	2	30,586	1	116	0	77,637	3
Unknown	508	0	562	0	400	0	1,471	0
All	1,345,001	52	1,248,497	48	3,985	0	2,597,485	100

Note:

Count represents the number of people tested



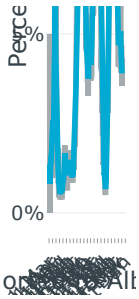


Figure 26: Cumulative and daily test positivity rate for COVID-19 in Alberta.

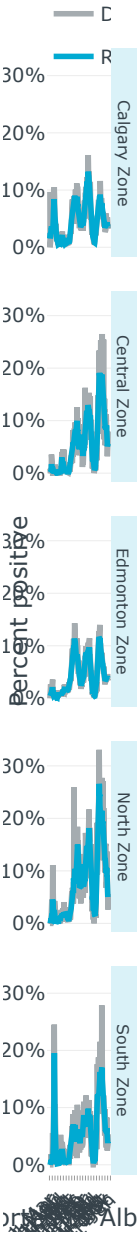


Figure 27: Positivity rate for COVID-19 in Alberta by zone.

Summary

NOTE: People are identified as COVID-19 cases prior to variant of concern identification. As such, variant of concern reporting is delayed compared to date the case was reported to Alberta Health.

Due to the large number of positive COVID-19 cases, the lab screened a sample of positive cases between May 1, 2021 and May 31, 2021 and again between

September 9 and November 23.

- **112,476** variants of concern identified
  - **3376** active cases
  - **1,140** died

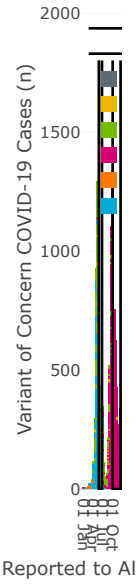


Figure 28: Variant of concern COVID-19 cases in Alberta by day. Note: cases are identified as COVID-19 positive prior to being identified as a variant of concern. Data included up to end of day December 06, 2021.

Table 23. Variants of concern COVID-19 cases identified in Alberta and by Zone

Zone	Alpha	Beta	Delta	Gamma	Kappa	Omicron	Total
Calgary Zone	20,046	79	14,389	802	6	8	35,330
Central Zone	5,459	2	7,920	193	0	0	13,574
Edmonton Zone	11,434	65	21,574	1,064	13	2	34,152
North Zone	6,249	34	13,677	768	0	1	20,729
South Zone	2,682	0	5,908	97	0	0	8,687
Unknown	0	0	4	0	0	0	4
Alberta	45,870	180	63,472	2,924	19	11	112,476

Table 21. Variants of concern COVID-19 cases identified who are active, recovered, or died in Alberta and by Zone

Zone	Active	Died	Recovered	Total
Calgary Zone	1,368	209	33,753	35,330
Central Zone	376	244	12,954	13,574
Edmonton Zone	1,007	305	32,840	34,152
North Zone	416	224	20,089	20,729
South Zone	208	158	8,321	8,687
Unknown	1	0	3	4
Alberta	3,376	1,140	107,960	112,476

Note: Active and recovered cases are now based on information on a sample of positive cases only and should be interpreted with caution.

Data are subject to change. Fluctuations are expected as cases are investigated and updated. Data are provided for export in csv format.

Case data

Data included up to end of day December 06, 2021.

Download

Summary data starting March 6, 2020

Data included up to end of day December 06, 2021.

Download

Geospatial data

Data included up to end of day December 06, 2021.

Download

Vaccine data

Data included up to end of day December 06, 2021.

Download

Data sources

The Provincial Surveillance Information system (PSI) is a laboratory surveillance system which receives positive results for all Notifiable Diseases and diseases under laboratory surveillance from Alberta Precision Labs (APL). The system also receives negative results for a subset of organisms such as COVID-19. The system contains basic information on characteristics and demographics such as age, zone and gender. The Communicable Disease Reporting System (CDRS) at Alberta Health and the Communicable Disease Outbreak Management (CDOM) system at Alberta Health Services contains information on COVID-19 cases. Data Integration and Measurement Reporting (DIMR) database at Alberta Health Services contains up to date information on people admitted and discharged from hospital in Alberta. Information such as hospitalizations and ICU admissions are received through enhanced case report forms sent by Alberta Health Services (AHS).

COVID-19 vaccinations and AEFIs are reported to the Provincial Immunization and Adverse Reaction to Immunization (Imm/ARI) repository. In Alberta, all health practitioners are required by law to report Adverse Events Following Immunization (AEFI) to Imm/ARI. The reporting requirements are outlined in the Immunization Regulation, under the Public Health Act. Case definitions are further defined in the AEFI Policy. As of January 1, 2021, all health practitioners are required to report all (both provincially funded and privately purchased) vaccinations electronically to Imm/ARI.

Definitions

Recovered

Active and recovered status is a surveillance definition to try to understand the number of active cases in the population. It is not related to clinical management of cases. It is based on the assumption that a case is recovered 14 days after a particular date. For confirmed cases, specimen collected date is used and for probable cases date reported to Alberta Health is used. If a case is hospitalized, the recovered date is when their symptoms have resolved based on case follow-up, or 10 days after being discharged.

COVID-19 Deaths

A death resulting from a clinically compatible illness, in a probable or confirmed COVID-19 case, unless there is a clear alternative cause of death identified (e.g., trauma, poisoning, drug overdose).

A Medical Officer of Health or relevant public health authority may use their discretion when determining if a death was due to COVID-19, and their judgement will supersede the above criteria.

A death due to COVID-19 may be attributed when COVID-19 is the cause of death or is a contributing factor.

Lab Positivity

COVID-19 percent positivity in Alberta is calculated using the Test Over Test method, which is the same method employed by the US Centers for Disease Control and Prevention. The calculation is as follows:

Daily Number of Positive Tests / (Daily Number of Positive Tests + Daily Number of Negative Tests) Q/RT-PCR tests are the only COVID-19 tests included in this calculation.

https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/calculating-percent-positivity-faq.html

Pre-existing Conditions

The following pre-existing conditions are included in respective analyses: diabetes, hypertension, COPD, cancer, dementia, stroke, liver cirrhosis, cardiovascular diseases (including IHD and congestive heart failure), chronic kidney disease, and immuno-deficiency diseases.

Vaccine coverage

Individuals who received at least one dose was calculated as (# of individuals who received at least one dose) / (population estimate). Those who received two doses was calculated as (# of individuals who received two doses) / (population estimate).

Disclaimer

The content and format of this report are subject to change. Cases are under investigation and numbers may fluctuate as cases are resolved. Data included in the interactive data application are up-to-date as of end of day December 06, 2021.

TAB 5

See Tab 4

TAB 6

National Collaborating Centre for Methods and Tools

Centre de collaboration nationale des méthodes et outils

School of Nursing | McMaster University

SPOR Evidence Alliance

SPOR Strategy for Patient-Oriented Research Putting Patients First

COVID-END COVID-19 Evidence Network to support Decision-making ... in Canada

Rapid Review Update 1: What is the ongoing effectiveness, immunogenicity, and safety of COVID-19 vaccines in persons who have had a prior, confirmed COVID-19 infection?

Prepared by: The National Collaborating Centre for Methods and Tools
Prepared for: National Advisory Committee on Immunization (NACI)

Date: October 15, 2021

Suggested Citation:

National Collaborating Centre for Methods and Tools. (2021, October 15). *Rapid Review Update 1: What is the effectiveness, immunogenicity, and safety of COVID-19 vaccines in persons who have had a prior, confirmed COVID-19 infection?* https://www.nccmt.ca/covid-19/covid-19-rapid-evidence-service/36

Please Note: An update of this review may be available. Access the most current version of this review by visiting the National Collaborating Centre for Methods and Tools COVID-19 Rapid Evidence Service at the above link.

This work was funded in collaboration with the SPOR Evidence Alliance (SPOR EA) and COVID-19 Evidence Network to support Decision-making (COVID-END), which are supported by the Canadian Institutes of Health Research (CIHR) through the Canadian 2019 Novel Coronavirus (COVID-19) Rapid Research Funding opportunity.

Executive Summary

Background

To date in Canada, four vaccines have been approved to prevent coronavirus disease 2019 (COVID-19): AstraZeneca/COVISHIELD, Janssen (Johnson & Johnson), Moderna and Pfizer-BioNTech. While their efficacy and effectiveness in preventing COVID-19 infections in the general population has been shown to be strong, questions remain as to the comparable effectiveness in those with prior confirmed COVID-19 infection. Given the immune system's previous exposure to the virus, it is not known whether the same vaccination schedule recommended for the general populations is appropriate for those with prior infection, what differences may exist in immunogenicity response between those with and without prior infection (infection naïve), and whether there may be differences in adverse events in response to vaccination in those with prior infection. As questions emerge about waning immunity over time, and booster shots are planned, it is also not known whether those with previous infection should receive boosters on the same schedule.

This rapid review was produced to support public health decision makers' response to the COVID-19 pandemic. This review seeks to identify, appraise, and summarize emerging research evidence to support evidence-informed decision making.

This rapid review includes evidence available up to October 6, 2021, to answer the question: **What is the ongoing effectiveness, immunogenicity, and safety of COVID-19 vaccines in persons who have had a prior, confirmed COVID-19 infection?**

What Has Changed in This Version?

- 15 new studies were identified and included in this updated review
- To address emerging questions about waning immunity and the need for booster shots in specific populations, additional exclusion criteria were applied. To be eligible for inclusion, studies must report data on outcomes of interest collected at least three months, 12 weeks, or 90 days post-completion of vaccination regime.
    - This resulted in 46 studies that were previously included being excluded from the current update, and 1 study remaining
- Given the limited data, the previous criteria which required a minimum sample size of 20 to be included has been removed. This did not result in any previously excluded studies being included in this review.

Key Points

- Only three studies were identified that compared the efficacy or effectiveness of vaccines in those with previous COVID-19 infection compared to those without previous infection. Vaccination in individuals with previous COVID-19 infection may be slightly more effective compared to those without previous infection, although the number of breakthrough infections was low in both groups. The certainty of evidence is low (GRADE).
- Only two studies compared rates of infection in those with previous COVID-19 infection who were vaccinated compared to those who were not vaccinated. Given the small

number of events in both groups, the effectiveness of vaccination in those with prior infection cannot be determined. The certainty of evidence is very low (GRADE).
- Across the 13 studies reporting on the humoral immune response to vaccination those with a prior COVID-19 infection likely have a stronger response than those without a prior infection after two doses, with the magnitude of the difference decreasing over time. The certainty of the evidence is moderate (GRADE).
- No studies compared humoral immune response in individuals with prior COVID-19 infection who had received vaccines to those who were not vaccinated with follow-up greater than three months.
- No studies reported on cellular immune responses with follow-up greater than three months.
- No studies compared local or systemic adverse effects with follow-up greater than three months.

Overview of Evidence and Knowledge Gaps

- There is very limited long-term (> 3 months) data on efficacy and effectiveness of vaccination to prevent infection specific to those with prior infection. The findings across studies were consistent: in all but one comparison, vaccinated individuals with prior infection had a small but statistically significant different decrease in the number of breakthrough infections compared to vaccinated individuals without prior infection. The largest difference was seen in residents (mean age 84.6) of a long-term care facility experiencing an outbreak of the delta variant of concern (1.3% vs. 53.7%). This suggests that any additional protection from prior infection may be more important in older adults.
- Within studies reporting on vaccine effectiveness, only the number of cases were reported without additional information on severity of infection, hospitalization, or death.
- Across all studies, vaccinated individuals with and without prior infection have vastly reduced rates of infection compared to unvaccinated individuals.
- Across immunogenicity studies, findings are consistent that those with a prior infection have a stronger response with follow-up periods closer to receipt of vaccination. The magnitude of the difference between groups appears to decrease over time, and in several studies was no longer statistically significant at the longest follow-up periods (5-7 months).
- Despite noted differences in immunogenicity, it is not clear whether the differences seen are meaningful in terms of protection offered against infection, severe infection, hospitalization, or death. One study found that IgG levels following vaccination did not predict protection in infection naïve older adults; it is not known whether this finding applies to other age groups or those with prior infection.
- Heterogeneity in findings across studies is likely influenced by variations in time since infection in previously infected individuals, interval between the first and second dose, the timing of data collection following vaccination and loss to follow-up which varies across studies. There is insufficient evidence available to draw conclusions as to whether interval between infection and vaccination, or vaccine product received, or interval between vaccine doses impacts effectiveness or immune response.

- No included studies reported on vaccine effectiveness or immunogenicity in populations where vaccines were mixed between first and second doses.
- Immunogenicity studies explored differences by age, or between groups representing older vs. younger populations (e.g., long-term care residents vs. staff). Findings suggest that humoral response to vaccination in those previously infected is lower in older age groups.
- Within the studies that compared immunogenicity response by severity of previous infection, findings were mixed, and no conclusions can be drawn based on severity of infection.
- Several studies collected data on either effectiveness and immunogenicity during periods where new variants of concern (VoC) were prevalent however effectiveness findings were generally not separated by VoC in those with and without prior infection.

Implications for Policy Making

- While the evidence included in this review suggests that vaccinated individuals with prior infection may have greater protection against COVID-19 and a stronger immune response than vaccinated individuals without prior infection, given the small number of infections in each group, short follow-up time and uncertainty with respect to how absolute values of humoral or cellular immune response markers correlate to or predict future infection, this data should be interpreted with caution with respect to recommendations about needs for additional booster doses in this population.

Methods

Research Question

What is the ongoing effectiveness, immunogenicity, and safety of COVID-19 vaccines in persons who have had a prior, confirmed COVID-19 infection?

Search

On October 6, 2021, the Public Health Agency of Canada's database of COVID-19 literature scan was searched. The search strategy for this database includes the following databases using key terms COVID-19, SARS-CoV-2, SARS-Coronavirus-2, nCov, "novel CoV", (novel AND coronavirus) for published and pre-print studies from January 28, 2021, through October 6, 2021. Systematic and rapid reviews are not included in this database.

- PubMed
- Scopus
- BioRxiv preprint server
- MedRxiv preprint server
- SSRN
- Research Square

We screened the database at the title and abstract level for studies related to immunogenicity, adverse events, and vaccine effectiveness/efficacy.

A copy of the full search strategy is available in Appendix 1.

Study Selection Criteria

English-language, peer-reviewed sources and sources published ahead-of-print before peer review were included. Surveillance sources were excluded.

Studies which did not report a statistical comparison between exposed and comparator groups were excluded.

	Inclusion Criteria	Exclusion Criteria
Population	Persons (any age) who had a prior, confirmed COVID-19 infection or are seropositive at the baseline of the study	
Exposure	COVID-19 vaccines which Canada has currently authorized for use (AstraZeneca, Janssen/J&J, Moderna, Pfizer/BioNTech)	Vaccines not approved in Canada
Comparisons	a) COVID-19 vaccination in persons without a previous confirmed SARS-CoV-2 infection or, persons with seronegative status at baseline b) Unvaccinated persons with a previous confirmed COVID-19 infection	
Outcomes	Effectiveness: • Confirmed COVID-19 infection (PCR or serologic), asymptomatic or symptomatic • Hospitalizations due to COVID-19 • ICU admissions due to COVID-19 • Deaths due to COVID-19 Immunogenicity: • Humoral immune responses (e.g., binding antibodies, neutralizing antibodies) • Cellular immune responses (e.g., B cells, CD4+ and CD8+ T-cells, and associated cytokine responses) Safety: • Local reactions due to vaccine • Systemic reactions due to vaccine • Serious adverse events due to vaccine	
Study designs	Interventional trials or observational studies with at least a 3-month follow-up period.	Case reports Case series

Data Extraction and Synthesis

Data relevant to the research question, such as study design, setting, location, population characteristics, interventions or exposure and outcomes were extracted when reported. We synthesized the results narratively due to the variation in methodology and outcomes for the included studies.

Appraisal of Evidence Quality

We evaluated the quality of included evidence using critical appraisal tools as indicated by the study design below. Quality assessment was completed by one reviewer and verified by a second reviewer. Conflicts were resolved through discussion.

Study Design	**Critical Appraisal Tool**
Cohort	Joanna Briggs Institute (JBI) Checklist for Cohort Studies
Cross-sectional	Joanna Briggs Institute (JBI) Checklist for Analytical Cross Sectional Studies

Completed quality assessments for each included study are available on request.

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) (Schünemann *et al.*, 2013) approach was used to assess the certainty in the findings based on eight key domains.

In the GRADE approach to quality of evidence, **observational studies,** as included in this review, provide **low quality** evidence, and this assessment can be further reduced based on other domains:

- High risk of bias
- Inconsistency in effects
- Indirectness of interventions/outcomes
- Imprecision in effect estimate
- Publication bias

and can be upgraded based on:

- Large effect
- Dose-response relationship
- Accounting for confounding.

The overall certainty in the evidence for each outcome was determined considering the characteristics of the available evidence (observational studies, some not peer-reviewed, unaccounted-for potential confounding factors, different tests and testing protocols, lack of valid comparison groups). A judgement of 'overall certainty is very low' means that the findings are very likely to change as more evidence accumulates.

Findings

Summary of the Certainty of Evidence

In this update, 15 new single studies were identified. 46 **previously included** studies were excluded based on new eligibility criteria, for a total of 16 publications addressing the research question.

A full list of studies that were previously included that are now excluded is available in Appendix 2.

Observational studies included cohort and cross-sectional designs. The certainty of the evidence included is as follows:

Outcome	Studies included		Overall certainty of evidence (GRADE)	Key findings
	Study design	n		
Risk of infection amongst vaccinated individuals, comparing those previously vs. not previously infected	Observational	3	⊕◯◯◯ Low[1]	Vaccination in individuals with previous COVID-19 infection may be slightly more effective compared to those without previous infection.
Risk of infection amongst those with previous infection, comparing those who received vaccination vs. unvaccinated	Observational	2	⊕◯◯◯ Very low[2]	The evidence is very uncertain about the risk of infection in individuals with previous COVID-19 infection who receive vaccination compared to those who remain unvaccinated.
Humoral immune responses (e.g., binding antibodies, neutralizing antibodies) amongst vaccinated individuals, comparing those previously vs. not previously infected	Observational	13	⊕⊕⊕◯ Moderate[2]	Those with prior infection likely have a stronger humoral immune response to vaccination than those with no prior infection.

[1]In the GRADE approach to quality of evidence, **observational studies,** as included in this review, provide **low quality** evidence, and this assessment was further downgraded due to imprecision
[2]In the GRADE approach to quality of evidence, **observational studies,** as included in this review, provide **low quality** evidence, and this assessment was further downgraded due to imprecision and risk of bias
[3]In the GRADE approach to quality of evidence, **observational studies,** as included in this review, provide **low quality** evidence, and this assessment was upgraded due to large effect.

Warning

Given the need to make emerging COVID-19 evidence quickly available, many emerging studies have not been peer reviewed. As such, we advise caution when using and interpreting the evidence included in this rapid review. We have provided a summary of overall certainty of the evidence to support the process of decision making. Where possible, make decisions using the highest quality evidence available.

Abbreviations

Ab: antibody
AU: arbitrary unit
Anti-S: anti-S antibodies
%B/B0: %bound/maximum bound
CI: confidence interval
dR: relative dissociation rate
GMC: geometric mean count
HCW: health care worker
IC_{50}: half maximal inhibitory concentration
IgG: immunoglobulin G
IQR: interquartile range
LTC: long-term care
mAb: monoclonal antibody
nAb: neutralizing antibody
NR: not reported
RFU: relative fluorescence unit
RT-PCR: real time polymerase chain reaction
RBD: receptor-binding domain
SD: standard deviation
SNAb: serum neutralizing antibody
Tab: total anti-capsid antibody
VoC: variant(s) of concern

Table 1: Clinical Effectiveness

Reference	Date Released	Study Design	Population	Case definition	Comparator	Vaccine	Effectiveness measure	Effect size	Notes	Quality Rating:
Risk of infection amongst those who are vaccinated, comparing those who had a previous infection vs. no infection (n=3)										
New evidence reported on October 15, 2021										
Blain, H., Tuaillon, E., Pisono, A., Soriteau, L., Million, E., Leglise, M., Bussereau, I., Miot, S., Rolland, Y., Picot, M., Christine, Jean, J. (2021). Prior Covid-19 and high RBD-IgG levels correlate with protection against VOC-δ SARS-CoV-2 infection in vaccinated nursing home residents. *Preprint.*	Sep 21, 2021	Cohort	Vaccinated nursing home residents during outbreak of delta-variant France Mean age 84.6 ±9.5	RT-PCR Confirmed seropositive n=44	RT-PCR Confirmed seronegative n=96	Pfizer-BioNTech 3-5 months prior to outbreak	Cumulative incidence	Previously infected: 1/44 (1.3%) Infection naïve: 55/96 (57.3%) p<0.0001	Delta-variant outbreak	Moderate ***PREPRINT***
Abu-Raddad, L.J., Chemaitelly, H., Ayoub, H.H., Yassine, H.M., Benslimane, F.M., Al Khatib, H.A. … Bertollini, R. (2021). Protection afforded by the BNT162b2 and mRNA-1273 COVID-19 vaccines	Jul 26, 2021	Cohort	Vaccinated adults Qatar Median age 39 (range 32-48)	Confirmed RT-PCR, seropositive n=24,052	Confirmed RT-PCR seronegative n=24,052	Pfizer/BioNTech or Moderna 14-146 days after 2nd dose Pfizer 14-60 days after 2nd dose Moderna	Cumulative incidence	Pfizer/BioNTech Previously infected: 0.16% (95% CI=0.11, 0.23) Naïve: 1.45% (95% CI=1.20, 1.76) p<0.05	Alpha and beta variants dominant in region during study follow-up period.	High ***PREPRINT***

in fully vaccinated cohorts with and without prior infection. *Preprint*.								Moderna: Previously infected: 0.06% (95% CI=0.03, 0.12) Naïve: 0.08% (95% CI=0.04, 0.15) *p-value NR*		
							Incident rate ratio	Pfizer-BioNTech: 0.15 (95% CI=0.11, 0.20)		
								Moderna: 0.85 (95% CI=0.34, 2.05)		
Previously reported evidence										
Shrestha, N. K., Burke, P. C., Nowacki, A. S., Terpeluk, P., Nowacki, A. S. & Gordon, S. M. (2021). Necessity of COVID-19 vaccination in previously infected individuals: A retrospective cohort study. *Preprint.*	Jun 19, 2021	Cohort	Vaccinated health system employees USA	Confirmed by RT-PCR n=1220 Mean age 39± SD 13 Time since infection: median 143 days (76,179)	COVID-19 infection naïve confirmed by nucleic acid amplification n=28 855 Mean age 42± SD 13	Pfizer/BioNTech (37%) Moderna (63%) Up to 108 days after the 2nd dose	Cumulative incidence of infection	Prior infection: 0/1220 (0%) Naïve: 15/28 855 (0.05%) *p-value NR*	Previously infected were younger (39±13 vs. 42±13, p<0.001), had patient-facing jobs (62% vs. 51%, p<0.001).	Moderate ***PREPRINT***

Risk of infection amongst those with previous infection, comparing those who received vaccination vs. unvaccinated (n = 2)										
New evidence reported on October 15, 2021										
Bruxvoort, K., Sy, L.S., Qian, L., Ackerson, B.K., Luo, Y., Lee, G.S., … Tseng, H.F. (2021). Real-World Effectiveness of the mRNA-1273 Vaccine Against COVID-19: Interim Results from a Prospective Observational Cohort Study. *Preprint*.	Sep 2, 2021	Cohort	Confirmed seropositive adults San Diego, USA Median age 65 (range 45-73)	Vaccinated (prior symptomatic infection) n=27	Unvaccinated (prior symptomatic infection) n=3	Moderna 14 days post index date to 3 months	Cumulative incidence	Vaccinated: 3.99 (95% CI=2.73,5.81) Unvaccinated: 5.48 (95% CI=3.85, 7.79)	This study was funded by Moderna Variants included delta (47.1%), alpha (21.4%), gamma (11.4%), epsilon (4.2%), Iota (4.3%) amongst vaccinated.	Moderate ***PREPRINT***
							Adjusted hazard ratio	0.66 (95% CI=0.38, 1.15)		
							Adjusted vaccine efficacy	33.6% (95% CI=0.0, 65.8)		
				Vaccinated (prior asymptomatic infection) n=44	Unvaccinated (prior asymptomatic infection) n=40	Moderna 14 days post index date to 3 months	Cumulative incidence	Vaccinated: 6.50 (95% CI=4.84, 8.763) Unvaccinated: 7.07 (95% CI: 5.19, 9.64)		
							Adjusted hazard ratio	0.92 (95% CI=0.58, 1.45)		
							Adjusted vaccine efficacy	8.2% (95% CI=0.0,47.3)		
Previously reported evidence										
Shrestha, N. K., Burke, P. C., Nowacki, A. S., Terpeluk, P., Nowacki, A. S. & Gordon, S. M. (2021). Necessity of COVID-19 vaccination in previously infected individuals: A retrospective cohort study. *Preprint.*	Jun 19, 2021	Cohort	Health system employees with confirmed RT-PCR infection, USA Time since infection: median 143 days (76,179)	Vaccinated n=1220 Mean age 39± SD 13	Unvaccinated N = 1359 Mean age 42± SD 13	Pfizer/BioNTech (37%), Moderna (63%)	Cumulative incidence of infection	Vaccinated: 0/1220 Unvaccinated: 0/1359 p>0.9999	-	Moderate ***PREPRINT***
							Adjusted hazard ratio	0.313 (95% CI=0, Infinity)		

Table 2: Immunogenicity

Reference	Date Released	Study Design	Population	Case definition	Comparator	Dose and follow-up	Immunogenicity measure	Unit	Effect size	Notes	Quality Rating:
Humoral immune responses (e.g., binding antibodies, neutralizing antibodies) amongst vaccinated individuals, comparing those previously vs. not previously infected (n = 13)											
New evidence reported on October 15, 2021											
Blain, H., Tuaillon, E., Pisono, A., Soriteau, L., Million, E., Leglise, M., Bussereau, I., Miot, S., Rolland, Y., Picot, M., Christine, Jean, J. (2021). Prior Covid-19 and high RBD-IgG levels correlate with protection against VOC-δ SARS-CoV-2 infection in vaccinated nursing home residents. *Preprint.*	Sep 21, 2021	Cohort	Vaccinated nursing home residents France Mean age 84.6 $\pm$9.5	RT-PCR Confirmed seropositive n=32	RT-PCR Confirmed seronegative n=25	Pfizer-BioNTech 6-weeks post 2nd dose	IgG (anti-RBD)	AU/mL Median (IQR)	Previously infected: 31,553 (19 667, 40 000) Naïve: 1050 (334, 3504) *p-value NR*	Naïve individual post-vaccination RBD IgG levels did not predict subsequent protection from Delta VoC infection.	Moderate ***PREPRINT***
						During outbreak, 3-5 months post 2nd dose (RT-PCR negative only)			Previously infected: 22,880 (12 296, 22 888) Naïve: 260 (79, 696) p<0.0001		
Kontopoulou, K., Nakas, C., Ntenti, C., Katsioulis, C., Goulas, A., & Papazisis, G. (2021). Antibody titers 3-months post-vaccination with the Pfizer/BioNTech vaccine in Greece. *Preprint.*	Sep 3, 2021	Cohort	Vaccinated HCW, Greece Vaccinated HCW, Greece	Confirmed seropositive n=38	Confirmed seronegative n=243	Pfizer-BioNTech 3 months post 2nd does (data not provided)	IgG-S (anti-RBD)	GMC (AU/mL)	Previously infected: 7460.91 (95% CI=5872.7, 9477.32) Naïve: 2534.43 (95% CI=2246.59, 2859.14) p<0.001	>99% of the study sample exceeded seropositivity threshold of 50 AU/mL. The authors conclude that although a decline in titers occurs at 6-months, these levels were still deemed.	High ***PREPRINT***
								GMC fold change relative to 2nd dose	Previously infected: 0.29 (95% CI=0.24, 0.33) Naïve: 0.17 (95% CI=0.16, 0.19) p<0.001		

Kontopoulou, K., Nakas, C., Ainatzoglou, A., Goudi, G., Katsioulis, C., & Papazisis, G. (2021). Evolution of Antibody Titers Up to 6 Months Post-Immunization with the BNT162b2 Pfizer/BioNTech Vaccine in Greece. *Preprint*. **Note, unique publications but from same study cohort as above*	Sep 15, 2021			N = 33	n = 213	6 months after 2nd dose	IgG	GMC (AU/mL)	Previously infected: 2848 (95% CI=2120.77, 3826.68) Naïve: 825.98 (95% CI=745.96, 914.60) p<0.001	satisfactory to prevent infection.	High ***PREPRINT***
								GMC fold change relative to 2nd dose	Previously infected: 0.10 (95% CI=0.08, 0.13) Naïve: 0.06 (95% CI=0.05, 0.06) p<0.05		
								GMC fold change relative to 3-months	Previously infected: 0.39 (95% CI=0.34, 0.45) Naïve: 0.33 (95% CI=0.31, 0.35) p<0.05		
Chen, Y., Tong, P., Whiteman, N.B., Moghaddam, A.S., Zuiani, A., Habibi, S., … Wesemann, D.R. (2021). Differential antibody dynamics to SARS-CoV-2 infection and vaccination. *Preprint*.	Sep 10, 2021	Cohort	Vaccinated adults, USA	Confirmed seropositive n=28 Median age 46.4 (range 23-77)	Confirmed seronegative n=18 Median age 39.8 (range 22-77)	Pfizer/BioNTech or Moderna 195 days after 2nd dose	IgG (anti-S and RBD)	mAb μg/mL	Previously infected had higher anti-S and anti-RBD than naïve up until 7 months (values NR). p<0.0001	-	High ***PREPRINT***

Racine-Brostek, S.E., Yee, J., Sukhu, A., Qiu, Y., Rand, S., Barone, P., ... Zhao, Z. (2021). More rapid, robust, and sustainable antibody responses to mRNA COVID-19 vaccine in convalescent COVID-19 individuals. *JCI Insight*. Epub ahead of print.	Sep 9, 2021	Cohort	Vaccinated HCW	Confirmed seropositive n=19 Mean age 42.5 ±11.6 Median days after onset of symptoms to 1st dose: 262 (range: 101.5, 275.0)	Confirmed seronegative n=49 Mean age 46.3 ±13.3	Pfizer-BioNTech 6-8 weeks post 2nd dose	TAb	RFU Median (IQR)	Previously infected higher than naïve (values NR) p<0.001	Naïve had a 50% decrease by 6 months.	Moderate
						~5 months post 1st dose			Previously infected: 8997 (7179, 9916) Naïve: 2706 (1667, 4511), Between-group difference 3.3-fold p<0.001		
						6-8 weeks post 2nd dose	SNAb	%B/B0 Median (IQR)	Previously infected: 0.8% (0.47, 1.22) Naïve: 17.35% (10.81, 28.76) p<0.001		
						~5 months post 2nd dose			Previously infected: 1.6% (1.359, 4.42) Naïve: 17.35% (10.81, 28.76) p<0.01		
						6-8 weeks post 2nd dose	Avidity	dR Median (IQR)	Previously infected: 3.89 (3.46, 4.89) Naïve: 7.0 (6.34, 3.38) p<0.001		
						~5 months post 2nd dose			Previously infected: 4.43 (3.39, 5.64) Naïve: 5.36 (4.5, 5.98) p=0.115		

						~5 months post 2nd dose	S-antibodies	U/mL	Previously infected: >2500 at all time points up to 6 months Naïve: 720 (565, 1269) p<0.001		
Erice, A., Varillas-Delgado, D., & Caballero, C. (2021). Decline of antibody titres 3 months after two doses of BNT162b2 in non-immunocompromised adults. *Clinical Microbiology and Infection*. Epub ahead of print.	Sep 8, 2021	Cohort	Vaccinated HCW, Spain Mean age=46±11	Confirmed by RT-PCR or seropositivity n=36	Confirmed seronegative n=194	Pfizer/BioNTech 1.5 months after 2nd dose	IgG (anti-RBD)	AU/mL Median (IQR)	Previously infected: 19,016 (7974,27 885) Naïve: 8,747 (5,631, 15,409) p<0.001	Median antibodies decreased by 58% in all participants (51% in previously infected). Titers higher in men, not statistically significant.	High
						3 months after 2nd dose			Previously infected: 9,364 (3975, 22 233) Naïve: 3,724 (2003, 7137) p<0.001		
Kertes, J., Gez, S.B., Saciuk, Y., Supino-Rosin, L., Stein, N.S. … Zohar, A.E. (2021). Effectiveness of the mRNA BNT162b2 vaccine six months after vaccination: findings from a large Israeli HMO. *Preprint*.	Sep 7, 2021	Cohort	Vaccinated individuals, Israel	Confirmed seropositive n = 365	Confirmed seronegative	Pfizer/BioNTech 7 days after 2nd dose 6 months after 2nd dose	IgG	% <300 AU/mL	Prior infection: 40.3% Naïve: 65.2% p<0.001	-	Moderate ***PREPRINT***

Bayart, J.L., Douxfils, J., Gillot, C., David, C., Mullier, F., Elsen, M., ... Favresse, J. (2021). Waning of IgG, total and neutralizing antibodies 6 months post-vaccination with BNT162b2 in healthcare workers. *Preprint*.	Sep 3, 2021	Cohort	Vaccinated HCW, Mean age 44	Confirmed seropositive n=73	Confirmed seronegative n=157	Pfizer-BioNTech Time after 2nd dose: 69 days	Mean total antibodies	U/mL Ratio (+/-)	Previously infected: 8,919 (95% CI=7201, 10637) Naïve: 1,262 (95% CI=1104, 1420) p<0.0001 Ratio: 7.1	-	Moderate ***PREPRINT***
						159 days			Previously infected: 4,270 (95% CI=3324, 5215) Naïve: 998 (95% CI=848, 1148) p<0.0001 Ratio: 4.3		
						69 days	IgG	AU/mL	Previously infected: 14,509 (95% CI=12 477, 16 541) Naïve: 6050 (95% CI=5371, 6729) p<0.001 Ratio 2.4		
						159 days			Previously infected: 6,333 (95% CI=5 072, 7 593) Naïve: 1,949 (95% CI=1 565, 2 332), p<0.342 Ratio: 3.2		

						69 days	NAbs	IC_{50} Median (IQR)	Previously infected: 163.1 (95% CI=83.5,243) Naïve: 127.6 (95% CI=84.3, 170.9) p=0.390 Ratio: 1.3		
						159 days			Previously infected: 30.5 (95% CI=18.2, 42.7) Naïve: 26.1 (95% CI=20.1, 32.1) p=0.4653 Ratio: 1.2		
Kosiorek, P., Kazberuk, D., Hrynieqicz, A., Milewski, R., Stróż, S., & Stasiak-Barmuta, A. (2021). Systemic COVID-19 vaccination also enhances the humoral immune response after SARS CoV-2 infection. An approach to criteria for COVID-19 re-immunization is needed. Do we need a third dose? *Preprint*.	Sep 2, 2021	Case-control	Vaccinated HCW, Poland Age range: 18-89 (45% >50)	Confirmed seropositive n=312	Confirmed seronegative n=472	Pfizer-BioNTech 90 days post 2nd dose	IgM IgG IgG (anti-S RBD)	AU/mL	IgM, IgG and S-RBD levels were significantly higher in those vaccinated and previously infected (values NR). p<0.0001	-	High ***PREPRINT***

Vicenti, I., Basso, M., Gatti, F., Scaggiante, R., Boccuto, A., Zago, D., ... Zazzi, M. (2021). Faster decay of neutralizing antibodies in never infected than previously infected healthcare workers three months after the second BNT162b2 mRNA COVID-19 vaccine dose. *International Journal of Infectious Diseases*. Epub ahead of print.	Sep 1, 2021	Cohort	Vaccinated HCW Veneto, Italy Median age 42 (range 33-47)	Confirmed seropositive, symptomatic n=9 Confirmed seropositive, asymptomatic n=14 Median time since infection 292 days (range 267-300)	Confirmed seronegative n=13	Pfizer/BioNTech or Moderna 20±3 days after 2nd dose	NtAbs	ID_{50} Median (range)	Previously infected, symptomatic: 1707.5 (1371.5, 3769.2) Previously infected, asymptomatic: 1450.3 (797.1, 2310) p=0.2076 Naïve: 176 (94.7, 299.7) vs. symptomatic p=0.0003 Naïve: 176 (94.7, 299.7) vs. asymptomatic p=0.0001	No difference between symptomatic and asymptomatic previously infected, but naïve participants had lower NtAbs than both.	High
						90±2 days after 2nd dose			Previously infected, symptomatic: 647 (308.4, 1439.7) Previously infected, asymptomatic: 520.5 (342,669.9) p=0.438 Naïve: 20 (17.5, 37) vs. symptomatic p<0.0001 Naïve: 20 (17.5, 37) vs. asymptomatic p=0.0001		

Tré-Hardy, M., Cupaiolo, R., Wilmet, A., Antoine-Moussiaux, T., Vecchia, A.D., ... Blairon, L. (2021). Six-month interim analysis of ongoing immunogenicity surveillance of the mRNA-1273 vaccine in healthcare workers: A third dose is expected. *Journal of Infection*. Epub ahead of print.	Aug 22, 2021	Cohort	Vaccinated HCW, Belgium Median age 50.1 (range: 46.9-52.4)	Confirmed seropositive n=43	Confirmed seronegative n=158	Moderna 2 months after 2nd dose 5 months after 2nd dose	IgG	AU/mL Median (IQR)	Previously infected: 400 (400, 400) Naïve: 400 (400, 400) Previously infected: 400 (365.5, 400) Naïve: 221.0 (202.3, 241.2) Decline from 2 to 5 months was greater in naïve vs. previously infected. p<0.0001	Among those previously infected, at 6 months 5/43 needed an additional booster to reach the 400 AU/mL threshold. All were >40 years (values not provided).	Moderate
Kannian, P., Mahanathi, P., Cohort Ashwini, V., & Kum Cohort arasamy, N. (2021). Booster and anergic effects of the Covishield vaccine among healthcare workers in South India. *Preprint*.	Aug 7, 2021	Cohort	Vaccinated HCW, South India	Confirmed seropositive Mild Covid n=13	No symptoms of COVID-19 n=88	AstraZeneca 14 days post 2nd dose 28 days post 2nd dose 3 months post 2nd dose	Anti-SARS-CoV2 spike antibodies	U/mL Median (IQR)	Previously infected: 13,584 (2692, 64 920) Naïve: 1206 (47,16 084) p<0.00001 Previously infected: 12,039 (3032, 37 476) Naïve: 870 (29, 12 824) p<0.00001 Previously infected: 6545 (1376, 22 004) Naïve: 306 (16, 2660) p=0.03	-	High ***PREPRINT***

Jeulin, H., Craus, D., Labat, C., & Benetos, A. (2021). Comparative analysis of post-vaccination anti-spike IgG antibodies in old Nursing Home Residents and in middle-aged Healthcare workers. *Preprint*.	Aug 4, 2021	Cohort	Vaccinated nursing home residents and HCW, France	Confirmed seropositive Residents n=109 median age 89 (range: 79-93) HCW n=21 median age 46 (range: 42-56)	Confirmed seronegative Residents, n=234 median age 88 (range: 83-92) HCW, n=187 median age 45 (Range: 38-54)	Not specified HCW: 123-141 days post 2nd dose Residents: 51-84 days post 2nd dose	IgG(S)	AIU Median (IQR)	*Residents:* Previously infected: 800 (800, 800) Naïve: 76 (20,287) p<0.01 *HCW:* Previously infected: 781 (481, 800) Naïve: 304 (182, 762) p<0.0001	Age was associated with IgG(S) decline only in naïve participants	Moderate ***PREPRINT***

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TAB 7

See Tab 6 at Pg. 3

TAB 8

COVID-19

Science Brief: SARS-CoV-2 Infection-induced and Vaccine-induced Immunity

Updated Oct. 29, 2021

This brief provides an overview of the current scientific evidence regarding infection-induced and vaccine-induced immunity, including both peer-reviewed and preprint publications, as well as unpublished CDC data. Although comprehensive, it is neither a formal systematic review nor meta-analysis. New data continue to emerge, and recommendations will be updated periodically, as needed.

Recovery from many viral infectious diseases is followed by a period of infection-induced immunologic protection against reinfection. This phenomenon is widely observed with many respiratory viral infections, including both influenza and the endemic coronaviruses, for which acquired immunity also wanes over time making individuals susceptible to reinfection.

CDC continues to recommend COVID-19 vaccination for all eligible persons, including those who have been previously infected with SARS-CoV-2.

Executive Summary

Key findings and considerations for this brief are as follows:

- Available evidence shows that fully vaccinated individuals and those previously infected with SARS-CoV-2 each have a low risk of subsequent infection for at least 6 months. Data are presently insufficient to determine an antibody titer threshold that indicates when an individual is protected from infection. At this time, there is no FDA-authorized or approved test that providers or the public can use to reliably determine whether a person is protected from infection.
  - The immunity provided by vaccine and prior infection are both high but not complete (i.e., not 100%).
  - Multiple studies have shown that antibody titers correlate with protection at a population level, but protective titers at the individual level remain unknown.
  - Whereas there is a wide range in antibody titers in response to infection with SARS-CoV-2, completion of a primary vaccine series, especially with mRNA vaccines, typically leads to a more consistent and higher-titer initial antibody response.
  - For certain populations, such as the elderly and immunocompromised, the levels of protection may be decreased following both vaccination and infection.
  - Current evidence indicates that the level of protection may not be the same for all viral variants.
  - The body of evidence for infection-induced immunity is more limited than that for vaccine-induced immunity in terms of the quality of evidence (e.g., probable bias towards symptomatic or medically-attended infections) and types of studies (e.g., observational cohort studies, mostly retrospective versus a mix of randomized controlled trials, case-control studies, and cohort studies for vaccine-induced immunity). There are insufficient data to extend the findings related to infection-induced immunity at this time to persons with very mild or asymptomatic infection or children.
- Substantial immunologic evidence and a growing body of epidemiologic evidence indicate that vaccination after infection significantly enhances protection and further reduces risk of reinfection, which lays the foundation for CDC recommendations.

Background

CDC recommends COVID-19 vaccination for all eligible persons, including those who have been previously infected with SARS-CoV-2 [1]. As of October 28, 2021, more than 45 million COVID-19 cases and over 740,000 deaths have been reported in the United States (US) [2]. Data from a seroprevalence survey that assessed for presence of antibodies and history of vaccination among US blood donors from January to August 2021 suggest that approximately half of previously infected adults in the US have not been vaccinated [3].

Both SARS-CoV-2 infection and COVID-19 vaccination induce an immune response that initially confers high levels of protection against symptomatic COVID-19 illness. This brief contains a review of evidence regarding vaccine-induced immunity and infection-induced immunity, including the initial immune response, antibody decay kinetics, protection from subsequent infection, impact of new variants, and effect of vaccinating previously infected individuals.

Separate overviews have been written on the types of assays used to assess the serologic response to SARS-CoV-2 (Interim Guidelines for COVID-19 Antibody Testing | CDC) and detailed evidence of the immunity provided specifically by vaccines (Science Brief: COVID-19 Vaccines and Vaccination).

Immune Response to Infection and Vaccination

Initial Immune Response to Infection

SARS-CoV-2 enters cells by binding to angiotensin converting enzyme-2 (ACE-2) receptors on the cell surface via the viral spike protein. As described in the Antibody Testing Guidelines, currently available serologic assays measure both overall production of antibodies against SARS-CoV-2 antigenic targets (binding antibodies) and functional ability to neutralize the SARS-CoV-2 virus via virus neutralization or pseudovirus neutralization tests (neutralizing antibodies). The antigenic targets most frequently assessed include those to the spike (S) protein, receptor binding domain (RBD) of the spike protein and nucleocapsid (N) core. IgM, IgA, and IgG isotypes may be developed against any of these antigens. As discussed below, serum binding antibodies to S and RBD and neutralizing antibodies have all been shown to correlate with protection against symptomatic SARS-CoV-2 infection.

SARS-CoV-2 infection induces a robust humoral and cellular immune response [4-8]. SARS-CoV-2-specific IgA and IgG have been detected from both mucosal sites and the serum of infected individuals [8]. IgM, IgA, and IgG can be detected in the blood 5–15 days following symptom onset or a positive reverse transcriptase polymerase chain reaction (RT-PCR) test, with IgM typically appearing first [6, 9]. IgM antibodies peak within the first few weeks following symptom onset, then fall below detectable limits 2–3 months after infection [6, 9, 10]. IgA antibodies also decrease rapidly, with some studies noting a return to undetectable levels within the first 3 months following infection [9]. IgG antibodies are more durable, though waning is also noted as described below. SARS-CoV-2-specific memory B- and T-cells also begin to appear within the first month following infection [11].

The vast majority of persons with SARS-CoV-2 infection generate detectable anti-SARS-CoV-2 antibodies, with multiple studies reporting seroconversion rates of 90% or higher [10, 12]. One large population-based study reported a lower seroconversion rate of 76%, though, among those who did not seroconvert in this study, only 21% reported symptoms, and authors noted that only 34% had strong evidence of a true-positive PCR [13]. Among individuals who seroconvert following infection with SARS-CoV-2, substantial heterogeneity exists, with a 200-fold difference in peak antibody titers noted in some studies [11].

Multiple factors contribute to the degree of immune response mounted following infection. Both binding and neutralizing antibody titers rise faster and reach a higher peak in persons with more severe COVID-19 [9, 10, 14]. People with symptomatic SARS-CoV-2 infection tend to have higher antibody titers than people who are asymptomatic, and people who are hospitalized tend to have higher antibody titers than people managed as outpatients [9, 10, 15, 16]. Studies have also demonstrated a correlation between cycle threshold (Ct) value and antibody titer, with lower Ct values being associated with higher antibody titers at the population level [9, 13].

Most studies did not find a relationship between sex and level of peak binding or neutralizing antibody titer. Increasing age has been associated with decreased likelihood of seroconversion [13] but higher peak antibody titers among those who do seroconvert [10, 11, 13, 15]. Lower rates of seroconversion have also been reported in persons with hematologic malignancies or receiving certain immunosuppressive medications [17, 18]. Data on the impact of other medical conditions is more variable and often confounded by the increased risk of severe disease in persons with certain underlying medical conditions

often confounded by the increased risk of severe disease in persons with certain underlying medical conditions.

Initial Immune Response to Vaccination

As of October 28, 2021, approximately 92% of people who have been vaccinated in the United States received one of two FDA-approved or authorized mRNA vaccines (Pfizer/BNT1272b2 and Moderna/mRNA-1273), and 8% received an adenovirus vector vaccine (Janssen/Ad26.COV2.S) [2]. Both vaccine types are designed to elicit an immune response against the spike protein that is required for SARS-CoV-2 binding, fusion, and cell entry. Consequently, vaccination induces the production of anti-S and anti-RBD binding and neutralizing antibodies in the blood, but not anti-N antibodies. Similar to infection, vaccines result in early production of serum IgA, IgM, and IgG antibodies [19, 20], and also induce long-lasting memory B- and T-cell responses [19, 21-23].

In immunogenicity analyses completed during phase I/II vaccine trials, 100% of participants developed both binding and neutralizing antibodies following vaccination with Pfizer-BioNTech and Moderna vaccines, and 90% of participants developed binding and neutralizing antibodies following vaccination with the Janssen vaccine [24-26]. Whereas there is a wide range in antibody titers in response to infection with SARS-CoV-2, completion of a primary vaccine series, especially with mRNA vaccines, typically leads to a more consistent, and higher-titer initial antibody response [24, 26-29]. However, similar to infection, this immune response may be decreased in older and immunosuppressed persons. Decreased rates of vaccine-induced seroconversion have been reported among persons with a variety of immune suppressing conditions, including those on certain immunosuppressive medications, post-solid organ transplant, and with hematologic cancers [30-34]. Studies have also found that persons aged 65-80 years and above have significantly lower peak anti-S and neutralizing antibody titers following vaccination than persons less than 65 years [35-40]. This is of particular concern given the increased risk of severe disease in older and immunosuppressed populations [41, 42].

Correlation of Immune Response Metrics to Protection

Multiple correlate-of-protection studies have demonstrated that higher antibody titers are associated with decreased risk of subsequent symptomatic SARS-CoV-2 infection. Data from both the phase 3 AZD1222 and mRNA-1273 vaccine efficacy trials demonstrated that quantitative titers of anti-S IgG, anti-RBD IgG, and pseudovirus and SARS-CoV-2 neutralizing antibody tests all correlate with protection against symptomatic infection (though not asymptomatic infection), with neutralizing antibodies having the strongest correlation in both of these studies [43, 44].

Analysis of data across studies has been difficult due to a lack of standardization of serologic assays [45]. Two different studies used data from seven vaccine efficacy studies (standardized against mean convalescent plasma titers) and one convalescent plasma/reinfection study to model effectiveness as a function of antibody titer [46, 47]. These found a high degree of correlation between mean peak neutralizing antibody titers and anti-S IgG binding antibodies within a population, and overall decrease in risk of infection. One study estimated that neutralizing antibody titers amounting to only 20% of the mean convalescent plasma neutralizing antibody titer (54 international units/ml using the WHO standard) correlated with a 50% reduction in infection risk; this appeared robust in predicting the effectiveness of vaccines not included in the model [46, 48]. Of note, the level of antibody associated with protection against severe disease was much lower than the level required to provide protection against infection, with only 3% of the mean convalescent antibody titer level correlating with 50% protection against severe disease [46].

Other immune mechanisms are also important in preventing SARS-CoV-2 infection and limiting COVID-19 illness severity, although their direct correlation with protection is less defined at this time. A study of rhesus macaques found that adaptive transfer of plasma with high titers of neutralizing antibodies was sufficient to protect from infection following a SARS-CoV-2 challenge. However, depleting CD8+ T cells compromised their ability to prevent infection once neutralizing antibodies had waned [49]. Analysis of antibody, B-cell and T-cell responses in acutely infected and convalescent humans has shown that protection depends on coordination of all three components of the immune response [50]. In the mRNA-1273 phase 3 clinical trial described above, investigators estimated that 68.5% (95% CI 58.5–78.4) of the protective effect of vaccination could be attributed to initial neutralization titers with some degree of protection occurring following vaccination, even when neutralization titers were not detected [43]. These, along with studies noted above, suggest that, while the magnitude of antibody response following infection or vaccination is correlated with protection and the absence of antibody with risk, antibody test results (particularly when not standardized nor quantitative) provide only a partial picture of an individual's immune response. At this time there is no specific antibody test or antibody threshold that can determine an individual's risk of subsequent infection.

Immune Response Kinetics and Duration of Protection

Immune Response Kinetics Following Infection

Antibody titers peak within 3-5 weeks following infection and then begin to wane in a manner that varies by individual, target antigen, antibody isotype, and assay used [6, 51]. Anti-N antibodies appear to wane fastest, followed by anti-RBD, then anti-S antibodies. Although at least 30% of persons may lose detectable anti-N antibodies within 10 months after infection, anti-S and overall SARS-CoV-2-specific IgG remain detectable in approximately 90% of persons who seroconvert up to 10 months to one year post-infection [16, 52]. Neutralizing antibodies appear to have a biphasic decline with an initial half-life of 2–3 months followed by a slower decline [11, 14, 15]. (**Table 1**)

For at least 2–3 months following infection, people with moderate-to-severe COVID-19 illness have higher titers of binding and neutralizing antibodies than people with mild illness [9, 14]; these differences may persist for 5–8 months following infection [11, 15].

B cells targeting SARS-CoV-2 increase in the first month and then remain at higher concentrations for at least 8 months post infection [11, 14, 53]. SARS-CoV-2-specific $CD4^+$ T cells increase then decline with a half-life of approximately 3-7 months; $CD8^+$ T cell measurements varied with at least one study reporting virtually no decline over the initial 4 months post-infection [11, 14]. (**Table 1**).

Protection from Reinfection in Cohort Studies

Multiple studies have compared the incidence of reinfection and primary infection during a specific time period to evaluate the level and duration of protection provided by initial infection with SARS-CoV-2. **Table 2** summarizes data from seven observational cohort studies from six countries, each with >10,000 participants, assessing the risk of reinfection over time. Five studies used RT-PCR positivity to define initial infection. In these studies, primary RT-PCR-confirmed SARS-CoV-2 infection decreased risk of subsequent infection by 80–93% for at least 6–9 months [54-58]. Studies specifically assessing persons seropositive with anti-N and anti-S antibodies following infection [16, 45] found slightly higher protective effects (89–93%). Most studies had a mean or median follow-up period of approximately 7 months; the longest reported follow-up was 12 months post-infection [58]. Three studies included sub-analysis to assess if the protection waned over time; none of these found a decline in protection within the follow-up period [54, 55, 57].

It is important to note that all of these studies were observational and all but two were retrospective. Low availability of testing early in the pandemic may have biased these studies toward populations that were more likely to have had symptomatic or medically attended primary infection. Most were unable to control for any potential differences in test- or healthcare-seeking behaviors between previously infected and naïve persons, though a large proportion of the reinfections reported across the studies were asymptomatic infections (**Table 2**). In one of the prospective cohort studies, over 25,000 healthcare workers were tested using RT-PCR testing every 2 weeks, allowing a more comprehensive ascertainment of reinfections. This study found that a history of previous RT-PCR-confirmed infection provided 93% protection against a subsequent symptomatic infection, 52% protection against asymptomatic infection, and 84% protection against overall infection with SARS-CoV-2 [54].

Many of these studies were completed just as vaccination was being rolled out in their respective countries, which makes it challenging to follow up and determine when immunity after infection wanes and what markers best predict this waning. Based on the trajectory of antibody decline, researchers have predicted that the immune response following infection would continue to provide at least 50% protection against reinfection for 1–2 years following initial infection with SARS-CoV-2 or vaccination [13, 46]. This would be similar to what is observed with seasonal coronaviruses [59]. Further epidemiologic analyses are needed to confirm these hypotheses.

Of note, these studies occurred when the ancestral strain and Alpha variant were the predominantly circulating variants. There is evidence that protection may decrease in the setting of more transmissible variants of concern (VoC) and variants being monitored (VBM), as discussed below.

Immune Response Kinetics Following Vaccination

Anti-S, anti-RBD and neutralizing antibodies remain detectable at least 6–8 months following vaccination [21, 22, 60]. Neutralizing titers following vaccination with the mRNA-1273 vaccine are estimated to decay with a half-life of 68–202 days, whereas binding anti-RBD antibodies decline with a half-life of 52–109 days [60]. These rates of antibody decay overlap with those reported for convalescent individuals (as shown in Table 1), though at least one preprint study reported less rapid decay among people recovered from infection compared with those vaccinated with BNT162b2 [28]. As with infection, the protective

among people recovered from infection compared with those vaccinated with BNT162b2 [20]. As with infection, the protective effect of vaccine-induced immunity is also supported by longer-term components of the humoral response, including memory B cells [21, 23, 61]; vaccine-induced CD4+ and CD8+ T cells continue to be relatively stable up to 6–8 months following vaccination [21, 61].

Although some studies have reported a faster decay of antibodies in persons 65 years or older, as compared to persons less than 65 years, lower anti-S and neutralizing antibodies at 2–6 months post vaccination appear to be at least partially attributable to lower peak antibody titers in this population [39, 40]. Nursing home residents are a unique population given age, co-morbidity, and congregate-setting associated risks. One study reported that detectable pseudovirus neutralization fell from 84% to 30% among nursing home residents (median age: 76 years, age range: 48–100 years) between 2 weeks and 6 months following vaccination; this was significantly faster than the rate of decline reported among staff-member controls (median age: 48 years, age range: 26–76 years), 81% of whom continued to have detectable neutralization at 6 months post-vaccination [42].

Duration of Immune Protection from Vaccination

Evidence is still accruing regarding the duration of protection following vaccination. Using antibody kinetics, one model predicted that an initial vaccine effectiveness of 90% would likely decline to approximately 70% around 250 days post-vaccination [46], not accounting for other factors such as non-serologic components of the immune response or the impact of new circulating variants.

Both Pfizer-BioNTech and Moderna released data from their phase 3 trials reporting overall high efficacy of mRNA vaccines against laboratory confirmed SARS-CoV-2 infection 5-6 months following vaccination. Pfizer-BioNTech reported an overall vaccine efficacy of 91% against infection and 97% against severe disease 6 months after vaccination with BNT162b2, though also reported a gradual decline in efficacy against infection from 96% at 7 days–2 months to 84% at 4–6months [62]. Moderna reported 93% efficacy at a median of 5 months after vaccination with mRNA-1273, without further details on the rate of decline in efficacy over time [63].

As described in greater detail in CDC's COVID-19 Vaccine and Vaccination Science Brief and in a October 2021 Advisory Committee on Immunization Practices presentation , recent studies have demonstrated waning of both antibody titers and vaccine effectiveness against infection over time, especially among older populations [42, 64]. Decreased vaccine effectiveness may reflect a combination of waning antibody titers and decreased neutralizing capacity in the setting of widespread circulation of variants with partial immune escape. Notably, multiple studies have found that vaccine effectiveness against hospitalization and/or severe disease continues to be high, ranging from 84–96%, up to 6 months following vaccination [65-68].

Impact of Variants on Infection- and Vaccine-induced Immunity

Variants of SARS-CoV-2 have emerged with multiple mutations in the spike protein that can result in decreased neutralization by antibodies, including those induced by either prior infection or vaccination [19, 69].

There is laboratory evidence that persons previously infected with the original lineage of SARS-CoV-2 have reduced neutralizing antibody titers against certain variants (i.e., Beta, Gamma, and Delta variants) [70-73]. One study found that among 367 unvaccinated persons assessed 12 months after infection, 98% had detectable anti-S IgG and 91% had neutralizing antibodies against wild-type virus. By comparison, among a subset of 78 persons assessed for neutralizing antibodies against particular variants, these were detectable in 84%, 68%, and 55% for Alpha, Delta, and Beta variants respectively [72]. Of note, absence of neutralization activity was higher among people reporting mild infection versus those with severe disease [72].

In studies examining neutralization from convalescent sera and vaccinated individuals together, the relative reduction in neutralization appears to be similar across both groups. A number of studies reported a 2- to 4-fold reduction in neutralization against Delta and a 6-fold (or higher) reduction in neutralization against Beta but minimal decreased neutralization against Alpha, as compared to the original SARS-CoV-2 lineage, for both convalescent and vaccinated individuals [70, 74, 75].

Decreased neutralization against Delta parallels reduced vaccine effectiveness against infection, but effectiveness remains high against hospitalization or severe disease [65, 66]. As highlighted in the COVID-19 Vaccine and Vaccination Science Brief, recent studies from the United States, United Kingdom, and Qatar have reported vaccine effectiveness of 54–85% against

SARS-CoV-2 infection compared with 90–100% against hospitalization/severe disease during periods of widespread circulation of Delta [65, 76-78]

Comparison of Infection- and Vaccine-induced Immune Responses

A systematic review and meta-analysis including data from three vaccine efficacy trials and four observational studies from the US, Israel, and the United Kingdom, found no significant difference in the overall level of protection provided by infection as compared with protection provided by vaccination; this included studies from both prior to and during the period in which Delta was the predominant variant [79]. In this review, the randomized controlled trials appeared to show higher protection from mRNA vaccines whereas the observational studies appeared to show protection to be higher following infection.

A more recent analysis of data from a network of 187 hospitals in the United States found that, among more than 7,000 COVID-19–like illness hospitalizations whose prior infection or vaccination occurred 90–179 days beforehand, there was a 5.5 times higher odds of laboratory-confirmed COVID-19 among previously infected patients than among fully vaccinated patients [80]. This study included data on persons more recently infected and/or vaccinated than the studies in the systematic review, though the authors noted one limitation of the design was the potential of missing testing that may have occurred outside of the healthcare network.

The Office of National Statistics in the United Kingdom used data from a large-scale longitudinal community survey of COVID-19 to compare the risk of infection among fully vaccinated, partially vaccinated, unvaccinated/previously infected, and unvaccinated/uninfected persons during two different periods 1) when Alpha was the predominant variant (December 2020–May 2021) and 2) when Delta was the predominant variant (May–August 2021) [81]. Based on results that included over 26,000 RT-PCR positive tests, they found full vaccination to provide the greatest protection during the Alpha predominant period (79% vs. 65% reduction in risk), but equivalent protection from full vaccination and infection during the Delta predominant period (67% vs. 71% reduction in risk).

Vaccine-induced Immune Responses after Previous Infection

Although there appears to be varying evidence regarding the relative protection that occurs after surviving COVID-19 as compared with completing vaccination, there is substantial immunologic and increasing epidemiologic evidence that vaccination following infection further increases protection against subsequent illness among those who have been previously infected.

Immunologic Data on Vaccination Following Infection

There is clear evidence that neutralizing antibody and memory B cell response elicited by a single dose of mRNA vaccine following previous infection with SARS-CoV-2 results in an increased antibody titer that is approximately equivalent to a two-dose vaccine regimen in individuals who were not previously infected (**Table 3**) [22, 23, 82-89]. In one study of healthcare workers vaccinated 7–11 months after infection with SARS-CoV-2, antibody titers measured 6 days following their first vaccination dose were twice as high as the antibody titers measured the month after their initial infection, and were able to neutralize wild-type, Alpha, and Beta variants, irrespective of vaccine type, number of doses, or pre-vaccination antibody titers [90].

Risk of Reinfection in Unvaccinated vs. Vaccinated Individuals with a History of Infection

In studies directly comparing risk of reinfection among previously infected individuals who were never vaccinated versus individuals who were vaccinated after infection, most, but not all, studies show a benefit of vaccination. One retrospective cohort study described risk of reinfection from December 2020–May 2021 among 2,579 US-based healthcare users previously infected with SARS-CoV-2, about 47% of whom were vaccinated over the course of the study. Investigators did not detect any cases of reinfection, regardless of vaccination status during 5 months of observation and so could not detect a benefit of vaccination [91]. In contrast, a case-control study conducted among 738 residents of Kentucky with reported infection during March–December 2020 found that previously infected persons who were unvaccinated had 2.3 times greater odds of reinfection during May–June 2021 than previously infected but vaccinated individuals [92]. Both studies occurred before Delta became the dominant variant in the United States.

More recent observational cohort studies including over 700,000 health system users in Israel and over 11,000 healthcare workers in India reported that history of prior infection provided greater protection from subsequent infection than vaccination alone, but overall risk of infection was lowest among those that were vaccinated following infection during periods of Delta predominance [93, 94]. In the systematic review described above, a pooled analysis across seven studies showed a modest but significant increase in protection from infection when previously infected individuals were vaccinated [79].

Limitations

This review summarizes characteristics of infection- and vaccine-induced immune responses, evidence regarding duration of immunity, and the potential impact of circulating variants. The approach was limited in scope focusing primarily on articles that were published in high-impact journals or novel in their findings; therefore, this does not represent a systematic review of all the scientific literature on SARS-CoV-2 infection-induced immunity. Particular biases related to observational study designs have been discussed above. The majority of studies included in this review came from a small number of countries, often with limited diversity in participants. Many of the immunologic studies did not include detailed demographic data. More consistent inclusion of descriptive data about demographics of participating populations (e.g., race/ethnicity, socioeconomic status, educational attainment) and conscious efforts to improve the racial, ethnic, and social diversity of participants in studies would be of great benefit in ensuring that related policies address the needs of all populations.

Conclusions

Multiple studies in different settings have consistently shown that infection with SARS-CoV-2 and vaccination each result in a low risk of subsequent infection with antigenically similar variants for at least 6 months. Numerous immunologic studies and a growing number of epidemiologic studies have shown that vaccinating previously infected individuals significantly enhances their immune response and effectively reduces the risk of subsequent infection, including in the setting of increased circulation of more infectious variants.

Although the Delta variant and some other variants have shown increased resistance to neutralization by both post-infection and post-vaccination sera in laboratory studies, observed reduction in effectiveness has been modest, with continued strong protection against hospitalization, severe disease, and death.

Multiple studies have shown that antibody titers correlate with protection at a population level; however, data are presently insufficient to determine an antibody titer threshold that indicates if an individual is protected from infection. At this time, there is no FDA-authorized or approved test that providers or the public can use to reliably determine whether a person is protected from infection.

CDC will continue to follow and evaluate evolving scientific evidence in these areas and update recommendations accordingly.

Table 1: Duration of various immune markers after infection, multiple studies

Immune marker	Half-life/Duration	Citation
Anti-nucleocapsid IgG	63–85 days	[11, 14, 15, 53]
Anti-spike IgG	126–229 days	[11, 13-15, 52, 53]
Anti-receptor binding domain	83–126 days	[11, 14, 53]
Neutralizing Abs	55 days (at <70 days post infection), then 519 days 150 days (at >42 days), then 254 days (at>120 days post symptom onset)	[14] [53]

Immune marker	Half-life/Duration	Citation
Pseudovirus neutralization	90–114 days	[11]
Memory B Cells	Increased over initial 4 months, then sustained	[11] [53]
CD4+ T Cells	Increased over first month then declined with half-life of 94–207 days	[11, 14, 53]
CD8+ T-Cells	Increased over first month then declined with half-life of 125–690 days	[11, 14, 53]

TTable 2: Summary of cohort studies with N>10,000 and population-level observational studies on reinfection, multiple locations

Study Design/ Location	Population/Sample Size	Definition of initial infection	Follow-up period	Definition of reinfection	Key Findings	Citation
Multicenter prospective cohort (SIREN) with routine RT-PCR and antibody testing every 2-4 weeks United Kingdom	Healthcare workers (HCWs) Median age: 46 yrs (Range: 18–84yrs) (N = 25,661)	RT-PCR or antibody positive (n = 8278)	Enrolled: Jun–Dec 2020 Data extracted Feb 2021	RT-PCR positive >90 days following previous positive RT-PCR or >4 weeks following prior positive antibody test (further classified as confirmed, probable, or possible from clinical review)	Incidence of reinfections: 7.6 per 100,000 person-days compared to 57.3 for per 100,000 person-days for primary infections SARS-CoV-2 infection offered 84% protection against infection (93% against symptomatic infection) at 7-months following primary infection Mean interval to reinfection was 200 days 50% of cases were symptomatic	[54]

Study Design/ Location	Population/Sample Size	Definition of initial infection	Follow-up period	Definition of reinfection	Key Findings	Citation
National-level observational study Denmark	Individuals tested nationally during 1st wave (N = 525,339)	RT-PCR positive during the 1st wave (Mar–May 2020) (n = 11,068)	Assessed for reinfections during 2nd wave (Sep–Dec 2020	RT-PCR positive during the 1st and 2nd wave (or subsequent positive >90 days later in alternative analysis)	Protection against repeat infection was 80.5% overall; 47.1% in persons >65years (in alternate analysis) No difference found when comparing 3-6 months to >7 months of follow-up	[55]
Retrospective observational study (national reporting system) Austria	Compared “COVID-19 survivors” from first wave to general population (N~8.9 million)	Positive RT-PCR during 1st wave (Feb to April 2020) excluding deaths (n = 14,840)	Assessed for reinfections during 2nd wave (Sep–Nov 2020)	RT-PCR positive during 1st and 2nd wave (did not track infections that occurred from May to Aug 2020)	Odds ratio (OR) for reinfection amongst COVID-19 survivors compared to general population was .09 Mean time to reinfection was 212 days Noted 5 hospitalizations and one death amongst 40 “tentative” reinfections, though death was thought to be unrelated	[56]
Retrospective cohort study (health system) United States	Healthcare users tested for COVID-19 from Mar to Aug 2020 Mean age: 51 years (SD: 22 years) (N = 150,325)	RT-PCR positive prior to Aug 30, 2020 (n=8,845)	Initial testing: Mar–Aug 2020 Follow-up through Feb 2021	RT-PCR positive ≥90 days after initial positive test	Protection against repeat infection was 81.8% overall and 84.5% against symptomatic infection Average time to reinfection was 139 days; protection increased over time 50% of possible reinfections were symptomatic	[57]

Study Design/ Location	Population/Sample Size	Definition of initial infection	Follow-up period	Definition of reinfection	Key Findings	Citation
Population-level observational study (using laboratory-system) Italy	Healthcare users Median age: 59 years (Range: 0-108 years) (N = 15,078)	RT-PCR positive during 1st wave (Feb–Jul 2020) (n = 1579)	Mean follow-up: 280 days	RT-PCR positive test >90 days after resolution of first infection (with at least 2 consecutive negative tests in-between)	Incidence of reinfections: 1.0 per 100,000 person days compared to 15.1 per 100,000 person days for primary infections Incidence rate ratio (IRR) 0.07 (93% reduction in risk) Mean interval between primary infection and reinfection was >230 days Of 5 reinfections, 1 required hospitalization	[58]
National-level observational study (using national laboratory) Qatar	Individuals with testing data in centralized national database, from April to Dec 2020 Median age: 35-38 years (N = 192,967)	Antibody positive from Apr–Dec 2020 (n = 43,044)	Median follow-up: 16.3 weeks (range: 0–34 weeks)	RT-PCR-positive >14 days after infection, assessed clinically for evidence of reinfection and then adjusted for proportion that were able to be confirmed as genetically distinct in paired genomic sequencing	Calculated incidence rate of reinfection as 0.66 per 10,000 person-weeks compared to 13.69 per 10,000 person weeks for primary infection Amongst antibody-positive individuals, protection was estimated at 95.2% for up to 7 months of follow-up Incidence of reinfections did not increase with time Reinfections were less severe than primary infections (none were critical or fatal)	[95]

Study Design/ Location	Population/Sample Size	Definition of initial infection	Follow-up period	Definition of reinfection	Key Findings	Citation
Prospective Cohort United Kingdom	HCWs at four Oxford University teaching hospitals Median age: 38 years (Range: 18-86 years) (N = 12,541)	Anti-S IgG positive (n = 1265)	Initial testing: Mar 2020 Follow-up until Nov 2020 (31 weeks)	RT-PCR positive 60 days or more after their first positive antibody test or RT-PCR test	Incidence of reinfection: 0.13 per 10,000 days at risk compared to 1.09 per 10,000 days at risk for seronegative participants aIRR of 0.11 (89% reduction in risk) All reinfections were asymptomatic	[96]

Table 3: Selected studies evaluating the immune response to a 1st and 2nd dose of mRNA vaccine following previous infection

Participants	Effect of 1st dose if previously infected vs. 2nd dose if SARS-CoV-2 naïve	Effect of if previously infected, 2nd dose vs. 1st dose	Notes	Citation
SARS-CoV-2 naïve (n=33) or previously infected (n=11; 65–275d prior); similar age and sex distribution who received two doses of Pfizer-BioNTech or Moderna vaccine	Antibody and memory B cell responses 2 weeks after 1st dose similar to SARS-CoV-2 naïve participants 1 week after 2nd dose	No increase in overall or neutralizing antibodies, or spike-specific memory B cells	Included assessment of response to B.1.351 variant	[22]
Study within cohort of participants who were SARS-CoV-2 naïve (n=490 post dose 1, n=228 post dose 2) or previously infected (n=35 post dose 1, n=11 post dose 2)	Anti-RBD IgG no difference ≤21d post 1st dose than for SARS-CoV-2 naïve participants ≤21d after 2nd dose (10.0 [9.2–10.4] vs. 9.9 [9.4-10.3)	No difference in Anti-RBD IgG (10.2[8.4–10.5] vs. 9.9 [9.4–10.3])	Sensitivity analysis including participants with data at all time points found similar results. Timing of previous infections not specified.	[86]
Study within cohort of participants who were SARS-CoV-2 naïve (n=67 post dose 1, n=36 post dose 2) with previously infected (n=43 post dose 1, n=19 post dose 2)	Median anti-spike IgG 6-fold higher after 2nd dose than SARS-CoV-2 naïve participants after 1st dose	No increase in antibody titers after 2nd dose	Assay measured by area under the curve; antibody levels 10–45 times higher at baseline if previous infection. Timing was soon after 2nd dose but was unspecified; timing of prior infection is also unknown.	[88]

Group receiving 2 doses of Pfizer-BioNTech vaccine, either previously infected (n=6, 2–7 months post-infection) or SARS-CoV-2 naïve (n=9)	Neutralizing anti-RBD IgG at day 7 post 1st vaccine dose in previously infected group no different to day 7 post 2nd dose in uninfected group (GMT, 95% CI: 906, 552–1348 vs. 670, 364–1228, p = NS)	Results chart indicates no difference between antibody titers after 1st vs. 2nd dose (numbers not provided)		[87]
Healthcare workers infected a median of 2 months previously (n=18), 9 months previously (n=19) or SARS-CoV-2 naïve (n=73) who received 2 doses of Pfizer-BioNTech vaccine.	(not assessed)	No substantial difference in binding assay (0.92-fold) or neutralizing titers (1.17-fold) between 21d after 1st dose and 28 days after 2nd dose	Similar antibody responses after vaccine by whether previous infection was ~2 months or ~9 months previously	[82]
Cohort of recipients of Pfizer-BioNTech vaccine previously infected (n=51; 25 in 1st wave, 26 in 2nd wave) or SARS-CoV-2 naïve (n=50)	Irrespective of time since infection, previously infected recipients had higher spike-specific IgG and pseudovirus neutralization than previously uninfected after 2nd dose.	Neutralization did not increase between 1st and 2nd doses.	This study noted similar trends for IgA, IgM, and IgG. There is limited information on timing of tests after vaccine doses.	[85]
Group of recipients of Pfizer-BioNTech vaccine previously infected (n=23; 1–9 months after infection) or uninfected (n=23)	Higher IFN-gamma 20 d after 1st dose if previous infection than 20d after 2nd if no previous infection	IFN-gamma declines after 2nd dose (but boosted after 1st dose)	IFN-gamma from CD4+ T cells assessed to SARS-CoV-2 spike and peptide pools. Note that a separate analysis indicates natural infection drives IFN-gamma responses more than vaccine-induced immunity.	[84]
Recipients of Pfizer-BioNTech vaccine, 1 dose if previously infected (n=43; 17 with severe illness 12 months prior; 17 with mild illness 12 months prior; 9 with mild illness 6 months prior); or 2 doses if SARS-CoV-2 naïve * (n=25)	Two months after 2nd dose without previous infection, similar antibody levels but lower neutralization against variants, lower proportion of anti-spike B cells that were anti-RBD, and less diverse responses. Neutralizing B-cell clones were present but less common without infection.	(Not assessed)	Stable IgG and memory B-cells 6 to 12 months after infection.	[23]

Recipients of Pfizer-BioNTech or Moderna vaccine, anti-nucleocapsid negative (n=148) or positive (n=20; mostly by RT-PCR)	Similar titers of anti-spike antibody if previously infected ~21 days post dose 1 compared with ~66 days after dose 2 if SARS-CoV-2 naïve.	No increase in median anti-spike or anti-RBD titers. However, no. post infection with neutralizing antibodies increased from 10/15 to 12/15 and varied by individual.	Timing of RT-PCR positive tests is unclear.	[89]

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TAB 9

Public Health England

Protecting and improving the nation's health

SARS-CoV-2 variants of concern and variants under investigation in England

Technical briefing 19

23 July 2021

This briefing provides an update on previous briefings up to 9 July 2021

Contents

Summary

There are 4 current variants of concern (VOCs) and 10 variants under investigation (VUIs) (Table 1).

This report has been published to continue to share the detailed variant surveillance analyses which contribute to the variant risk assessments and designation of new VOCs and VUIs. The risk assessments updated this week are for Beta and Delta and there is one new VUI.

A separate report is published covering our routine data on all other variants of concern and variants under investigation. The specialist technical briefings contain early data and analysis on emerging variants and findings have a high level of uncertainty.

Principal changes and findings this week are:

- the number of genome sequence results available is maintained but the coverage has fallen with the increasing case numbers
- Delta variant accounted for approximately 99% of sequenced and 96% genotyped cases from 4 July to 10 July 2021
- distinct clades within Delta have been identified in the UK, which are primarily distinguished by changes outside spike – additional spike mutations on Delta occur at relatively low frequencies at present
- preliminary analysis of national surveillance data finds an increased risk of reinfection with Delta, compared to Alpha
- B.1.621 has been designated a VUI on 21 July 2021, previously being a signal in monitoring. The new designation is based on international spread, importation to the UK, and mutations of concern
- one new variant in monitoring has been designated (C.1.2)

All risk assessments are published separately, except for Gamma, which was published within Technical Briefing 7 and Alpha within Technical Briefing 9.

All risk assessments are published separately here, except for Gamma, which was published within Technical Briefing 7, Alpha within Technical Briefing 9, and Delta in Technical Briefing 10. As Delta is the dominant variant in the UK, epidemiological data in the weekly surveillance report is highly relevant and available.

Published information on variants

The collection page gives content on variants, including prior technical briefings. Definitions for variants of concern, variants under investigation, and signals in monitoring are detailed in technical briefing 8. Data on variants not detailed here is published in the variant data update. Variant risk assessments are available in prior technical briefings.

Public Health England (PHE) curated a repository on the 5 March 2021 containing the up-to-date genomic definitions for all VOCs and VUIs. The repository is accessible on GitHub.

World Health Organization (WHO) nomenclature from 31 May 2021 is incorporated. A table incorporating WHO and UK designations with Pango lineages is provided below (Table 1). Following the table, variants are referred to using their WHO designation where this exists and the UK designation where it does not.

Technical briefings are published periodically. From 15 onwards, briefings include variant diagnoses made by whole-genome sequencing and a genotyping PCR test, including the categorisation of confirmed and probable variant results and a rules-based decision algorithm (RBDA) to identify variant and mutation (VAM) profiles from genotype assay mutation profiles. Genotyping is used to identify variants Alpha, Beta, Delta, and Gamma. Targets were updated in mid-May 2021 to prioritise accurate identification of Delta over Alpha.

Part 1: Surveillance overview

1.1 Variants under surveillance

Table 1 shows the current VOC, VUI, and variants in monitoring as of 21 July. Figure 1 shows the proportion of cases sequenced over time. Figure 2 shows the proportion of cases sequenced over time by regions. Figure 3 shows the proportion of cases sequenced amongst cases who tested positive while in hospital. Summary epidemiology on Delta is shown in Table 2 and for each variant is shown in Table 3, case numbers are also updated online.

Figure 4 shows cumulative cases of variants over time.

Table 1. Variant lineage and designation as of 21 July 2021

WHO nomenclature as of 19 July 2021	Lineage	Designation	Status
Alpha	B.1.1.7	VOC-20DEC-01	VOC
Beta	B.1.351	VOC-20DEC-02	VOC
Gamma	P.1	VOC-21JAN-02	VOC
Delta	B.1.617.2, AY.1 and AY.2	VOC-21APR-02	VOC
Zeta	P.2	VUI-21JAN-01	VUI
Eta	B.1.525	VUI-21FEB-03	VUI
	B.1.1.318	VUI-21FEB-04	VUI
Theta	P.3	VUI-21MAR-02	VUI
Kappa	B.1.617.1	VUI-21APR-01	VUI
	B.1.617.3	VUI-21APR-03	VUI
	AV.1	VUI-21MAY-01	VUI
	C.36.3	VUI-21MAY-02	VUI
Lambda	C.37	VUI-21JUN-01	VUI
	B.1.621	VUI-21JUL-01	VUI
	B.1.1.7 with E484K	VOC-21FEB-02	*Monitoring
Epsilon	B.1.427/B.1.429		Monitoring

WHO nomenclature as of 19 July 2021	Lineage	Designation	Status
	B.1.1.7 with S494P		Monitoring
	A.27		Monitoring
Iota	B.1.526		Monitoring
	B.1.1.7 with Q677H		Monitoring
	B.1.620		Monitoring
	B.1.214.2		Monitoring
	R.1		Monitoring
	B.1 with 214insQAS		Monitoring
	AT.1		Monitoring
	Lineage A with R346K, T478R and E484K		Monitoring
	Delta like variant with E484A		Monitoring
	P.1 + N501T and E484Q		Monitoring
	B.1.629		Monitoring
	B.1.619		Monitoring
	C.1.2		Monitoring

Note that provisionally extinct variants are excluded from this table.

*VOC-21FEB-02 (B.1.1.7 with E484K). This specific clade of B.1.1.7 with E484K has not been detected in England since 1 March 2021. There is apparent transmission outside the UK based on international sequence data. It is no longer included in the data update but monitoring of international data continues.

1.2 Sequencing coverage

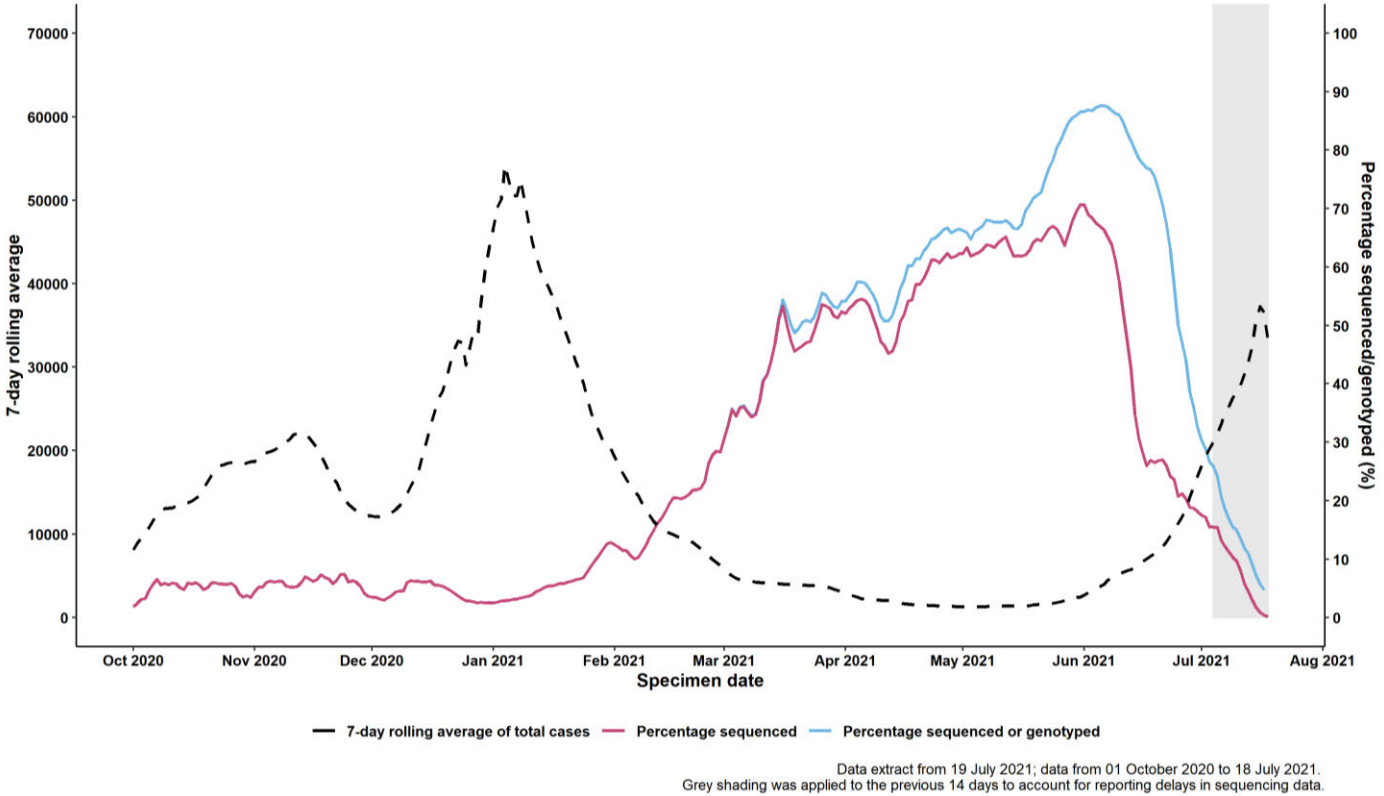
Sequencing capacity has been maintained, but the proportion of cases sequenced has fallen with increasing case numbers.

There is a reduction in overall sequencing coverage (Figure 1). Sequencing coverage is slightly higher for cases in hospital (Figure 3). During the current surge period, the sequencing strategy is:

- hospitalised cases and hospital staff
- imported cases
- national core priority studies
- as near random a sample as possible from each region, to the maximum coverage allowed by laboratory capacity

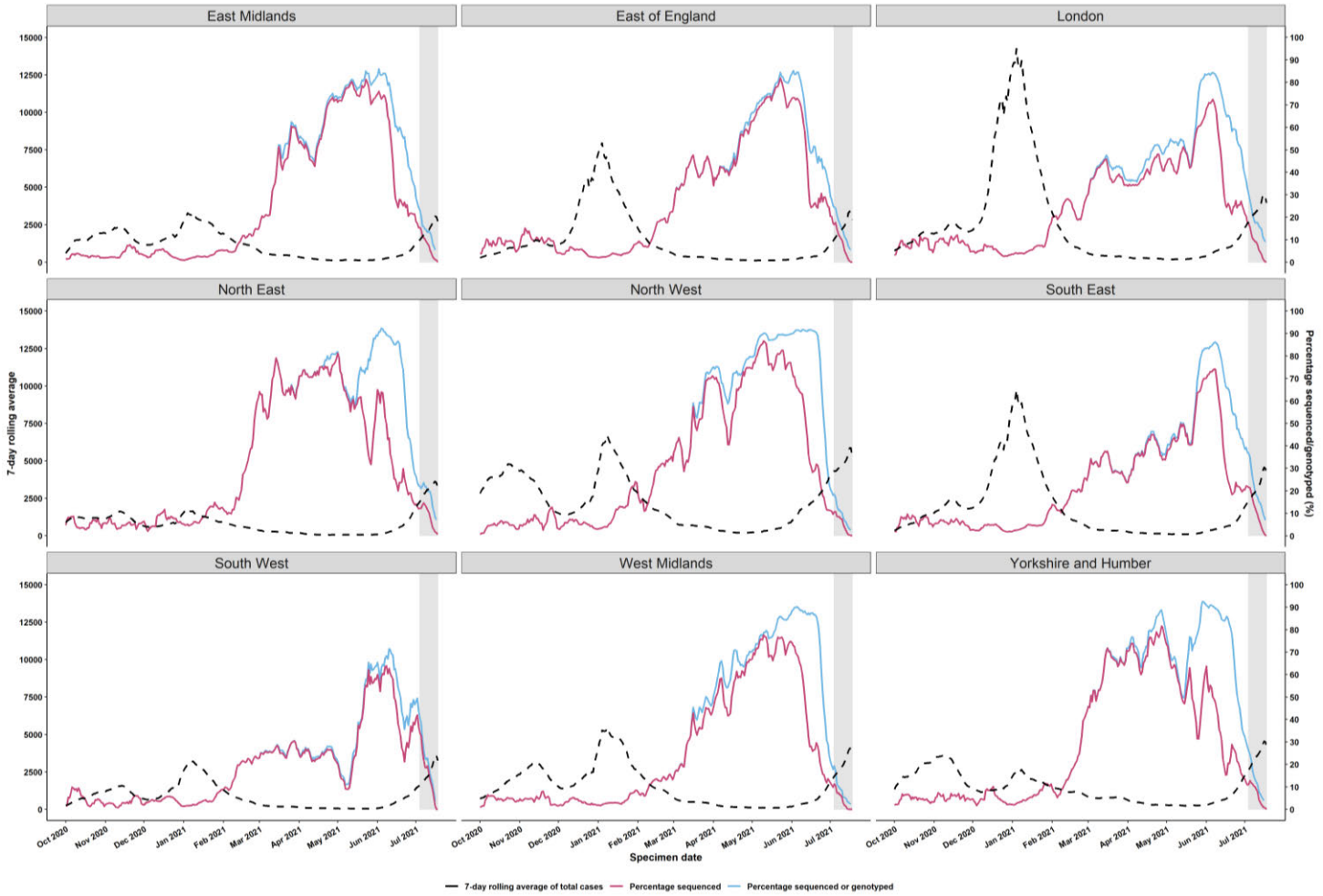
The increase in cases observed in England since the middle of June has resulted in a lower proportion of samples being sent for whole-genome sequencing (WGS) and genotyping. On July 4, 2021, 25.8% of new samples had further typing information of which 15.5 % of which was derived from WGS and an additional 10.3% provided by genotyping.

Figure 1. Coverage of sequencing and genotyping: percentage of SARS-CoV-2 cases sequenced over time as of 19 July 2021
(Find accessible data used in this graph in underlying data)[1]



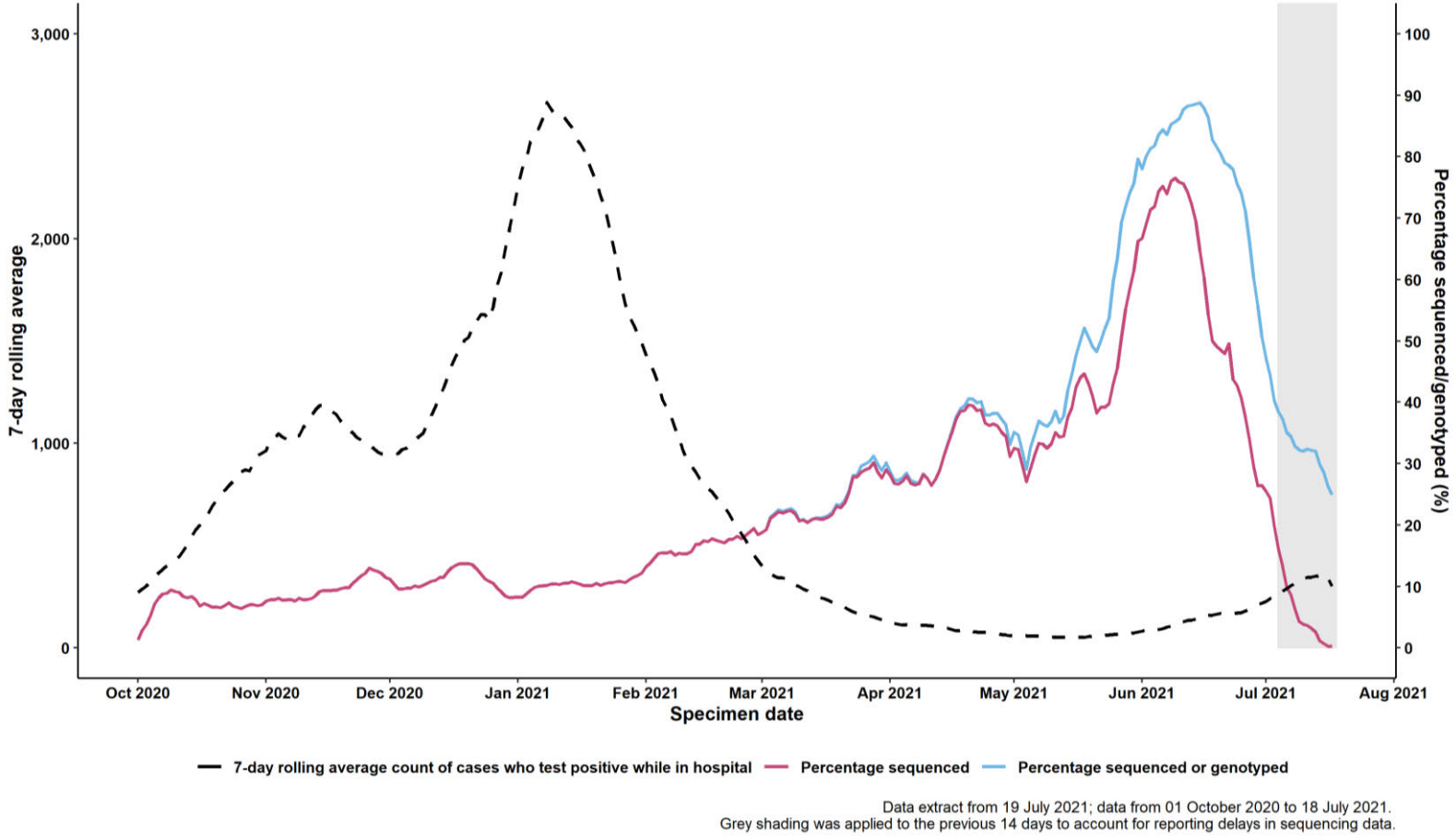
[1] From 14 to 18 June 2021 an operational issue at a sequencing site resulted in a reduction in the number of samples with sequencing data of sufficient quality for variant assignment. There were 19,502 samples reported to PHE as impacted by the incident. PHE has received approximately 10,000 sample identifiers from the list of those affected of which sequencing data has been obtained for approximately 4,300 and genotyping data for 3,300 have a reflex assay result. Approximately 9,000 samples are pending analysis and for approximately 2,400 samples variant assignment is not possible. This issue resulted in a reduction in genome coverage for specimen dates 10 to 15 June 2021 and may impact variant counts in figures and tables for this limited period. The unusable samples were from locations distributed around the UK and the proportions of different variants by region should be correct. In addition, the genotyping results means that this has limited impact in the interpretation of the overall data.

Figure 2. Coverage of sequencing and genotyping: percentage of SARS-CoV-2 cases sequenced over time by region as of 19 July 2021 (Find accessible data used in this graph in underlying data)



Date extract from 19 July 2021, data from 01 October 2020 to 18 July 2021.
Grey shading was applied to the previous 14 days to account for reporting delays in sequencing data.
There were 5095 cases missing PHEC that were excluded.

Figure 3. Coverage of sequencing and genotyping: percentage of SARS-CoV-2 cases sequenced among cases who test positive while in hospital as of 19 July 2021 (Find accessible data used in this graph in underlying data)



[1] From 14 to 18 June 2021 an operational issue at a sequencing site resulted in a reduction in the number of samples with sequencing data of sufficient quality for variant assignment. There were 19,502 samples reported to PHE as impacted by the incident. PHE has received approximately 10,000 sample identifiers from the list of those affected of which sequencing data has been obtained for approximately 4,300 and genotyping data for 3,300 have a reflex assay result. For approximately 2,400 samples variant assignment is not possible. This issue resulted in a reduction in genome coverage for specimen dates 10 to 15 June 2021 and may impact variant counts in figures and tables for this limited period. The unusable samples were from locations distributed around the UK and the proportions of different variants by region should be correct. In addition, the genotyping results means that this has limited impact in the interpretation of the overall data.

1.3 VOC and VUI case numbers, proportion, deaths and case fatality rate

Table 3 shows the number of cases and deaths associated with each VOC and VUI, and the proportion of total sequenced cases accounted for by each variant. Note case fatality rates are not comparable across variants (see Table 3 footnote). Tables 4 and 5 show the number of cases known to be infected with a VOC or VUI who visited an NHS Emergency Department, the number who were admitted, and the number who died in any setting (note data is shown from 1 February 2021 onwards to enable comparison). Figure 4 shows the cumulative number of cases per variant indexed by days since first report.

Hospitalisation data are subject to reporting delays as hospitals typically submit data once a month, although some may provide daily updates. The data show only cases who have been hospitalised and not those who are currently in hospital with COVID-19. As such, it is not appropriate for use for surveillance of those currently hospitalised with COVID-19. In addition, the data will not show cases who were directly admitted as inpatients without presenting to emergency care.

Attended emergency care are those cases with a record in the Emergency Care Data Set showing that they presented to emergency care one to 28 days after the specimen date. The Emergency Care Data Set is updated weekly, and sequence data are linked to the data daily.

Figure 4 shows cumulative case numbers per variant indexed by days since the fifth reported case.

Table 2. Number of confirmed and provisional Delta cases by region of residence as of 19 July 2021

Region	Confirmed case number	Provisional case number	Total case number	Proportion of total cases
East Midlands	8,192	4,936	13,128	5.7%
East of England	9,218	4,515	13,733	6.0%
London	18,248	15,099	33,347	14.5%
North East	8,765	10,264	19,029	8.3%
North West	35,996	30,425	66,421	29.0%
South East	13,903	10,868	24,771	10.8%
South West	12,875	3,139	16,014	7.0%
West Midlands	8,702	8,801	17,503	7.6%
Yorkshire and Humber	10,864	13,325	24,189	10.5%
Unknown region	573	594	1,167	0.5%
Total	127,336	101,966	229,302	n/a

Table 3. Number of confirmed (sequencing) and probable (genotyping) cases by variant as of 19 July 2021

Variant	Confirmed (sequencing) case number	Probable (genotyping) case number[1]	Total case number	Proportion of total cases	Deaths
Alpha	220,500	5,677	226,177	49.3%	4,265
Beta	898	71	969	0.2%	13
Delta	127,336	101,966	229,302	50.0%	461
Eta	443	0	443	0.1%	12
Gamma	189	42	231	0.1%	0
Kappa	446	0	446	0.1%	1
Lambda	8	0	8	0.0%	0
Theta	7	0	7	0.0%	0
VOC-21FEB-02	45	0	45	0.0%	1
VUI-21APR-03	13	0	13	0.0%	0
VUI-21FEB-01	79	0	79	0.0%	2
VUI-21FEB-04	292	0	292	0.1%	1
VUI-21MAR-01	2	0	2	0.0%	0
VUI-21MAY-01	184	0	184	0.0%	1
VUI-21MAY-02	140	0	140	0.0%	0
Zeta	54	0	54	0.0%	1

[1]Genotyping is used to identify variants Alpha, Beta, Delta and Gamma; targets were updated in mid-May 2021 to prioritise accurate identification of Delta over Alpha.

Table 4. Attendance to emergency care and deaths among all sequenced and genotyped COVID-19 cases in England, 1 February 2021 to 19 July 2021

Variant	Age Group (years)	Cases Since 1 Feb	Cases with specimen date in past 28 days		Cases with an A&E visit§ (exclusion‡)		Cases with an A&E visit§ (inclusion#)		Cases where presentation to A&E resulted in overnight inpatient admission§ (exclusion‡)		Cases where presentation to A&E resulted in overnight inpatient admission§ (inclusion#)		Deaths^	
			n	%	n	%	n	%	n	%	n	%	n	%
Alpha (VOC-20DEC-01)	<50	118,082	331	0.3	4,963	4.2	5,808	4.9	1,230	1.0	1,680	1.4	66	0.1
	≥50	32,265	29	0.1	3,125	9.7	4,586	14.2	1,713	5.3	2,779	8.6	1,548	4.8
	All cases	150,436	361	0.2	8,088	5.4	10,394	6.9	2,943	2.0	4,459	3.0	1,614	1.1
Beta (VOC-20DEC-02)	<50	595	15	2.5	24	4.0	26	4.4	5	0.8	8	1.3	1	0.2
	≥50	161	2	1.2	17	10.6	25	15.5	7	4.3	15	9.3	7	4.3
	All cases	763	18	2.4	41	5.4	51	6.7	12	1.6	23	3.0	8	1.0
Gamma (VOC-21JAN-02)	<50	209	3	1.4	9	4.3	9	4.3	1	0.5	1	0.5	-	0.0
	≥50	21	3	14.3	1	4.8	1	4.8	-	0.0	-	0.0	-	0.0
	All cases	230	6	2.6	10	4.3	10	4.3	1	0.4	1	0.4	-	0.0
Delta (VOC-21APR-02)	<50	205,549	94,294	45.9	6,471	3.1	8,325	4.1	1,529	0.7	2,327	1.1	45	0.0
	≥50	23,379	10,933	46.8	1,319	5.6	2,263	9.7	687	2.9	1,365	5.8	415	1.8

Variant	Age Group (years)	Cases Since 1 Feb	Cases with specimen date in past 28 days		Cases with an A&E visit§ (exclusion‡)		Cases with an A&E visit§ (inclusion#)		Cases where presentation to A&E resulted in overnight inpatient admission§ (exclusion‡)		Cases where presentation to A&E resulted in overnight inpatient admission§ (inclusion#)		Deaths^	
			n	%	n	%	n	%	n	%	n	%	n	%
	All cases	229,218	105,298	45.9	7,790	3.4	10,588	4.6	2,216	1.0	3,692	1.6	460	0.2
Zeta (VUI-21JAN-01)	<50	16	-	0.0	0	0.0	-	0.0	0	0.0	0	0.0	0	0.0
	≥50	8	-	0.0	1	12.5	1	12.5	1	12.5	1	12.5	0	0.0
	All cases	24	-	0.0	1	4.2	1	4.2	1	4.2	1	4.2	0	0.0
Eta (VUI-21FEB-03)	<50	273	-	0.0	11	4.0	13	4.8	5	1.8	6	2.2	0	0.0
	≥50	114	-	0.0	4	3.5	7	6.1	1	0.9	3	2.6	6	5.3
	All cases	389	-	0.0	15	3.9	20	5.1	6	1.5	9	2.3	6	1.5
VUI-21FEB-04	<50	230	1	0.4	6	2.6	9	3.9	1	0.4	2	0.9	0	0.0
	≥50	54	-	0.0	1	1.9	2	3.7	0	0.0	1	1.9	1	1.9
	All cases	285	1	0.4	7	2.5	11	3.9	1	0.4	3	1.1	1	0.4
Theta (VUI-21MAR-02)	<50	4	0	0.0	1	25.0	1	25.0	0	0.0	0	0.0	0	0.0
	≥50	3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Variant	Age Group (years)	Cases Since 1 Feb	Cases with specimen date in past 28 days		Cases with an A&E visit§ (exclusion‡)		Cases with an A&E visit§ (inclusion#)		Cases where presentation to A&E resulted in overnight inpatient admission§ (exclusion‡)		Cases where presentation to A&E resulted in overnight inpatient admission§ (inclusion#)		Deaths^	
			n	%	n	%	n	%	n	%	n	%	n	%
	All cases	7	0	0.0	1	14.3	1	14.3	0	0.0	0	0.0	0	0.0
Kappa (VUI-21APR-01)	<50	382	0	0.0	10	2.6	11	2.9	1	0.3	2	0.5	0	0.0
	≥50	64	0	0.0	5	7.8	5	7.8	2	3.1	2	3.1	1	1.6
	All cases	446	0	0.0	15	3.4	16	3.6	3	0.7	4	0.9	1	0.2
VUI-21APR-03	<50	11	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	≥50	2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	All cases	13	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
VUI-21MAY-01	<50	161	0	0.0	1	0.6	2	1.2	0	0.0	1	0.6	0	0.0
	≥50	23	-	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	4.3
	All cases	184	-	0.0	1	0.5	2	1.1	0	0.0	1	0.5	1	0.5
VUI-21MAY-02	<50	109	4	3.7	8	7.3	9	8.3	2	1.8	3	2.8	0	0.0
	≥50	30	-	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Variant	Age Group (years)	Cases Since 1 Feb	Cases with specimen date in past 28 days		Cases with an A&E visit§ (exclusion‡)		Cases with an A&E visit§ (inclusion#)		Cases where presentation to A&E resulted in overnight inpatient admission§ (exclusion‡)		Cases where presentation to A&E resulted in overnight inpatient admission§ (inclusion#)		Deaths^	
			n	%	n	%	n	%	n	%	n	%	n	%
	All cases	140	4	2.9	8	5.7	9	6.4	2	1.4	3	2.1	0	0.0
Lambda (VUI-21JUN-01)	<50	8	0	0.0	1	12.5	1	12.5	1	12.5	1	12.5	0	0.0
	≥50	-	-	-	-	-	-	-	-	-	-	-	-	-
	All cases	8	0	0.0	1	12.5	1	12.5	1	12.5	1	12.5	0	0.0

Data sources: Emergency care attendance and admissions from Emergency Care Dataset (ECDS), deaths from PHE daily death data series (deaths within 28 days). NHS trusts are required to submit emergency care attendances by the 21st of each month. As a result, the number of cases with attendances may show substantial increases in technical briefs prepared after the monthly cut-off, compared with other briefs from the same month.
¥ Cases without specimen dates and unlinked sequences (sequenced samples that could not be matched to individuals) are excluded from this table.
* Cases are assessed for any emergency care attendance within 28 days of their positive specimen date. Cases still undergoing within 28-day period may have an emergency care attendance reported at a later date.
§ At least 1 attendance or admission within 28 days of positive specimen date
# Inclusion: Including cases with the same specimen and attendance dates
‡ Exclusion: Excluding cases with the same specimen and attendance dates. Cases where specimen date is the same as date of emergency care visit are excluded to help remove cases picked up via routine testing in healthcare settings whose primary cause of attendance is not COVID-19. This underestimates the number of individuals in hospital with COVID-19 but only includes those who tested positive prior to the day of their emergency care visit. Some of the cases detected on the day of admission may have attended for a diagnosis unrelated to COVID-19.
^ Total deaths in any setting (regardless of hospitalisation status) within 28 days of positive specimen date.

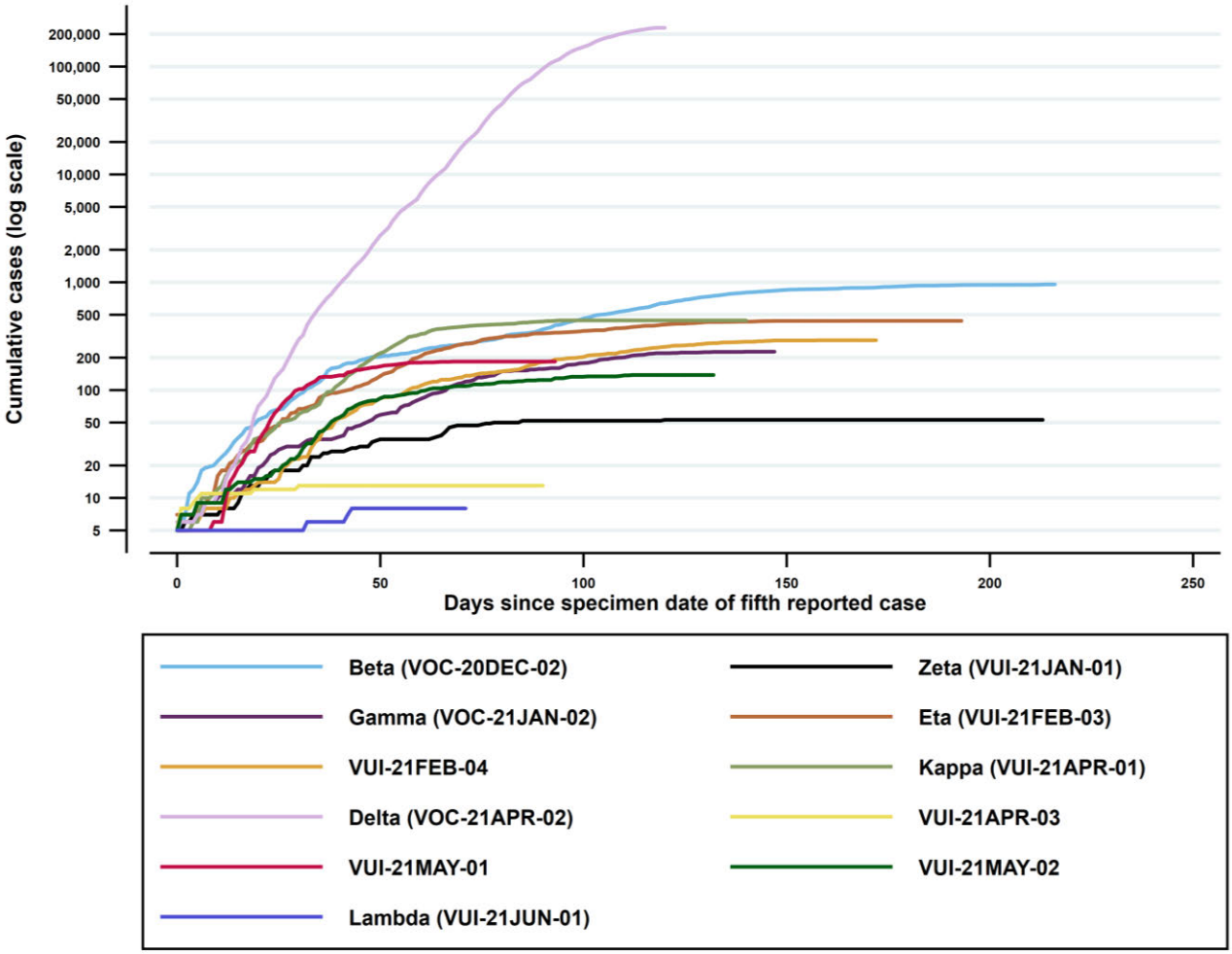
Table 5. Attendance to emergency care and deaths by vaccination status among all sequenced and genotyped Delta cases in England from 1 February 2021 to 19 July 2021

Variant	Age group (years)**	Total	Cases with specimen date in past 28 days	Unlinked	<21 days post dose 1	≥21 days post dose 1	Received 2 doses	Unvaccinated
Delta cases	<50	205,549	94,294	22,496	20,930	27,714	15,346	119,063
	≥50	23,379	10,933	2,169	157	5,289	13,427	2,337
	All cases	229,218	105,298	24,952	21,088	33,003	28,773	121,402
Cases with an emergency care visit§ (exclusion‡)	<50	6,471	N/A	73	597	851	429	4,521
	≥50	1,319	N/A	7	11	297	672	332
	All cases	7,790	N/A	80	608	1,148	1,101	4,853
Cases with an emergency care visit§ (inclusion#)	<50	8,325	N/A	110	756	1,025	531	5,903
	≥50	2,263	N/A	18	22	435	1,125	663
	All cases	10,588	N/A	128	778	1,460	1,656	6,566
Cases where presentation to emergency care resulted in overnight inpatient admission§ ((exclusion‡)	<50	1,529	N/A	36	127	158	103	1,105
	≥50	687	N/A	4	9	107	371	196
	All cases	2,216	N/A	40	136	265	474	1,301
Cases where presentation to emergency care resulted in	<50	2,327	N/A	51	185	239	140	1,712

overnight inpatient admission§ (inclusion#)	≥50	1,365	N/A	13	18	191	703	440
	All cases	3,692	N/A	64	203	430	843	2,152
Deaths within 28 days of positive specimen date	<50	45	N/A	1	3	3	4	34
	≥50	415	N/A	5	2	57	220	131
	All cases	460	N/A	6	5	60	224	165

Data sources: Emergency care attendance and admissions from Emergency Care Dataset (ECDS), deaths from PHE daily death data series (deaths within 28 days). NHS trusts are required to submit emergency care attendances by the 21st of each month. As a result, the number of cases with attendances may show substantial increases in technical briefs prepared after the monthly cut-off, compared with other briefs from the same month.
¥ Cases without specimen dates and unlinked sequences (sequenced samples that could not be matched to individuals) are excluded from this table.
* Cases are assessed for any emergency care attendance within 28 days of their positive specimen date. Cases still undergoing within 28-day period may have an emergency care attendance reported at a later date.
§ At least 1 attendance or admission within 28 days of positive specimen date
# Inclusion: Including cases with the same specimen and attendance dates
‡ Exclusion: Excluding cases with the same specimen and attendance dates. Cases where specimen date is the same as date of emergency care visit are excluded to help remove cases picked up via routine testing in healthcare settings whose primary cause of attendance is not COVID-19. This underestimates the number of individuals in hospital with COVID-19 but only includes those who tested positive prior to the day of their emergency care visit. Some of the cases detected on the day of admission may have attended for a diagnosis unrelated to COVID-19.
^ Total deaths in any setting (regardless of hospitalisation status) within 28 days of positive specimen date.
** Age <50 + >50 do not total ‘all cases’ per category as some cases lack reported age data

Figure 4. Cumulative cases in England of variants indexed by days since the fifth reported case as of 19 July 2021
(Find accessible data used in this graph in underlying data)



1.4 Variant prevalence

The prevalence of different variants amongst all genotyped and sequenced cases is presented in Figures 5 and 6 and split by region in Figures 7 and 8. Genotyping allows a shorter turnaround time of 12 to 24 hours (after initial confirmation of COVID-19) for a probable variant result. The initial panel of targets began trials in March 2021, using single nucleotide polymorphisms that included N501Y, E484K, K417N, and K417T. Results have been reported and used for public health action since 29 March 2021. On 11 May 2021, after rapid validation of targets to allow identification of Delta variant, P681R was introduced in the panel to replace N501Y. Genotyping results have now been fully integrated into the variant data reports and analyses. Changes in the use of genotyping over time should be considered when interpreting prevalence from genotyped data.

The ‘Other’ category in Figures 5 to 8 includes genomes where the quality is insufficient to determine variant status and genomes that do not meet the current definition for a VUI or VOC. Sequencing numbers and coverage fall in the last week shown due partly to sequencing lag time, and new sequences are still being produced relating to sample dates in that week. The supplementary data for figures are available.

Delta variant accounted for approximately 99% of sequenced and 96% genotyped cases from 4 July to 10 July 2021.

Figure 5. Variant prevalence for all England available genotyped cases from 1 February 2021 to 19 July 2021
(Find accessible data used in this graph in underlying data)

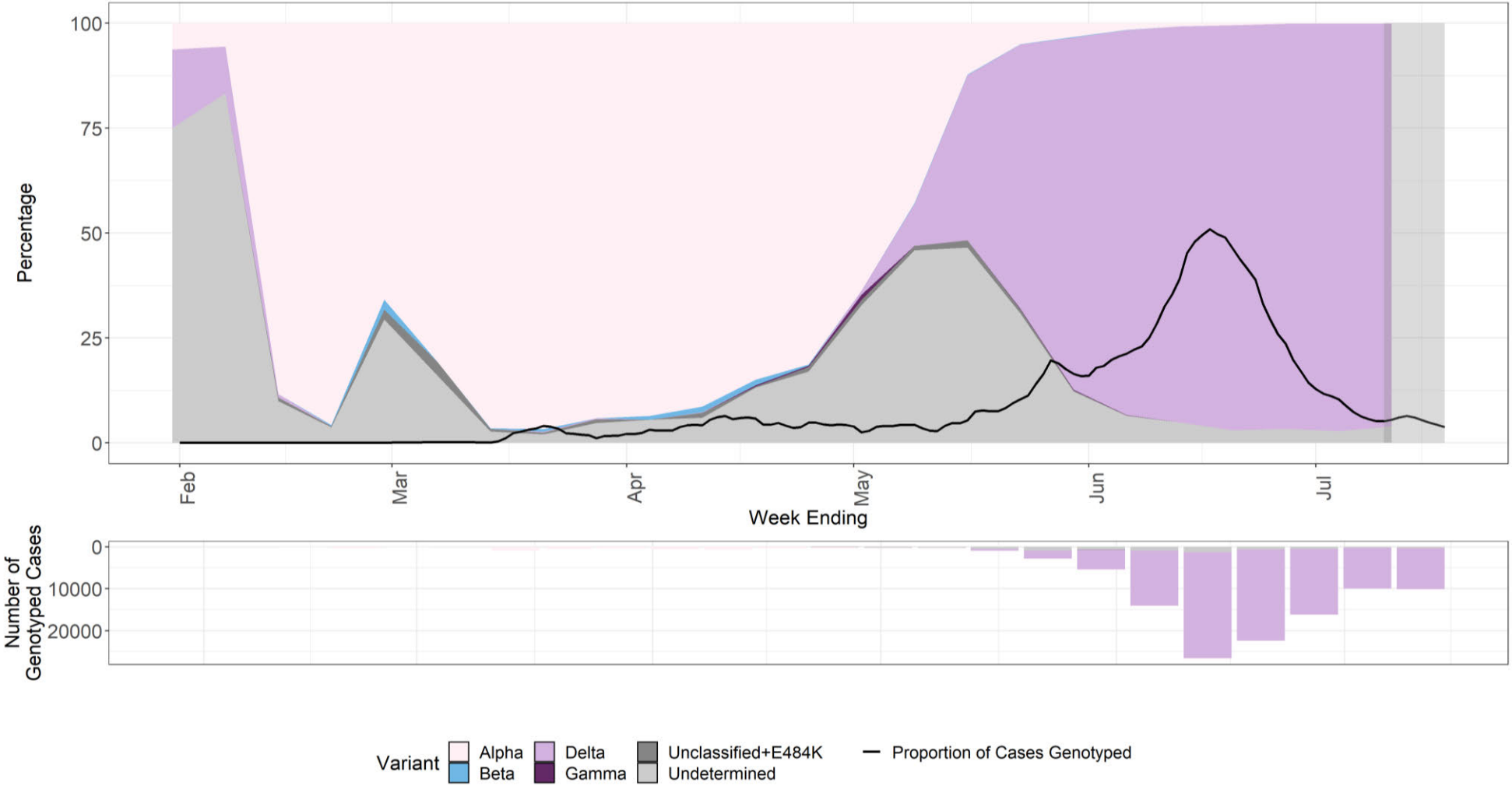


Figure 6. Variant prevalence for all England available sequenced cases from 1 February 2021 as of 19 July 2021
Dashed lines indicate period incorporating issue at a sequencing site. (Find accessible data used in this graph in underlying data).

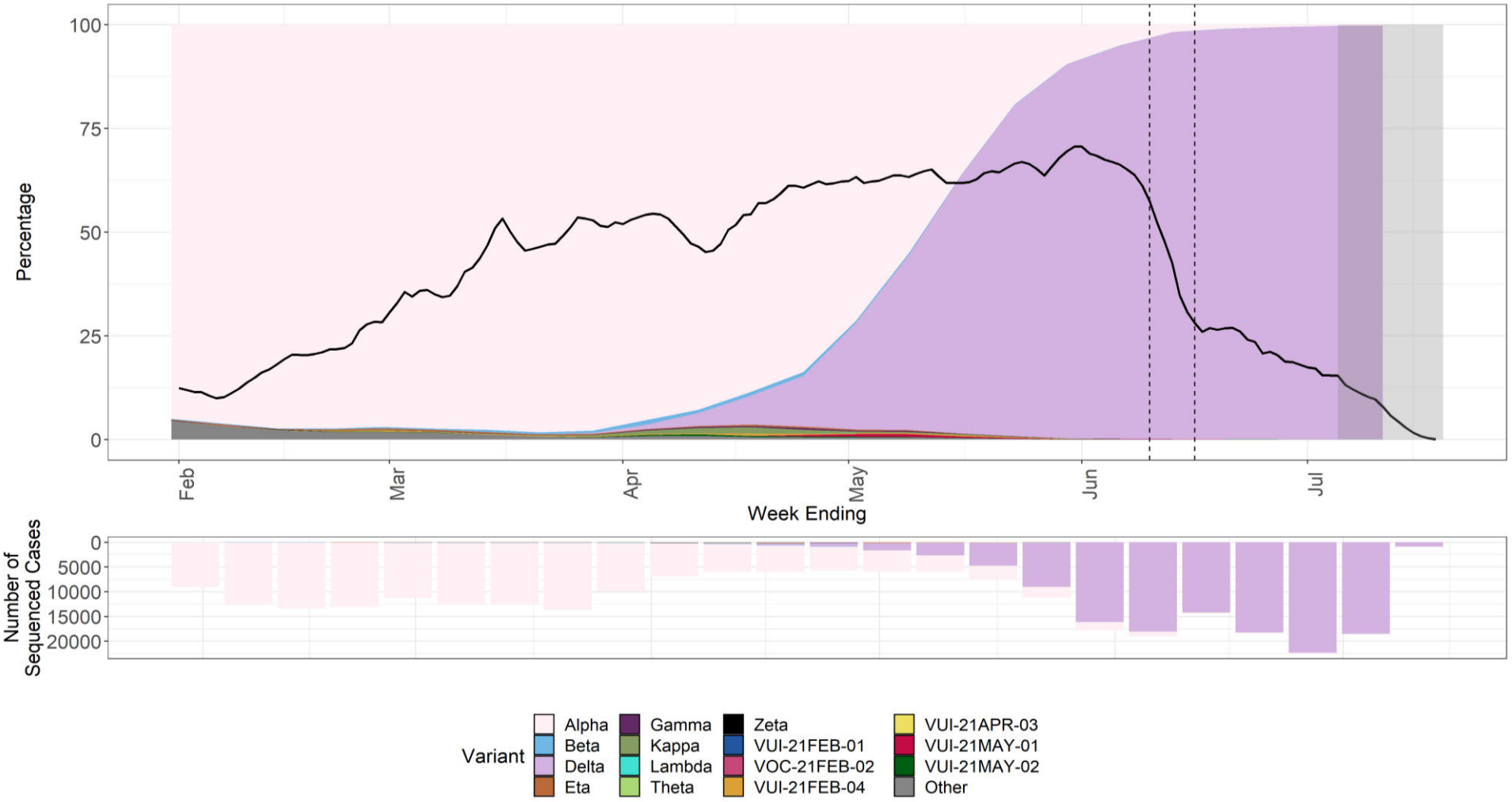
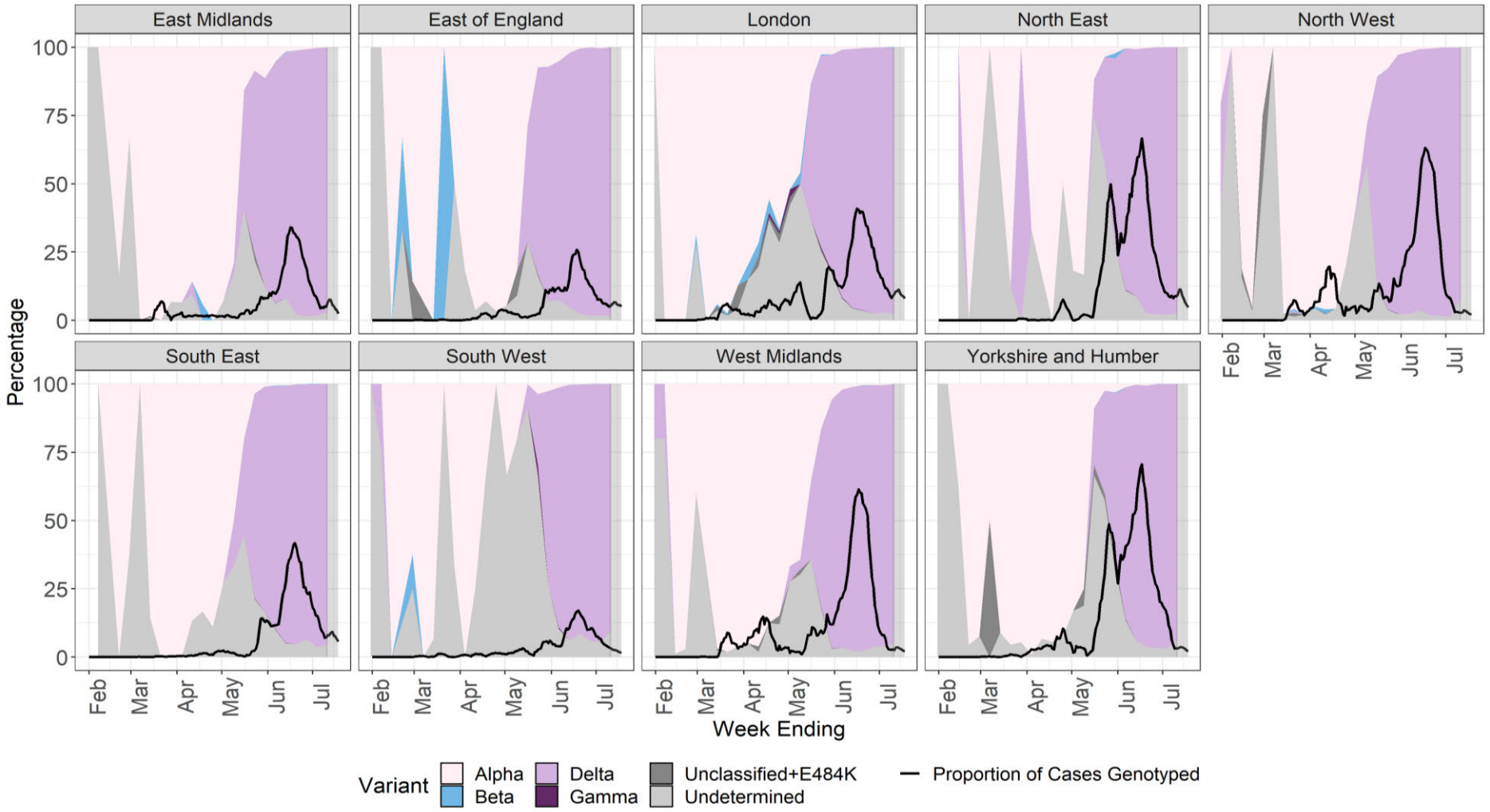
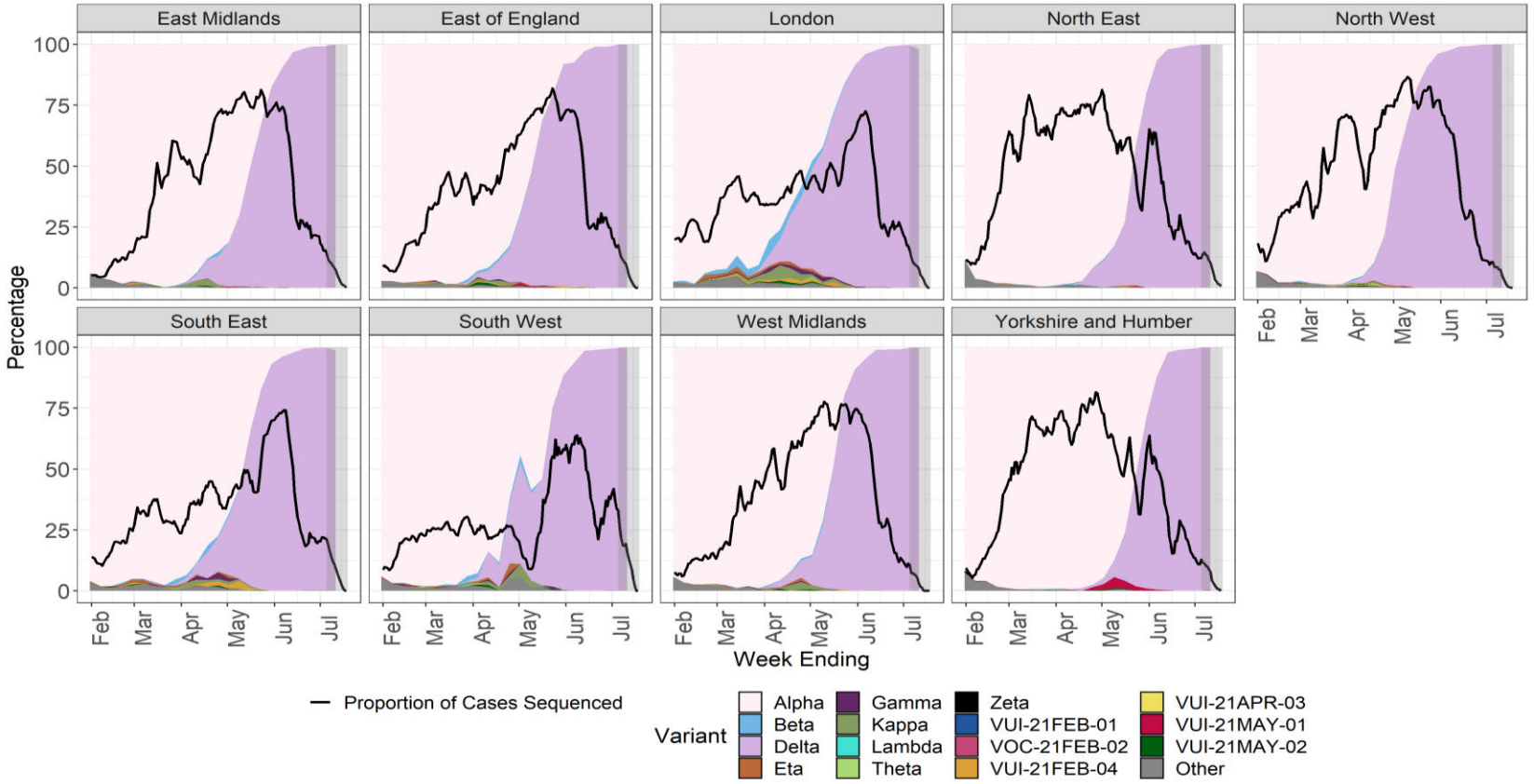


Figure 7. Variant prevalence from 1 February 2021 as of 19 July 2021 by region for all genotyped cases in England
(Find accessible data used in this graph in underlying data)



Note that 717 cases were excluded due to missing region or specimen date information.

Figure 8. Variant prevalence from 1 February 2021 as of 19 July 2021 by region for all sequenced cases in England
(Find accessible data used in this graph in underlying data)



Note that 1166 cases were excluded due to missing region or specimen date information. Travel status is assigned based on an interval of ≤14 days between the arrival and positive specimen date. Travel information is derived from Passenger Locator Forms (PLF), contact tracing and international arrivals. Where people indicate that they have not travelled in response to contact tracing and do not have associated PLF data, they are categorised as not-travel associated. Cases for which there is no matching PLFs or information about travel status from other sources are marked as awaiting information. Travel status was assigned based on the individual's history of travel (including transit), rather than contact with a traveller. The area in grey shows weeks where sequence data are still accumulating. Therefore, the proportions are less likely to reflect prevalence accurately. The total number of sequencing cases in each week is shown in the bars below, split by travel status.

1.5 Antigenic change over time (international)

A list of mutations of potential antigenic significance has been compiled using the available published evidence. The full list of mutations of potential antigenic significance is compiled and continuously updated by an expert group comprising members of the variant technical group, COG-UK, and UK-G2P using literature searches and data mining from publicly available datasets. Data analysis includes GISAID data uploaded before 16 July 2021 (excluding UK data). The increase in the number of antigenic mutations over time is illustrated for all variants in Figure 9 and for all variants, excluding VOCs and VUIs in Figure 10.

The plots in Figures 9 and 10 were obtained by first counting the number of high confidence antigenic mutations for each sequence. The sequences were then grouped and the prevalence for each number of mutations was estimated weekly from March 2020 until 16 June 2021. All non-synonymous mutations at positions in the spike protein that have been associated with antigenicity were considered antigenic. VOCs or VUIs were identified by analysing their spike mutation profile to deal with low-quality and partial sequences.

Figure 9. Prevalence of antigenic mutations over time for all genomes in GISAID (excluding UK data), as of 16 July 2021
(Find accessible data used in this graph in underlying data)

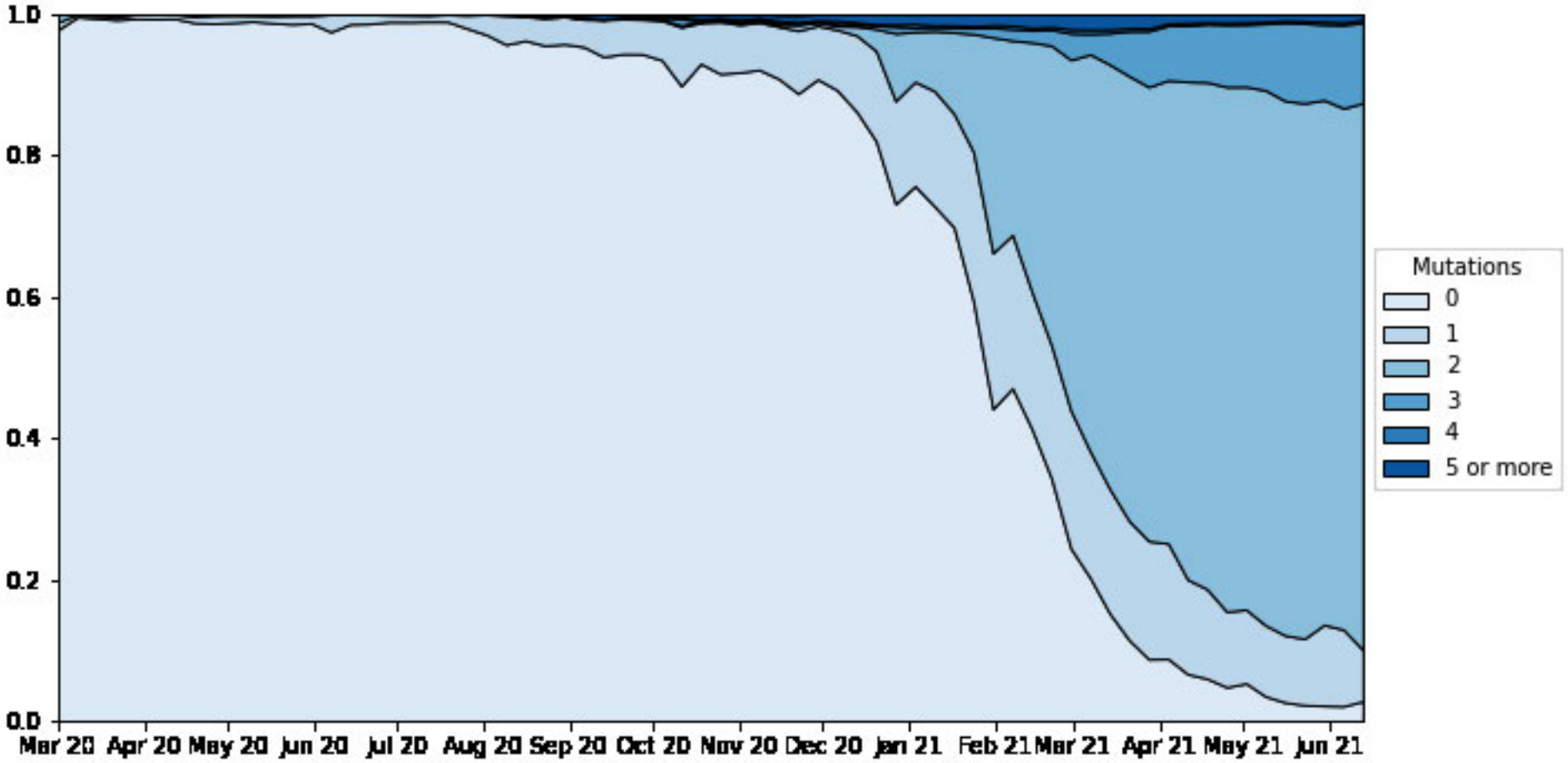
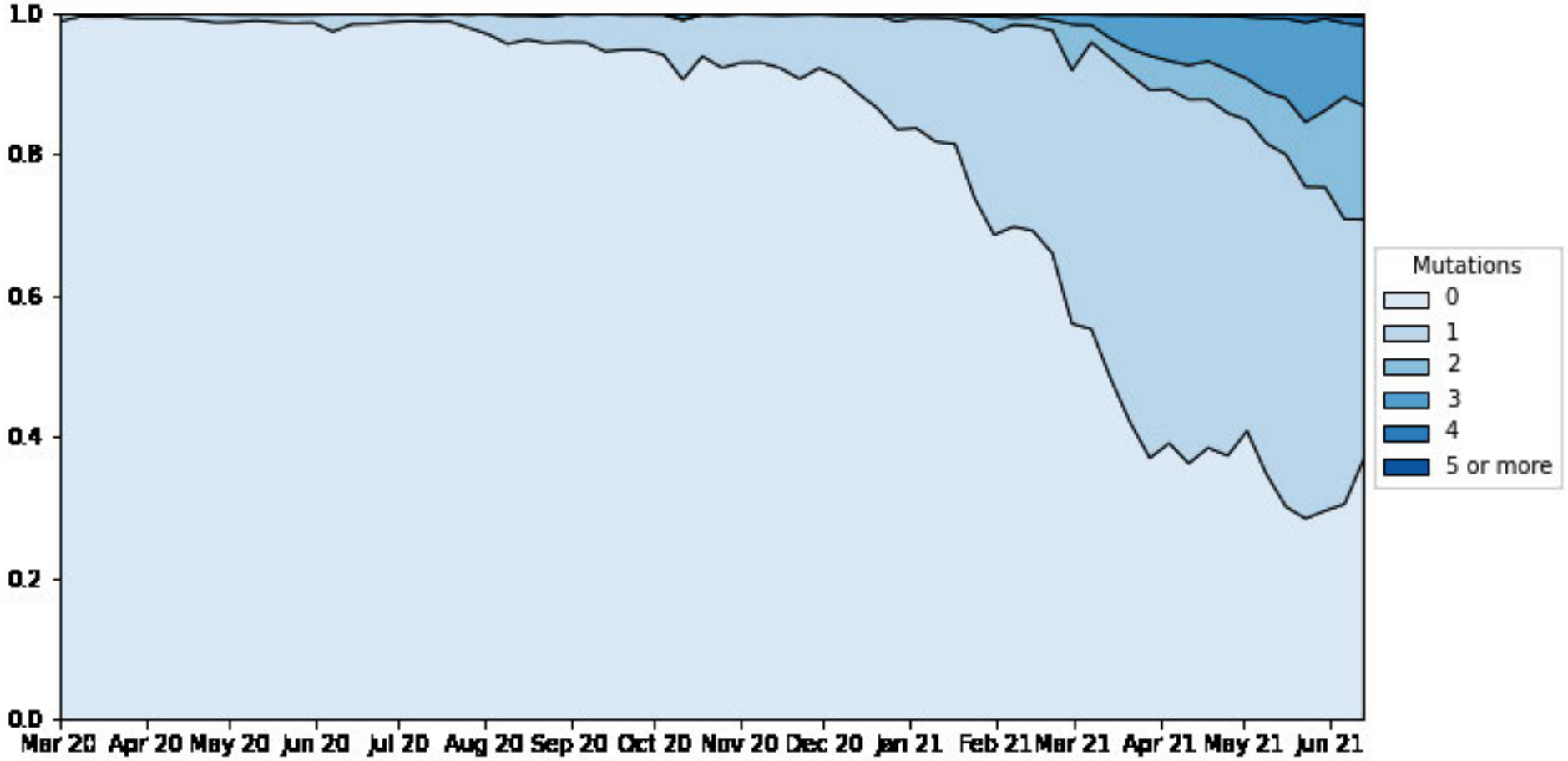


Figure 10. Prevalence of antigenic mutations over time for all genomes in GISAID (excluding UK data), excluding VOCs and VUIs, as of 16 July 2021

(Find accessible data used in this graph in underlying data)



1.6 Secondary attack rates

This section includes secondary attack rates for traveller and non-traveller cases, and separate household contact rates, including new analysis of rates for household and non-household contacts of non-traveller cases over time for Delta and Alpha variants.

Secondary attack rates are based on positive tests amongst contacts named to NHS Test and Trace by an original case identified with a confirmed or probable VOC or VUI. Variant cases are identified using confirmed (sequencing) results supplemented with probable (genotyping) results as of 19 July 2021 and exclude low-quality results.

Secondary attack rates are shown for cases with and without travel history. In non-travel settings, only close contacts named by the original case are included, that is, household members, face-to-face contact, people within one metre of the case for one minute or longer, or people within 2 metres for 15 minutes. In travel settings, the contacts reported are not restricted to only close contacts named by the case. For example, they may include contacts on a plane linked by additional contact tracing efforts. This likely deflates secondary attack rates amongst travellers compared to non-travellers. In addition, people recently returning from overseas are subject to stricter quarantine measures and may moderate their behaviour towards contacts. Travel history suggests where infection of the original case may have occurred.

Table 6 shows secondary attack rates for all variants. The time period of study for secondary attack rates is between 5 January 2021 and 30 June 2021 to capture data for all variants. Vaccination levels and social restrictions in England have varied over this period, so comparisons between variants prevalent during different periods are not valid. Estimates of secondary attack rates for contacts of those that have travelled with variants of concern or variants under investigation were all considerably lower than those that have not travelled, due to the difference in contact definition.

Figure 11 shows the secondary attack rates amongst household and non-household contacts of non-travel cases with Delta and Alpha over time for the period 29 March 2021 to 27 June 2021, with 95% confidence intervals. A modest increase in secondary attack rate amongst household contacts of cases with Delta in the most recent 2 weeks of reporting is observed, with an estimate of 11.1% (10.9% to 11.4%) for exposure events in week commencing 21 June 2021 compared to 10.3% (10.1% to 10.6%) in the week commencing 7 June 2021. Over the period presented, secondary attack rates for household contacts of cases with Delta remain higher than for Alpha.

Table 6. Secondary attack rates for all variants
(5 January 2021 to 30 June 2021, variant data as of 19 July 2021, contact tracing data as of 21 July 2021)

Variant	Cases in those that have travelled (with contacts)	Cases in those that have not travelled or unknown (with contacts)	Case proportion that have travelled	Secondary attack rate among contacts of cases that have travelled (95% CI) [secondary cases/contacts]	Secondary Attack Rate among household contacts of cases that have not travelled or unknown (95% CI) [secondary cases/contacts]	Secondary Attack Rate among non-household contacts of cases that have not travelled or unknown (95% CI) [secondary cases/contacts]
Alpha (VOC-20DEC-01)	4388 (76.6% with contacts)	184,980 (73.0% with household, 14.0% with non-household contacts)	2.3%	1.5% (1.4% to 1.6%) [1,249/81,942]	10.2% (10.1% to 10.3%) [34596/338352]	5.6% (5.5% to 5.8%) [3303/58625]
Beta (VOC-20DEC-02)	341 (69.8% with contacts)	420 (64.5% with household, 14.5% with non-household contacts)	44.8%	1.8% (1.5% to 2.2%) [110/6,027]	10.0% (8.0% to 12.4%) [74/741]	3.0% (1.4% to 6.3%) [6/202]
Zeta (VUI-21JAN-01)	4 (75.0% with contacts)	27 (70.4% with household, 3.7% with non-household contacts)	12.9%	Unavailable [0/159]	Unavailable [4/51]	Unavailable [0/1]

Gamma (VOC-21JAN-02)	72 (63.9% with contacts)	146 (71.9% with household, 15.8% with non-household contacts)	33.0%	1.0% (0.5% to 1.9%) [9/889]	10.3% (7.1% to 14.8%) [25/242]	3.4% (1.2% to 9.4%) [3/89]
VUI-21FEB-01	0 (0 with contacts)	63 (57.1% with household, 12.7% with non-household contacts)	0.0%	Unavailable [0/0]	9.9% (5.1% to 18.3%) [8/81]	Unavailable [1/12]
Eta (VUI-21FEB-03)	196 (70.4% with contacts)	198 (70.7% with household, 12.6% with non-household contacts)	49.7%	1.1% (0.8% to 1.5%) [47/4,281]	9.8% (7.1% to 13.4%) [33/337]	Unavailable [1/43]
VUI-21FEB-04	113 (69.0% with contacts)	159 (76.7% with household, 20.1% with non-household contacts)	41.5%	0.5% (0.3% to 0.8%) [16/3,106]	8.5% (5.8% to 12.1%) [26/307]	6.5% (3.0% to 13.4%) [6/93]
VUI-21MAR-01	1 (100.0% with contacts)	0 (0 with household, 0 with non-household contacts)	100.0%	Unavailable [0/7]	Unavailable [0/0]	Unavailable [0/0]
Theta (VUI-21MAR-02)	5 (40.0% with contacts)	1 (100.0% with household, 0.0% with	83.3%	Unavailable [0/4]	Unavailable [0/3]	Unavailable [0/0]

		non-household contacts)				
Kappa (VUI-21APR-01)	233 (77.3% with contacts)	173 (74.6% with household, 13.3% with non-household contacts)	57.4%	1.9% (1.5% to 2.3%) [83/4,449]	9.7% (7.1% to 13.0%) [38/392]	Unavailable [3/45]
Delta (VOC-21APR-02)	1387 (69.9% with contacts)	174632 (76.8% with household, 22.9% with non-household contacts)	0.8%	1.7% (1.5% to1.9%) [429/25,424]	11.0% (10.9% to 11.1%) [37440/341069]	5.8% (5.6% to 5.9%) [7119/123393]
VUI-21APR-03	7 (14.3% with contacts)	5 (100.0% with household, 0.0% with non-household contacts)	58.3%	Unavailable [1/201]	Unavailable [1/12]	Unavailable [0/0]
VUI-21MAY-01	2 (0.0% with contacts)	176 (83.0% with household, 17.6% with non-household contacts)	1.1%	Unavailable [0/0]	8.0% (5.8% to 11.1%) [33/411]	2.4% (0.8% to 6.9%) [3/124]
VUI-21MAY-02	68 (73.5% with contacts)	54 (81.5% with household, 9.3% with non-household contacts)	55.7%	0.8% (0.5% to1.5%) [11/1,298]	8.2% (4.4% to14.8%) [9/110]	Unavailable [0/13]
Lambda (VUI-21JUN-01)	8	0	100.0%	Unavailable [1/193]	Unavailable [0/0]	Unavailable [0/0]

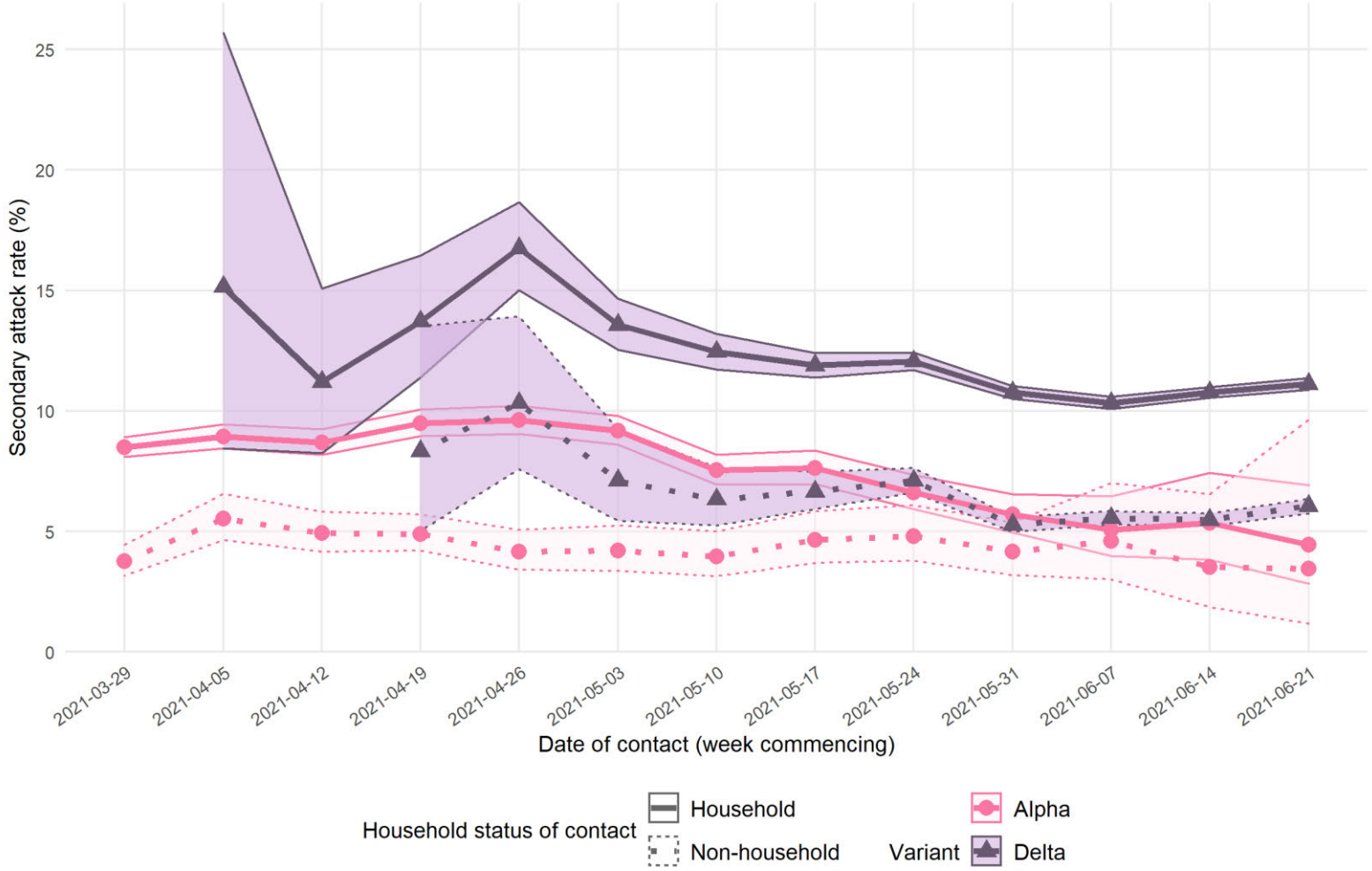
	(62.5% with contacts)	(0 with household, 0 with non-household contacts)				

Footnote to table 6: Secondary attack rates are marked as ‘Unavailable’ when count of contacts is fewer than 50 or count of cases is fewer than 20. Travel-linked cases for secondary attack rates are identified positively in NHS Test and Trace data using multiple PHE sources. A case is considered as being travel-linked if EpiCell or Health Protection Teams have found evidence of international travel, their NHS Test and Trace record mentions an event associated with international travel, their NHS Test and Trace record was created after notification via International Health Regulations National Focal Point, their contacts were traced by the international contact tracing team, or they have been marked for priority contact tracing in NHS Test and Trace for reasons of travel. Some travel-linked cases may be missed by these methods and would be marked as non-travel-linked or unknown.

Secondary attack rates from NHS Test and Trace should generally be considered lower bounds due to the nature of contact tracing and testing. Data provided is for period until 30 June 2021 in order to allow time for contacts to become cases, hence case counts are lower than other sources. Cases are included in case counts if their onset or (if asymptomatic) test is during the period of study
Contacts are included in secondary attack rates if their exposure date or onset or test of exposing case if the contact is a household contact is during the period of study. Probable (genotyping) results are included, but low-quality genomic results are excluded.
Secondary attack rates are suppressed when count of contacts is less than 50 or count of cases is less than 20. Data provided is for period until 27 June 2021 in order to allow time for contacts to become cases and complete weeks to be shown. Probable (genotyping) results are included, low quality genomic results are not.

Figure 11. Secondary attack rates amongst household and non-household contacts of non-travel cases of Alpha and Delta, with 95% confidence intervals (29 March 2021 to 27 June 2021, variant data as of 19 July 2021, contact tracing data as of 21 July 2021)

(Find accessible data used in this graph in underlying data)



1.7 Reinfections

1.7.1 National Surveillance of Reinfections

Symptomatic SARS-CoV-2 cases in persons aged ≥15 years identified as PCR positive through the Pillar 2 route between 12 April and 27 June 2021 were compiled. Cases were identified as having an Alpha or Delta variant through sequencing or inferred through s-gene target data. All previous SARS-CoV2 positive PCR and/or LFD test results for these cases were scrutinised for possible reinfections, where a previous positive result had occurred at least 90 days earlier. Multivariable logistic regression models in Stata were used to assess the risk of reinfection with the Alpha and Delta variants. The models were adjusted for age (<30 or ≥30 years), sex, region of residence, vaccination status (any vaccine at least 14 days earlier or no vaccine), ethnicity, and week of test. The model was also run separately for cases of reinfection with shorter (90 to 179 days) and longer (≥180 days) intervals between episodes. There were 83,197 people who tested positive in the 11-week period, of whom 980 (1.2%) were possible reinfections.

The adjusted odds ratio of reinfection with the Delta variant was 1.46 (95% CI 1.03 to 2.05) compared to the Alpha variant. The risk of reinfection was not elevated for Delta if the primary infection was <180 days (adjusted odds ratio = 0.79, 95% CI 0.49 to1.28) but was higher for those with a prior infection ≥180 days earlier (adjusted odds ratio = 2.37, 95%CI 1.43 to 3.93). Further work to examine the risk of reinfection is being undertaken.

Table 7: Multivariable logistic regression model of the risk of reinfection with alpha and delta variants during a period of emergent delta infection in England

			Risk of reinfection-week 2021-15 to 2021-25		
		Totals	Crude OR	aOR (95% CI)*	aP-Value
Definition of reinfection applied	All possible reinfections	980 (1.2%)			
	All first infections	82,217 (98.8%)			
All possible reinfections arising at least 90 days after prior infection	Alpha variant	83/14,509 (0.6%)	1	1	
	Delta variant	897/68,688 (1.3%)	2.30 (1.84 to 2.88)	1.46 (1.03 to 2.05)	0.031
Possible reinfections arising between 90-179 days after prior infection	Alpha variant	54/14,480 (0.4%)	1	1	
	Delta variant	243/68,034 (0.4%)	0.96 (0.71to 1.29)	0.79 (0.49 to1.28)	0.342
Possible reinfections arising at least 180 days after prior infection	Alpha variant	29/14,455 (0.2%)	1	1	
	Delta variant	654/68,445 (1.0%)	4.80 (3.31 to 6.96)	2.37 (1.43 to 3.93)	0.001

*adjusted for age group (<30 years, 30+years), sex, Region, vaccination status (any vaccine at least 14 days earlier vs no vaccine), ethnicity and week

1.7.2 SARS-CoV-2 Immunity and Reinfection Evaluation (the SIREN study) cohort monitoring

The SIREN study is a cohort of National Health Service healthcare workers, including 135 sites and 44,546 participants across the UK, 35,684* in England, who remain under active follow-up with PCR testing every 2 weeks for COVID-19 by PCR. This cohort had high seropositivity on recruitment (30% before the second wave) and is now highly vaccinated (95%). The incidence of new infections and potential reinfections in SIREN is monitored and would be expected to rise if a new variant became highly prevalent and was able to escape predominantly vaccine-derived immunity.

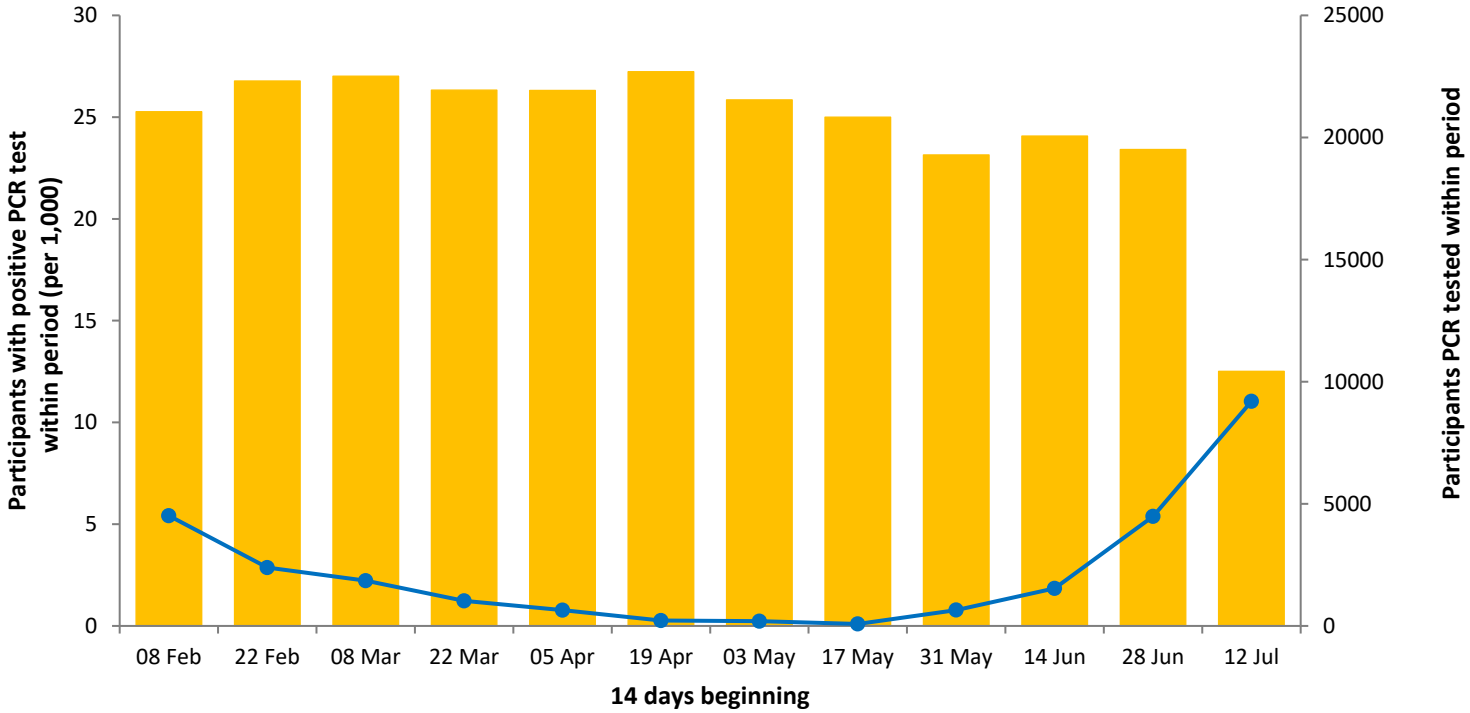
The frequency of PCR positivity in the SIREN cohort overall has increased in June 2021, with 5.4 PCR positives per 1000 tested between 28 June 2021 and 11 July 2021 after low levels in April and May (0.1 PCR positives per 1000 tested between 17 May 2021 and 30 May 2021) (Figure 12). Of the 263 participants with a PCR positive sample since April 2021 in the SIREN cohort overall, 221 (84%) occurred 14 days or more following their

second vaccine dose. Please note that historical infections and reinfections have increased since the last Technical Briefing due to improvements in data linkage.

Of the SIREN cohort, 9,813 (31%) had evidence of prior infection (previous PCR positive or antibody positive) at enrolment. This number has increased during follow-up as participants move from the negative to positive cohort after a primary infection. Up to the 11 July 2021, there were 301 potential reinfections (blue line) identified in England (Figure 13). This is provisional data as potential reinfection cases flagged are undergoing further investigation, and some may subsequently be excluded. Reinfections in the SIREN cohort have been increasing since June 2021 (20 cases in June and 24 cases in July), after low levels in April 2021 (3 cases) and May 2021 (4 cases). Of the 51 potential reinfection events since April 2021, 3 were at least 21 days after the 1st vaccine dose and 42 (82%) were at least 14 days after the 2nd vaccine dose.

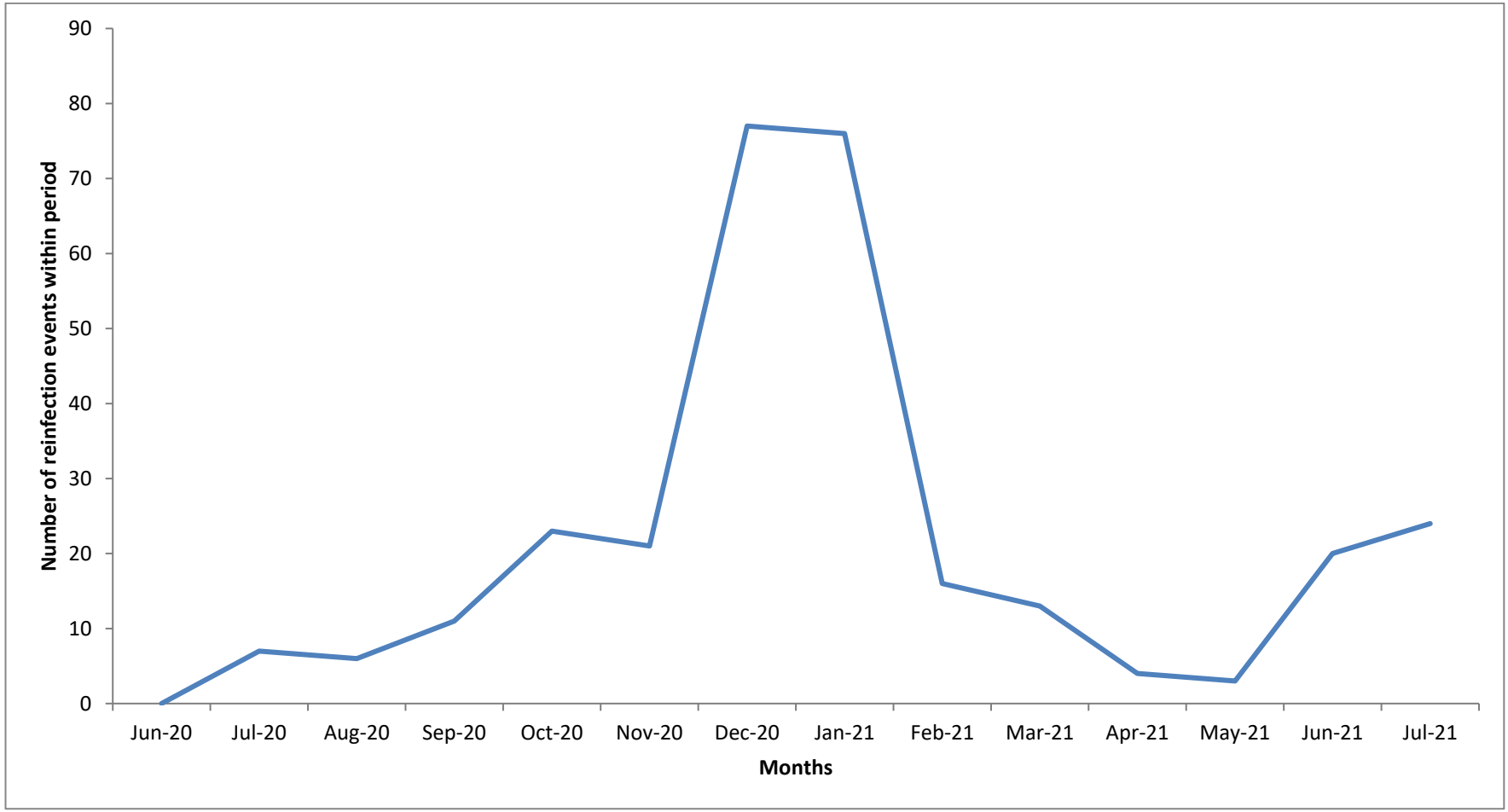
*Number excludes participants who have withdrawn from the study and requested their data to be removed and participants recruited in hospitals in the devolved administrations.

Figure 12. PCR positivity within the SIREN study for all regions, England (fortnightly testing interval) data up to 18 July 2021
(Find accessible data used in this graph in underlying data)



*Incomplete week commencing 28 June 2021
Yellow bars indicate participants PCR-tested within period (right axis), Blue line indicates participants with positive PCR within period (per 1,000) (left axis). Please note that Figure 15 only contains data from participants with at least one PCR test within the given period. Participants are counted as positive if at least one PCR test within the given period is positive. The data has not been restricted by antibody status or vaccination status, and only includes participants from trusts in England.

Figure 13. Monthly frequency of potential reinfection events within SIREN data up to 11 July 2021
(Find accessible data used in this graph in underlying data)



1.8 Updates from Variant Technical Group Members

This section contains summaries of key information reported by Variant Technical Group members for use in the variant risk assessments. Links to full published data will be provided once available.

1.8.1 Genotype to Phenotype (G2P) Consortium

The G2P consortium reports experimental data (growth in airway epithelium, and animal to animal transmission) suggesting that Beta is not highly fit and is likely to be less transmissible than Alpha.

1.8.2 University of Oxford

The University of Oxford reports preliminary findings that convalescent sera from individuals with Delta infection neutralises Beta and Gamma less effectively than convalescent sera from individuals with Alpha infection (all cases were unvaccinated). This is data from a single laboratory with limited numbers of samples tested at present.

1.8.3 MRC Biostatistics Unit, University of Cambridge

The MRC Biostatistics Unit reported preliminary findings from analysis of deaths data. Analysis of deaths in England is limited by low numbers, but suggests that Delta has at least an equivalent case fatality rate to Alpha. There is currently a high level of uncertainty and further analyses will be undertaken.

Part 2: Surveillance of individual variants

2.1 Delta (B.1.617.2) surveillance

The lineage B.1.617.2 was escalated to a VOC in the UK on 6 May 2021 (VOC-21APR-02). This variant was named Delta by WHO on 31 May 2021.

2.1.1 Diversity in Delta

Table 8 shows additional spike mutations with a potential impact on antigenicity, avidity or the furin cleavage site significance that have been acquired by Delta in the UK. This data uses the numbers of genomes in the national genomic data set rather than case numbers. Only mutations associated with antigenic change (for example, through published literature) are presented. The number of unlinked sequences represents the number of sequences not present within the English surveillance system. These sequences include those samples from the Devolved Administrations and cannot be associated with a date by PHE.

Figure 14 shows the phylogeny of Delta in the UK, which is dominated by a large distinct clade. The clade has distinguishing mutations outside spike with uncertain biological significance, including NSP3: A488S, P1228L, P1469S; NSP4: D144D, V167L, T492I; NSP6: T77A, V120V; NSP14:A394V; ORF7b: T40I; N: G215C. The dominance of this clade in the UK may relate to epidemiological or biological effects or both. Further investigations are being undertaken. Figure 15 shows the percentage of sequences in each clade over time.

Table 8. Additional spike mutations of interest detected in Delta genomes in the UK as of 20 July 2021

Amino acid change	Nucleotide change	Total number of sequences (UK)	Number of unlinked sequences	Number of sequences 21April to 20 May 2021	Number of sequences 21 May to 20 June 2021	Number of sequences 21 June to 20 July 2021
P251L	C22314T	1,159	968	1	36	154
G446V	G22899T	490	277	5	105	103
L18F	C21614T	271	89	0	31	151
D253G	A22320G	193	13	0	31	149
R683Q	G23610A	162	5	1	55	101
S255F	C22326T	151	18	6	14	113
N148S	A22005G	87	12	0	4	71
R158G	A22034G	77	3	4	70	0
T716I	C23709T	73	24	0	12	37
P479S	C22997T	57	7	1	13	36
Q677H	G23593T	55	10	4	25	16
K417N	G22813T	52	8	33	11	0
P479L	C22998T	41	2	0	15	24
V483F	G23009T	40	5	0	6	29
S477I	G22992T	40	7	1	14	18
S494L	C23043T	24	9	3	6	6
S477G	A22991G	20	1	0	5	14
K458N	G22936T	20	0	0	2	18
P681L	C23604T	20	1	0	12	7
Total Sequences	**C23604G**	**165,981**	**165,981**	**9,266**	**64,316**	**57,865**

Note that G142D is in a part of the genome with consistently reduced coverage in the Delta variant due to the lineage-defining deletion from position 22029 to 22035, which affects one of the PCR primer sites in the ARTIC v3 protocol. While it is only reported as detected in ~60% of sequences, the remaining 40% of sequences are almost all “N” at that position (the code for ‘insufficient data’), rather than being confirmed ”G” (the reference allele). As the mutation occurred early in the history of the lineage the majority of sequences (>99%) in this lineage can be assumed to harbour the mutation.

Figure 14. Maximum likelihood tree of all UK Delta sequences
Phylogenetic tree showing clades are defined using the clusterfunk method. Clades defined by the clusterfunk method are shown in separate colours (N.B. these do not relate to Pangolin lineage names). The clade in green is predominant in the UK. (There is no underlying data for this figure)

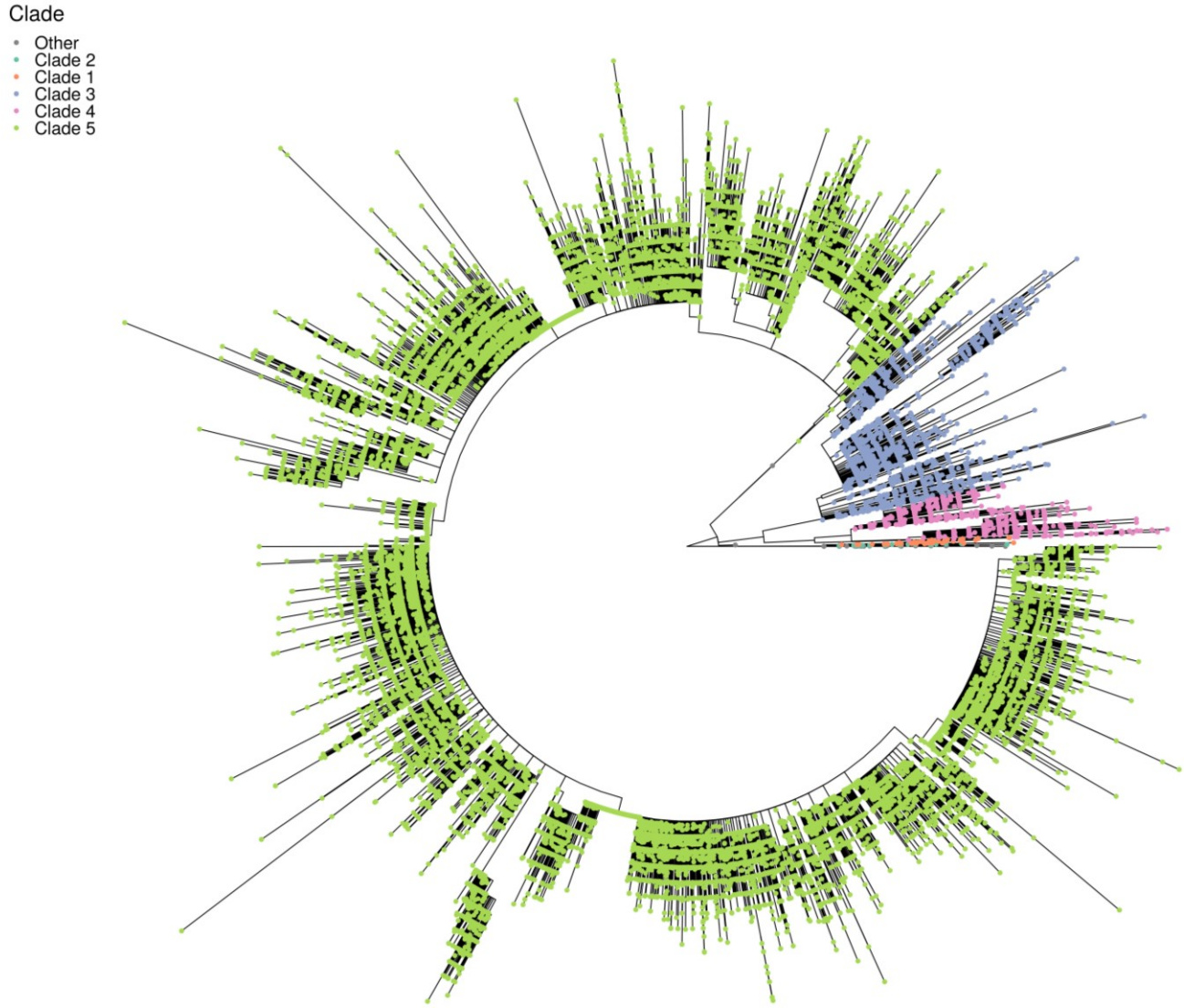
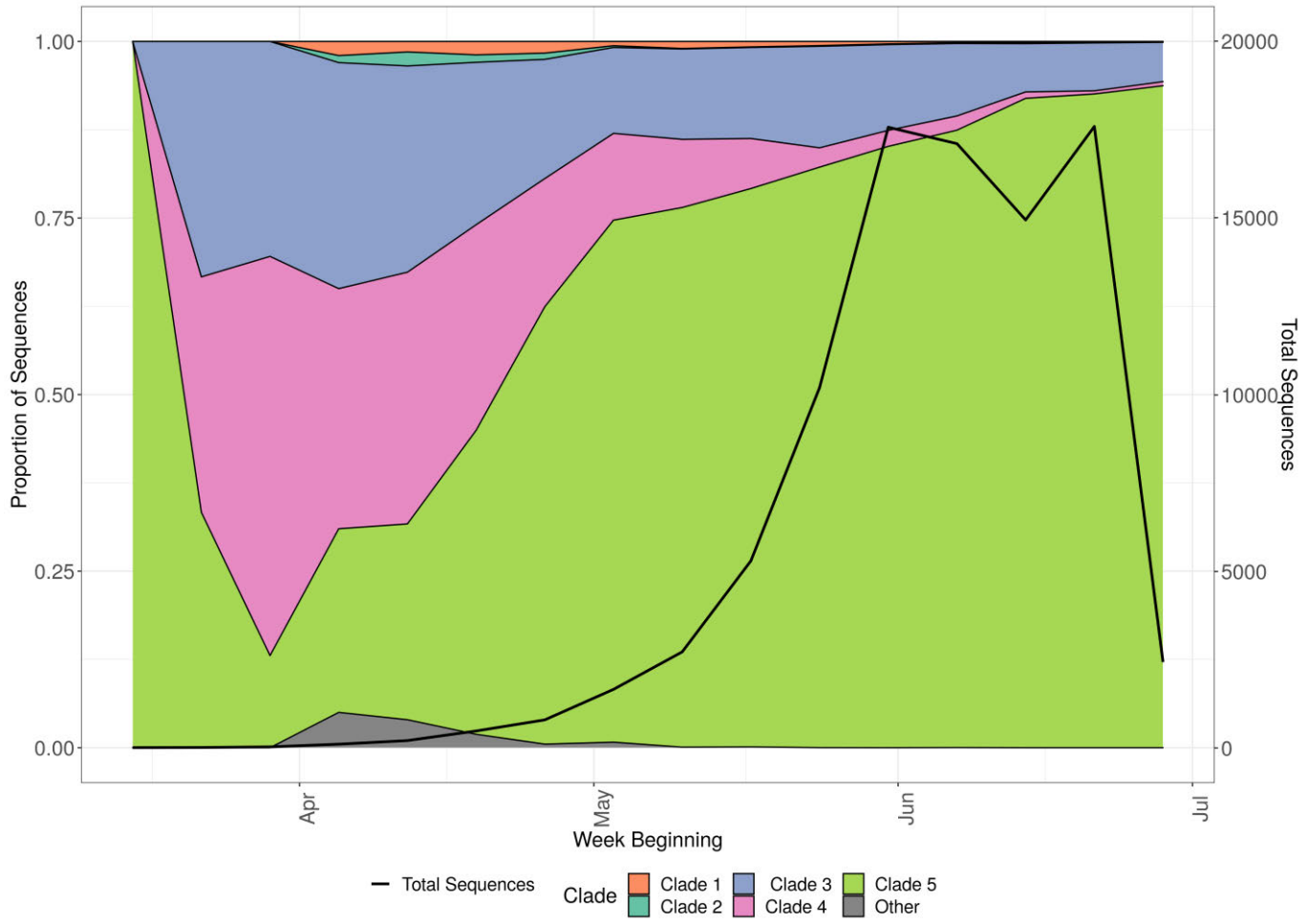


Figure 15. Proportion of Delta sequences in each clade over time
Sequences are grouped by week and any clades with fewer than 100 sequences are grouped into “other”. Total sequences for each week are indicated by the black line.



2.1.2 Delta with K417N

Through routine scanning of variation in Delta a small number of sequences were detected with the K417N spike protein mutation.

Data suggest that there are at least 2 separate clades of Delta with K417N. One clade is large and internationally distributed with the PANGO lineage designation AY.1. A second clade found in sequences uploaded to GISAID from the US, which is now designated AY.2.

Preliminary results for live virus neutralisation of AY.1 with a small number of sera from vaccine recipients are reassuring, however further testing is required (data provided by G2P consortium).

2.1.2.1 International epidemiology

GISAID includes data on sequences available internationally. As of 16 July 2021, 828 genomes of Delta-with K417N have been identified in GISAID internationally, excluding the UK: US (592), Portugal (56), Japan (47), Switzerland (41), Poland (27), India (23), France (11), Nepal (11), Germany (3), Netherlands (2), Spain (2), Qatar (2), Australia (2), Mexico (2), Canada (1), Kuwait (1), Ecuador (1), Romania (1), Russia (1), Denmark (1), and Czech Republic (1).

2.1.2.2 Epidemiology

There are currently 45 cases of Delta with K417N in England (39 confirmed sequencing and 6 probable genotyping). Cases have been detected in 7 different regions in England (Table 9, Figure 16).

Delta with K417N can be detected by genotyping assay, which means that rapid case identification and response activities can be undertaken. Until laboratory characterisation has been undertaken, Health Protection Teams will respond with high priority to case finding and control measures for cases of Delta with K417N. Neutralisation assays are underway for Delta-AY.1

Table 9. Number of confirmed (sequencing) and probable (genotyping) Delta cases with K417N mutation, by region of residence as of 19 July 2021

Region	Confirmed (sequencing) case number	Probable (genotyping) case number[1]	Total case number	Case Proportion
East Midlands	1	0	1	2.2%
East of England	0	1	1	2.2%
London	7	1	8	17.8%
North East	0	2	2	4.4%
North West	3	0	3	6.7%
South East	15	1	16	35.6%
South West	2	1	3	6.7%
West Midlands	10	0	10	22.2%
Yorkshire and Humber	0		0	0.0%
Unknown region	1	0	1	2.2%
Total	39	6	45	-

[1]Genotyping is used to identify variants Alpha, Beta, Delta and Gamma; targets were updated in mid-May 2021 to prioritise accurate identification of Delta over Alpha

Figure 16. Confirmed (sequencing) and probable (genotyping) Delta cases with K417N cases by specimen date and region of residence as of 19 July 2021

Larger plot includes last 60 days only. (Find accessible data used in this graph in underlying data)

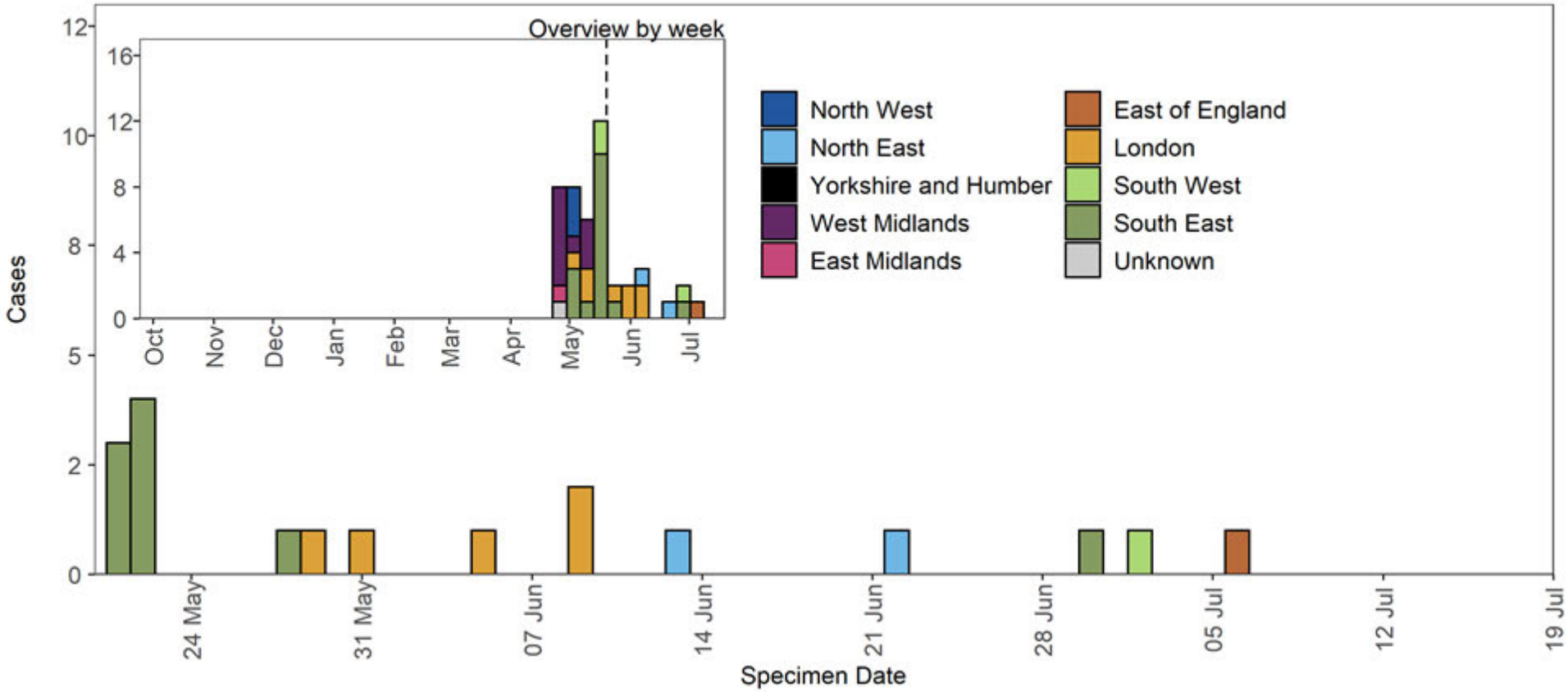


Figure 17. Confirmed (sequencing) and probable (genotyping) Delta cases with K417N cases by specimen date and detection method as of 19 July 2021 (Find accessible data used in this graph in underlying data)

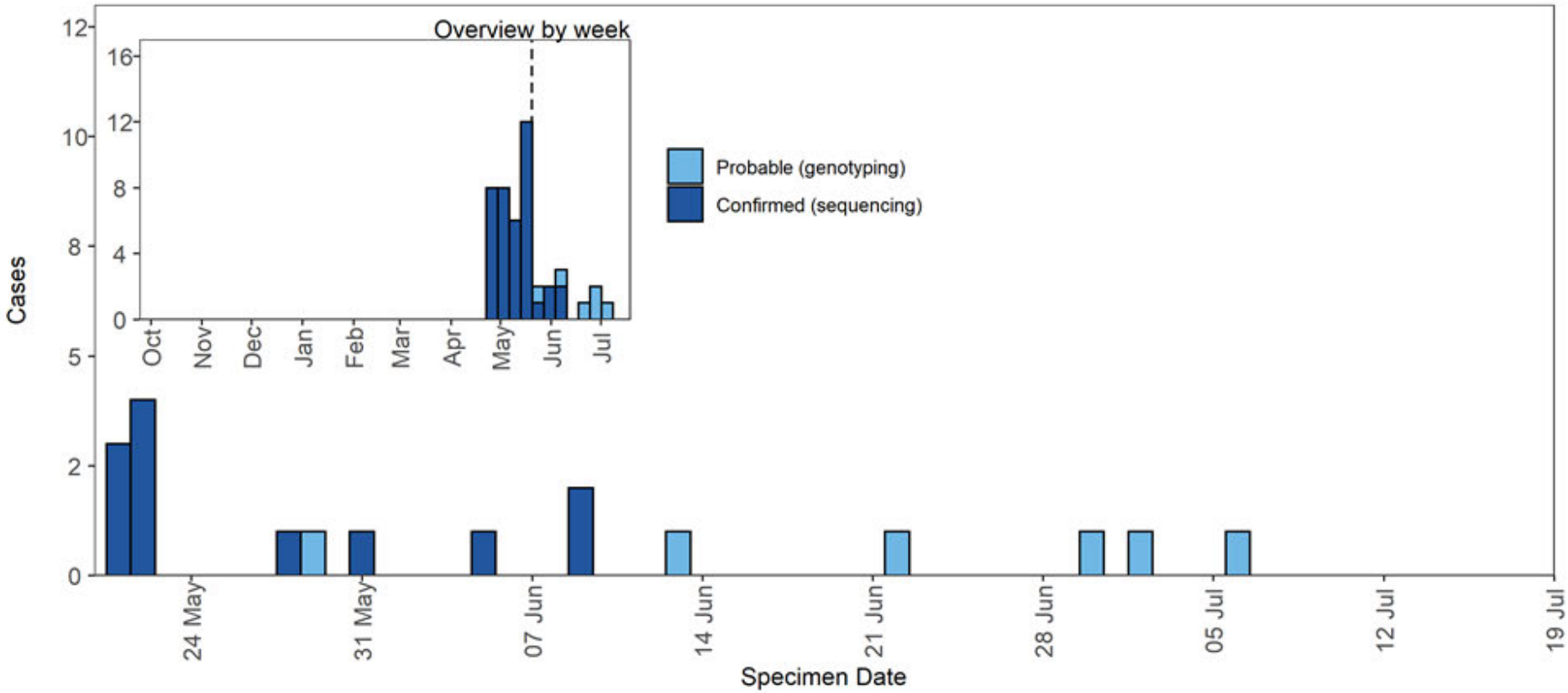
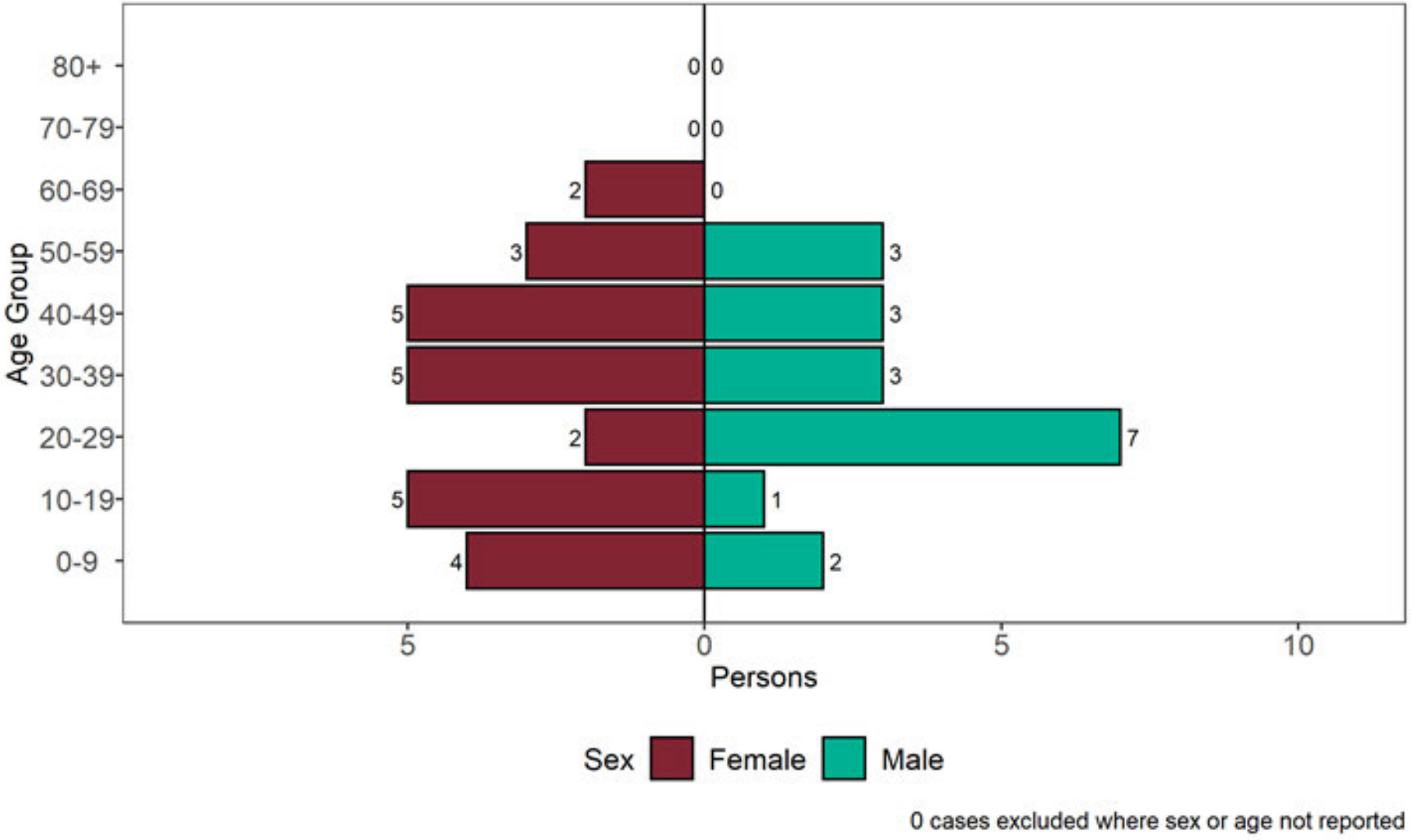


Figure 18. Age and sex pyramid of confirmed (sequencing) and probable (genotyping) Delta cases with K417N cases as of 19 July 2021 (Find accessible data used in this graph in underlying data)



2.2 VUI-21JUL-01 Surveillance

VUI-21JUL-01 was identified through international variant horizon scanning and was made a signal in monitoring by PHE on 7 June 2021 (lineage B.1.621 at the time). On 20 July 2021, PHE designated lineage B.1.621 as a new variant of interest, VUI-21JUL-01, based on apparent spread into multiple countries, importation to the UK and mutations of concern.

VUI-21JUL-01 is characterised by the non-synonymous mutations NSP3; T237A, T720I. NSP4;T492I. NSP6; Q160R. NSP12; P323L. NSP13; P419S, T95I. S; R346K, E484K, N501Y, D614G, P681H, D950N. ORF3a; Q57H, ORF8; T11K, P38S, S67F, and N; T205I as well as an insertion in S at 144. Recent sequences identified as B.1.621 have also contained the K417N S gene mutation.

2.2.1. International epidemiology

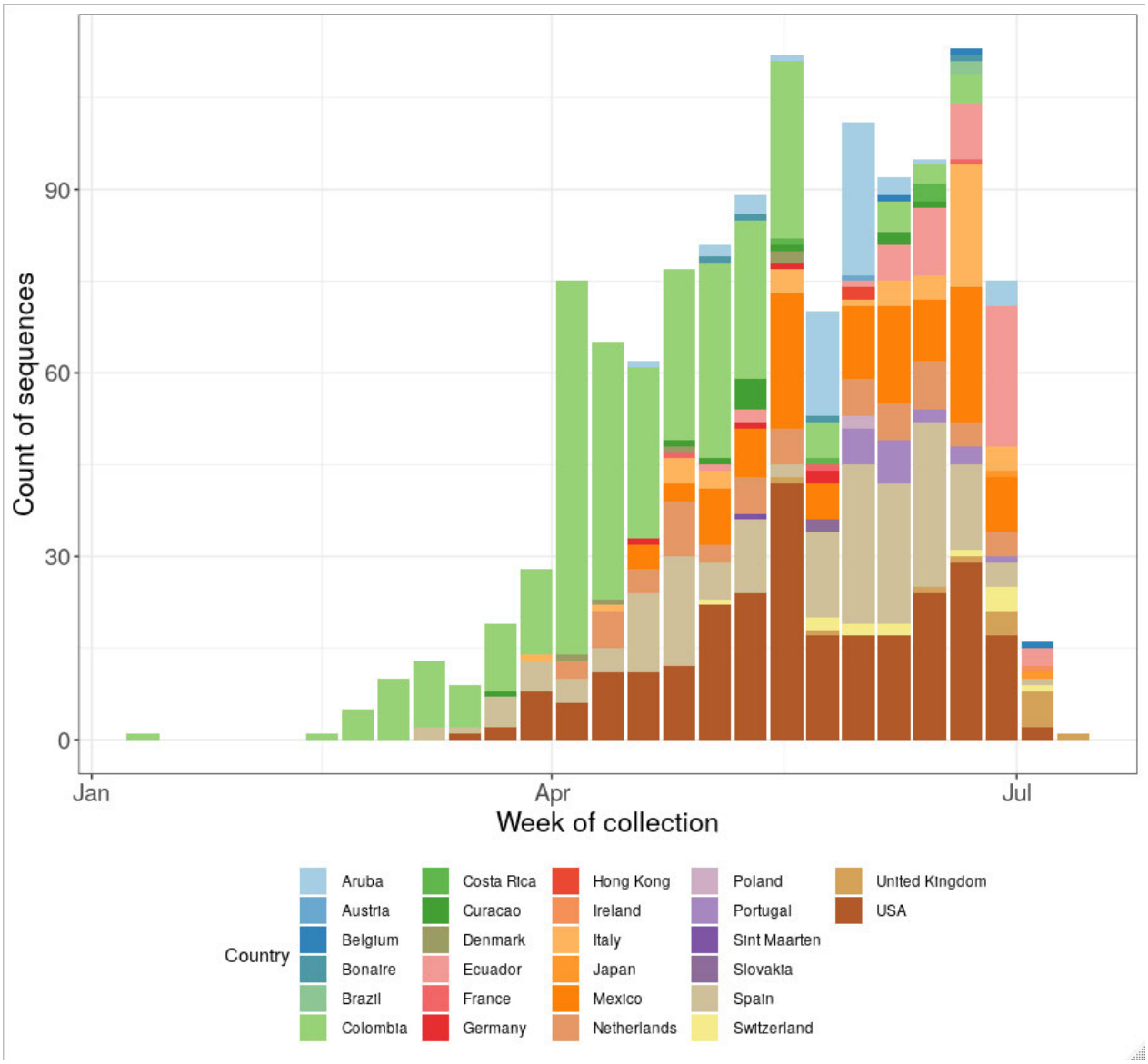
As of 20 July 2021**,** 1,230 sequences on GISAID have been assigned to the B.1.621 lineage. B.1.621 sequences have been uploaded from Colombia (325), US (264), Spain (196), Mexico (122), Netherlands (65), Aruba (57), Ecuador (56), Italy (47), Portugal (19) United Kingdom (16), Switzerland (13), Curacao (12), Costa Rica (5), Denmark (5),Germany (5) Bonaire (4), Belgium (3), France (3), Brazil (2), Hong Kong (2), Japan (2), Poland (2), Slovakia (2), Austria (1), Ireland (1), and Sint Maarten (1). Figure 19 shows the distribution of case per country over time, based on GISAID data, indicating that an increasing number of countries reported cases in June and July.

2.2.2 Epidemiology in England

As of 22 July 2021, there are 16 cases of VUI-21JUL-01 in England plus an additional 6 genomes for which case data is being sought. Cases have been detected in 3 different regions in England, with the majority of cases detected in London (10, 63%). The 20-to-29 years age group formed the largest age group (6 cases). Three of the 16 cases have history of travel which include travel from or transit through Mexico, Spain, Dominican Republic and Colombia.

Of the 16 cases, 10 cases were known to have a vaccination status within the National Immunisation Management System (NIMS), when linked on NHS number. Of these, 3 cases occurred in people who were not vaccinated, 3 cases in people who had received their first dose within 21 days at the time of testing positive, 2 cases in people who had received their first dose more than 21 days before testing positive, and 2 cases where there were more than 14 days after their second dose of vaccine at the time of testing positive. No deaths have been recorded amongst the 16 cases.

Figure 19. Count of B.1.621 classified sequences by week of collection uploaded to GISAID by week as of 20 July 2021



Sources and acknowledgments

Data sources

Data used in this investigation is derived from the COG-UK dataset, the PHE Second Generation Surveillance System (SGSS), NHS Test and Trace, the Secondary Uses Service (SUS) dataset, Emergency Care Data Set (ECDS), and the PHE Case and Incident Management System (CIMS). Data on international cases are derived from reports in GISAID, the media and information received via the International Health Regulations National Focal Point (IHRNFP) and Early Warning and Response System (EWRS).

Repository of human and machine-readable genomic case definitions

Genomic definitions for all VOC and VUI are provided in order to facilitate standardised VOC and VUI calling across sequencing sites and bioinformatics pipelines and are the same definitions used internally at PHE. Definition files are provided in YAML format so are compatible with a range of computational platforms. The repository will be regularly updated. The genomic and biological profiles of VOC and VUI are also detailed on first description in prior technical briefings.

Variant Technical Group

Authors of this report

PHE Genomics Cell
PHE Outbreak Surveillance Team
PHE Epidemiology Cell
PHE Contact Tracing Data Team
PHE Health Protection Data Science Team
PHE International Cell
Contributions from the Variant Technical Group Members

Variant Technical Group members and contributors

The PHE Variant Technical Group includes members and contributors from the following organisations: PHE, Public Health Wales, Public Health Scotland, Public Health Agency Northern Ireland, the Department of Health and Social Care, Imperial College London, London School of Hygiene and Tropical Medicine, University of Birmingham, University of Cambridge (including the MRC Biostatistics Unit), University of Edinburgh, University of Liverpool, the Wellcome Sanger Institute, the NHS Test and Trace Joint Biosecurity Centre, Genotype to Phenotype Consortium, SPI-M

Acknowledgements

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Public Health England
Wellington House
133-155 Waterloo Road
London SE1 8UG
Tel: 020 7654 8000

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SUSTAINABLE DEVELOPMENT GOALS

TAB 10

See Tab 6

TAB 11

See Tab 6 at Pg. 8

TAB 12

Previous COVID-19 infection but not Long-COVID is associated with increased adverse events following BNT162b2/Pfizer vaccination.

Rachael K. Raw (PhD)[1*], Clive Kelly (MD)[2], Jon Rees (MBBS)[3], Caroline Wroe (PhD)[4] and David R. Chadwick (PhD)[5]

[1] School of Medicine and Health, Newcastle University, Newcastle upon Tyne, UK

[2]The Department of Rheumatology, James Cook University Hospital, Middlesbrough, UK

[3]The School of Psychology, University of Sunderland, UK

[4]The Department of Nephrology, James Cook University Hospital, Middlesbrough, UK

[5]Centre for Clinical Infection, James Cook University Hospital, Middlesbrough, UK

*** Corresponding author**

Rachael Kathleen Raw

Email: Rachael.raw3@nhs.net

Telephone: +447780652723

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Manuscript length: 14 pages

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Number of figures: 1

Number of tables: 1

Key Points

Question: Does previous COVID-19 infection or 'Long-COVID' increase the frequency of Adverse Events (AEs) following first dose of BNT162b2/Pfizer vaccination?

Findings: In a survey-based observational study, healthcare workers in the United Kingdom reported AEs experienced after their first dose of BNT162b2/Pfizer vaccine. Prior COVID-19 infection, but not Long-COVID, were associated with increased risk of self-reported AEs including lymphadenopathy post-vaccination. Duration since COVID-19 infection did not affect severity of AEs.

Meaning*:* Our study can inform education and understanding of AEs associated with COVID-19 vaccination and help to combat vaccine hesitancy.

Abstract

Importance: Understanding Adverse Events (AEs) associated with SARS-CoV-2 vaccination has public health implications, especially with regards to vaccine hesitancy.

Objective: To establish whether individuals with prior history of COVID-19 were more likely to experience AEs after BNT162b2/Pfizer vaccination, than those without previous COVID-19, and whether COVID-19-vaccination interval influenced AE severity.

Design: An observational study explored AEs after vaccination. Participants were invited to complete an electronic survey, capturing self-reported COVID-19 symptoms, PCR/antibody results, and AEs following first dose of BNT162b2/Pfizer vaccine. In a subset where PCR/antibody results could be verified, a sensitivity analysis was conducted.

Setting: Three North-East England hospital Trusts in the United Kingdom.

Participants: Healthcare workers formed an opportunistic sample – 265 of 974 reported prior positive SARS-CoV-2 PCR and/or antibody.

Exposure: All participants had received their first dose of BNT162b2/Pfizer vaccine.

Main Outcomes and Measures: Nature, severity, duration, and onset of self-reported AEs (reported via a modified version of the FDA Toxicity Grading Scale for vaccine-associated AEs), was compared between those with and without a prior history of COVID-19, using 2-way ANCOVA and logistic regression. Effects of age, gender, illness-vaccine interval, and ongoing symptoms ('Long-COVID') on AEs, were also explored.

Results: Of 974 respondents (81% female, mean age 48), 265 (27%) reported previous COVID-19 infection. Within this group (symptoms median 8.9 months pre-vaccination), 30 (11%) complained of Long-COVID. The proportion reporting one moderate/severe symptom was higher in the previous COVID-19 group (56% v 47%, OR=1.5 [95%CI, 1.1–2.0], p=.009), with fever, fatigue, myalgia-arthralgia and lymphadenopathy significantly more common. There was no significant relationship between illness-vaccine interval and symptom composite score (r_s=0.09, p=.44). Long-COVID was not associated with worse AEs in

comparison to the group without previous COVID-19. In the smaller sensitivity analysis cohort (412 people) similar findings were obtained although only myalgia and arthralgia remained significant.

***Conclusions and Relevance*:** Prior COVID-19 infection but not ongoing Long-COVID symptoms were associated with an increase in the risk of self-reported adverse events following BNT162b2/Pfizer vaccination. COVID-19 illness-vaccination interval did not significantly influence AEs. This data can support education around vaccine-associated AEs and, through improved understanding, help to combat vaccine hesitancy.

Introduction

The BNT162b2/Pfizer and mRNA-1273/Moderna COVID-19 vaccines[1,2] were recently approved for use in the UK, with the former widely used amongst priority groups. While safety profiles were deemed acceptable (following phase 3 trials), participants with previous COVID-19 infection were excluded. Recent evidence suggests mRNA vaccines may cause more Adverse Events (AEs) in those with a history of COVID-19.[3-5] A small study found that AEs reported after the first dose of mRNA vaccine in seropositive individuals, were greater than in those with no prior COVID-19.[3] The 'ZOE COVID-19 Symptom Study' also observed similar outcomes via a self-reporting app.[4] Most recently in a larger study, 532 out of 2002 participants with prior COVID-19 reported increased (mostly systemic) AEs after either an mRNA or vector-based (AZD1222/AstraZeneca) vaccine.[5]

These preliminary studies suggest a need for further investigation into the effect of prior COVID-19 history on vaccine-related AEs. Consideration of whether time between previous infection and vaccination administration or the presence of 'Long-COVID'[6-8] can predict AEs, is also warranted. This information is important, as it could assist in identifying individuals who are more likely to experience side effects to COVID-19 vaccines. Furthermore, there are public health implications with regards to vaccine hesitancy, which is somewhat driven by fear of AEs.[9-11] As part of a longitudinal observational study of COVID-19 in healthcare workers in North-East England, we evaluated AEs following first doses of BNT162b2/Pfizer vaccine, with particular reference to previous COVID-19 and Long-COVID.

Method

National Health Service (NHS) workers (employed by 3 North-East Trusts in the UK) completed an electronic survey on AEs following COVID-19 vaccination. The survey captured self-reported COVID-19 symptoms, PCR/antibody results, and AEs following the first dose. The FDA Toxicity Grading Scale[12] (with simplified language) was modified allowing participants to self-report AEs for severity (mild/moderate/severe/very severe),

duration (≤24 hours/>24 hours) and onset (≤24 hours/>24 hours); lymphadenopathy was included as an additional symptom.

A composite score for symptom nature and severity was calculated, to provide an overall estimate of AE-related morbidity, for the former by adding number of moderate/severe symptoms, and the latter by multiplying this by symptom duration. Individual and composite AE scores were compared between those with and without a prior history of COVID-19, as indicated by self-reported prior positive antibody and/or PCR result. Long-COVID was defined as symptoms persisting >2 months to vaccination. Effects of age, gender and time between past infection to vaccination were also considered.

Respondents who had permitted laboratory results to be accessed (SARS-CoV-2 PCR and antibody), formed a subgroup for sensitivity analysis. Statistical analysis was carried out using JASP v0.14.1.0. Composite scores were compared using 2-way ANCOVA. Multivariable logistic regressions were performed to identify the relationship between COVID-19 status and the presence of moderate/severe symptoms in each category, and the Bonferroni correction applied to the resulting significance and confidence intervals. The study was approved by Cambridge East Research Ethics Committee.

Results

Of 974 healthcare workers (aged 19-72-years) responding to the survey and providing complete data for analysis, 265 (27%) participants (84% female, mean age 48.9) reported a prior positive PCR and/or antibody result, and 709 (80% female, mean age 47.0) had no COVID-19 history. Within the previous COVID-19 group (symptoms median 8.9 months

before vaccination), 30 (83% female, mean age 48.8) complained of Long-COVID (median duration 9.3 months, range 2.8–10.4).

Figure 1A shows frequencies of each symptom by COVID-19 status. The proportion of participants reporting at least one moderate-to-severe symptom was higher in the previous COVID-19 group (56% v 47%, OR=1.5 [95%CI, 1.1–2.0], p=.009). Symptom onset was mostly within 24 hours (75%) with no onset >48 hours. Number and total duration of reported symptoms was greater in women (1.24 (1.67) v 0.84 (1.46) symptoms, d=0.25 [0.09–0.42], p=.002; 2.10 (2.99) v 1.39 (2.54) symptom-days, d=0.22 [0.09–0.42], p=.001) and significantly decreased with age (symptoms: r_s=-0.25, p<.001; symptom-days: r_s=-0.24, p<.001). After controlling for age and sex, higher symptom number (1.61 (2.26) v 0.89 (2.02) symptoms, d=0.34 [0.20-0.49], p<.001) and severity (2.7 (6.65) v 1.5 (2.21) symptom-days, d=0.41 [0.27-0.55], p<.001) were significantly associated with reporting previous COVID-19.

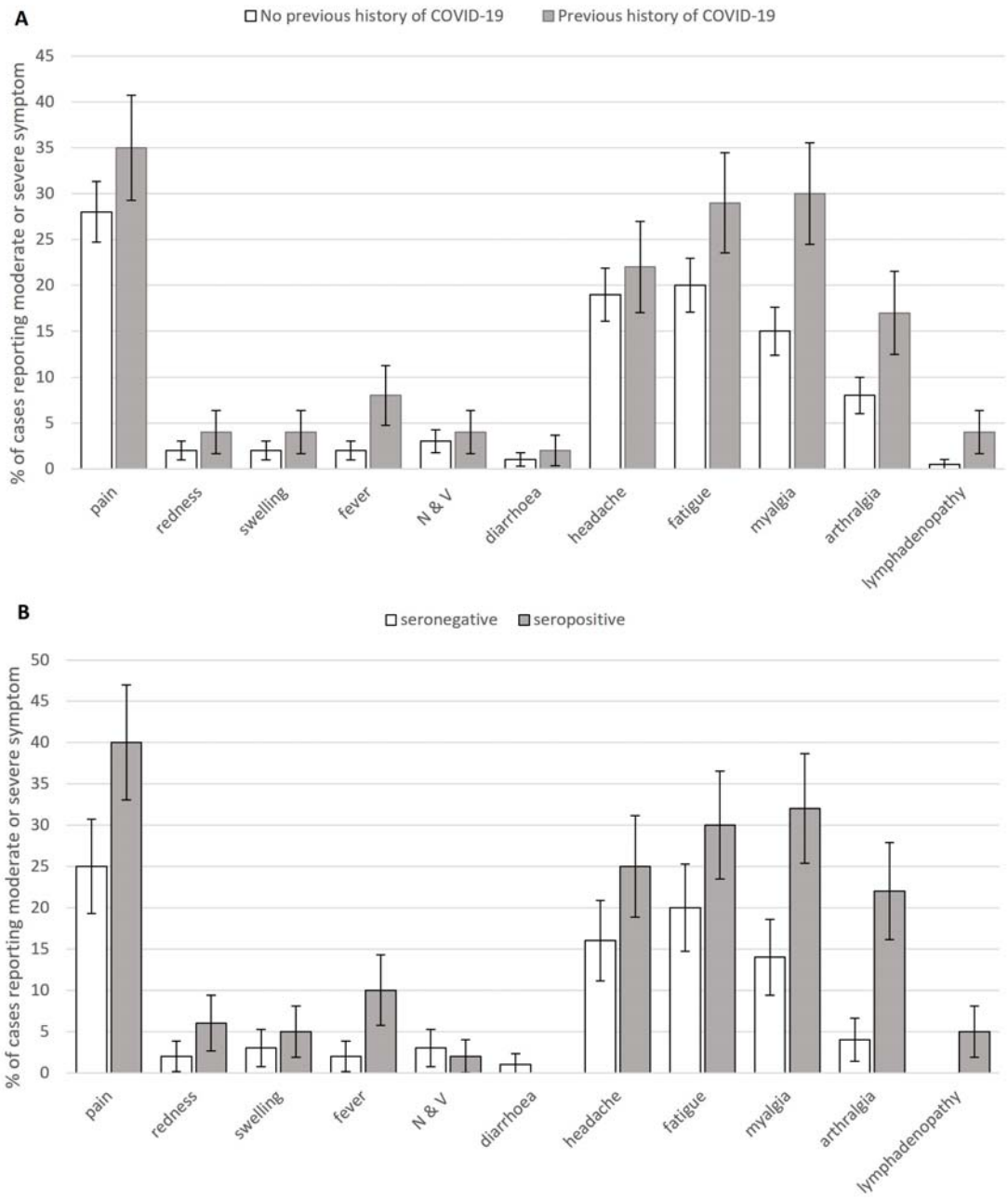

Figure 1. ***Moderate and Severe Symptoms by COVID-19 Status***: Percentage of cases reporting moderate or severe symptoms (95% CI) in those with and without a history of COVID-19. N & V: nausea and vomiting. Upper panel (A): entire cohort; lower panel (B): sensitivity analysis subset

Logistic regressions (Table 1) controlling for age and sex showed five systemic symptoms were significantly associated with previous COVID-19 status: fever, fatigue, myalgia, arthralgia and lymphadenopathy. Arthralgia was regularly co-reported with myalgia (87 cases) but rarely alone and was not independently associated (OR 1.4 [95%CI 0.86–2.37], p=0.49) with COVID-19 exposure once myalgia was controlled for. Neither local nor gastrointestinal symptoms were significantly associated with previous COVID-19 history.

	Whole cohort		**Sensitivity Analysis Subset**	
	Odds Ratio (95% C.I.)	p	Odds Ratio (95% C.I.)	p
Fever	2.87 (1.10 – 7.51)	.044	5.68 (0.69 – 46.65)	.32
Fatigue	1.78 (1.12 – 2.84)	.011	2.17 (0.85– 5.54)	.31
Myalgia	2.34 (1.44 – 3.88)	<.001	3.18 (1.16 – 8.69)	.02
Arthralgia	2.25 (1.23 – 4.12)	.004	7.06 (2.05 – 36.91)	.01
Lymphadenopathy	5.18 (1.19 – 22.63)	.033	****	****
Local Pain	1.55 (0.99 – 2.40)	.09	2.28 (0.96 – 5.43)	.11
Local Redness	2.93 (0.84 – 10.20)	.24	3.92 (0.43 – 35.79)	>.99
Local Swelling	2.0 (0.64 – 6.27)	.14	2.1 (0.29 – 15.33)	>.99
N & V	1.47 (0.48 – 4.42)	>.99	0.72 (0.05 – 8.81)	>.99
Diarrhoea	2.35 (0.30 – 18.25)	>.99	****	****
Headache	1.31 (0.80 – 2.15)	>.99	1.78 (0.65 – 4.83)	>.99

**** No model could be calculated due to absence of cases in this cohort. In all cases age and gender were included in the null model as nuisance variables. Adjusted P values and adjusted confidence intervals corrected (Bonferroni) for 11 outcomes in each case.

Table 1. ***Results of Logistic Regression Analyses***: Logistic regressions showing those symptoms significantly predicted by previous history of COVID-19 after controlling for differences in age and gender and with p values and confidence intervals corrected (Bonferroni) for multiple comparisons.

Symptom number and duration was not significantly higher in those with Long-COVID after accounting for gender and age effects and no individual symptom was significantly associated with this condition. Importantly, among those with prior COVID-19, there was no significant relationship between illness-vaccine time interval and either composite score (r_s=0.09 p=.44 for symptoms; r_s=0.10, p=.42 for symptom–days) nor any difference in mean time interval based on presence of any of the symptoms (all p>0.05).

For the sensitivity analysis, 412 participants had verified PCR/antibody results. Of this subgroup, 228 (55%) were PCR/antibody negative (80% female, mean (SD) age 47.0 [11.1]) and 184 (45%) PCR or antibody positive (91% female, mean (SD) age 47.3 [11.5]). Nine (5%) complained of Long-COVID (range 2.8–10.4 months). The pattern of results was broadly replicated in this subgroup analysis (Figure 1B), with more previous-COVID-19 individuals reporting at least one moderate symptom (63% v 43%, OR=2.2 [1.2–4.0], p=.006) and previous-COVID-19 being associated with higher symptom number (1.81 (3.09) v 0.85 (4.12) symptoms, d=0.25 [0.05–0.44] p=.012) and severity (3.0 (8.3) v 1.5 (5.6) symptom days d=0.2 [95% CI 0.02–0.41], p=.0350). Only myalgia and arthralgia remain as significant outcomes once multiple comparisons were controlled for though pattern of outcomes remains similar.

Discussion

This study of healthcare workers demonstrated that prior COVID-19 infection, but not Long-COVID, is associated with increased risk of AEs including lymphadenopathy following BNT162b2/Pfizer vaccination, although there was no relationship with duration since COVID-19 illness. Women and younger individuals were also more likely to experience vaccine-related AEs. Our findings add to other reports supporting wider understanding of AEs following COVID-19 vaccination.[3-5] Importantly, given the hesitancy surrounding COVID-19

vaccination,[9-11] our findings may help inform those with previous COVID-19, including Long-COVID, of increased susceptibility to certain AEs. Our study also adds weight to the question of whether a second dose of mRNA vaccine is necessary in those with previous COVID-19, assuming effective immunity is established after the first dose.[3,14] This is relevant, given that another study has suggested worse AEs following the second dose.[5]

Our study has several limitations. Firstly, some non-responder bias[13] is likely, with 27% of participants reporting previous COVID-19. This is slightly higher than in UK healthcare workers.[15] Nevertheless, the sample was broadly representative of UK healthcare employees and likely generalizable. Secondly, information on AEs was gathered via self-reported questionnaires, and hence subjective. Thirdly, PCR and antibody results were self-reported. We addressed this via a sensitivity analysis on a subset of participants with laboratory data available, which mostly confirmed the findings in the entire sample. Finally, the numbers with Long-COVID were relative small for comparison.

In conclusion, this large study shows an association of previous COVID-19 with increased AEs and will help those with previous COVID-19 infection understand better what to expect following vaccination.

Author Contributions

DRC/CK/RKR conceived the study and DRC is chief investigator of CHOIS. RKR acted as site principal investigator. DRC/RKR/CW contributed to the study protocol, design, and data collection. JR/RKR/DRC did the statistical analysis. RKR/JR/DRC prepared the manuscript. All authors critically reviewed and approved the final version.

Declarations of Interest

No conflicts of interest.

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TAB 13

See Tab 12 at

Abstract Pg. 6

TAB 14

We have archived this page and will not be updating it.

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Archived 21: National Advisory Committee on Immunization statement: Interim guidance on booster COVID-19 vaccine doses in Canada [2021-10-29]

Published: October 29, 2021

Notice to reader

This is an archived version. Please refer to NACI statements and publications for current COVID-19 vaccine statements.

On this page

Preamble

The National Advisory Committee on Immunization (NACI) is an External Advisory Body that provides the Public Health Agency of Canada (PHAC) with independent, ongoing and timely medical, scientific, and public health advice in response to questions from PHAC relating to immunization.

In addition to burden of disease and vaccine characteristics, PHAC has expanded the mandate of NACI to include the systematic consideration of programmatic factors in developing evidence-based recommendations to facilitate timely decision-making for publicly funded vaccine programs at provincial and territorial levels.

The additional factors to be systematically considered by NACI include: economics, ethics, equity, feasibility, and acceptability. Not all NACI Statements will require in-depth analyses of all programmatic factors. While systematic consideration of programmatic factors will be conducted using evidence-informed tools to identify distinct issues that could impact decision-making for recommendation development, only distinct issues identified as being specific to the vaccine or vaccine-preventable disease will be included.

This statement contains NACI's independent advice and recommendations, which are based upon the best current available scientific knowledge. This document is being disseminated for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph. Recommendations for use and other information set out herein may differ from that set out in the product monographs of the Canadian manufacturers of the vaccines. Manufacturer(s) have sought approval of the vaccines and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

Background

NACI's recommendations on booster doses will be based on the decision-making framework outlined in this document, triggered by evidence of the need for (e.g., evidence of decreased vaccine effectiveness against severe illness and/or infection depending on the population) and

benefit of (e.g., safety and effectiveness) a booster dose in the Canadian context.

The public health goal of Canada's pandemic response is to minimize serious illness and death while minimizing societal disruption as a result of the COVID-19 pandemic. COVID-19 vaccines have played a vital role in the response and have been shown to be very effective against symptomatic laboratory confirmed SARS-CoV-2 infection, severe disease, hospitalization, and death from COVID-19. Unfortunately, the COVID-19 pandemic is ongoing and continues to cause significant morbidity and mortality, as well as social and economic disruption in Canada and worldwide (including impacts on health system capacity). COVID-19 vaccination with a complete primary series is critical. Fully vaccinated individuals have much lower rates of SARS-CoV-2 hospitalizations, ICU admission and mortality compared to those who are unvaccinated. In addition, those who have been vaccinated are less likely to get infected, and therefore less likely to transmit SARS-CoV-2 infection to others. NACI continues to strongly recommend that all individuals in the authorized age groups should be immunized with a primary series of an authorized COVID-19 vaccine, and preferably with mRNA COVID-19 vaccines (Moderna Spikevax and Pfizer-BioNTech Comirnaty) [1].

To date, COVID-19 vaccines have been shown to maintain high vaccine effectiveness (VE) against serious illness, hospitalization, and death from COVID-19 in most populations. However, evidence is emerging that VE against asymptomatic infection and mild COVID-19 disease may decrease with time, and that currently authorized COVID-19 vaccines may be less effective against the highly transmissible Delta variant (B.1.617.2), which could contribute to increased transmission of infection. Therefore, an additional or booster dose may be needed to obtain more durable protection in some populations.

Evidence from clinical trials suggests that booster doses of mRNA vaccines given six months after the primary series elicited a robust immune response against the wild type strain and variants of Concern (VoC), with titres often higher after the booster dose than after the primary series. Real-world data from Israel suggest that a booster dose provides good short-term effectiveness against SARS-CoV-2 infection and has a safety profile comparable to that observed after the second dose of the vaccine.

The intent of a booster dose is to restore protection that may have decreased over time to a level that is no longer deemed sufficient in individuals who initially responded adequately to a complete primary vaccine series. This is distinguished from the intent of an additional dose which might be added to the standard primary vaccine series with the aim of enhancing the immune response and establishing an adequate level of protection. For example, evidence suggests that compared to the general population, individuals who are moderately to severely immunocompromised have lower immune responses to COVID-19 vaccines. Therefore, NACI has

recommended that moderately to severely immunocompromised individuals in the authorized age groups should be immunized with a primary series of three doses of an authorized mRNA vaccine.

Historically in other vaccine programs, it can take years of post-market use to determine the optimal intervals and dose number needed for a complete primary series to sustain long-term protection. At present, there is scientific debate about whether a third dose for COVID-19 vaccines truly constitutes a booster dose in the traditional sense. NACI continues to monitor the emerging scientific data on how best to use these vaccines, and will study the important differences between a primary series (to establish strong immune memory), versus a booster (to stimulate the memory response once protection has truly waned). Over time, it may be learned that a short 2-dose primary series, with a booster at least 6 months after the second dose, can in fact be adjusted to achieve durable protection with a more streamlined primary series. For example, NACI has already highlighted benefit in terms of longer-term protection when the second dose is provided at least 8 weeks after the first dose. In this guidance document, additional doses of COVID-19 vaccines after the authorized series are being described as booster doses but it should be acknowledged that over time, what defines an optimal primary series could also evolve and be refined.

NACI's recommendations on booster doses are occurring in the context of the World Health Organization's (WHO's) call for global vaccine equity, and take into consideration conclusions in its Interim statement on booster doses for COVID-19 vaccination including the call for evidence-based decisions: "Introducing booster doses should be firmly evidence-driven and targeted to the population groups in greatest need. The rationale for implementing booster doses should be guided by evidence on waning vaccine effectiveness, in particular a decline in protection against severe disease in the general population and in high-risk populations, or due to a circulating VoC. To date, the evidence remains limited and still inconclusive on any widespread need for booster doses following a primary vaccination series. The focus remains on urgently increasing global vaccination coverage with the primary series [2]." NACI's recommendations on booster doses in those who have completed a primary series will be triggered by evidence on the need for a booster dose (in key populations at increased risk or in the general population), as well as the benefit of a booster dose.

Internationally, several countries, including the United States [3], the United Kingdom [4], France [5], and Germany [6], have recently recommended booster doses of COVID-19 vaccines at least 6 months following a primary vaccine series for certain high-risk groups, such as older adults, long-term care residents, and healthcare workers. Israel initially recommended a booster dose in

adults 60 years of age and older and subsequently recommended a booster dose for the general population 12 years of age and over, at least 5 months following the primary series administered at the authorized dosage interval [7].

Countries that have rolled out primary series of COVID-19 vaccines using different vaccines and different intervals between doses of vaccines are experiencing different levels of protection over time, which is to be expected. NACI's recommendations for booster doses will differ from recommendations in other countries because of differences in a number of contextual factors including:

- the vaccine product(s) used to complete the primary series,
- the time that has elapsed since last dose in the primary series,
- the intervals between the first and second doses in the primary series,
- indirect protection from high vaccination coverage, and
- the use of other public health measures such as masking and physical distancing policies.

NACI reviewed available evidence on the factors presented in Table 1 in the context of the current Canadian epidemiology, vaccine programs, and vaccine schedules. Over 80% of Canadians aged 12 years and older have completed a primary COVID-19 vaccine series. Most are at a lower risk of declining protection due to receipt of mRNA vaccines (following NACI's preferential recommendation for mRNA vaccines [1]) or a combination of vaccine products in some instances (following NACI's recommendation on the interchangeability of authorized COVID-19 vaccines [8]), and at intervals longer than the manufacturer authorized intervals (following NACI's recommendation for extended intervals [9]). Furthermore, the Moderna Spikevax vaccine, authorized for use in Canada, appears to offer more durable protection against severe disease and asymptomatic infection [10]. There is no evidence of decreasing protection over time against severe disease in the general Canadian population who have been vaccinated against COVID-19 disease. To date, Health Canada has not authorized booster doses of COVID-19 vaccines. NACI will continue to closely monitor the evidence and encourages a coordinated evidence-informed national approach.

On September 28, 2021, NACI recommended that a booster dose of an authorized mRNA vaccine should be offered to all long-term care residents and seniors living in other congregate settings who have received a primary COVID-19 vaccine series (with the primary series being a homologous or heterologous schedule using mRNA and/or viral vector vaccines) at an interval of at least 6 months after the primary series has been completed [11]. This population was also initially prioritized as a key population to receive initial doses of a primary series of COVID-19 vaccines based on evidence of an increased risk of severe illness and death and increased risk of exposure to SARS-CoV-2. The recommendation for a booster dose was triggered by increases in COVID-19 cases and outbreaks in long-term care homes with signs emerging that protection

from vaccination might not persist as long in this population compared to other populations in Canada. In addition, long-term care residents are at high risk of exposure to SARS-CoV-2 due to their congregate living environment and at high risk of severe outcomes due to age and underlying health status. Longer time since last dose and shorter intervals between doses in the primary series, as well as older age/immunosenescence, also contribute to waning vaccine protection against infection and severe outcomes in this population. Assessment of the need for and benefit of a booster dose in other populations based on the criteria in Table 1 in the Canadian context and NACI's decision-making framework inform and guide NACI's recommendations herein subsequent to the Rapid response: Booster doses in long-term care residents and seniors living in other congregate care settings.

Guidance objective

The objective of this advisory committee statement is to provide evidence-informed guidance on the equitable, ethical, and effective use of additional doses of authorized COVID-19 vaccines in the Canadian context based on the need for, and benefit of, booster doses to minimize serious illness and deaths while minimizing societal disruption as a result of COVID-19.

Methods

The evidence pertaining to COVID-19 and COVID-19 vaccines is rapidly evolving. NACI reviewed the decision-making framework and evidence on the need for and benefit of additional doses of COVID-19 vaccines in various populations on September 7, 14, 27, October 12 and 15, 2021. NACI consulted with the Public Health Ethics Consultative Group (PHECG) on the ethical implications of booster dose recommendations in various populations on September 2 and 21, 2021. Following a comprehensive review of available evidence and consultations with the provinces and territories through the Canadian Immunization Committee (CIC) and the Chief Medical Officers of Health (CMOH), NACI made and approved these recommendations on October 22, 2021.

NACI's decision-making framework on booster doses was modified from NACI's original prioritization framework of key populations for COVID-19 vaccination. The evidence supporting the development of the original framework is summarized in NACI's previously published guidance:

1. Preliminary guidance on key populations for early COVID-19 immunization (November 2020)
2. Guidance on the prioritization of initial doses of COVID-19 vaccines (December 2020)
3. Guidance on the prioritization of key populations for COVID-19 immunization (February 2021)

To guide ethical decisions that are based on evidence and on clear, transparent criteria, NACI developed a decision-making framework for booster doses modified from its original evidence-informed prioritization framework for COVID-19 vaccination [12]. NACI's recommendations on booster doses will be based on this decision-making framework, triggered by evidence of the need for, and benefit of, a booster dose in the Canadian context (Table 1).

Key populations prioritized for a primary series of COVID-19 vaccination in NACI's original framework were based on evidence of increased risk of severe illness and death from COVID-19 and increased risk of exposure to SARS-CoV-2, summarized in NACI's 2020 guidance [12] [13] [14] [15] [16] [17]. NACI's decision-making framework on booster doses also considered populations with emerging evidence suggesting decreased protection from the primary series (e.g., vaccination with only viral vector vaccines, a longer time since completion of the primary series, shorter interval between doses of the primary series). NACI's recommendations are also guided by ethics and rooted in the foundational elements of equity, feasibility and acceptability

Table 1. Underlying factors for consideration based on evolving evidence to determine the need for and benefit of a booster dose of COVID-19 vaccine in various populations

Underlying factors for consideration	Evidence reviewed to determine the need for and benefit of a booster dose of COVID-19 vaccine
Risk benefit analysis	• Risk of severe illness and death • Risk of exposure (including ability to physically distance and access to infection prevention and control • measures and healthcare) • Risk of transmission to vulnerable populations • Risk of societal disruption
Vaccine characteristics in different groups against wild-type and VoC	• Duration of protection • Immunogenicity • Efficacy/effectiveness • Safety and reactogenicity of boosters • Effect of vaccine in preventing transmission
Vaccine supply/types/intervals	• Number and type of available vaccines • Initial vaccination series (type, interval between doses, time since initial series)

Underlying factors for consideration	Evidence reviewed to determine the need for and benefit of a booster dose of COVID-19 vaccine
COVID-19 epidemic conditions	• Circulation of SARS-CoV-2 wild-type and VoC • Breakthrough cases, outbreaks • Case rates and implications for health system capacity

NACI recommendations on the use of COVID-19 vaccines are available.

Data on COVID-19 vaccination coverage and doses administered in various key populations in jurisdictions across Canada is available.

Further information on NACI's process and procedures is available elsewhere [18] [19].

Summary of evidence

Vaccine principles for booster doses

The immune responses to a vaccine are determined by a number of factors including vaccine type, interval between doses in the primary series, time since completion of the primary series, and underlying health status and age.

Higher antibody titres occur with the Moderna vaccine compared to the Pfizer-BioNTech vaccine and both have a higher titre than the viral vector vaccines [20]. A longer interval between the first and second doses also results in higher titres [21] [22]. Although correlates of protection against SARS-CoV-2 have not yet been clearly defined, a higher antibody titre appears to be associated with longer duration of protection against symptomatic infection, including against VoC.

While there are various studies showing decreasing levels of circulating neutralizing antibodies as well as binding antibodies over time, studies also show that the mRNA vaccines elicit a memory B and T cell response [23] [24]. Even if circulating antibodies decrease, future exposure to SARS-CoV-2 is expected to drive a 'recall' response and long-lived memory T and B cells will help produce new antibodies. Therefore, even if a vaccinated individual is infected with SARS-CoV-2, vaccine-induced immunity through immune memory is expected to help to prevent progression to severe disease in most individuals, although the duration of immune memory is not known at this time.

For more information on vaccine principles, please consult the chapter on basic immunology and vaccinology in the Canadian Immunization Guide.

Recent COVID-19 epidemiological trends

There is currently a resurgence of COVID-19 cases in regions of Canada fuelled by the highly transmissible Delta variant. Outbreaks continue to occur in multiple settings, including long-term care homes and retirement residences, industrial settings, school and daycare settings, as well as other settings that are enclosed and crowded, and can be a significant source of spread of SARS-CoV-2 infection. School and daycare settings have experienced an increasing number of outbreaks since mid-August [25] due in part to a large proportion of ineligible and unvaccinated population (children under 12). In early August, the rate of active cases started rising in First Nations communities for the first time since mid-January 2021, and was 4.2 times higher than the rate in the general population as of October 12 [26]. As such, this NACI guidance is provided in the midst of the fourth COVID-19 pandemic wave driven by the Delta variant.

Canadian surveillance data up to October 2, 2021 shows that rates of new SARS-CoV-2 infection are highest among persons who are unvaccinated and lowest in persons who are fully vaccinated. Unvaccinated persons have also had much higher rates of hospitalizations, ICU admission and deaths compared to those fully vaccinated. Compared to those who are fully vaccinated, the rate of SARS-CoV-2 infection in unvaccinated persons was 8 times higher and the rate of COVID-19 related hospitalization in unvaccinated persons was 25 times higher, on average, for each week during the period of September 5 to October 2, 2021. While the incidence rate of infection is much lower in fully vaccinated people, it increased slightly across all age groups since mid-July, but has declined as of the week of September 26 - October 2, 2021 for all age groups.

Compared to fully vaccinated younger age groups, fully vaccinated cases 80 years of age and over have the highest rates of hospitalizations and deaths, followed by those aged 70 to 79 years. Among the fully vaccinated, these older age groups have the highest proportion of cases who are hospitalized and who have died from COVID-19. The weekly proportions of fully vaccinated cases who are hospitalized or who died has remained relatively low and stable since mid-July and the case fatality has decreased more recently in the older age groups, indicating that fully vaccinated people who become infected do not appear to be getting more severely ill over time.

Duration of COVID-19 vaccine protection against infection

Emerging evidence suggests a decrease in COVID-19 vaccine protection against SARS-CoV-2 infection over time following completion of the primary series. However, it can be challenging to distinguish potential signals of waning from increasing case numbers driven by community spread during the fourth wave of the pandemic and the rise of the Delta variant. Evidence on increasing incidence of infection in vaccinated individuals coincides with periods when the Delta variant predominated, and estimates of lower VE may be a reflection of decreased effectiveness against the Delta variant rather than waning in COVID-19 vaccine protection. Further, increasing incidence in vaccinated individuals may also be observed in areas with lower vaccine coverage as

a result of overall higher community rates driven by SARS-CoV-2 infection in the unvaccinated population. Continued research evaluating VE is needed to accurately determine trends in protection over time, as well as to learn more about the effects on transmission and the magnitude, if any, of potential decrease in protection. Immunogenicity data alone is insufficient to assess waning of protection against disease, and may not be indicative of protection against severe outcomes. To date, protection against severe COVID-19 outcomes, such as hospitalization and death, consistently appear to be more durable than protection against infection. There are some data that suggest decreases in protection may be greater in older age groups and in individuals with clinical risk factors for more severe outcomes [27] [28].

A recent rapid review [29] on vaccine efficacy/effectiveness over time in COVID-19 vaccinated individuals identified seven studies that examined vaccine efficacy/effectiveness longitudinally over a period of 4 months or longer and provided both baseline and follow-up data. Studies that reported on confirmed infection [30] [31] [32] as an outcome generally indicated a decrease in VE against SARS-CoV-2 infection at 4 and 6 months after primary series completion compared to 7 to 14 days after primary series completion. Trends were similar for studies reporting on symptomatic infection [27] [30] [33] [34]. In contrast, the studies that reported on COVID-19 related hospitalization [27] [31] [32] [35] and deaths [27] [30] [32] indicated that VE against severe COVID-19 outcomes remained stable over time thus far. These patterns were generally similar across vaccine products and in individuals over 60 years old. However, evidence was limited by the small number of heterogeneous studies, which were observational in design.

Studies on duration of protection have typically examined protection after a manufacturer-recommended dosing interval of 3 or 4 weeks between first and second doses for mRNA vaccines. It is currently uncertain how a longer interval between first and second vaccine doses in a primary series might affect the duration of protection. Provincial data from British Columbia and Quebec found that shorter intervals between doses in a primary series result in lower VE against SARS-CoV-2 infection and COVID-19 related hospitalizations compared to extended intervals. Further, emerging evidence suggests that shorter intervals between doses may be associated with lower VE against infection over time [27] [28]. Evidence to date suggests that delaying the second dose by several weeks leads to higher antibody titres and greater VE of the series [22] [36] [37] which is likely to result in a more durable immune response and longer protection over time.

It is currently unclear to what extent the duration of protection may vary by vaccine product. In general, VE against symptomatic SARS-CoV-2 infection and severe COVID-19 outcomes has consistently been somewhat lower with viral vector vaccines compared to mRNA vaccines [38]. Emerging data on effectiveness suggests that vaccine protection against infection and symptomatic disease decreases more quickly with viral vector vaccines in comparison to mRNA

vaccines, whereas the difference is less pronounced for severe disease [27] [28]. Limited real-world data from Canada and the United States suggests that protection from Moderna Spikevax may be more durable compared to Pfizer-BioNTech Comirnaty [28] [39], but more research is required.

There is limited evidence on duration of protection following a mixed COVID-19 vaccination schedule. Data from two studies indicate that VE for those who received a mixed schedule of AstraZeneca Vaxzevria/COVISHIELD followed by an mRNA vaccine is similar compared to those who received a complete series of mRNA vaccines [28] [40].

Despite some evidence of increasing risk of breakthrough infection over time, those vaccinated against COVID-19 with a two-dose series continue to demonstrate significantly lower odds of SARS-CoV-2 infection compared to unvaccinated individuals and, when infections occur, symptoms tend to be milder in vaccinated cases [41]. VE against severe COVID-19 outcomes with all vaccine types remains high, even in the context of the Delta variant. Breakthrough infections in vaccinated persons could contribute to ongoing transmission of SARS-CoV-2. Early evidence from when the Alpha variant predominated suggested that vaccinated individuals who became infected were less infectious [42]. The evidence on transmission with the Delta variant is less clear, with some studies suggesting the differences in viral load between vaccinated and unvaccinated persons who become infected may be less compared to when the Alpha variant was predominant [42] [43] [44] [45] [46].

Immunogenicity, safety, and effectiveness of COVID-19 vaccine booster doses

Ongoing manufacturer-sponsored trials on mRNA vaccines have reported higher titres following the third doses compared to those after the initial series [47] [48] of two doses (administered at manufacturer authorized intervals), suggesting that the higher titres produced by a booster dose may lead to longer lasting protection than the primary series administered at manufacturer authorized intervals. Early results also show a favourable reactogenicity profile for booster mRNA vaccine doses, similar to that of the second dose in the primary series [47] [48]. Evidence from these trial data is limited by small sample size (less than 350 participants in each published manufacturer-sponsored trial [49] [50]) and short duration of follow-up of study populations. Pfizer-BioNTech Comirnaty and Moderna Spikevax have filed submissions for booster doses ≥ 6 months after the primary series to Health Canada for regulatory approval as of October 1 and 5, 2021 respectively. The regulatory submission for a Moderna Spikevax booster dose is for half the current dosage of Moderna Spikevax primary series dose (i.e., a 50 mcg booster dose vs. 100 mcg full dose). The regulatory submission for a Pfizer-BioNTech Comirnaty booster dose is the same as the current dosage of the primary series dose for this vaccine (i.e., a 30 mcg booster dose).

Emerging real-world data from Israel's booster dose program with Pfizer-BioNTech Comirnaty indicates that a third dose (after a primary series using the manufacturer authorized interval of 21 days between doses) resulted in improved short-term vaccine effectiveness against infection and severe illness [51]. In one Israeli study of individuals ≥ 60 years of age, a booster dose of Pfizer-BioNTech Comirnaty at least 5 months after the primary series decreased the relative risk of confirmed SARS-CoV-2 infection by 11.3-fold and of severe illness by 19.5-fold at 12 or more days from the booster dose, compared to those with two doses [52]. An extension of this analysis [53] found that, compared to a two-dose series, a booster dose resulted in about a 10-fold reduction in confirmed infection rates in persons ≥ 16 years of age. In another Israeli study of persons ≥ 40 years of age, those who received a third dose had a 70 to 84% reduction in the odds of testing positive for SARS-CoV-2 infection 14 to 20 days after receiving the booster compared to people who received two doses of Pfizer-BioNTech Comirnaty [54]. There are no data currently on the long-term effectiveness of booster doses so it remains unknown at this time how long benefit might last. The effect of booster doses on transmission is unknown.

Studies evaluating boosters following different primary series vaccine schedules are ongoing [55] [56]. Unpublished data from the Cov-Boost trial presented to the United Kingdom's Joint Committee on Vaccination and Immunisation (JCVI) suggest that mRNA booster doses are generally well tolerated and provide a strong booster effect regardless of the vaccine used in the primary series [4]. Similarly, recent data from the US National Institutes of Health "Mix and Match" trial indicates that heterologous booster doses given at least 12 weeks following completion of the primary series of mRNA vaccines or Janssen COVID-19 vaccine were well-tolerated and immunogenic. Additionally, those who received an mRNA booster following a dose of Janssen COVID-19 vaccine had higher antibody titres compared to those who received a second dose of Janssen as a booster [57].

The safety and effectiveness of a third dose in persons who had a previous SARS-CoV-2 infection is currently unknown.

Rare cases of myocarditis and pericarditis following vaccination with COVID-19 mRNA vaccines have been reported, more frequently after the second dose compared to the first dose, and more commonly in younger males and adolescents. Canadian data also suggest that myocarditis/pericarditis occur more frequently after Moderna Spikevax compared to Pfizer Comirnaty COVID-19 vaccines. The rate of myocarditis and pericarditis following a booster dose of a COVID-19 mRNA vaccine is currently unknown. Initial surveillance data from Israel up to October 10, 2021 has reported 17 cases of myocarditis or peri-myocarditis out of approximately 3.7 million booster doses of Pfizer-BioNTech Comirnaty administered [51]. In Israel, this rate is

lower than observed after the second dose, but higher than observed after the first dose. Data collection is ongoing. NACI will continue to monitor the evidence and update recommendations as needed.

Optimal primary series to booster dose interval

There are currently limited data to determine the optimal interval between the completion of the primary series and administration of the booster dose. Most studies on mRNA COVID-19 vaccine booster doses have used an interval of 6 months or more following the completion of the primary series, although some have used an interval as short as 3 months [55] [56]. Submissions filed with regulatory authorities in the US, EU and Canada are for 6 months or more following the second dose, which was the interval used in booster doses trials for Pfizer-BioNTech Comirnaty and Moderna Spikevax [49] [50]. However, it is currently unknown at what interval a maximum boosting effect is achieved. For older adults who may have a decrease in protection over time, delaying the booster dose will increase the period during which individuals may have reduced protection against SARS-CoV-2 infection, although to date protection against severe outcomes has been shown to be more durable than protection against infection.

Summary of primary COVID-19 vaccine series that have been used in Canada to date

Vaccine types received in the primary series in Canada

As of October 9, 2021, 82% of eligible Canadians have been fully vaccinated with a COVID-19 vaccine, while 87% have received at least one dose. Of those fully vaccinated, the majority received a complete two-dose series of mRNA vaccines. A small percentage received a complete series with a viral vector vaccine. At least 469,371 Canadians have received a viral vector vaccine primary series and 1,395,324 Canadians have received a heterologous primary series containing both a viral vector vaccine and an mRNA vaccine. Almost all viral vector primary series were with AstraZeneca Vaxzevria/COVISHIELD vaccines. Data on vaccination coverage by vaccine product was missing for two provinces.

Refer to COVID-19 vaccination in Canada for the most current information on vaccination coverage.

Intervals between doses in the primary series of COVID-19 vaccines in Canada

Shorter intervals between doses results in lower antibody titres which may wane to below protective levels over time. While individuals who received their second dose in the primary COVID-19 vaccine series at a shorter interval from the first dose were well protected in the short-term, they may have produced lower antibody levels, which may decrease over time compared with those who had a longer interval between doses.

Intervals between the first and second doses of a two-dose primary series of COVID-19 vaccines varied across Canada as vaccine supply and evidence evolved. Groups prioritized for vaccination early in the vaccine roll-out [12] often received their vaccines using the manufacturers' recommended interval of 21 days for Pfizer-BioNTech Comirnaty and 28 days (or as short as 21 days) for Moderna Spikevax. Subsequently, intervals between doses were extended up to 16 weeks to optimize early vaccine rollout and population protection in Canada in the context of limited vaccine supply [9]. As vaccine supply was no longer limited, and in the context of the increasing prevalence of the Delta variant, jurisdictions accelerated second doses with shorter intervals. Aggregated vaccination coverage data obtained from provincial and territorial vaccination registries up to August 14, 2021, showed that an interval of 7-11 weeks between first and second doses was the most common dosing interval across all vaccine products. Dosing intervals varied widely by jurisdiction and age group. Most notably, 66% of vaccinated adults aged 80 years old and older had an interval of 12 weeks or more between first and second dose, while 9% had an interval of 28 days or less. Data on vaccination coverage by dosing interval was missing for one province.

There is evidence that the Moderna Spikevax vaccine remains efficacious against severe disease and asymptomatic infection at more than 5 months when given at the authorized interval of 28 days between doses [10]. There is evidence that while the Pfizer-BioNTech Comirnaty vaccine prevents COVID-19 for up to 6 months, there is a gradual decline in efficacy when given at the authorized interval of 21 days between doses [34]. Though limited data suggests that protection from Moderna Spikevax may be more durable compared to Pfizer-BioNTech Comirnaty [28] [39], more research is required.

Time since completion of primary COVID-19 vaccine series in Canada

As noted above, protection against infection may decrease with time since completion of the second dose of vaccine. Key populations at highest risk of severe illness due to COVID-19 and/or highest risk of exposure to SARS-CoV-2 (e.g., residents and staff of congregate living settings that provide care for seniors, older adults, frontline healthcare workers, adults in or from Indigenous communities) were prioritized to receive COVID-19 vaccines earlier than others when initial vaccine supply was limited [12]. Therefore, many in these populations would have completed their primary series longer than 6-8 months ago. A number of these key populations received their second doses between January and April 2021. The vast majority of Canadians who are fully vaccinated completed their primary series in June or July 2021 (84%). Only 4% received their second doses between January and April 2021. Data on vaccination coverage by time since last dose was missing for one province.

Ethics, equity, feasibility and acceptability considerations

Ethics

Advice provided to NACI by the PHAC Public Health Ethics Consultative Group (PHECG) on the ethical implications of booster dose recommendations included the following [58] [59]:

- Decisions about extending boosters ought to be evidence-informed and fair, and clearly communicate why and when groups will become eligible for boosters. It is necessary to be clear about the rationale for offering an additional dose, including how the criteria fit within, and are consistent with, a broader booster framework, if and when such a recommendation is made.
- Besides a general duty to protect the public's health, Canada also has a duty to protect the most vulnerable. The precautionary principle supports offering a booster dose of a COVID-19 vaccine to those who are at greatest risk of serious harms due to COVID-19, prior to a significant degree of waning VE against severe outcomes being observed.

Equity

Global equity

- On September 8, 2021 the WHO called for a global moratorium on booster doses until at least the end of 2021, to enable every country to vaccinate at least 40 percent of its population [60]. NACI acknowledges the importance of global equity in this pandemic, although global vaccine supply considerations are outside the purview of NACI's mandate. As advised by the PHECG, global vaccine equity requires that need (e.g., risk of severe illness and death and risk of exposure) be taken into account when allocating vaccines. This includes prioritizing high-risk groups globally who have not yet received first or second doses over individuals who are at lower risk due to having completed a primary vaccine series [58].

Domestic equity

- Inter-jurisdictional equity is also a relevant consideration both for reasons of promoting fairness and fostering trust. As advised by the PHECG, consistency and transparency in public health messaging and programs contribute to public trust in public health advice. Equity may not necessarily require a uniform response across all jurisdictions, since there are a variety of ethically-relevant factors that could justify triggering a recommendation for one jurisdiction but not in another. For example, in order to offer equitable protection against risk of COVID-19-related harms, disparate recommendations across jurisdictions may be justified when the populations in these jurisdictions face disparate levels of risk [58]. This includes the continued allocation of resources to encourage high acceptance and uptake of the primary series, which offers the most benefit against severe outcomes and deaths due to COVID-19, for those who have not yet received the vaccine. However, where possible,

alignment across jurisdictions is expected to positively impact inter-jurisdictional equity and public trust in public health advice.

Feasibility

- COVID-19 vaccine supply in Canada has increased and mechanisms for distributing and administering vaccines have been established. However, if boosters are administered all at once for the general population, there may be operational challenges with implementation. Consideration should also be given to minimizing wastage of product reaching its expiry date and open vials that need to be used within a specified period of time.

Acceptability

- According to survey data from August 2021, there is generally high acceptability for COVID-19 booster doses amongst Canadians. Approximately 80% of individuals, regardless of vaccination status, are willing to get an annual booster or booster doses now or within the next year; and those aged 65 or older are the most likely to be willing to take a booster shot (92%) [61] [62].
- Of those who are already fully vaccinated, around 80-93% are willing to get a booster dose [61] [63]. Of those who received a mixed schedule with AstraZeneca and an mRNA COVID-19 vaccine, 58% agreed to get a third dose if studies show that a third dose is required [64].
- Most Canadians (74%) agree that the priority for vaccines should be first doses for those who want them before making booster shots available [63].

Refer to NACI's previous guidance for a comprehensive overview of the ethical, equity, feasibility and acceptability considerations for prioritizing key populations for COVID-19 vaccination [12] [13] [16] [17].

Recommendations

Please see Table 2 for an explanation of strong vs discretionary NACI recommendations.

NACI strongly reiterates its previous evidence-informed recommendations for the primary series of COVID-19 vaccines in all authorized age groups:

1. NACI preferentially recommends [1] that a complete series with an mRNA COVID-19 vaccine should be offered to individuals in the authorized age group without contraindications to the vaccine. (Strong NACI Recommendation)

Additional details are available in the NACI statement on Recommendations on the use of COVID-19 vaccines.

2. NACI recommends [65] that moderately to severely immunocompromised individuals [i] in the authorized age groups should be immunized with a primary series of three doses of an authorized mRNA vaccine. For those who have previously received a 1- or 2-dose complete primary COVID-19 vaccine series (with a homologous or heterologous schedule using mRNA or viral vector vaccines), NACI recommends that an additional dose of an authorized mRNA COVID-19 vaccine should be offered. (Strong NACI Recommendation)

Additional details are available in the NACI rapid response: Additional dose of COVID-19 vaccine in immunocompromised individuals following 1- or 2- dose primary series.

NACI's evidence-informed recommendations for booster doses of COVID-19 vaccines:

NACI recognizes that epidemiological and logistical/operational contexts, as well as impacts on health system capacity, vary between provinces and territories across Canada. NACI encourages jurisdictions to align with these recommendations as much as possible to ensure the equitable, ethical and effective use of booster doses of COVID-19 vaccines in Canada, maintaining vaccine acceptance and confidence, while considering their local contexts.

NACI also acknowledges that the epidemiology of COVID-19 (including the impact of SARS-CoV-2 variants of concern) and the evidence on booster doses of COVID-19 vaccines are rapidly evolving, and will continue to monitor the evidence in the Canadian context and provide additional recommendations and updates subsequent to this interim statement as data emerge.

Following an evaluation of the need for, and benefit of, additional doses of COVID-19 vaccines based on evolving evidence on the criteria outlined in Table 1, as well as the systematic assessment of ethics, equity, feasibility and acceptability considerations with the EEFA framework [19], NACI makes the following evidence-informed recommendations on booster doses of authorized COVID-19 vaccines in the context of ongoing risk of severe illness from COVID-19 and exposure to SARS-CoV-2 and VoCs in Canada:

For key populations at highest risk of severe illness from COVID-19 and highest risk of waning protection:

3. NACI recommends that a booster dose of an authorized mRNA COVID-19 vaccine [*] should be offered ≥6 months after completion of a primary COVID-19 vaccine series (where the primary series consisted of a homologous or heterologous schedule using mRNA or viral vector vaccines) to individuals in the following key populations:

- Adults living in long-term care homes for seniors or other congregate living settings that provide care for seniors (as previously recommended by NACI)
- Adults ≥80 years of age

(Strong NACI Recommendation)

For key populations at increased risk of severe illness from COVID-19 and increased risk of waning and/or lower protection:

4. NACI recommends that a booster dose of an authorized mRNA COVID-19 vaccine * may be offered ≥6 months after completion of a primary COVID-19 vaccine series to individuals in the following key populations:

- Adults 70-79 years of age (whose primary series consisted of a homologous or heterologous schedule using mRNA or viral vector vaccines)
- Recipients of a viral vector vaccine series completed with only viral vector vaccines (AstraZeneca/COVISHIELD or Janssen COVID-19 vaccine), regardless of age based on local epidemiology and any evidence of diminished protection, and with consideration of individual risks and potential benefits.

(Discretionary NACI Recommendation)

For key populations who may be at increased risk of severe illness from COVID-19 (due to intersecting social and health risk factors [13]) and waning protection (due to increased time since completion of the primary COVID-19 vaccine series after a shorter interval between doses) where infection can have disproportionate consequences [12]:

5. NACI recommends that a booster dose of an authorized mRNA COVID-19 vaccine * may be offered ≥6 months after completion of a primary COVID-19 vaccine series (where the primary series consisted of a homologous or heterologous schedule using mRNA or viral vector vaccines) to individuals in the following key population:

- Adults in or from First Nations, Inuit and Métis communities based on local epidemiology, vaccine coverage, any evidence of waning protection and with consideration of individual risks and potential benefits. Whether or not booster dose vaccine programs are needed in distinct Indigenous communities should be determined by Indigenous leaders and communities, considering these same factors, and with the support of public health partners.

(Discretionary NACI Recommendation)

For key populations who are essential for maintaining health system capacity and who may be at increased risk of waning protection (due to increased time since completion of the primary COVID-19 vaccine series after a shorter interval between doses) and who could pose increased risk of transmission to vulnerable populations:

6. NACI recommends that a booster dose of an authorized mRNA COVID-19 vaccine * may be offered ≥6 months after completion of a primary COVID-19 vaccine series (where the primary series consisted of a homologous or heterologous schedule using mRNA or viral vector vaccines)

to individuals in the following key population:

- Adults who are frontline healthcare workers (having direct close physical contact with patients) and who were vaccinated with a very short minimum interval (less than 28 days) between the first and second doses of an mRNA COVID-19 primary vaccine series, based on local epidemiology, any evidence of waning protection, and impacts on health system capacity, and with consideration of individual risks and potential benefits.

(Discretionary NACI Recommendation)

For other populations not included in the above recommendations for a booster dose, NACI will continue to closely monitor the evidence and will make additional recommendations if there is evidence of the need for, and benefit of, a booster dose. This includes monitoring the specific evidence for:

- Individuals who have had previously PCR-confirmed SARS-CoV-2 infection and have completed a primary series of COVID-19 vaccines.
- Moderately to severely immunocompromised individuals who have completed a 3-dose primary series of COVID-19 vaccines. Populations with underlying medical conditions that may be at higher risk of severe disease after breakthrough infection

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* Either Moderna Spikevax or Pfizer-BioNTech Comirnaty vaccines may be used as a booster dose (regardless of which COVID-19 vaccine was used in the primary series). As previously recommended, adults living in long-term care homes for seniors or other congregate living settings that provide care for seniors are recommended to receive the full dose (100 mcg) if being offered Moderna Spikevax. For other adults recommended to receive a booster dose, the full dose (100 mcg) is recommended for adults 70 years of age or older, if offering Moderna Spikevax, while a half dose (50 mcg) is recommended for those less than 70 years of age. If offering Pfizer-BioNTech Comirnaty, the full dose (30 mcg) is recommended.

Individuals who had a severe immediate allergic reaction (e.g., anaphylaxis) to a previous mRNA vaccine or who have a severe immediate allergic reaction (e.g., anaphylaxis) to a component of the mRNA vaccine should consult with an allergist or other appropriate physician as vaccination with an mRNA has been safely performed in these populations. Additional guidance for individuals with myocarditis/pericarditis after a previous dose of an mRNA vaccine is under consideration and will be forthcoming.

Summary of evidence and rationale

- To date, almost 2 in 10 eligible Canadians have not been fully vaccinated. Efforts should be made to encourage vaccination of those unvaccinated with a primary COVID-19 vaccine series.
- Unvaccinated individuals are at highest risk of SARS-CoV-2 infection and severe outcomes from COVID-19. There is no evidence to date of waning of protection against severe disease in the general Canadian population who have been vaccinated against COVID-19 disease.
- NACI continues to strongly recommend that all individuals in the authorized age groups should be immunized with a primary series of an authorized COVID-19 vaccine, and preferably with mRNA COVID-19 vaccines (Moderna Spikevax and Pfizer-BioNTech Comirnaty) [1].
- Fully vaccinated individuals are less likely to get infected, and therefore are less likely to transmit infection to others.
- Emerging evidence suggests a waning in COVID-19 vaccine immunogenicity and effectiveness against SARS-CoV-2 infection over time following completion of the primary series, although protection against severe COVID-19 outcomes appears to be more durable than protection against infection.
- Increased incidence of breakthrough infections amongst those fully vaccinated is expected in the context of high community rates of SARS-CoV-2 (especially where vaccination coverage rates for the primary COVID-19 vaccine series are low) and the predominance of the Delta variant in Canada, given the somewhat lower vaccine effectiveness against infection with this VoC.
- Decreased protection against infection could contribute to more transmission which can have significant impacts especially on some populations and on health system capacity. Vaccinated individuals infected with the Delta variant are less likely to develop severe disease. However, vaccinated individuals infected with this highly transmissible variant may be more infectious to others, potentially facilitating transmission if infected [66].
- Decreased protection against infection over time has been noted to potentially occur more quickly with the viral vector vaccines than the mRNA vaccines, while protection with Moderna Spikevax may be more durable than with Pfizer-BioNTech Comirnaty. Shorter intervals between the first and second dose for 2-dose COVID-19 vaccine series result in lower initial titres that may result in protection that decreases sooner.
- Studies suggest that booster doses of mRNA vaccines elicit a robust immune response, have a favourable safety profile (comparable to that of the second dose of the primary series) and provide good short-term effectiveness against SARS-CoV-2 infection and severe disease. Health Canada is reviewing the evidence submitted by Moderna and Pfizer BioNTech for regulatory approval of a booster dose, but neither vaccine is currently authorized for use as a booster dose in Canada. Post-market safety surveillance on mRNA COVID-19 vaccines

found an increased frequency of myocarditis and pericarditis following a second dose of a COVID-19 mRNA vaccine in younger males and adolescents. Higher unadjusted rates of cases of myocarditis and/or pericarditis have been reported after the Moderna vaccine compared to Pfizer-BioNTech vaccine in some jurisdictions [67] [68]. Additional analyses are ongoing. The majority of cases reported while hospitalized were relatively mild and individuals tended to recover quickly. The rate of myocarditis and pericarditis following a booster dose of a COVID-19 mRNA vaccine is currently unknown, although initial data from Israel to date has shown lower rates of myocarditis/pericarditis after the booster dose than after the second dose, but higher than after the first dose; data collection is ongoing. Informed consent for vaccination with a booster dose should include that a primary series of COVID-19 vaccines remains effective against severe COVID-19, and that a booster dose is intended to restore protection against infection that may have decreased over time. However, the effectiveness against transmission of infection, long-term effectiveness against infection and severe disease, and rate of myocarditis and pericarditis after a booster dose are currently unknown. In addition, recommendations for a booster dose of COVID-19 vaccines are currently off-label in Canada.

Key populations included in this initial guidance on booster doses of COVID-19 vaccine

- The key populations identified by NACI for early COVID-19 immunization were prioritized due to an increased risk of severe illness and exposure. The evidence and rationale for prioritizing these groups is summarized in Table 2 of NACI's previous guidance. Those prioritized in the earliest stages may now be at an increased risk of waning of protection because for some of them, more time has elapsed since their second dose and a number of them were vaccinated with a very short interval between doses to optimize protection as quickly as possible.
- The combined factors of high risk of severe outcomes, high risk of exposure, increased time since completion of primary series, shorter interval between doses in the primary series (in some cases), and immunosenescence in older age can contribute to decreased protection and increase the risk for infection and possibly severe outcomes in the key populations for whom NACI recommends a booster dose of COVID-19 vaccine.
- An individual's risk benefit analysis for a booster dose recommended in key populations should include an assessment of:
    - Risk of severe illness from COVID-19 (e.g., older age, underlying medical condition)
    - Risk of increased waning of protection (e.g., shorter interval between doses, longer time since completion of primary series, vaccination with only viral vector COVID-19 vaccines)
    - Local epidemiology (e.g., circulation of VoC, evidence of waning protection)

- Vaccine coverage of primary series in the community (e.g., the risk of breakthrough infection in fully vaccinated individuals is higher in the context of high community rates of SARS-CoV-2 especially where vaccination coverage rates for the primary COVID-19 vaccine series are low)
- Health system capacity

Long-term care residents and seniors living in other congregate settings

- Refer to NACI's Rapid response: Booster dose in long-term care residents and seniors living in other congregate settings for a summary of the evidence and rationale for booster doses in this population.

Older age

- There are some signs that decreasing protection may be greater in older age groups and in individuals with clinical risk factors for more severe outcomes [27] [28]. Among the fully vaccinated, older age groups (80 years of age and over, followed by those 70 to 79 years of age) have the highest hospitalization and mortality rates from COVID-19 compared to younger age groups who are fully vaccinated.
- There was a large independent association of severe COVID-19 with increasing age and moderate certainty of evidence for a very large association of hospitalization and mortality particularly in those over 70 years of age in OECD countries before vaccination [69].
- The proportion of individuals with at least one underlying medical condition associated with an increased risk of severe COVID-19 increases with increasing age [70].
- It is important to acknowledge that the regulatory submission for a Moderna booster dose is for half the current dosage of Moderna Spikevax (i.e., a 50 mcg booster dose vs. 100 mcg full dose). However, as older adults have dampened immune function, and may need to receive a higher dose formulation of a vaccine or an immunostimulatory adjuvant to increase the potency of their response to vaccines, this population may benefit from a full dose (100 mcg) of Moderna Spikevax as a booster dose [11].

Recipients of only viral vector vaccines

- Individuals who received a complete series with only a viral vector vaccine have somewhat lower initial VE and may experience waning protection. Emerging data suggests vaccine protection against infection and symptomatic infection decreases more quickly with viral vector vaccines in comparison to mRNA vaccines.
- NACI preferentially recommended COVID-19 vaccination with mRNA vaccines [1] due to their high efficacy and safety and the availability of mRNA vaccine supply in Canada. Only a small

percentage of fully vaccinated Canadians to date (<1%) have been vaccinated with only viral vector vaccines.

Adults in or from First Nations, Inuit and Métis communities

- The rate of active COVID-19 cases started rising in First Nations communities in August 2021 and was 4.2 times higher than the rate in the general population as of October.
- Racialized and marginalized populations such as Indigenous Peoples have been disproportionately affected by COVID-19 due to a number of intersecting equity factors.
- The proportion of Canadians who identify as Indigenous and have at least one underlying medical condition associated with severe COVID-19 is higher compared to other Canadians for every age category above 20 years of age. This increases the risk of severe outcomes for COVID-19 in this population.
- Remote or isolated communities may not have ready access to sufficient healthcare infrastructure. Therefore, their risk for severe outcomes, including death, and societal disruption is proportionally greater than in other communities.
- The risk of transmission is higher in settings where physical distancing and other infection prevention and control measures are challenging and individuals may not be able to exercise sufficient precautions to adequately protect themselves from infection.
- Immunization of individuals in this population has the potential to reduce or prevent the exacerbation of intersecting health and social inequities.
- Adults in or from Indigenous communities were included in the earliest stages of initial COVID-19 immunization and may be at increased risk of waning of protection because for some of them, more time has elapsed since their second dose and a number of them were vaccinated with a very short interval between doses to optimize protection as quickly as possible.
- Autonomous decisions should be made by Indigenous Peoples with the support of healthcare and public health partners in accordance with the United Nations Declaration on the Rights of Indigenous Peoples [71].

Frontline healthcare workers

- Maintaining health system capacity is crucial to minimize serious illness and overall deaths while minimizing societal disruption as a result of the COVID-19 pandemic.
- Frontline healthcare workers can be at risk for occupational exposure and can potentially transmit infection to vulnerable populations. Healthcare workers are essential to the provision of healthcare, and their absence due to illness could compromise health system capacity. At present, the health system continues to be strained due to the hospitalization of people with COVID-19, especially where infection rates have been high during the fourth

(Delta) wave in Canada. Optimizing the protection of healthcare workers can help to balance any disproportionate burden of those taking on additional risks to protect the public, thereby upholding the ethical principle of reciprocity.

- The risk of waning of protection is associated with shorter intervals between doses in the primary vaccine series. Therefore, while frontline healthcare workers who received their second dose at very short minimum intervals (less than 28 days) from the first dose were well protected in the short-term, the durability of that protection may wane more quickly than those who had a longer interval between doses.
- There is evidence that the Moderna Spikevax vaccine remains efficacious against severe disease and asymptomatic infection at more than 5 months when given at the authorized interval of 28 days between doses [10]. There is evidence that while the Pfizer-BioNTech Comirnaty vaccine prevents COVID-19 effectively for up to 6 months, there is a gradual decline in efficacy when given at the authorized interval of 21 days between doses [34]. Emerging data also suggest that protection from Moderna Spikevax may be more durable compared to Pfizer-BioNTech Comirnaty [28] [39]; more research is required.

NACI is continuing to monitor the evidence related to waning immunity in various populations and the evidence on immunogenicity, safety and effectiveness of booster doses (including those who have been previously infected with SARS-CoV-2 and have received a complete primary vaccine series with authorized COVID-19 vaccines). NACI will update guidance as required.

Refer to NACI's Recommendations on the use of COVID-19 vaccines for further information on COVID-19 vaccines.

Refer to NACI's Guidance on the prioritization of key populations for COVID-19 immunization for further information on NACI's initial framework and foundational elements guiding ethical decision-making.

Table 2. Strength of NACI recommendations

Strength of NACI recommendation based on factors not isolated to strength of evidence(e.g., public health need)	**Strong**	**Discretionary**
Wording	"should/should not be offered"	"may/may not be offered"

Strength of NACI recommendation based on factors not isolated to strength of evidence(e.g., public health need)	**Strong**	**Discretionary**
Rationale	Known/anticipated advantages outweigh known/anticipated disadvantages ("should"), OR Known/Anticipated disadvantages outweigh known/anticipated advantages ("should not")	Known/anticipated advantages are closely balanced with known/anticipated disadvantages, OR uncertainty in the evidence of advantages and disadvantages exists
Implication	A strong recommendation applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present.	A discretionary recommendation may/may not be offered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

Research priorities

1. What is the efficacy, effectiveness, immunogenicity and safety of booster dose COVID-19 vaccine individuals who have had a previous laboratory-confirmed SARS-CoV-2 infection?
2. What is the effect of booster doses of COVID-19 vaccines on transmission of infection at a population level? How long do any beneficial effects on transmission last?
3. Is a booster dose required after a 3-dose primary series of COVID-19 vaccines in those who are moderately to severely immunocompromised?
4. What is the optimal product (including the booster vaccine in relation to the product(s) received for the primary series), booster vaccine dose, interval between doses in the primary series, interval between the primary series and additional/booster dose, and potential need for (and frequency of) future booster doses in groups at high risk for severe COVID-19 outcomes and in the general population to ensure protection against SARS-CoV-2?
5. What is the optimal timing and trigger for booster doses? What are the risks associated with providing a booster dose earlier than necessary?
6. Will special adverse events that have been associated with the primary series (e.g., myocarditis/pericarditis) also be associated with additional/booster doses? Will any new or previously unrecognized adverse event occur with booster doses?

7. What is the efficacy, effectiveness, immunogenicity, and safety of booster doses of COVID-19 vaccine following a complete series across diverse population groups (e.g., adults of advanced age, those with high-risk medical conditions including autoimmune conditions and transplant recipients, individuals with social or occupational vulnerabilities, individuals who are pregnant or breastfeeding, adolescents, frailty)?

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NACI members: S Deeks (Chair), R Harrison (Vice-Chair), J Bettinger, N Brousseau, P De Wals, E Dubé, V Dubey, K Hildebrand, K Klein, J Papenburg, A Pham-Huy, C Rotstein, B Sander, S Smith, and S Wilson.

Liaison representatives: LM Bucci (Canadian Public Health Association), E Castillo (Society of Obstetricians and Gynaecologists of Canada), A Cohn (Centers for Disease Control and Prevention, United States), L Dupuis (Canadian Nurses Association), J Emili (College of Family Physicians of Canada), D Fell (Canadian Association for Immunization Research and Evaluation), M Lavoie (Council of Chief Medical Officers of Health), D Moore (Canadian Paediatric Society), M Naus (Canadian Immunization Committee), P Emberley (Canadian Pharmacists Association), L Bill (Canadian Indigenous Nurses Association), and S Funnel (Indigenous Physicians Association of Canada).

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NACI High Consequence Infectious Disease Working Group

Members: R Harrison (Chair), Y-G Bui, S Deeks, K Dooling, K Hildebrand, M Miller, M Murti, J Papenburg, R Pless, S Ramanathan, N Stall, and S Vaughan.

PHAC participants: N Abraham, L Coward, N Forbes, C Jensen, A Killikelly, R Krishnan, J Montroy, A Nam, M Patel, M Salvadori, A Sinilaite, R Stirling, E Tice, B Warshawsky, R Ximenes MW Yeung, and J Zafack.

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Endnotes

i Moderately to severely immunosuppressed includes individuals with the following conditions:

- Active treatment for solid tumour or hematologic malignancies
- Receipt of solid-organ transplant and taking immunosuppressive therapy
- Receipt of chimeric antigen receptor (CAR)-T-cell therapy or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)
- Moderate to severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Stage 3 or advanced untreated HIV infection and those with acquired immunodeficiency syndrome
- Active treatment with the following categories of immunosuppressive therapies: anti-B cell therapies (monoclonal antibodies targeting CD19, CD20 and CD22), high-dose systemic corticosteroids (refer to the CIG for suggested definition of high dose steroids), alkylating agents, antimetabolites, or tumor-necrosis factor (TNF) inhibitors and other biologic agents that are significantly immunosuppressive.

Date modified:

2021-12-01

TAB 15

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TAB 16

Centers for Disease Control and Prevention

COVID-19

Preparing for Your COVID-19 Vaccination

Updated Dec. 3, 2021

COVID-19 vaccines are effective at protecting you from getting sick even if you have had COVID-19. Vaccination is an important tool to help us get back to normal. This information will help you prepare for your COVID-19 vaccination.

Learn more about the different types of COVID-19 vaccines and how they work.

- Pfizer-BioNTech COVID-19 vaccine for everyone ages 5 years and older
- Moderna COVID-19 vaccine for adults ages 18 years and older
- Johnson & Johnson's Janssen COVID-19 vaccine for adults ages 18 years and older

Learn more about the benefits of getting a COVID-19 vaccination.

Find a COVID-19 vaccine: Search vaccines.gov, text your ZIP code to 438829, or call 1-800-232-0233 to find locations near you.

Plan and Prepare for Your COVID-19 Vaccination

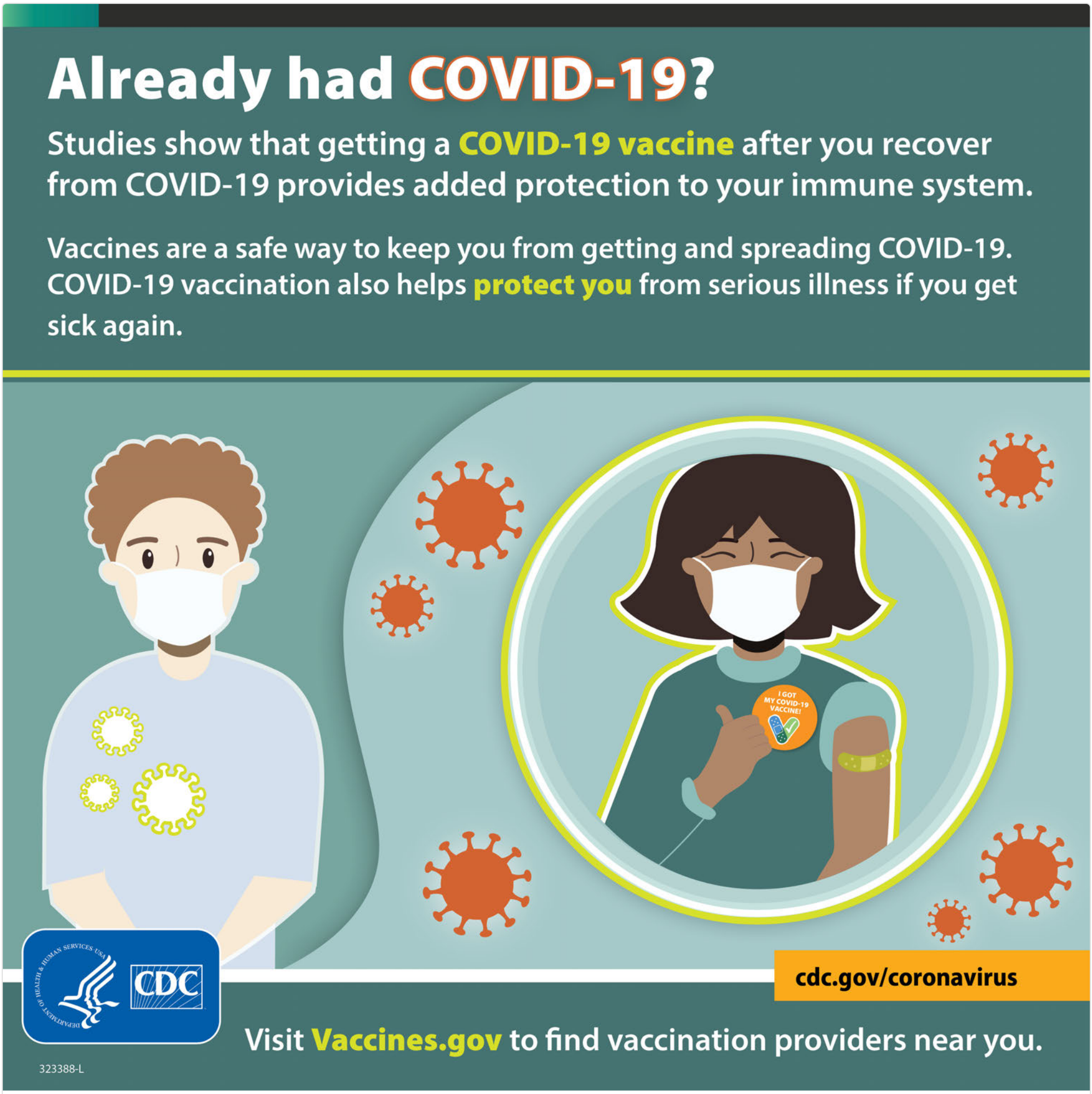
- Find out how to get a COVID-19 vaccine.
- Get vaccinated even if you have already had COVID-19.
- If you are getting a COVID-19 vaccine that requires two doses, be sure to schedule an appointment for your second shot.
- Get a COVID-19 vaccine and any other recommended vaccines, including a flu vaccine, at the same visit.
- Learn more about routine medical procedures and screenings and COVID-19 vaccination.

Watch Video: What to Expect at Your COVID-19 Vaccination Appointment [00:00:48]

Who Should Get a COVID-19 Vaccine

- COVID-19 vaccination is recommended for everyone ages 5 years and older.
- Moderately or severely immunocompromised people who are ages 12 years and older and received a Pfizer-BioNTech primary vaccine series or ages 18 years and older and received a Moderna primary vaccine series should receive an additional primary dose of the same vaccine at least 28 days after their second dose.
- Everyone ages 18 years and older who is fully vaccinated against COVID-19 should get a booster shot. Learn more about booster shots.

Get Vaccinated Even If You Had COVID-19 and Think You Have Natural Immunity



[JPG - 2 MB]

Get vaccinated to protect against serious illness.

You should get a COVID-19 vaccine even if you already had COVID-19.

Getting sick with COVID-19 offers some protection from future illness with COVID-19, sometimes called “natural immunity.” The level of protection people get from having COVID-19 may vary depending on how mild or severe their illness was, the time since their infection, and their age; and no currently available test can reliably determine if you are protected after a COVID-19 infection.

All COVID-19 vaccines currently available in the United States are effective at preventing COVID-19. Getting a COVID-19 vaccine gives most people a high level of protection against COVID-19, even in people who have already been sick with COVID-19.

Emerging evidence shows that getting a COVID-19 vaccine after you recover from COVID-19 infection provides added protection to your immune system. One study showed that, for people who already had COVID-19, those who do not get vaccinated after their recovery are more than 2 times as likely to get COVID-19 again than those who get fully vaccinated after

their recovery.

People Who Should Wait to Get Vaccinated

If you were treated for COVID-19 with monoclonal antibodies or convalescent plasma while sick with COVID-19, you should wait 90 days before getting a COVID-19 vaccine. If you received monoclonal antibodies or convalescent plasma after you were exposed to someone with COVID-19 to prevent you from getting sick, you should wait 30 days before getting a COVID-19 vaccine. Talk to your healthcare professional if you are unsure what treatments you received or if you have more questions about getting a COVID-19 vaccine.

If you or your child have a history of multisystem inflammatory syndrome in adults or children (MIS-A or MIS-C), consider delaying vaccination until you have recovered from being sick and for 90 days after the date of diagnosis of MIS-A or MIS-C. Learn more about the clinical considerations for people with a history of MIS-A or MIS-C.

Considerations for Taking Medication before Getting Vaccinated

It is not recommended you take over-the-counter medicine (such as ibuprofen, aspirin, or acetaminophen) before vaccination for the purpose of trying to prevent vaccine-related side effects. It is not known how these medications might affect how well the vaccine works. If you take these medications regularly for other reasons, you should keep taking them before you get vaccinated. It is also not recommended to take antihistamines before getting a COVID-19 vaccine to try to prevent allergic reactions.

Learn more about medications to relieve post-vaccination side effects.

For most people, it is not recommended to avoid, discontinue, or delay medications that you are routinely taking for prevention or treatment of other medical conditions around the time of COVID-19 vaccination.

If you are taking medications that suppress the immune system, you should talk to your healthcare provider about what is currently known and not known about the effectiveness of getting a COVID-19 vaccine. Ask about the best timing for receiving a vaccine. Learn more about COVID-19 vaccines for moderately to severely immunocompromised people.

Most people who take medication can get a COVID-19 vaccine. Taking one of the following medications is not, on its own, a reason to avoid getting your COVID-19 vaccination:

- Over-the-counter medications (non-prescription)
- Non-steroidal anti-inflammatory drugs (NSAIDs) (naproxen, ibuprofen, aspirin, etc.)
- Acetaminophen (Tylenol, etc.)
- Biologics or biologic response modifiers that treat autoimmune diseases
- Chemotherapy or other cancer treatment medications
- Antiviral medication
- Antibiotics
- Statins
- Blood pressure medications/antihypertensives (amlodipine, lisinopril, etc.)
- Diuretics
- Thyroid medications
- Antidepressants
- Metformin
- Diabetic medications
- Insulin
- Steroids (prednisone, etc.)

This is not a complete list. It is meant to provide some examples of common medications. Taking any of these medications will not make COVID-19 vaccination harmful or dangerous.

will not make COVID-19 vaccination harmful or dangerous.

If you have questions about medications that you are taking, talk to your healthcare professional or your vaccination provider.

Last Updated Dec. 3, 2021

TAB 17

Weekly / August 13, 2021 / 70(32);1081-1083

On August 6, 2021, this report was posted online as an MMWR *Early Release.*

Alyson M. Cavanaugh, DPT, PhD[1,2]; Kevin B. Spicer, MD, PhD[2,3]; Douglas Thoroughman, PhD[2,4]; Connor Glick, MS[2]; Kathleen Winter, PhD[2,5] (View author affiliations)

View suggested citation

Summary

What is already known about this topic?

Reinfection with human coronaviruses, including SARS-CoV-2, the virus that causes COVID-19, has been documented. Currently, limited evidence concerning the protection afforded by vaccination against reinfection with SARS-CoV-2 is available.

What is added by this report?

Among Kentucky residents infected with SARS-CoV-2 in 2020, vaccination status of those reinfected during May–June 2021 was compared with that of residents who were not reinfected. In this case-control study, being unvaccinated was associated with 2.34 times the odds of reinfection compared with being fully vaccinated.

What are the implications for public health practice?

To reduce their likelihood for future infection, all eligible persons should be offered COVID-19 vaccine, even those with previous SARS-CoV-2 infection.

Although laboratory evidence suggests that antibody responses following COVID-19 vaccination provide better neutralization of some circulating variants than does natural infection (*1*,*2*), few real-world epidemiologic studies exist to support the benefit of vaccination for previously infected persons. This report details the findings of a case-control evaluation of the association between vaccination and SARS-CoV-2 reinfection in Kentucky during May–June 2021 among persons previously infected with SARS-CoV-2 in 2020. Kentucky residents who were not vaccinated had 2.34 times the odds of reinfection compared with those who were fully vaccinated (odds ratio [OR] = 2.34; 95% confidence interval [CI] = 1.58–3.47). These findings suggest that among persons with previous SARS-CoV-2 infection, full vaccination provides additional protection against reinfection. To reduce their risk of infection, all eligible persons should be offered vaccination, even if they have been previously infected with SARS-CoV-2.*

Tables

Table 1

Table 2

References

Related Materials

PDF [89K]

Kentucky residents aged ≥18 years with SARS-CoV-2 infection confirmed by positive nucleic acid amplification test (NAAT) or antigen test results† reported in Kentucky's National Electronic Disease Surveillance System (NEDSS) during March–December 2020 were eligible for inclusion. NEDSS data for all Kentucky COVID-19 cases were imported into a REDCap database that contains laboratory test results and case investigation data, including dates of death for deceased patients reported to public health authorities (*3*). The REDCap database was queried to identify previously infected persons, excluding COVID-19 cases resulting in death before May 1, 2021. A case-patient was defined as a Kentucky resident with laboratory-confirmed SARS-CoV-2 infection in 2020 and a subsequent positive NAAT or antigen test result during May 1–June 30, 2021. May and June were selected because of vaccine supply and eligibility requirement considerations; this period was more likely to reflect resident choice to be vaccinated, rather than eligibility to receive vaccine.§ Control participants were Kentucky residents with laboratory-confirmed SARS-CoV-2 infection in 2020 who were not reinfected through June 30, 2021. Case-

patients and controls were matched on a 1:2 ratio based on sex, age (within 3 years), and date of initial positive SARS-CoV-2 test (within 1 week). Date of initial positive test result refers to the specimen collection date, if available. The report date in NEDSS was used if specimen collection date was missing. Random matching was performed to select controls when multiple possible controls were available to match per case (*4*).

Vaccination status was determined using data from the Kentucky Immunization Registry (KYIR). Case-patients and controls were matched to the KYIR database using first name, last name, and date of birth. Case-patients were considered fully vaccinated if a single dose of Janssen (Johnson & Johnson) or a second dose of an mRNA vaccine (Pfizer-BioNTech or Moderna) was received ≥14 days before the reinfection date. For controls, the same definition was applied, using the reinfection date of the matched case-patient. Partial vaccination was defined as receipt of ≥1 dose of vaccine, but either the vaccination series was not completed or the final dose was received <14 days before the case-patient's reinfection date. Using conditional logistic regression, ORs and CIs were used to compare no vaccination and partial vaccination with full vaccination among case-patients and controls. SAS (version 9.4; SAS Institute) was used for matching and statistical analyses. This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.¶

Overall, 246 case-patients met eligibility requirements and were successfully matched by age, sex, and date of initial infection with 492 controls. Among the population included in the analysis, 60.6% were female, and 204 (82.9%) case-patients were initially infected during October–December 2020 (Table 1). Among case-patients, 20.3% were fully vaccinated, compared with 34.3% of controls (Table 2). Kentucky residents with previous infections who were unvaccinated had 2.34 times the odds of reinfection (OR = 2.34; 95% CI = 1.58–3.47) compared with those who were fully vaccinated; partial vaccination was not significantly associated with reinfection (OR = 1.56; 95% CI = 0.81–3.01).

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Discussion

This study found that among Kentucky residents who were previously infected with SARS-CoV-2 in 2020, those who were unvaccinated against COVID-19 had significantly higher likelihood of reinfection during May and June 2021. This finding supports the CDC recommendation that all eligible persons be offered COVID-19 vaccination, regardless of previous SARS-CoV-2 infection status.

Reinfection with SARS-CoV-2 has been documented, but the scientific understanding of natural infection-derived immunity is still emerging (*5*). The duration of immunity resulting from natural infection, although not well understood, is suspected to persist for ≥90 days in most persons.** The emergence of new variants might affect the duration of infection-acquired immunity, and laboratory studies have shown that sera from previously infected persons might offer weak or inconsistent responses against several variants of concern (*2*,*6*). For example, a recent laboratory study found that sera collected from previously infected persons before they were vaccinated provided a relatively weaker, and in some cases absent, neutralization response to the B.1.351 (Beta) variant when compared with the original Wuhan-Hu-1 strain (*1*). Sera from the same persons after vaccination showed a heightened neutralization response to the Beta variant, suggesting that vaccination enhances the immune response even to a variant to which the infected person had not been previously exposed. Although such laboratory evidence continues to suggest that vaccination provides improved neutralization of SARS-CoV-2 variants, limited evidence in real-world settings to date corroborates the findings that vaccination can provide improved protection for previously infected persons. The findings from this study suggest that among previously infected persons, full vaccination is associated with reduced likelihood of reinfection, and, conversely, being unvaccinated is associated with higher likelihood of being reinfected.

The lack of a significant association with partial versus full vaccination should be interpreted with caution given the small numbers of partially vaccinated persons included in the analysis (6.9% of case-patients and 7.9% of controls), which limited statistical power. The lower odds of reinfection among the partially vaccinated group compared with the unvaccinated group is suggestive of a protective effect and consistent with findings from previous studies indicating higher titers after the first mRNA vaccine dose in persons who were previously infected (*7*,*8*).

The findings in this report are subject to at least five limitations. First, reinfection was not confirmed through whole genome sequencing, which would be necessary to definitively prove that the reinfection was caused from a distinct virus relative to the first infection. Although in some cases the repeat positive test could be indicative of prolonged viral shedding or failure to clear the initial viral infection (*9*), given the time between initial and subsequent positive molecular tests among participants in this study, reinfection is the most likely explanation. Second, persons who have been vaccinated are possibly less likely to get tested. Therefore, the association of reinfection and lack of vaccination might be overestimated. Third, vaccine doses administered at federal or out-of-state sites are not typically entered in KYIR, so vaccination data are possibly missing for some persons in these analyses. In addition, inconsistencies in name and date of birth between KYIR and NEDSS might limit

some persons in these analyses. In addition, inconsistencies in name and date of birth between KYIR and NEDSS might limit ability to match the two databases. Because case investigations include questions regarding vaccination, and KYIR might be updated during the case investigation process, vaccination data might be more likely to be missing for controls. Thus, the OR might be even more favorable for vaccination. Fourth, although case-patients and controls were matched based on age, sex, and date of initial infection, other unknown confounders might be present. Finally, this is a retrospective study design using data from a single state during a 2-month period; therefore, these findings cannot be used to infer causation. Additional prospective studies with larger populations are warranted to support these findings.

These findings suggest that among persons with previous SARS-CoV-2 infection, full vaccination provides additional protection against reinfection. Among previously infected Kentucky residents, those who were not vaccinated were more than twice as likely to be reinfected compared with those with full vaccination. All eligible persons should be offered vaccination, including those with previous SARS-CoV-2 infection, to reduce their risk for future infection.

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Corresponding author: Alyson M. Cavanaugh, qds1@cdc.gov.

[1]Epidemic Intelligence Service, CDC; [2]Kentucky Department for Public Health; [3]Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, CDC; [4]Division of State and Local Readiness, Center for Preparedness and Response, CDC; [5]College of Public Health, University of Kentucky, Lexington, Kentucky.

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All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflicts of interest were disclosed.

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* https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Fcovid-19%2Finfo-by-product%2Fclinical-considerations.html#CoV-19-vaccination

† https://www.cdc.gov/coronavirus/2019-ncov/hcp/testing-overview.html

§ May and June were selected for two primary reasons. First, when vaccination supplies were low, some previously infected persons were deferring vaccination for 90 days to allow never-infected persons priority for available vaccine; however, by May 2021, deferral for 90 days was no longer a reason for those infected in 2020 to remain unvaccinated. Second, although vaccination eligibility was initially restricted based on age, comorbidities, and occupation, by April 5, 2021, all Kentucky residents aged ≥16 years became eligible for vaccination (https://chfs.ky.gov/agencies/dph/covid19/Cv19VaccineFAskedQ.pdf). Thus, vaccination status in May or June 2021 might more accurately reflect choice rather than eligibility to be vaccinated.

¶ 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

** https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html

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TABLE 1. Demographic characteristics of COVID-19 patients with reinfection (case-patients) and COVID-19 patients who were not reinfected (control participants) — Kentucky, May–June 2021

Return

Characteristic	No. (%)	
	Case-patients* (n = 246)	Control participants† (n = 492)
Age group, yrs		
18–29	46 (18.7)	89 (18.1)
30–39	37 (15.0)	83 (16.9)
40–49	43 (17.5)	80 (16.3)
50–59	44 (17.9)	88 (17.9)
60–69	27 (11.0)	51 (10.4)
70–79	28 (11.4)	58 (11.8)
≥80	21 (8.5)	43 (8.7)
Sex		
Female	149 (60.6)	298 (60.6)
Month of initial infection in 2020		
March	0 (0)	3 (0.6)
April	7 (2.8)	11 (2.2)
May	2 (0.8)	2 (0.4)
June	4 (1.6)	11 (2.2)
July	8 (3.3)	17 (3.5)

Characteristic	No. (%)	
	Case-patients* (n = 246)	Control participants† (n = 492)
August	8 (3.3)	13 (2.6)
September	13 (5.3)	22 (4.5)
October	36 (14.6)	78 (15.9)
November	72 (29.3)	141 (28.7)
December	96 (39.0)	194 (39.4)

* Case-patients were eligible for inclusion if initial infection occurred during March–December 2020, and a subsequent positive nucleic acid amplification or antigen test result was received during May–June 2021 (using date of specimen collection). Cases for analyses were restricted to persons aged ≥18 years at time of reinfection.

† Controls were matched by sex, age (within 3 years), and time of initial infection diagnosis (within 7 days).

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TABLE 2. Association of SARS-CoV-2 reinfection* with COVID-19 vaccination status — Kentucky, May–June 2021

Return

Vaccination status	No. (%)		OR (95% CI)†
	Case-patients	Control participants	
Not vaccinated	179 (72.8)	284 (57.7)	2.34 (1.58–3.47)
Partially vaccinated¶	17 (6.9)	39 (7.9)	1.56 (0.81–3.01)
Fully vaccinated§	50 (20.3)	169 (34.3)	Ref
Total	**246 (100)**	**492 (100)**	**—**

Abbreviations: CI = confidence interval; NAAT = nucleic acid amplification test; OR = odds ratio; Ref = referent group.

*All case-patients (reinfected) and control participants (not reinfected) had previous SARS-CoV-2 infection documented by positive NAAT or antigen test results during March–December 2020. Reinfection was defined as receipt of positive NAAT or antigen test results during May 1–June 30, 2021.

† Estimated based on conditional logistic regression.

§ Case-patients were considered partially vaccinated if ≥1 dose of vaccine was received, but the vaccination series was either not completed or the final dose was received <14 days before their reinfection date. For control participants, the same criteria were applied, using the matched case-patient's reinfection date.

¶ Case-patients and control participants were considered fully vaccinated if a complete COVID-19 vaccine series was received ≥14 days before the case-patient's reinfection date.

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Suggested citation for this article: Cavanaugh AM, Spicer KB, Thoroughman D, Glick C, Winter K. Reduced Risk of Reinfection with SARS-CoV-2 After COVID-19 Vaccination — Kentucky, May–June 2021. MMWR Morb Mortal Wkly Rep 2021;70:1081-1083. DOI: http://dx.doi.org/10.15585/mmwr.mm7032e1 .

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TAB 19

RAPID RISK ASSESSMENT

Assessing SARS-CoV-2 circulation, variants of concern, non-pharmaceutical interventions and vaccine rollout in the EU/EEA, 16th update

30 September 2021

Summary

Since its emergence in March 2021, the B.1.617.2 (Delta) variant of concern (VOC) has rapidly become predominant across the European Union/European Economic Area (EU/EEA). More than 99% of newly reported cases are attributed to this variant. The Delta variant has demonstrated a significant transmission advantage relative to previously circulating SARS-CoV-2 strains. However, full vaccination remains protective against severe outcomes such as hospitalisation, admission to intensive care and death. Currently available vaccines have played a crucial role in limiting viral circulation and in particular, limiting the impact of infections by the Delta variant.

Despite the fact that over 565 million vaccine doses have been administered in the EU/EEA so far, only 61.1% (range: 18.4–79.4%) of the total population in the EU/EEA have been fully vaccinated to date. The total population includes children and adolescents for whom the vaccine is not available or who may not be included in national target groups yet. There is considerable inter-country and sub-national variation in vaccine uptake, resulting in large proportions of the EU/EEA population remaining susceptible to SARS-CoV-2 infection.

Modelling scenarios that consider vaccination coverage, vaccine effectiveness, natural immunity and population contact rates—in the context of continued Delta circulation—indicate that the potential burden of disease risk in the EU/EEA from the Delta variant is high between now to the end of November, unless vaccination coverage can be increased rapidly in the total population in the next few weeks.

Risk assessed in this update

The risk assessed in this update is as follows: based on current levels of vaccination coverage and the dominance of the Delta variant in the EU/EEA, what risk does SARS-CoV-2 pose to the general population and the vulnerable population in the coming months?

This update was prompted by the forecast modelling undertaken by ECDC and the planned relaxation of non-pharmaceutical and other measures announced by EU/EEA countries.

Suggested citation: European Centre for Disease Prevention and Control. Assessing SARS-CoV-2 circulation, variants of concern, non-pharmaceutical interventions and vaccine rollout in the EU/EEA, 16th update – 30 September 2021. ECDC: Stockholm; 2021.

Our previous assessment published on 10 June 2021 (15th update) described the risk at that point in time, and classified EU/EEA countries based on SARS-CoV-2 transmission (expressed as low, moderate, high and very high concern). Here we assess the risk to broad groupings of EU/EEA countries based on their current and projected levels of vaccination coverage for the total population (low <45% total population; average 55-65% total population; high >75% total population). Through mathematical modelling, we forecast the disease burden between now and the end of November 2021. The assessment of risk posed by the SARS-CoV-2 pandemic is further stratified for the following groups in the total population: the vaccinated and the unvaccinated general population; the vaccinated and the unvaccinated vulnerable population. The assessment is based on the following elements: i) the vaccinated have a lower probability of infection and ii) a lower impact of such infection than the unvaccinated, while iii) the vulnerable population suffers a higher impact if infection occurs, when compared with the general population.

Based on modelling projections, virus circulation and disease burden between now and end of November 2021, the following can be anticipated:

- Countries with COVID-19 vaccination coverage at or below the current EU average level in the total population and who are planning to relax non-pharmaceutical interventions (NPIs) have a high risk of experiencing a significant surge of cases, hospitalisations and mortality from now until the end of November 2021. In such a scenario, due to very high virus circulation, fully vaccinated vulnerable populations are also at risk of experiencing infection with a severe outcome.
- Countries with COVID-19 vaccination coverage above the current EU average level, and particularly those with the highest current coverage, in the total population have a lower, manageable risk of experiencing a severe surge of cases, hospitalisations and mortality from now until the end of November 2021, unless there is a rapid decline of vaccine effectiveness due to waning immunity.

Options for response

- Countries should continuously strive to increase their COVID-19 vaccination coverage in all eligible age groups, to limit the burden of infections posed by the Delta variant in the autumn. This requires continuous monitoring of vaccine uptake and associated social determinants to understand where and in which population groups and communities an immunity gap persists.
- According to the current ECDC forecast, depending on the local epidemiological and COVID-19 vaccination coverage situation, non-pharmaceutical interventions will still be needed between now and the end of November to control the circulation and impact of the Delta variant.
- Closing any COVID-19 vaccination gaps in vulnerable populations and healthcare workers before the winter months is also critical to mitigate the risks to healthcare systems, which may be impacted by influenza and other respiratory viruses, in addition to SARS-CoV-2, as the winter season approaches, posing the risk of further increasing the demand for care.
- To increase vaccination coverage, it will be key to address inequalities in access to COVID-19 vaccination in different population groups. It is also important to understand the factors that determine low vaccine uptake in some population groups, including issues around vaccine acceptance and access so that targeted, context-specific and effective interventions can be developed.
- Risk communication activities should clearly and consistently stress the important role that existing COVID-19 and influenza vaccines play in protecting people against severe disease. Messaging should also highlight the fact that although many countries have relaxed public health measures in recent months, maintaining hygiene measures and avoidance of unnecessary physical crowding remains prudent.
- Given the continuing risk of transmission among unvaccinated children, high levels of prevention and preparedness are required in the educational system.
- In addition to these response options, it remains crucial that COVID-19 surveillance systems are able to effectively monitor and report on COVID-19 cases, hospitalisations and deaths, in order to guide decisions on public health measures and to understand their impact. Vaccine effectiveness should also be monitored to inform vaccination programme strategies.
- Genomic sequencing of samples remains of high importance to characterise currently circulating variants, and to detect the emergence of novel variants with concerning characteristics.

What is new in this assessment?

- This Rapid Risk Assessment assesses the risk posed by the circulation of the Delta variant of SARS-CoV-2 from now until the end of November 2021, based on modelling scenarios and projected levels of vaccine coverage
- Updated data on seroprevalence and re-infection by SARS-CoV-2 are included, as well as available evidence on COVID-19 vaccine effectiveness, waning immunity and breakthrough infections.
- Information on vaccine hesitancy and good practice to approach hesitant populations and address misinformation are included, as well as risk communication advice and a list of proposed key messages.

Event background

Since 31 December 2019 and as of week 2021-37, 229 415 774 cases of COVID-19 have been reported, including 4 699 359 deaths. As of week 2021-37, EU/EEA countries have reported 37 863 314 cases and 764 710 deaths due to COVID-19, representing 16.5% of all cases and 16.3% of all deaths reported worldwide.

These global and EU/EEA figures are likely an underestimate of the true number of COVID-19 cases and deaths, due to various degrees of under-ascertainment and under-reporting. The timeline of the major events in the COVID-19 pandemic can be found on ECDC's website: https://www.ecdc.europa.eu/en/covid-19/timeline-ecdc-response.

The latest available data on the number of cases and the number of deaths globally are published daily on ECDC's website: https://www.ecdc.europa.eu/en/covid-19/situation-updates. Detailed epidemiological information on laboratory-confirmed cases reported to The European Surveillance System (TESSy) is published in ECDC's weekly COVID-19 surveillance report: https://www.ecdc.europa.eu/en/covid-19/surveillance/weekly-surveillance-report

The overview of the epidemiological situation in relation to the COVID-19 pandemic, by country, is published in ECDC's weekly COVID-19 country overview: http://covid19-country-overviews.ecdc.europa.eu/

The latest available data on the number of COVID-19 vaccine doses administered in the EU/EEA reported to TESSy are available on ECDC's website: https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#uptake-tab

Trends in reported cases, testing, hospitalisation and mortality

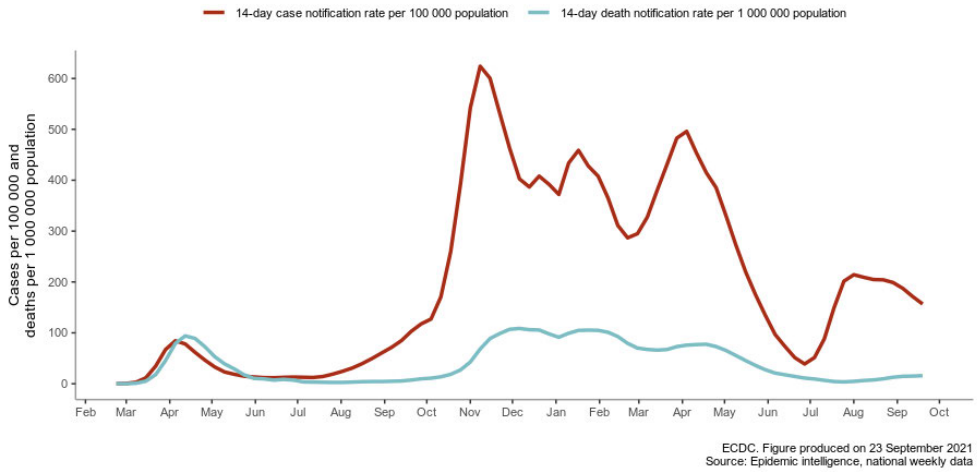
By the end of week 37, 2021 (19 September 2021), the 14-day case notification rate for the EU/EEA was 157 per 100 000 population (country range: 20–652) and the 14-day death rate was 16 deaths per million population (Figure 1a). The overall epidemiological situation in the EU/EEA was characterised by a high and slowly decreasing overall case notification rate and a low, stable death rate (Figure 1a).

Currently, the age groups with the highest reported incidence of infection are those aged 15 to 24 years. The notification rate in this age group has been decreasing across the EU/EEA since week 30, 2021. The increase observed in July and August 2021 amongst children under 15 years of age has begun to level off. Age-specific hospitalisation rates have risen in all ages in line with increases in case rates, but absolute rates of hospital admission remain very low in young age groups (Figure 1b i). Younger age groups account for an increasing proportion of hospital admissions (Figure 1b ii), which is due to comparatively lower hospitalisation rates in older age groups because of vaccination. There is no indication in surveillance data submitted to ECDC by EU/EEA countries of increasing COVID-19 mortality rates among people under 25 years of age.

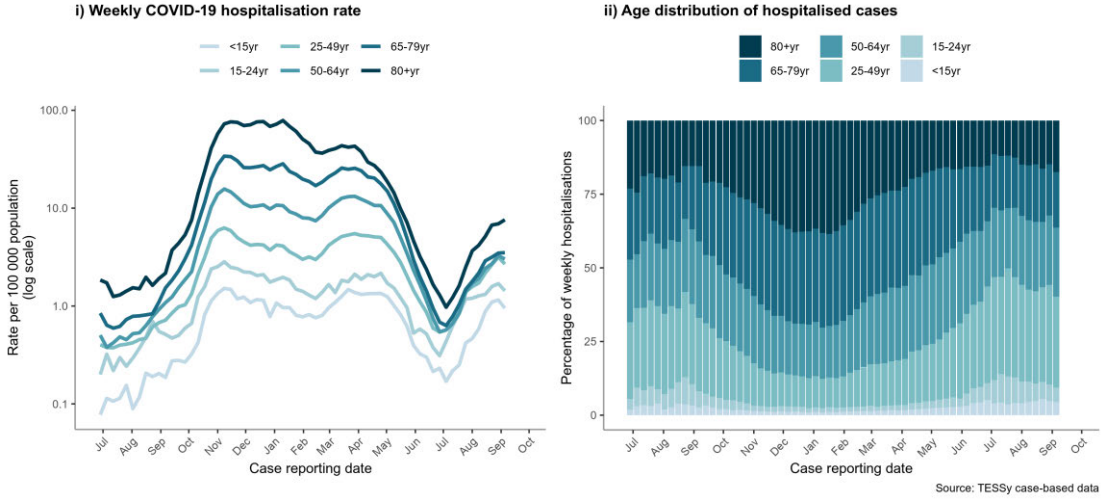
The pooled testing rate for the EU/EEA in week 37, 2021 was high, at 3 573 tests per 100 000 population, but varied markedly by country, from 689 to 42 656 per 100 000 population. Pooled test positivity for the EU/EEA was 2.1% (country range: 0.3–10.2%) and has been stable for nine weeks. Testing rates and test positivity by country need to be interpreted with caution as testing strategies are heterogenous, for example in the use of rapid antigen detection tests (RADTs) or use of self-testing RADTs in settings such as schools and workplaces.

Figure 1. (a) 14-day overall case and death notification rates in the EU/EEA to week 37, 2021, b) age-specific distribution and rates of hospitalised cases, 12 EU/EEA countries, to week 35, 2021

a)



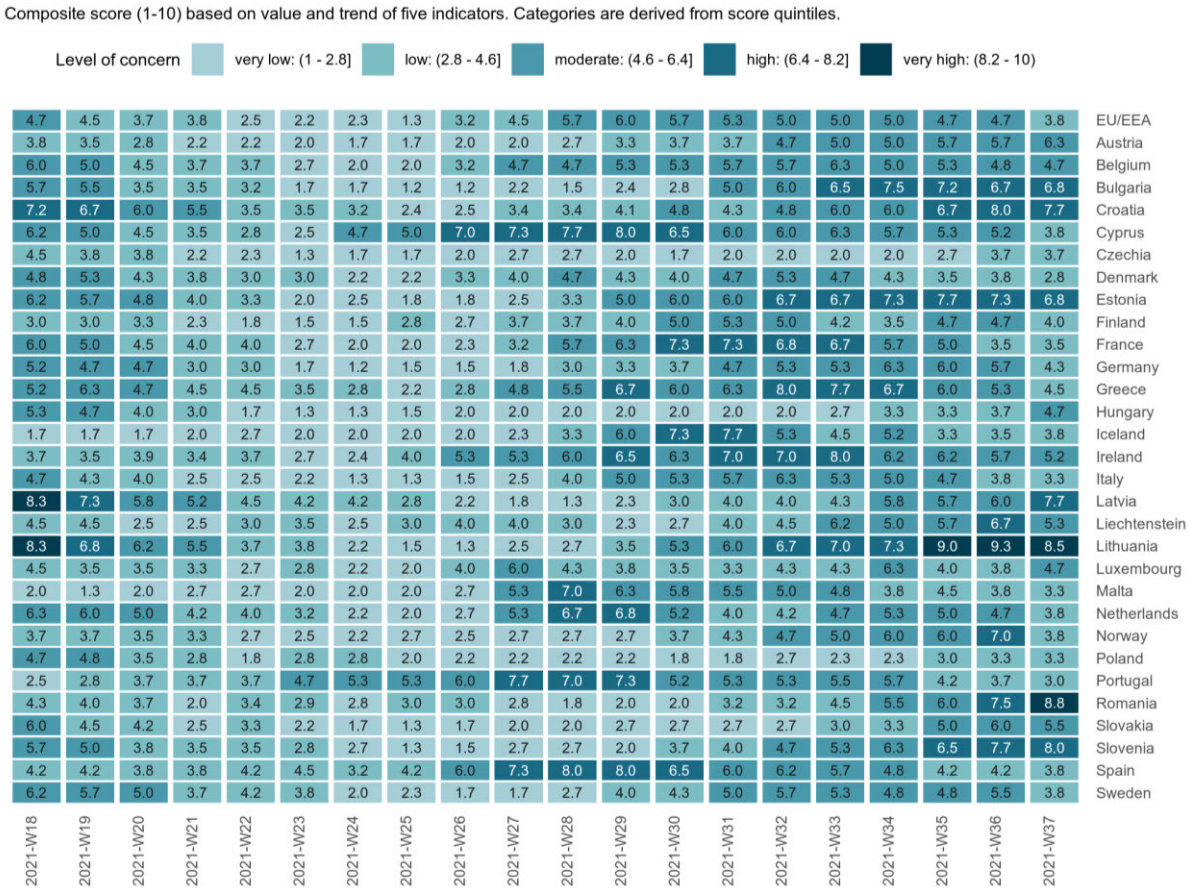
b)



Note: Figure a) is based on pooled data for 30 EU/EEA countries. Figure b) is based on pooled case-based data submitted to TESSy by 12 countries (Austria, Cyprus, Czechia, Finland, Germany, Italy, Luxembourg, Malta, Norway, Portugal, Slovakia and Sweden). Data from weeks 36 and 37 were censored to account for possible delayed reporting of hospitalisation status.

The trends vary considerably at Member State level, with increasing trends in case notification rates mainly reported in eastern parts of the EU/EEA. Several countries also report increases in severity indicators including cases in older age groups, hospitalisation and mortality. Figure 2 shows a composite score for each country based on the absolute value and trend of five COVID-19 epidemiological indicators (intensity indicators: test positivity and total case notification rates; and severity indicators: hospital or ICU admissions or occupancy, death rates, case rates amongst people aged 65 years and above) [1]. In week 37, the epidemiological situation in the EU/EEA overall was categorised as of low concern. In the same week, two countries were categorised as of very high concern (Lithuania and Romania), five countries as of high concern (Bulgaria, Croatia, Estonia, Latvia and Slovenia), seven countries as of moderate concern (Austria, Belgium, Hungary, Ireland, Liechtenstein, Luxembourg, and Slovakia) and 16 countries as of low concern (Cyprus, Czechia, Denmark, Finland, France, Germany, Greece, Iceland, Italy, Malta, Netherlands, Norway, Poland, Portugal, Spain and Sweden) (Figure 2). No country was categorised as of very low concern.

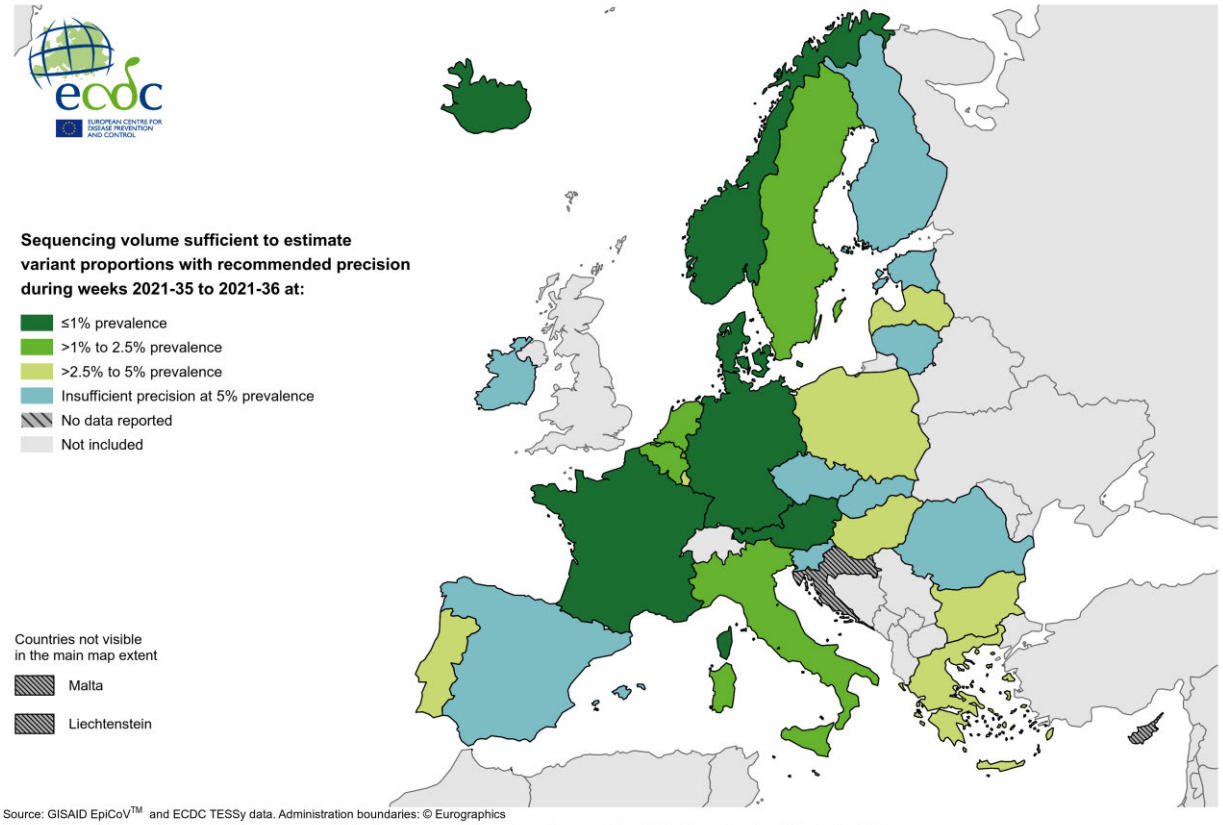
Figure 2. Weekly COVID-19 epidemiological classification and score by country in the EU/EEA, weeks 18 to 37, 2021



SARS-CoV-2 variants of concern

Sequencing capacity varies greatly across the EU/EEA. ECDC uses data reported to the GISAID EpiCoV database or to TESSy, to estimate the distribution of variants in countries reporting an adequate average weekly volume of sequenced SARS-CoV-2-positive cases [2]. In weeks 35-36, 2021, 17 countries reported an adequate average weekly sequencing volume (six with sufficient precision at a variant prevalence of 1% or lower, four with sufficient precision at a variant prevalence of >1-2.5%, and seven with sufficient precision at a variant prevalence of >2.5-5%), nine countries reported an inadequate sequencing volume (with insufficient precision at a variant prevalence of 5%), and four did not report any data (Figure 3) [3].

Figure 3. Distribution of SARS-CoV-2 sequencing volume of sufficient precision by EU/EEA country, weeks 35-36, 2021



Source: GISAID EpiCoV™ and ECDC TESSy data. Administration boundaries: © Eurographics
The boundaries and names shown on this map do not imply official endorsement or acceptance by the European Union. ECDC. Map produced on 22 September 2021

Among the variants of concern (VOC), Delta (B.1.617.2) dominates in all EU/EEA countries, accounting for a median of 99.6% (range 72.0–100.0%) of sequenced samples in the 17 countries with sufficient sequencing volume and a valid denominator in week 35-36, 2021. In the same weeks, Alpha, Beta and Gamma accounted for <1% of the cases. The current dominance of Delta across the EU/EEA is a marked change from the variant prevalence reported in our previous Risk Assessment, for the period 10 to 23 May 2021, when Alpha was the dominant VOC, accounting for 91.6% (70.2–97.1%) of the sequenced samples, while Delta accounted for 0.2% (0.0–10.1) [1].

Estimates for the basic reproductive number (R_0) for Delta range from 3.2 to 8, with a mean of 5.08 [4]. Delta is estimated to have a relative increase in the pooled basic reproductive number compared with the Alpha (+29%, 95% CI 24-33%) and wild type variants (+97%, 95% CI 76-117%) [5]. This increased transmissibility, which is nearly double that of the wild type SARS-CoV-2 virus that circulated during autumn 2020, is a key factor in Delta's rapid dominance.

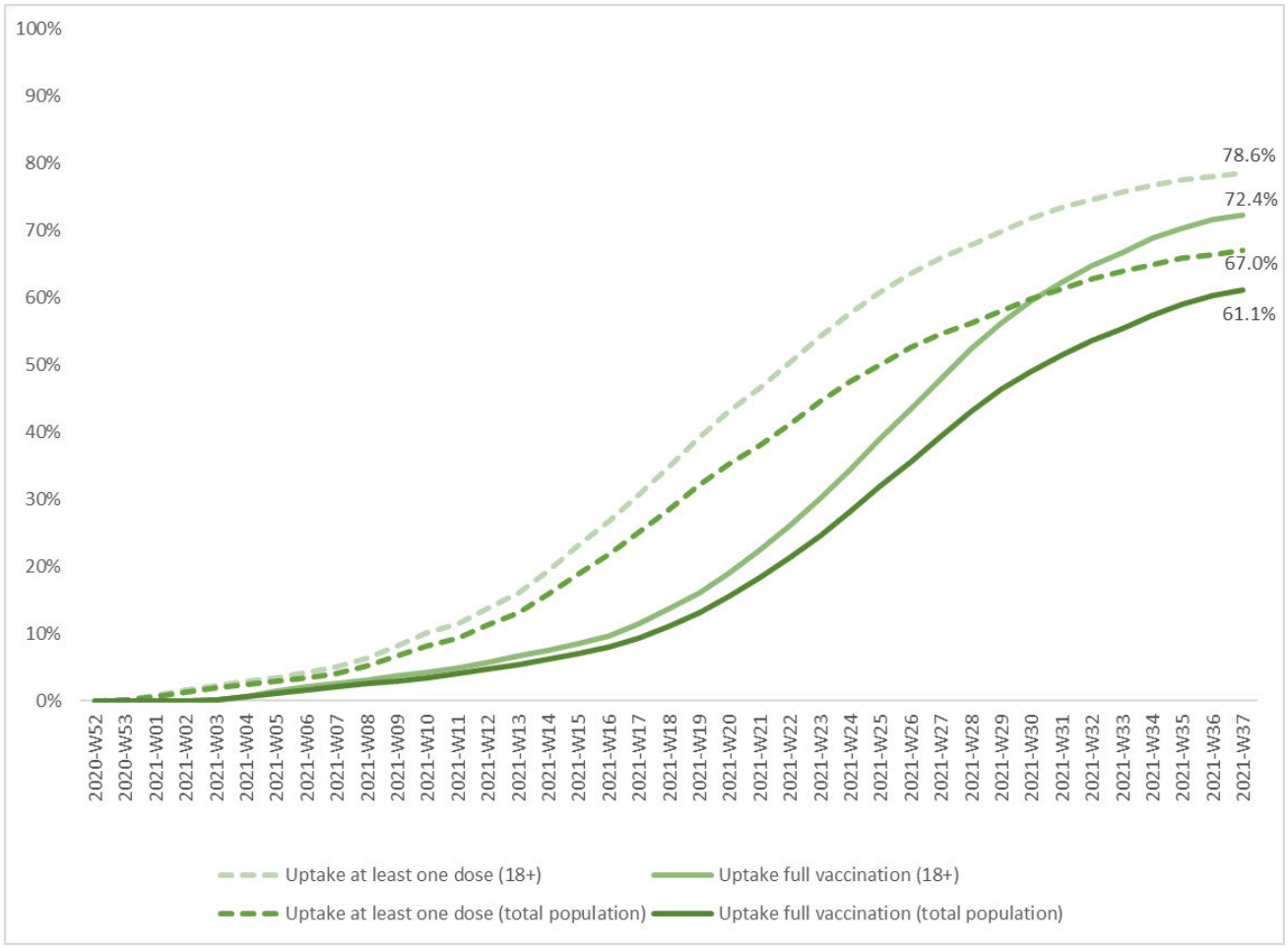
In studies in Scotland and England, the Delta variant has been associated with a two-fold increase in the risk of hospitalisation and emergency care compared with the Alpha variant [6,7], although a similar study from Norway found no difference in the risk for hospitalisation for cases with the Delta variant [8]. Analysis of the impact of the Delta variant on the risk of death due to COVID-19 is affected by the rollout of vaccination programmes at the same time as the variant emerged [6].

If a new variant (including a current VOC with additional mutations) with a significant transmissibility advantage over Delta starts circulating in the EU/EEA, it is likely that it will take at least two to three months from the initial detection of an increasing trend to it becoming dominant based on previous introductions of VOCs and modelling over a range of levels of transmission advantages. There is also a possibility that new variants with a lower R_0 than Delta but associated with significantly reduced vaccine effectiveness and/or increased risk for reinfections could be introduced and start to co-circulate with Delta as levels of immunity increase in the population. However, there are currently no concerning signals for other variants in the EU/EEA, so no major impact on the epidemiological situation in the EU/EEA before the end of 2021 is expected from emerging VOCs.

Vaccination

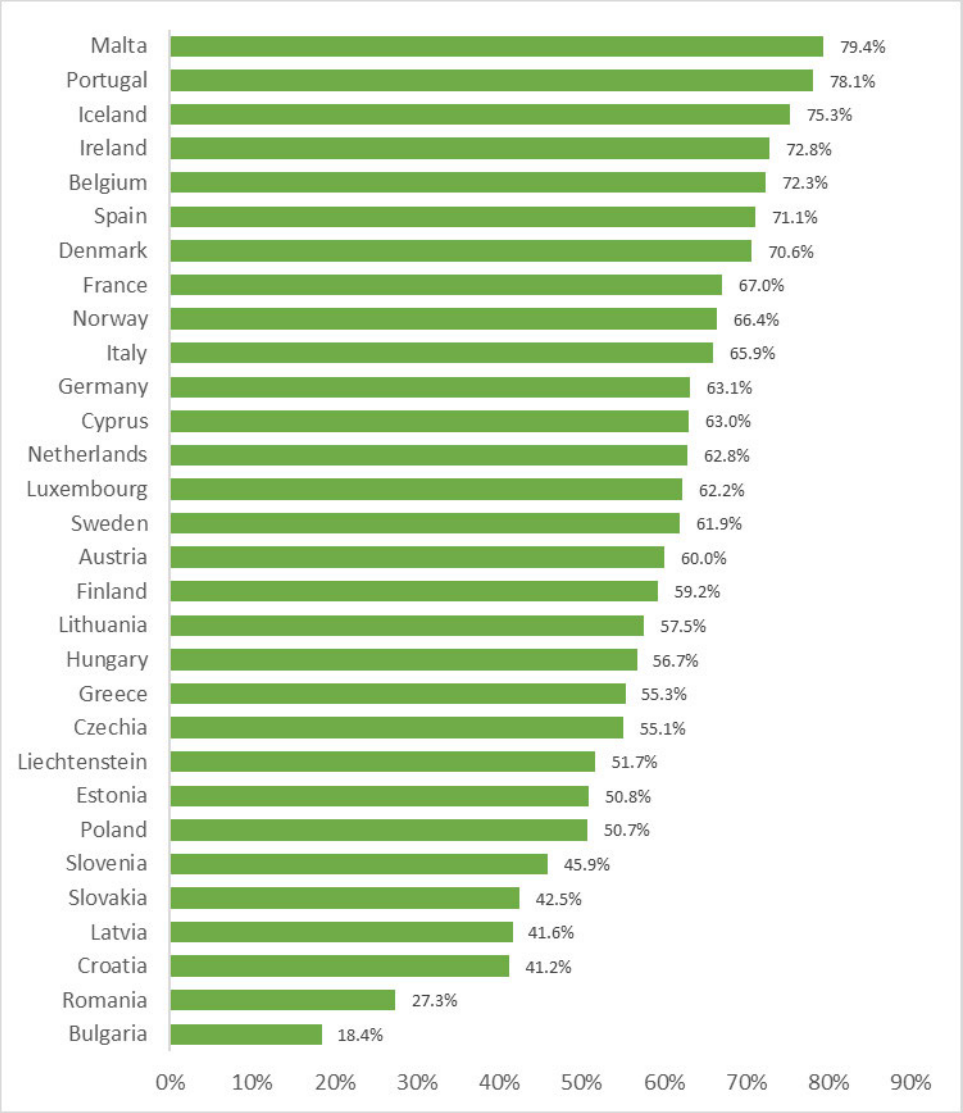
As of 19 September 2021, 43.1% of the world population are reported to have received at least one dose of a COVID-19 vaccine, including only 1.9% of people in low-income countries [9]. As of 19 September 2021 (week 37, 2021), over 565 million vaccine doses have been administered in the EU/EEA. Since the start of the COVID-19 vaccine deployment in December 2020, the cumulative vaccine uptake in the adult population (aged 18 years and older) in the EU/EEA has reached 78.6% for at least one vaccine dose (range 23.5-97.3%) and 72.4% for the full vaccination course (range: 22-90.7%) (30 reporting countries). When estimated over the total population, including children and adolescents for whom the vaccine is not available or who may not be included in national target groups yet, the cumulative vaccine uptake in the EU/EEA is 67% (range 19.8-86.5%) for at least one vaccine dose and 61.1% (range: 18.4-79.4%) for the full vaccination course (30 reporting countries). Approximately 26 million people in the EU/EEA have received their first dose but have not yet completed their primary vaccination course. As the overall cumulative uptake in the adult population reaches above 70%, the pace of weekly increase in uptake is decreasing (Figure 4). Furthermore, progress with vaccination rollout is unequal across EU/EEA countries (Figure 5) and is plateauing at low levels in some of them (Appendix 1) [10].

Figure 4. Cumulative uptake (%) of at least one COVID-19 vaccine dose and full vaccination course amongst adults (18+) and total population in EU/EEA countries as of week 37, 2021



Source: TESSy; data reported by 30 countries as of week 37, 2021.

Figure 5. Cumulative uptake of full COVID-19 vaccination course in the total population by EU/EEA country as of week 37, 2021

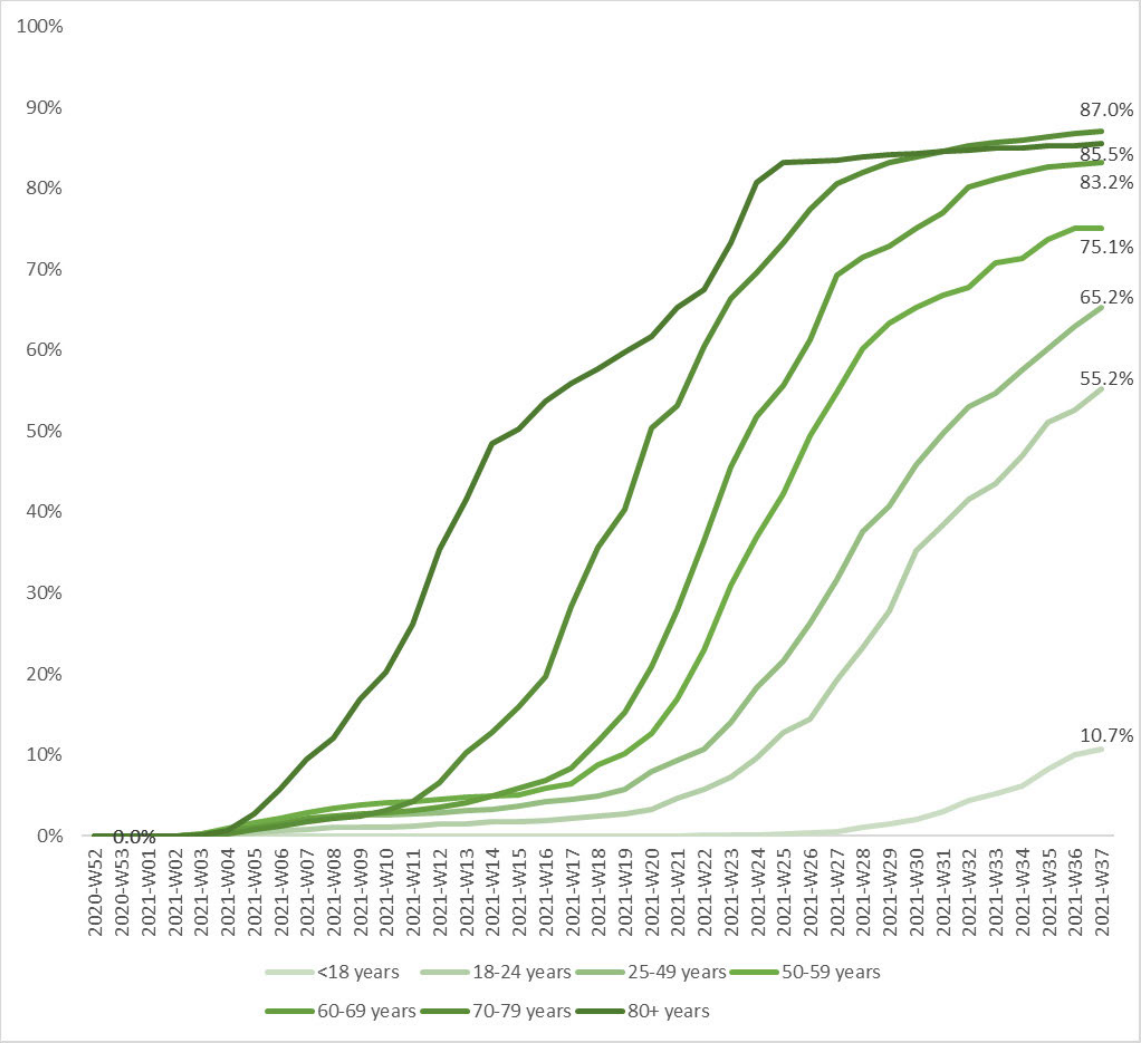


Source: TESSy; data reported by 30 countries as of week 37, 2021. See the Notes on data in the ECDC Vaccine Tracker for country specific disclaimers.

Cumulative vaccine uptake is higher in target groups that have been prioritised since the beginning of vaccine rollout, such as the elderly and healthcare workers (HCWs). In people aged 80 years and above, the median vaccine uptake amongst EU/EEA countries is 87.1% (range 20.1–100%) for at least one dose, and 85.3% (range 19.4–100%) for the full vaccination course (27 countries reporting). For people 60 years and above, the median vaccine uptake is 88.6% (range: 29.8–100%) for at least one dose and 85% (range: 28-100%) for the full vaccination course (27 countries reporting). Sixteen countries have already administered the full vaccination course to more than 80% of the population aged 60 years and above. [11].

As vaccine uptake increased in priority groups (the elderly, residents in long-term care facilities, HCWs, etc.), countries have progressively expanded rollout to include younger age groups, in some cases to the entire population including children aged 12 years and above. Figure 6 presents the median cumulative uptake of full vaccination by age group amongst EU/EEA countries.

Figure 6. Median cumulative uptake of full COVID-19 vaccination course by age group, EU/EEA, week 52, 2020 - week 37, 2021



Source: TESSy; data reported by 27 countries as of week 37, 2021 (missing Germany, Liechtenstein and the Netherlands; for the age group <18 also missing Denmark and Poland).

Of note, in many countries the rollout of COVID-19 vaccines has been unequal at subnational level and significant differences in vaccine uptake at population level may be observed across regions. For example, in Italy, against a national full vaccination coverage of approximately 77.7% in the population over 12 years of age, vaccine uptake in Sicily has reached 69.6% (accessed on 27 September 2021) [12]. In Germany, vaccine uptake in the total population also greatly varies across federal states from 57.5% in Saxony to 78.5% in Bremen (63.9% at national level) (accessed on 27 September 2021) [13]. Similarly in Austria, vaccine coverage in the total population ranges from 55.5% in Upper Austria to 67.9% in Burgenland (60.4% at national level) (accessed on 28 September 2021) [14]. In Belgium, vaccine coverage in the adult population has exceeded 90% in Flanders but is lagging behind in Brussels (64%) (accessed on 27 September 2021) [15].

Most EU/EEA countries report that vaccine supply is no longer an issue, with challenges now mainly related to communication, vaccination acceptance and low vaccine uptake in certain population groups, communities and geographical areas due to hesitancy and access issues [16].

More country-specific data on vaccine uptake, can be found in ECDC's vaccine tracker [10] and the related weekly vaccine rollout overview [11].

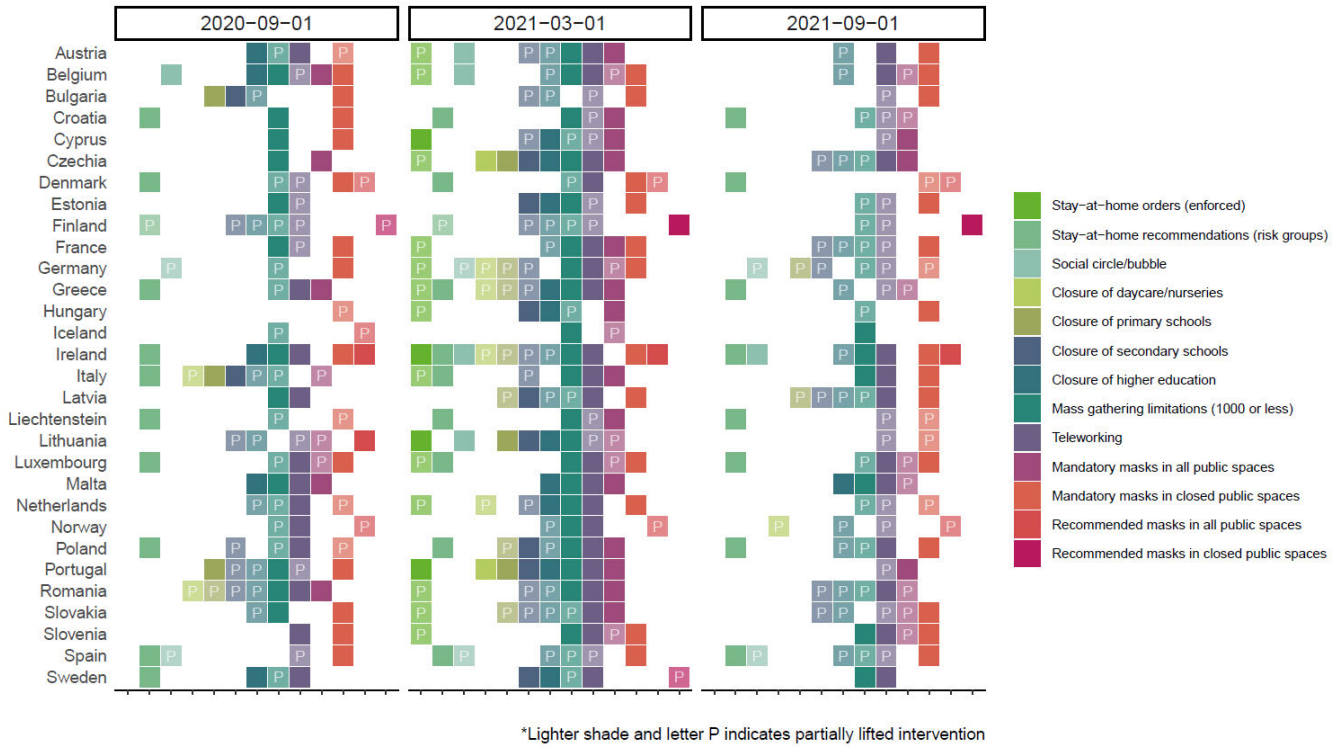
Non-pharmaceutical interventions

Non-pharmaceutical interventions (NPIs) such as the use of face masks, improved ventilation in closed spaces and physical distancing measures are fundamental elements of the public health response to controlling COVID-19. Non-pharmaceutical interventions have proven valuable tools for the public health response if implemented swiftly and decisively with the appropriate risk communication and community engagement. In addition, these measures are similarly effective against other respiratory viruses including influenza.

The ECDC Response Measure Database collects the different NPIs implemented by country in the EU/EEA since January 2020 to prevent the spread of the SARS-CoV-2 virus. Figure 7 shows the different NPIs in place at three points in time: 1 September 2020, 1 March 2021 and 1 September 2021.

Several NPIs have been relaxed or fully lifted in a number of EU/EEA countries, with less measures in place overall (n=113) in September 2021 compared with March 2021 (n=183). In addition, 58% of the NPI measures which remained in place in September 2021 were recorded as partially lifted compared with 40% of measures partially lifted in March 2021.

Figure 7. Comparison of implementation of NPIs for the control of COVID-19 in EU/EEA countries in September 2020, March 2021 and September 2021



Note: the visualisation above is a comparison at three points in time, and not a period analysis. Several countries have introduced various measures between or after the dates selected

Stay-at-home orders and recommendations: Stay-at-home orders are the clearest example of the differences between time points, with 17 countries implementing such partial or full orders in March 2021 and no countries doing so in September 2021. Regarding stay-at-home recommendations for risk groups, 10 countries had these in place in March 2021 and eight countries still had these recommendations in September 2021.

Mass gatherings: During the spring of 2021, nearly all EU/EEA countries introduced limitations on the number of people allowed to gather at public events, both indoors and outdoors. In September 2021, these measures have been either eased (allowing a larger number of people to gather in public spaces or introducing other partial measures) or lifted in most countries, with six Member States still reporting full closure and 13 partial closure of events up to 1 000 participants or less.

Teleworking: Recommendations have largely remained in place between 1 March and 1 September 2021, however, in September the recommendation is reported as partial in more countries.

Use of facemasks in community settings: The mandatory use of facemasks has also decreased from 17 countries having full or partial mask mandates in all public spaces in March 2021 to 11 countries in September 2021. Furthermore, there is variation in the degree to which the mandates are implemented.

Exemptions to NPIs: In Spring 2021, 23 countries introduced varied exemptions to implemented NPIs for the total population when fully vaccinated, ranging from requiring digital covid certificates to attend public gatherings for example, to lifting quarantine requirements or allowing different sized gatherings or social encounters for those that are vaccinated.

Schools: By September 2021, only one country had partial closure of daycare facilities, in contrast to six countries having had partial or wider closures in March 2021. Similarly, in primary and secondary schools, fewer countries had partial or full closures in September 2021 compared with March 2021. For higher education, fewer countries had remaining partial or full closures, although 12 countries still reported partial closures and one country full closure in September 2021.

Regional implementation: Since the end of 2020, a rising number of measures have been implemented at a lower geographical level. This reflects regional differences in incidence within countries and detection of local outbreaks and is not fully captured by the ECDC Response Measure Database.

Use of self-tests in specific settings: In a survey performed by ECDC in July 2021, 12 out of 22 countries responded that they were using RADT self-tests in different settings. In seven countries, self-tests were either mandatory (4) or recommended (3) in schools and six countries had mandatory (2) or recommended (4) use in workplaces. Other settings mentioned were LTCF, kindergartens, restaurants, hotels, airports etc. As the information was gathered through a survey, no more recent update is available.

Potential co-circulation of SARS-CoV-2 with influenza and other respiratory viruses

Since the implementation of strict public health and physical distancing measures in February 2020, seasonal influenza virus circulation has been significantly reduced in the EU/EEA as well as globally. This situation of very low influenza circulation continued during the 2020/21 season and the summer months 2021 [17-19]. However, in recent weeks, an increasing number of cases due to influenza A(H3N2) virus have been reported from several countries across the European Region [18]. These cases were reported from sentinel and non-sentinel surveillance system including hospital settings. Influenza A(H3N2) viruses have been shown in the past to primarily affect the elderly and the very young (i.e. children below five years of age), cause severe and large outbreaks in long-term care facilities [20-22], lead to high excess mortality in the elderly population [23-25] and increase pressure on healthcare systems. Vaccine effectiveness (VE) data from previous regular influenza seasons for A(H3N2) viruses have been overall low to moderate and low to very low, particularly in the elderly who are most at risk of severe disease [26-31]. The limited circulation during this and last year might also contribute to a higher susceptibility in the population with less people being exposed to influenza viruses.

Due to lack of influenza circulation in the past year, the timing of an eventual influenza epidemic in Europe is difficult to predict. An earlier onset of the seasonal influenza epidemic (usually peaking around weeks 49-06) than in pre-COVID-19 seasons is possible, potentially adding pressure and burden on healthcare settings.

Influenza and SARS-CoV-2 co-infections have been only documented rarely, which is likely due to the limited circulation of influenza viruses during this pandemic. One study in the United Kingdom showed higher severity in these co-infected cases early in the pandemic when influenza was still circulating [32]. The risk groups for severe influenza disease largely overlap with groups most at risk of severe COVID-19 disease and death. Therefore, there could be several benefits to the co-administration of COVID-19 vaccines with seasonal influenza vaccination campaigns. The infrastructure for seasonal influenza vaccination is already in place and can be modified according to the epidemiological context of COVID-19. Previous evidence from co-administration of other vaccines has not shown any safety or effectiveness concerns, although evidence from the co-administration of mRNA vaccines with other vaccines is still scarce. The US American Committee on Immunisation Practices (ACIP) stated in their recommendations that COVID-19 vaccines and other vaccines may be administered at the same time [33]. Results from the phase three randomised trial (preprint) of the safety and efficacy of NVX-CoV2373 (Novavax; currently not authorised for use in the EU) shows that the safety, immunogenicity, and efficacy profile of the COVID-19 vaccine is maintained while co-administered with the seasonal influenza vaccine, with only a slight decrease in vaccine efficacy from 89.8% (95% CI: 79.7–95.5) to 87.5% (95% CI: -0.2–98.4) [34]. In the UK, preliminary (unpublished) evidence from the ComFluCOV trial [35] indicates that co-administration of the influenza and COVID-19 vaccines is generally well tolerated with no reduction in immunogenicity, the two vaccines may be co-administered where operationally practical [36,37].

Similar to seasonal influenza, respiratory syncytial virus (RSV) detection levels were significantly lower during the 2020/21 season in many countries around the world including in EU/EEA countries. Non-pharmaceutical interventions implemented to control SARS-CoV-2 transmission are believed to prevent the transmission of RSV; with measures in daycare centres and schools possibly playing a bigger role in this [38]. However, a number of countries reported out-of-season RSV epidemics in 2021 [39,40].

Societal and healthcare worker fatigue

Several studies have shown increases in HCW fatigue during the pandemic in terms of stress, anxiety and burn out as well as other metrics [41,42]. As the strain on healthcare systems has continued in several countries in 2021, it is expected that fatigue amongst HCWs has only further increased. Whilst some studies have shown opposite effects, possibly because of an increased sense of motivation and recognition by society, the future workload and fatigue within healthcare is likely to remain high due to the COVID-19 pandemic but also possibly in terms of other communicable diseases such as influenza or respiratory syncytial virus (RSV), as already seen in some areas [39,43-45]. Further increases in the healthcare burden will happen due to backlog of diagnosis and treatment for non-communicable diseases such as cancer, during the pandemic in 2020-2021 [46].

Pandemic fatigue was identified almost a year ago by WHO as a significant factor of 'de-motivation to follow recommended protective measures' and continues to be a significant challenge for countries [47]. Pandemic fatigue brings with it the risk of increased infection rates, increased strains on healthcare capacity, increased impact on the economy and society, and the likelihood that even stricter measures may be needed in the near future to control the further spread of the virus [48].

Disease background

For additional information on the latest scientific evidence relating to COVID-19, SARS-CoV-2, virus transmission, diagnostic testing, infection, clinical characteristics, risk factors and risk groups, immunity, treatment and vaccines please visit ECDC's website: https://www.ecdc.europa.eu/en/covid-19/latest-evidence.

Impact of Delta on COVID-19 vaccine effectiveness

An update of the evidence of vaccine effectiveness against SARS-CoV-2 infection by severity (mild/moderate disease, severe disease, hospitalisation, death) and variants of concern was included in the recently published ECDC technical report 'Interim public health considerations for the provision of additional COVID-19 vaccine doses' [49].

Multiple studies indicate a decrease in vaccine effectiveness against SARS-CoV-2 infection with the Delta variant compared with wild-type and Alpha. The impact of the Delta variant on vaccine effectiveness against severe disease, hospitalisation and death was less pronounced with high effectiveness maintained overall. However, this needs to be carefully monitored over time, particularly amongst older adults where some signs of decreased protection against hospitalisations have now been reported by some countries. Below we present a few relevant updates on vaccine effectiveness in the context of the current dominance of the Delta variant.

The Danish Public Health Institute published an official communication of an analysis of data from 2 000 breakthrough infections between 1 March and 3 August 2021, including the periods when Alpha and then Delta variants were dominant in Denmark. They found a high vaccine effectiveness against hospitalisations due to the Delta variant following two doses of Comirnaty (94.4%; 95% CI: 91.1–96.5) or Vaxzevria (96.6%; 95% CI: 75.3–99.5) (not possible to estimate for Spikevax as there were no cases during the study period) with slightly lower effectiveness for the Alpha VOC after two doses of Comirnaty (85.6%; 95% CI: 80.4–89.5) (not possible to estimate for Vaxzevria as there were no cases during the study period). These findings may be partly due to people who were vaccinated during the Delta variant study period being considerably younger than those who were vaccinated during the Alpha variant study period. However, the estimates of vaccine effectiveness against infection were slightly lower for the Delta variant (Comirnaty: 78.8%, 95% CI: 77.2–80.4; Spikevax: 88.1%, 95% CI: 83.6–91.4; Vaxzevria: 73.7%, 95% CI: 70–77) compared with the Alpha variant (Comirnaty: 81%, 95% CI: 79.4–82.4; Spikevax: 95.9%, 95% CI: 91.4–98.1; Vaxzevria: 93.2%, 95% CI: 89.5–95.5) [50].

A recent study conducted in Portugal estimated vaccine effectiveness against hospitalisation and deaths in adults 65 years and older, receiving either Comirnaty or Spikevax, between February and August 2021 and found slightly lower vaccine effectiveness estimates in the ≥80 years olds compared with younger age groups 14 days after the administration of the second dose, but overall sustained protection against hospitalisations and deaths up to 98 days (three months) from the administration of the second dose in all age groups [51].

Studies from Israel [52,53] and the US [54,55] on waning immunity showed evidence of reductions in effectiveness of Comirnaty against infections ≥5 months after being fully vaccinated, but still high vaccine effectiveness against hospitalisation and severe disease overall.

In older age groups and in residents of long-term care facilities there is some emerging evidence of possibly decreased effectiveness of COVID-19 vaccines against not only infections, but also against hospitalisation. A study from the US amongst nursing home residents found that protection from Comirnaty or Spikevax against SARS CoV-2 infection for the fully vaccinated in the pre-Delta period was 75%, declining to 53% in the Delta period [56]. In addition, two recent studies from the US have shown that vaccine effectiveness against hospitalisation is lower in older adults (Bajema et al: VE ≥65 years: 79.8% vs 18–64 years: 95.1%; Grannis et al: VE ≥75 years: 76% vs 18–74 years: 89%) with Comirnaty or Spikevax [57,58].

On 9 September 2021, Public Health England released new data on the duration of immunity after full vaccination with Comirnaty or Vaxzevria, which are similar to those from Israel and the US. For both vaccines, waning of vaccine effectiveness against symptomatic disease is seen from around 10 weeks after the second dose and is mostly observed in older adults. Vaccine effectiveness against symptomatic disease due to Delta variant peaked in the early weeks after the second dose and then fell to 47.3% (95% CI: 45–49.6) and 69.7% (95% CI: 68.7–70.5) beyond 20 weeks after completion of the primary series with Vaxzevria and Comirnaty, respectively. Waning of vaccine effectiveness against symptomatic disease was greater for individuals aged 65 and above compared with 40-64-year-olds. Nevertheless, after completion of the primary series, protection against hospitalisations remained high throughout the follow-up period, at 77.0% (95% CI: 70.3–82.3) and 92.7% (95% CI: 90.3–94.6) with Vaxzevria and Comirnaty, respectively. Greater waning of vaccine effectiveness against hospitalisation was observed amongst individuals aged 65 and above, in vulnerable and frail individuals and 40-64-year-olds with underlying medical conditions compared with healthy adults [59].

It is difficult to ascertain if reductions in effectiveness against SARS-CoV-2 infections over time are due to waning immunity or Delta partially escaping vaccine protection. The Delta variant is characterised by higher transmissibility, higher viral loads in the respiratory tract, as well as partial escape from cellular and humoral responses which could contribute to lower VE, particularly in the elderly.

Natural immunity to SARS-CoV-2

Prevalence of SARS-CoV-2 antibodies in Europe

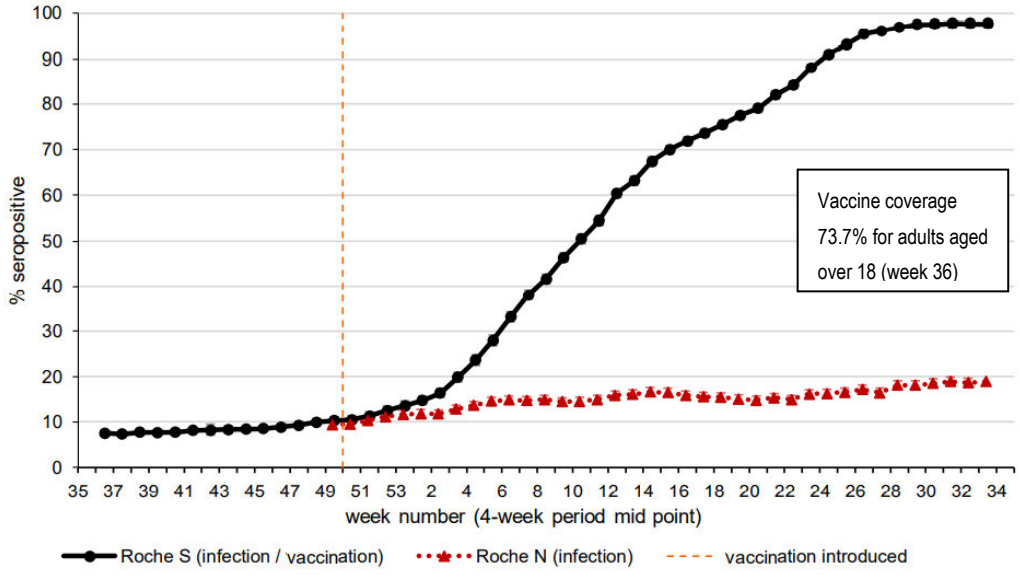
Seroprevalence studies, in which infection- or vaccination-derived serum antibody levels are determined for representative subsets of a population can provide useful estimates of existing population exposure to, and protection against, infection with SARS-CoV-2 [60].

Data from studies conducted during 2020 showed evidence of low national seroprevalence (<10%) across the WHO European region, except for a few sub-national populations that had experienced intense community transmission, with estimates ranging up to 52% [61]. Although seroprevalence varied markedly between and within countries, the overall results indicate that during 2020, only a low proportion of the European population had evidence of immunity to SARS-CoV-2. During 2020, estimates of seroprevalence varied by age across studies with no obvious overall trends.

Data from SARS-CoV-2 serosurveys conducted around the world are systematically collected by Serotracker [62]. Many of these studies have been classified as having a medium or high risk of bias, with weak methodological approaches including the use of convenience sampling, low sample sizes and suboptimal laboratory assays. Nevertheless, the results from studies within the EU/EEA all show a steady increase in the seroprevalence from April 2021 onwards (estimates between 32.8% in Sweden [63] up to 68% in Estonia [64] during June). The sharp increases in seropositivity observed correspond closely to the rollout of COVID-19 vaccination programs across the region, with the highest seroprevalence currently observed amongst older age groups who were vaccinated first. Findings from a study among blood donors in Sweden in March 2021, just prior to the widespread rollout of vaccination in the population, found a seroprevalence of around 22% which probably reflects the baseline level of natural immunity amongst adults at that time [65]. Later results from the same study showed a seroprevalence of 51.9% amongst the Swedish blood donors for the period of June 24 to 4 August 2021.

Most of the published seroprevalence studies in the EU/EEA region do not yet differentiate the level of natural versus vaccine-induced immunity, even though this is potentially possible using different serological assays for research purposes. The UK have conducted longitudinal testing of blood donor samples using nucleoprotein (nucleocapsid antigen) (N) and spike (S) assays to differentiate natural and vaccine-induced immunity, with the N assays detecting antibodies from natural infection and S assays detecting both post-infection and vaccine-induced antibodies [66]. This testing has shown a dramatic rise in antibodies since the introduction of vaccination with the latest data (see Figure 8) indicating that 97.7% of donors aged 17 and over have antibodies from either infection or vaccination. The data suggest that these antibodies are mostly related to vaccination, with a seroprevalence of around 20% due to natural infection.

Figure 8. Four-weekly rolling SARS-CoV-2 antibody seroprevalence (% seropositive) in blood donors in England, 2020 -2021 [66]



Estimates of seroprevalence have been compared with the corresponding global cumulative incidence of confirmed COVID-19 infections. These comparisons have shown large variations with seroprevalence estimates generally considerably higher than the reported cumulative incidence, with one study estimating the median ratio of seroprevalence to cumulative incidence of SARS-CoV-2 infection to be almost 18 [67]. Other systematic reviews have shown a broad range of ratios with all findings suggesting a high level of case under-ascertainment due to insufficient testing in some locations and the fact that many cases that are pauci- or asymptomatic go undetected [68,69].

Taken together, estimates of existing population exposure to, and protection against, infection with SARS-CoV-2 via seroprevalence studies are challenging because of wide variability in seroprevalence estimates, largely driven by biases in population sampling. Furthermore, use of case notification rates to determine true population exposure to SARS-CoV-2 can be misleading because of under-ascertainment, given that not all SARS-CoV-2 infected individuals undergo testing or seroconvert. The extent of under-ascertainment is driven by context-specific factors that change over time, such as testing strategy and capacity. Additional research is needed to better understand the consequence of waning antibody responses for serosurveys and for accurate extrapolation of results from seroprevalence studies to the level of protection in the population.

Reinfection with SARS-CoV-2

Evidence on duration of immunity for recovered individuals is ideally drawn from longitudinal cohorts comparing infection risk amongst naïve and recovered individuals at three or six monthly intervals. Unfortunately, such studies are sparse. A systematic review of 11 key studies conducted by Health Information and Quality Authority in Ireland suggests that the reinfection risk amongst recovered individuals is low (absolute rate 0%–1.1%), with protection maintained for up to 10 months post initial infection [70]. More recently, Vitale et al. observed protection from reinfection for recovered individuals for a period of at least 12 months [71]. However, a critical limitation of these studies is that their observation periods predate the emergence and subsequent dominance of the Delta variant across the EU/EEA.

Preliminary analysis of national surveillance data from the UK indicates that recovered individuals have an increased risk of reinfection with Delta compared with the previously dominant Alpha strain, with the overall odds approximately 46% higher [72]. The Public Health England analysis included 83 197 individuals ≥15 years of age, who became SARS-CoV-2 PCR positive during an 11-week observation period (12 April and 27 June 2021), of whom 980 (1.2%) were possible reinfections. The adjusted odds ratio of reinfection with the Delta variant was 1.46 (95% CI 1.03 to 2.05) compared with the previously dominant Alpha variant. The risk of reinfection was not elevated for Delta if the primary infection occurred <180 days earlier (adjusted odds ratio = 0.79, 95% CI 0.49–1.28) but was higher for those with a prior infection ≥180 days earlier (adjusted odds ratio = 2.37, 95%CI 1.43–3.93). This finding has not yet been replicated in other settings, and additional age-stratified data on reinfection risk over time, specifically in the context of the Delta variant, is needed.

In the absence of a universal immune correlate which can be measured in recovered individuals to infer protection, the virus-neutralising capability of serum antibodies provide the best current indication of protection from reinfection. Whilst most SARS-CoV-2 infected individuals will develop serum antibodies, recovered individuals demonstrate highly variable antibody dynamics over time [73], with waning of neutralising antibodies widely documented [74]. In a key study by Planas *et al.*, sera collected from 56 convalescent individuals six months post-symptom onset were shown to be four-fold less potent against the Delta variant relative to the Alpha variant. The authors also observed a similar four-fold reduction in a separate cohort of 26 convalescent individuals evaluated 12 months post-symptom onset, stressing that neutralisation activity was globally low by month 12 [75].

Waning of serum antibodies may be entirely mitigated by the presence of SARS-CoV-2-specific memory B cells, which can rapidly expand when supported by SARS-CoV-2-specific memory T cells. Memory T cells may also contribute to protection and recovery from infection by directly lysing SARS-CoV-2 infected cells. However, specific T cell correlates remain elusive [76-78].

Taken together, the risk of reinfection with the Delta variant remains low, albeit with evidence of increased risk relative to the previously circulating Alpha variant.

Modelling forecasts

As EU/EEA countries are entering the autumn months of 2021, COVID-19 vaccination coverage appears to be reaching a plateau, with the rate of weekly increase slowing in most age groups, following a large-scale vaccination programme. Since last spring, many NPIs have been lifted (see above 'Non-pharmaceutical interventions') and contact rates have increased steadily across the EU/EEA, as can be seen in contact surveys [79] as well as mobility data [80]. The future course of the pandemic will be determined largely by the contact rates between people and by immunity conferred through vaccination and/or past infection. Importantly, the Delta variant, estimated to be twice as transmissible as the wild type variant that was circulating last autumn, is dominant across all EU/EEA Member States.

In view of the high transmissibility of the Delta variant, stagnating vaccination coverage and relaxation of NPIs, we estimate the number of cases, deaths, and hospitalisations in the EU/EEA until the end of November 2021, taking into account available epidemiological and vaccination data up to 8 September 2021. A crucial challenge for trying to predict the course of COVID-19 are the uncertainties regarding: vaccine effectiveness, the number of recovered individuals with natural immunity, human mobility patterns and the seasonal effects of the viral spread. We take these uncertainties into account by considering different prediction scenarios (Table 1). By exploring all scenarios, we obtain a predicted landscape of COVID-19 in Autumn 2021. For simplicity, for all scenarios we consider an optimistic set of assumptions: natural immunity protects 100% against reinfection, there is cross-protection across variants, and there is no waning of natural immunity within one year. Thus, our predictions, which are based on this optimistic setting, yield a lower bound on the COVID-19 burden.

Furthermore, we assume that Delta remains the dominant variant, and that this variant is twice as infective as the wildtype SARS-CoV-2 [5], which was dominant last autumn. We further assume that vaccination programmes continue with a good supply of vaccine doses, but vaccination coverage starts to stagnate. These vaccination projections take into account the current prioritisation of age groups and dose spacing [10]. We use studies of vaccine efficacy against the Delta variant and weigh estimates for the different vaccine products according to their distribution in the EU/EEA [10]. We use a bootstrap method to obtain effectiveness mean and range estimates, and repeat this for effectiveness against cases, hospitalisation, and death. We use mean values in our baseline forecast scenario and the range estimates in additional scenarios.

We then generate COVID-19 cases by age-group, considering shifted age case distribution due to vaccination. We further estimate projected hospitalisations from the age-based case-hospitalisation rates, which are obtained from data during the dominance of wildtype SARS-CoV-2 in October and November 2020; we adjust those rates according to severity of the Delta variant as well as vaccine protection against severe outcomes by this variant, including for partially and fully vaccinated individuals. We simulate forecasts for the 11 different scenarios to capture the uncertainty in our key model assumptions (see Table 1).

In our baseline scenario (scenario 1, Table 1), we assume that contact rates (rates of transmission-relevant contacts between people) stay the same as those observed at the beginning of September 2021. We use Google mobility data [80] to inform changes in viral transmission in the forecast period compared with last year. Additional scenarios consider high and low VE against infection and against severe disease (scenarios 2-5, Table 1). To reflect current case detection rates, we use serological survey studies conducted in 2021 (see references and discussion in 'Natural immunity to SARS-CoV-2' section) and cumulative detected cases to estimate that for each detected case in the EU/EEA, 2.2 additional undetected individuals developed natural immunity. To reflect variability and uncertainty of this under-detection factor, we use a bootstrap method and obtain a value range that we include as additional scenarios (scenarios 6-9, Table 1). In one additional scenario we assume a seasonal forcing of transmission that we estimated in an analysis that adjusts for NPI and other effects. In another scenario we apply half of that seasonal forcing (scenarios 10 and 11, Table 1).

Table 1. Baseline and alternative forecast scenarios for COVID-19 in the EU/EEA, Autumn 2021

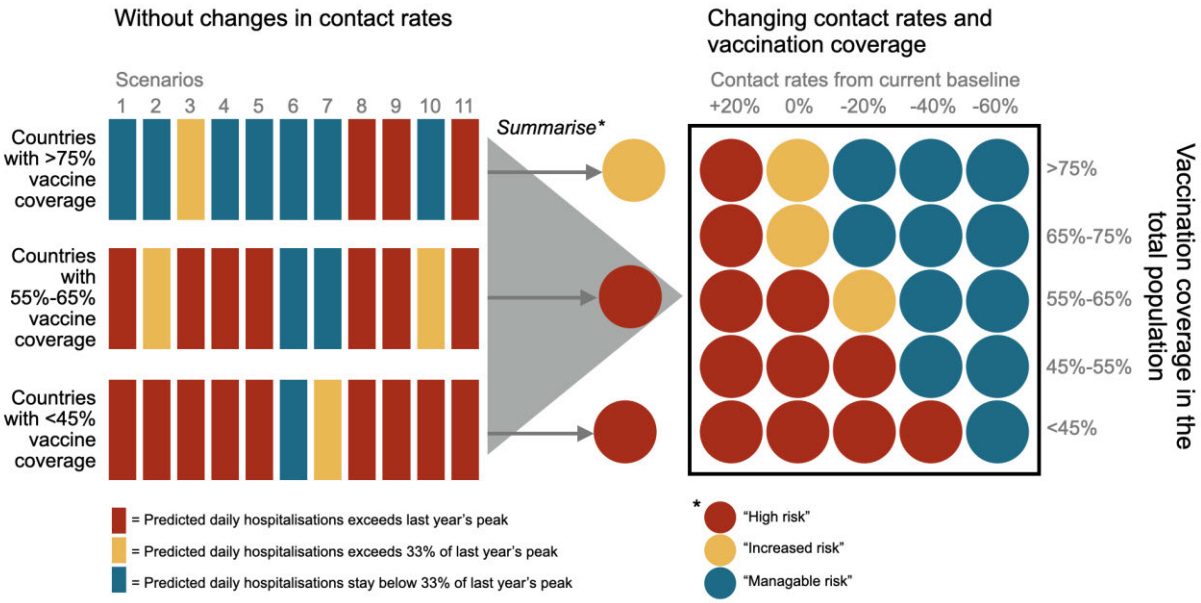
Scenario	1	2	3	4	5	6	7	8	9	10	11
Scenario name	*Baseline*	*High VE cases*	*Low VE cases*	*High VE severe*	*Low VE severe*	*Very high natural immunity*	*High natural immunity*	*Low natural immunity*	*Very low natural immunity*	*Half seasonal forcing*	*Seasonal forcing*
Contact rates between people	Current mobility	Current mobility	Current mobility	Current mobility	Current mobility	Current mobility	Current mobility	Current mobility	Current mobility	0.5xSeasonality	1xSeasonality
Natural immunity	3.2 x cases	3.2 x cases	3.2 x cases	3.2 x cases	3.2 x cases	10.7 x cases	6 x cases	1.7 x cases	1 x cases	3.2 x cases	3.2 x cases
VE cases	71%	76%	66%	71%	71%	71%	71%	71%	71%	71%	71%
VE severe (hospitalisation/death)	82%/82%	82%/82%	82%/82%	90%/90%	74%/74%	82%/82%	82%/82%	82%/82%	82%/82%	82%/82%	82%/82%

Note to Table 1: Gives the parameters used in the different forecast scenarios with one baseline scenario (scenario 1) and ten alternative scenarios. These scenarios reflect uncertain factors which cannot be modified by Member States such as vaccine efficacy against the Delta variant. Scenario 10 applies seasonal forcing estimated elsewhere, and scenario 11 applies half of this seasonal forcing. VE: vaccine efficacy.

We show the model predictions based on full course vaccine coverage in the total population. For easier readability, the left side of Figure 9 shows the main three vaccination coverage levels while all five levels are considered on the right-hand side. Note that we do not model future vaccination in <18-year-old populations as that varies greatly between Member States. Moreover, projections are based on a mean vaccination coverage for each country group, such that for countries with a coverage below this mean, prediction would be worse. The thresholds of the qualitative classification by vaccination coverage are based on the distribution of vaccine coverage levels assessed at the time of the modelling. Overall, countries with <45% vaccination coverage in total population fall into the low coverage group, those with 45–55% into low-intermediate coverage, countries with 55–65% into intermediate coverage, those with 65–75% into intermediate-high coverage, and countries with >75% vaccination coverage in the total population are seen in a high vaccination group.

For every predicted scenario, we visualise our forecasts with a rectangle whose colour indicates the hospitalisation burden (assuming unchanged contact rates from those currently observed): blue indicates low daily hospitalisations (below 33% of the past EU/EEA peak during the COVID-19 pandemic), yellow indicates substantial hospitalisation burden (over 33%, but not exceeding the past EU/EEA peak), and red indicates very high hospitalisation burden (exceeding the past EU/EEA peak). The left-hand side of Figure 9 shows the predicted burden of the 11 scenarios and the three main vaccination levels. We then summarise the predictions across modelling scenarios (Figure 9, arrows to circles): Without changes in contact rates from current levels, the countries at the highest level of vaccination coverage are at 'increased risk', while those at average or low vaccination coverage are at 'high risk' (Figure 9). From this we show predicted risk of healthcare burden based on different vaccination coverage and contact pattern levels (Figure 9, right-hand side).

Figure 9. Projected burden of COVID-19 hospitalisations in relation to vaccination coverage between now and the end of November 2021.



Note: The left subfigure shows model projections (assuming unchanged current contact rates) as rectangles in blue (predicted burden that stays below 33% of the COVID-19 pandemic's peak hospitalisation rate), yellow (burden above 33% but below peak rate), and red (burden exceeds the peak rate). These projections are shown for three levels of vaccination coverage (rows, full vaccination course in the total population), and across 11 different scenarios (columns) that vary parameters (see Table 1). While the vaccination levels can be increased by Member States, the parameters are a biological reality and cannot be influenced. The different scenario outcomes are then summarised into single categories (depicted as circles).
The right-hand side shows the risk for hospital burden as circles in blue ('manageable risk'), yellow ('increased risk'), and red ('high risk'), across different vaccination coverages as well as different changes in contact rates from the current baseline. The vaccination coverage range represent current coverage, but as the projected values change only by few %, the range also represents the future vaccination coverage.

Our forecasts show that a combination of high vaccination coverage and effective contact reduction (see section 'Options for response - Non-pharmaceutical interventions') is crucial for reducing the risk of high COVID-19 burden on healthcare systems in Autumn 2021 (see Figure 9). EU/EEA countries with low vaccination coverage will likely require substantial reductions in contacts between people or otherwise risk a high burden on their healthcare system. Similarly, countries with intermediate vaccination coverage will also likely require contact reductions to avoid a high burden. Lastly, EU/EEA countries with high vaccination coverage could experience a manageable burden at current contact rates, but this burden would increase if contact rates increase further. Moreover, even in countries with high vaccination coverage, a high burden is possible due to potential waning of vaccine effectiveness (see Appendix 2) or low levels of natural immunity. Because vaccines offer high protection against severe outcomes of COVID-19 infection, a large proportion of COVID-19 hospital admissions will be unvaccinated individuals, in particular unvaccinated individuals in risk groups. This will especially be true in countries with low vaccination coverage, where a high burden of severe illness is projected. A high burden of severe illness, however, is also a risk for intermediate and high vaccination locations. This is because the high transmissibility of Delta roughly outweighs the reduction in transmission achieved by the current vaccination rollout. The key impact of vaccination is indeed the reduction of the case-hospitalisation and case-fatality rates, thus decoupling case burden and burden of severe disease. Nonetheless, our modelling shows that Delta's transmissibility as well as increasing contact rates could combine to pose a significant risk for exponential growth of cases this autumn. Such growth may lead to a burden of cases that outweighs the reduction in case-hospitalisation rates, thereby leading to a comparable or higher burden than last winter.

This risk for exponential growth will be further exacerbated by the potential for waning of vaccine effectiveness against transmission. We estimate that if substantial waning of vaccine immunity occurs, the risk of high healthcare burden strongly increases for all vaccination scenarios, thus requiring even further contact reduction (see Appendix 2). Furthermore, hospitalisation rates for COVID-19 infection modelled here do not account for further pressures that health systems may face through, for example, increased hospitalisations due to a moderate or severe influenza season. Finally, any country, including those with high vaccination coverage, is likely to have communities with low vaccination coverage. Our results suggest that those communities are at a high risk for a substantial burden of severe illness. A combination of targeted vaccination campaigns and NPIs could help reduce this risk. This may further require close monitoring of COVID-19 cases on a local scale.

Limitations

There are a number limitations to this modelling. We use estimates of vaccine efficacy from trials, but those only give an imperfect picture of real-world vaccine effectiveness. Moreover, due to lack of accurate data, we do not use age-stratified vaccine efficacies. More observational studies on the effectiveness of vaccines are needed. Behaviour is extremely difficult to measure and to predict and here google mobility data is used as a proxy for contact rates. Additionally, there are still many unknowns around natural immunity to SARS-CoV-2, which we are trying to capture through a wide range of natural immunity scenarios. Finally, it remains unclear to what extent viral transmission of SARS-CoV-2 is affected by climate and other seasonal factors. Our forecasts should therefore be interpreted in the light of these uncertainties.

ECDC risk assessment for the EU/EEA

This assessment is based on evidence available to ECDC at the time of publication and is informed by mathematical modelling of projected disease burden for scenarios that consider vaccination coverage, vaccine effectiveness, natural immunity, and population contact rates—in the context of the continued circulation of the Delta variant. Unlike the previous Risk Assessments, which provided a risk estimate for a single point in time, this assessment of risk covers the period between now and the end of November 2021. Nonetheless, assessment follows the same ECDC risk assessment methodology as in the previous Risk Assessments, with the overall risk determined by a combination of the probability of an event occurring (infection with SARS-CoV-2) and its impact for a given population [81].

The current assessment of the risk posed by the SARS-CoV-2 pandemic is stratified by four population groups: the vaccinated and the unvaccinated general population; the vaccinated and the unvaccinated vulnerable population. The assessment is based on the following principles: i) the vaccinated have a lower probability of infection and ii) a lower impact of such infection than the unvaccinated, while iii) whether vaccinated or not, the vulnerable population suffers a higher impact of such infection when compared with the general population. Following the current ECDC forecast (see section on 'Modelling') the risk to EU/EEA countries is assessed based on their current levels of full COVID-19 vaccination coverage in their total population, grouped into three categories (low, average, high). Appendix 3 includes a detailed description of the assessment process per population and vaccination coverage group, where the low and average vaccination coverage countries have been combined to facilitate presentation.

Risk assessment question

Based on current vaccination coverage and the circulating Delta variant in the EU/EEA, what risk does SARS-CoV-2 pose to the general population and to vulnerable population?

Countries with low vaccination coverage

Current ECDC modelling indicates that without substantial changes in population contact rates, countries or regions with vaccination coverage in the total population that is below the current EU average level are projected to experience a high burden of hospitalisations and deaths between now and end of November 2021.

<u>General population</u>

- Fully vaccinated: probability of infection HIGH + impact of infection LOW ➔ **LOW-MODERATE RISK**
- Unvaccinated: probability of infection VERY HIGH + impact of infection HIGH ➔ **HIGH-to-VERY HIGH RISK**

<u>Vulnerable population</u>

- Fully vaccinated: probability of infection HIGH + impact of infection VERY HIGH ➔ **HIGH-to-VERY HIGH RISK**
- Unvaccinated: probability of infection VERY HIGH + impact of infection VERY HIGH ➔ **VERY HIGH RISK**

Countries with average vaccination coverage

Without moderate changes in contact rates, countries or regions with vaccination coverage in the total population that is at the EU average level are projected to experience a high burden of hospitalisations and deaths unless their population has high natural immunity from previous SARS-CoV-2 infections.

General population

- Fully vaccinated: probability of infection HIGH + impact of infection LOW ➔ **LOW-MODERATE RISK**
- Unvaccinated: probability of infection VERY HIGH + impact of infection HIGH ➔ **HIGH-to-VERY HIGH RISK**

Vulnerable population

- Fully vaccinated: probability of infection HIGH + impact of infection VERY HIGH ➔ **HIGH-to-VERY HIGH RISK**
- Unvaccinated: probability of infection VERY HIGH + impact of infection VERY HIGH ➔ **VERY HIGH RISK**

Countries with high vaccination coverage

Countries or regions with levels of vaccination coverage in the total population that is above the current EU average level, and particularly those with the highest levels of coverage, may have a manageable burden of hospitalisations and deaths unless there is strong waning of immunity post-vaccination and/or their population has low natural immunity.

General population

- Fully vaccinated: probability of infection MODERATE + impact of infection LOW ➔ **LOW RISK**
- Unvaccinated: probability of infection HIGH + impact of infection MODERATE ➔ **MODERATE RISK**

Vulnerable population

- Fully vaccinated: probability of infection MODERATE + impact of infection HIGH ➔ **MODERATE**
- Unvaccinated: probability of infection HIGH + impact of infection VERY HIGH ➔ **HIGH-to-VERY HIGH RISK**

Additional risk considerations

The assessment of risk, as outlined above, is at the population level and does not correspond to the individual risk of a vaccinated person.

In case of substantial waning of vaccine efficacy against infection and/or seasonal transmission, the likelihood of high disease burden and need for reduced contact rates increases for all countries at all levels of vaccination coverage.

In the context of possible circulation of other seasonal respiratory viruses, the projected increase in SARS-CoV-2 cases may place additional strain on healthcare systems and healthcare system capacity. As such, non-pharmaceutical measures, coupled with efforts to address low national and sub-national vaccination coverage, will continue to play an important role in limiting disease burden across the EU/EEA in the autumn.

Options for response

In view of the dominant circulation of the Delta variant, the unequal COVID-19 vaccine uptake across and within EU/EEA countries and the forecast of increased burden of SARS-Cov-2 cases in the next two months, improving national vaccination coverage should be the absolute priority for all public health authorities in Autumn 2021. A possible early start of the influenza season and the potential co-circulation of the two viruses may further stress healthcare systems. Furthermore, if A(H3N2) viruses are the dominant virus subtype as detected until now, the elderly would also be disproportionately affected. Non-pharmaceutical interventions (NPIs) such as use of face masks, improved ventilation in closed spaces and physical distancing measures should remain in the response toolbox to be tailored to the needs of the community. Testing for SARS-CoV-2 should continue to be available using accredited testing methods. Surveillance systems should continue to monitor primary, secondary and tertiary care, and disease incidence by severity, in order to guide decisions on public health measures and to understand their impact. Finally, risk communication should try to keep a balance between optimism while maintaining awareness that 'the pandemic in not over, yet'.

Vaccination

Considering the overall progress in national COVID-19 vaccination programmes in the EU/EEA and the increased availability of vaccine supplies, the current priority for EU/EEA countries remains to increase vaccination coverage, close the immunity gaps and ensure that all eligible individuals receive a full course of vaccination, especially those individuals at higher risk of severe COVID-19 disease who have not yet been reached. While increasing overall population coverage to the maximum level possible is critically important, as shown by the modelling forecast scenarios in this assessment, priority needs to continue to be given to ensuring that all those most vulnerable to COVID-19 infection and its consequences are fully vaccinated.

Despite overall progress in vaccination coverage, the progress in vaccine uptake in the adult population and specific priority groups (i.e., elderly and residents in LTCFs, HCW) has been unequal across EU/EEA countries and at subnational level, where pockets of geographic areas or population groups with low uptake persist, including in countries that have reached high levels of vaccination coverage overall. In order to expand the vaccine rollout, it will be especially important to continuously monitor vaccine uptake and associated social determinants to understand where and in which population groups and communities the immunity gap persists. The extent and characteristics of unvaccinated individuals will play a major role in the future dynamic of the pandemic and it should be monitored to inform vaccination strategies.

As recently published in a ECDC technical report [49], strategies should include the administration of additional vaccine doses as part of a primary vaccination series for people with severely weakened immune systems (e.g., solid organ transplant recipients), as they may not achieve an adequate level of protection from the standard primary vaccination. Full vaccination against COVID-19 of all eligible family contacts and close contacts, including professionals providing care, of immunocompromised and vulnerable individuals should also be considered. Consideration could also be given to providing an additional dose as a precautionary measure to older frail individuals, in particular those living in closed settings (e.g. residents of long-term care facilities). In light of emerging evidence of waning immunity after vaccination and of reduced vaccine effectiveness against the currently dominant Delta variant, monitoring of vaccine effectiveness data and description of breakthrough infections, particularly amongst vulnerable groups at risk of severe COVID-19 and amongst those living in closed settings, is ongoing in EU/EEA countries and at ECDC to continue to inform policy decisions on the use of additional doses. Other groups for consideration for the use of additional doses could be healthcare workers and other staff who work in close contact with individuals at risk of severe COVID-19.

Finally, the co-circulation and a potential rise in influenza infections during the ongoing COVID-19 pandemic in the autumn and winter months could have severe consequences for vulnerable populations and place an additional burden on health systems already strained by COVID-19. Seasonal influenza vaccination campaigns are well established in EU/EEA countries and are usually organised during the autumn to provide adequate protection in time for the start of the influenza season. Given the possibility of co-circulation of SARS-CoV-2 and influenza viruses in the autumn, capacity building for influenza diagnostic testing should be planned and Member States should ensure that optimal influenza vaccine coverage is achieved before the start of the winter influenza season. EU Member states have agreed to have policies and programmes in place to target healthcare workers, older adults, and individuals with chronic health conditions for influenza vaccination. Many Member States also include children and pregnant women in their programmes. In addition to influenza vaccines, two antiviral medicines are authorised in the EU to prevent severe influenza disease [82].

Increasing vaccination uptake

Efforts should be made to ensure that as many eligible citizens as possible are protected by full COVID-19 vaccination. A key principle to consider when seeking to facilitate vaccination uptake is that populations are diverse, and interventions need to be targeted and context-specific: a one-size-fits-all strategy is unlikely to be optimally effective. It is therefore necessary to diagnose the reasons for under-vaccination in a given sub-population in order to plan the most appropriate intervention. The '3Cs' model, as suggested by the WHO's SAGE Working Group on Vaccine Hesitancy, offers a potentially useful framework for diagnosis and then action (Appendix 4) [83]. This model identifies Convenience, Complacency and Confidence as key factors associated with vaccine uptake. The relative importance of the 3Cs can change over time in a certain sub-population, so it is important for the authorities to conduct regular diagnoses of the reasons for under-vaccination, thereby providing a basis for adapting the interventions as necessary.

Healthcare workers are widely trusted within the EU/EEA for information on vaccination, and they therefore play a particularly critical role in promoting COVID-19 vaccination and in addressing people's questions or concerns about the vaccines. They should also be a key target for tailored communication and community engagement efforts to address any acceptance issues that they may face themselves, both to avoid putting themselves, their families, their colleagues and patients at risk of SARS-CoV-2 infection, but also as any concerns that they have may be amplified if they communicate these to their patients. Some EU/EEA countries have issued COVID-19 vaccination mandates for healthcare workers and personnel working in long-term care facilities. However, it is important to note the potential negative effects of such mandates, whether ethical, political, or legal.

This issue is discussed further in Appendix 4, which also presents strategies implemented in EU/EEA countries to address hesitant populations as well as key strategies to address misinformation. It is hoped that other Member States may learn from and apply these in their own context to increase COVID-19 vaccine uptake.

Non-pharmaceutical interventions

Non-pharmaceutical interventions such as the use of face masks, improved ventilation in closed spaces and physical distancing measures as well as contact tracing should continue to be implemented in accordance with the local epidemiological situation, the vaccination coverage in the total population and taking into account the increased transmissibility of the Delta variant. The forecasts presented in this assessment indicate that until and unless sufficiently high vaccination coverage has been achieved, it will be necessary to maintain, or strengthen NPIs through the coming autumn months, according to assessments of vulnerability considering the vaccination coverage, the epidemiological situation, public health and healthcare system capacity in a country or region.

Fully vaccinated individuals with underlying diseases and risk factors may be increasingly vulnerable in the coming months, given the increased likelihood of exposure to the Delta variant combined with the potential for waning immunity. Therefore, vulnerable groups, independent of their vaccination status, should be advised to continue adhering to NPIs such as use of face masks when in crowded situations as a means of personal protection, physical distancing and personal hygiene measures like appropriate handwashing.

Continued mitigation efforts and strengthening of healthcare systems and HCW resilience remain important during autumn and winter 2021-2022. Interventions to support HCWs should consider organisational, social, personal, and psychological aspects, and continue to be researched to determine the effectiveness of different interventions [41,84] .

According to the ECDC forecast (See 'Modelling' and Figure 9), some measures to limit physical contacts will be needed in the next months to avoid an increased burden of COVID-19 hospitalisations and potentially deaths. However, in countries where the epidemiological situation and the vaccination coverage of the total population allows (regions with high vaccination coverage), authorities may consider a gradual relaxation of NPIs. Measures that can be considered in order to avoid increases in cases, if the epidemiological situation and vaccine coverage levels are at a level likely to be associated with the further rises indicated in the ECDC forecast, include physical distancing measures such as permitting teleworking and distance education, particularly for those vulnerable to severe COVID-19 outcomes, or those living with vulnerable people. Other measures include modifications to public transportation to decrease crowding, such as increasing its availability. If gatherings are allowed (e.g., social and cultural events, entertainment, etc) their preparations should aim to prevent or minimise crowding, with gatherings outdoors preferred. Recommendations to stay home from school and work when ill with COVID-19 compatible symptoms should also continue.

Surveillance, identification of cases, contact tracing and quarantine of contacts remain key for monitoring the epidemiological situation and preventing a further surge of cases while measures are lifted or adapted [85].

In countries or regions where the epidemiological situation remains concerning and vaccination uptake remains at the current average level or below, NPIs should be maintained. Efforts should focus on enhancing adherence to the current measures, protecting vulnerable populations (e.g., LTCF residents and unvaccinated vulnerable groups) and ensuring healthcare capacity. In particular, these countries/regions should consider maintaining physical distancing measures between individuals as much as possible, maintaining limits on the size of public gatherings, especially those indoors, as well as recommending only limited size private gatherings, providing advice on the appropriate use of face masks where necessary, continuing with contact tracing, quarantine of contacts and isolation of cases, as well as limiting transmission in workplaces by encouraging teleworking whenever possible and promoting hand hygiene and respiratory etiquette for all. Additional targeted voluntary measures could also be considered.

For analysis and available evidence on NPIs used to respond to the COVID-19 pandemic, please refer to ECDC's technical document 'Guidelines for the implementation of NPIs against COVID-19' [86]. For analysis and available evidence on the impact of vaccination on NPIs, please refer to ECDC's 'Interim guidance on the benefits of full vaccination against COVID-19 for transmission and implications for non-pharmaceutical interventions' [87].

Schools

As ECDC outlined in July 2021, in regions where an increasing percentage of adults are fully vaccinated against COVID-19 but where children are not vaccinated or vaccinated at low levels, it may be anticipated that in the coming months increasingly greater proportions of reported SARS-CoV-2 cases will be amongst children [88]. Given this continued risk of transmission amongst unvaccinated children, a high level of preparedness is required in the educational system for the 2021/2022 school year [88].

The high transmissibility of the Delta variant means that the risk of transmission in school settings is higher than with previously circulating SARS-CoV-2 strains, given comparable control measures in place [89,90]. While severe COVID-19 outcomes in children remain relatively rare compared with other age groups [91], increases in case numbers amongst children could lead to higher absolute numbers of severe outcomes, notably hospitalisations, in this age group. In the US, the number of children and adolescents hospitalised due to COVID-19 increased nearly five-fold during late-June to mid-August 2021 due to the circulation of the Delta variant, but the proportion of children and adolescents having severe disease due to COVID-19 infection was noted to be similar to periods prior to the dominance of Delta [92].

School closures have been shown to have significant negative physical, mental and educational impacts on children, as well as the economic impact on society more broadly, and therefore alternative mitigation and response strategies should be given priority, as outlined below.

Combinations of NPIs in the form of physical distancing to prevent crowding, as well as hygiene, improved ventilation, masks and other measures remain important tools for the prevention of transmission in school settings. Measures should be adapted to levels of community SARS-CoV-2 transmission and healthcare system utilisation, as well as to the educational setting and age group, and their implementation should consider the need to provide an optimal learning and social environment while reducing transmission risks [88]. Measures to reduce SARS-CoV-2 transmission in school settings may also help to mitigate the transmission of other respiratory viruses commonly circulating in the autumn and winter months amongst the paediatric population. 'Test-to-stay' strategies could additionally be considered in an attempt to minimise disruption and school absenteeism in school settings while also limiting opportunities for further transmission [88,93,94]. Daily testing has been used successfully to keep children in schools, despite positive cases in a class. In a UK open-label cluster-randomised trial, daily contact testing of school-based contacts was found to be a non-inferior safe alternative to self-isolation [93].

Testing, surveillance and monitoring

Testing strategies

Testing of people with symptoms, through improving access to testing and encouraging people to seek testing as soon as possible after symptom onset remains important to enable rapid identification of cases and initiation of contact tracing to limit the spread of SARS-CoV-2. Depending on available resources, testing strategies could include additional objectives, such as outbreak analyses, asymptomatic case detection, phylodynamic analyses and other studies. While RT-PCR tests remain the gold standard in COVID-19 testing because of their high sensitivity and specificity, several EU/EEA countries have introduced the use of RADTs and self-RADTs as a way of further strengthening countries' overall testing capacity, particularly in case of limited RT-PCR capacities or where prolonged testing turnaround times result in no clinical utility [95].

In January 2021, Member States agreed to maintain a common and updated list of COVID-19 RADTs that are considered appropriate for use and are in line with countries' testing strategies. This common list of RADTs is regularly being reviewed by Member States through the Health Security Committee (HSC), and, if necessary, being updated in line with new results from independent validation studies becoming available and new tests entering the market.

Diagnostic laboratories should remain vigilant to detect any mismatches of specific RT-PCR assay primers and probes in comparison to circulating virus genomes. It should be noted that the majority of primer/probe binding sites of commercial assays are not publicly known. For in-house or commercial RT-PCR assays for which the primer/probe sequences are available, validation can be done via the ECDC PrimerScan [96] or similar tools that identify mismatches. For commercial assays where the primer/probe sequences are unknown, a validation procedure for the capacity of the molecular assays to detect variants is needed. For laboratories using the ARCTIC protocol for sequencing of SARS-CoV-2 it is important to use the latest version of the primers as mismatches may occur with variant viruses [97].

During the ongoing COVID-19 pandemic period, and as influenza is already being detected in some countries ahead of the normal start of the influenza season, when the number of cases presenting to sentinel surveillance sites are low, all patients with influenza-like illness (ILI) or acute respiratory illness (ARI) symptoms in sentinel primary care surveillance sites as well as severe acute respiratory illness (SARI) patients in secondary care should be sampled and tested concurrently for influenza and SARS-CoV-2 viruses; a multiplex RT-PCR assay can be considered [98]. Representative influenza positive specimens should be sent to the influenza reference laboratories for further genetic and antigenic characterisation as well as antiviral resistance monitoring.

In general, laboratories should have a quality assurance system in place and are encouraged to participate in external quality assessment (EQA) schemes or perform result comparisons between laboratories for a subset of samples. The ECDC funded External Quality Assessment (EQA) on molecular detection of SARS-CoV-2 with the focus on variants for national COVID-19 laboratory panels was distributed in the week of 13 September 2021.

Community-level screening can be performed by sequencing SARS-CoV-2 from wastewater and the presence of signature mutations can be used to assess the presence of variants, although this technique is still under development [99]. The European Commission has published a Recommendation to support EU/EEA countries in establishing wastewater surveillance systems across the EU [100]. For more information on RADTs, self-test RADTs, assessment of the circulation of VOCs in the community and community level screening from wastewater, please refer to the testing strategy section of the 15th update of the Rapid Risk Assessment [1].

Sequencing capacity

Genomic surveillance of currently circulating variants (including regular representative samples and targeted samples from special settings and populations) is of high importance for early detection of the presence and epidemiological trends of specific VOCs, VOIs and variants under monitoring, or the emergence of novel variants with concerning characteristics.

General considerations regarding testing strategies, diagnostic assays, sequencing and antigenic characterisation with relevance for circulating SARS-CoV-2 variants are provided in the latest ECDC rapid risk assessment [1] and in the ECDC guidance for representative and targeted genomic SARS-CoV-2 monitoring [2].

A representative sample with a sufficient sample size (optimally each week) and targeted samples from special settings or populations (e.g., all travel-related cases, a representative sample of outbreak cases, cases with unusual clinical presentation) of PCR-positive specimens should be sequenced according to the recommendations of the ECDC guidance for representative and targeted genomic SARS-CoV-2 monitoring [2]. This allows for early identification and monitoring of emerging variants or of known variants with novel mutations that may have a potential impact on phenotypic characteristics of the virus. All or a representative subset of viruses detected in samples from sentinel sources should be sequenced.

Furthermore, Member States who need support to reach sequencing targets can use ECDC services for sequencing of SARS-CoV-2 samples by writing an email to typing@ecdc.europa.eu.

Surveillance and monitoring

Considering a potential increase in the incidence of SARS-CoV-2 over the autumn and winter, COVID-19 surveillance systems need to be able to effectively monitor disease incidence by severity, to guide decisions on public health measures and to understand their impact. Vaccine effectiveness needs to be monitored to determine the need for additional doses and inform optimal vaccination programmes and strategies.

In order to achieve these objectives, comprehensive surveillance or sentinel surveillance systems with high population coverage covering primary (such as expanded sentinel influenza surveillance), secondary and tertiary care (for example SARI surveillance) should be in place. Particular focus should be placed on collecting complete data on key variables, such as severity of infection and vaccination history, ideally linked to sequencing results where available [101]. Sentinel influenza surveillance systems and SARI surveillance systems also need to be strengthened in anticipation of potential co-occurring outbreaks and circulation of other respiratory viruses such as influenza or respiratory syncytial virus (RSV). Surveillance of all-cause mortality (such as carried out by the EuroMOMO network [102]) should continue in order to rapidly detect and quantify excess mortality from COVID-19.

In the event a new SARS-CoV-2 variant emerges, monitoring their spread and rapid assessment of their characteristics remains important in order to issue potential containment measures.

Monitoring of COVID-19 outbreaks in long-term care facilities (LTCFs) is also important. While these settings have in general the highest vaccine coverage, they are also home to those with the highest risk for severe COVID-19 outcomes. Numerous outbreaks in LTCFs have been reported in the EU/EEA during the summer and early autumn, with breakthrough infections being reported in fully vaccinated residents and sometimes with fatalities [103]. ECDC issued a specific protocol on data collection of COVID-19 outbreaks in LTCFs on 6 May 2021, and an update on 3 September 2021. Its main aim is to collect information on the severity of breakthrough COVID-19 infections in outbreaks at LTCFs and to obtain a timely estimate of vaccine effectiveness in these settings, by SARS-CoV-2 variant and vaccine product. This activity is not intended to capture all outbreaks, generate comparative statistics, or obtain a (sub-)nationally representative sample [104].

Historically, outbreaks of influenza in LTCFs with high morbidity and mortality have been observed when influenza A(H3N2) circulated. Outbreaks of A(H3N2) virus in LTCFs are early signals of a severe influenza season and healthcare providers should consider influenza testing as well as vaccination and possibly pre-and postexposure prophylaxis with antivirals (neuraminidase or cap-dependent endonuclease inhibitors) [105,106].

Travel measures

Travel measures are unlikely to have any long-term major impact on the timing or intensity of local epidemics in comparison to rigorous local implementation of NPIs, particularly in view of the dominance of the Delta variant in all EU/EEA countries. Travel measures would be important if implemented very early, consistently and completely, if there was evidence of circulation of a new SARS-CoV-2 variant, particularly an immune escaping one, to delay its introduction.

ECDC has published a guidance for COVID-19 quarantine and testing of travellers [107], also highlighting the considerations around the use of RADTs for travelling. RADTs can be useful for detection of infectious cases in the first five days from disease onset, they have, however, reduced sensitivity for detecting asymptomatic cases [108].

During travel, NPIs should be maintained regardless of the vaccination status of the traveller. In particular, the use of face masks, avoidance of crowding and maintaining physical distancing as well as improved ventilation in stations and transportation modes (airplanes, trains, buses etc) should be maintained. Fully- vaccinated travellers should also respect any NPIs for fully- vaccinated people in the country of destination. Documents informing about which give more information on the safety measures on various travel conveyances have been developed in collaboration with other EU agencies: air travel [109], cruises [110] and railways [111].

The EU digital COVID certificate (EU-DCC) has been in use in the EU/EEA countries and a number of third countries since 1 July 2021, as proof that a person has been vaccinated against COVID-19, has recovered from COVID-19 or has had a recent negative test result with the aim to facilitate safe and free movement. When travelling, every EU citizen or third-country national legally staying or residing in the EU, who holds an EU digital COVID certificate, should be exempt from free movement restrictions in the same way as citizens of the visited EU country [112].

Risk communication

With the dominance of the Delta variant across the EU/EEA, continued community transmission, and pockets of low vaccination coverage across most countries, it is important to maintain the overarching message to the population that 'the pandemic is not yet over'. This is a challenging message to disseminate, given widespread expectations that increasing overall vaccination rates would, in broad terms, allow people to return to a relatively 'normal' life again.

However, the epidemiological situation needs to be balanced against these expectations. Authorities may want to consider the potentially substantial risks in over-promising what may be possible in terms of re-opening society. The Canadian province of Alberta provides a recent example of what can happen if COVID-19 restrictions are loosened too soon, with the healthcare system struggling to manage the highest rate of hospitalisations yet seen in the pandemic. 61% of eligible Albertans are fully vaccinated (as of September 19), but approximately 91% of those in Intensive Care Units over the past 120 days have been unvaccinated [113]. The province's political leadership has found it necessary to issue a public apology for opening up too much too soon, and has reimposed COVID-19 restrictions in a reversal of previous policy [114].

Consistency in messaging, within the confines of what is known scientifically, has been stressed throughout the pandemic as a key principle for facilitating trust in the authorities, and thereby for adherence to the recommended measures [115]. As such, efforts should be made to avoid circumstances that may require back-tracking over promises made regarding the re-opening of society. Populations that are weary of living under pandemic restrictions may not respond well if the restrictions are first removed and then re-imposed [116].

There is also a communication challenge to be addressed in situations where some restrictions remain in place even though there is good overall vaccination coverage. People may question the vaccine's effectiveness under such circumstances, especially when the original message was that vaccination would lead to a return to normality. In these circumstances, it is important to clarify that the Delta variant is now dominant throughout most of the EU/EEA [117], which it was not earlier in the year, and that the vaccines are now working well to mitigate against this more challenging epidemiological situation.

Proposed key messages

Key messages for citizens

- Public health authorities need to continuously remind all eligible citizens of the importance of being fully vaccinated. Vaccines are the key tool to controlling this pandemic. Those who remain unvaccinated are putting themselves and people close to them at risk. Safe and effective vaccines are available and are highly protective against COVID-19 related severe disease, hospitalisation and death.
- Those partially vaccinated need to be reminded of the importance of completing their vaccination course, as evidence shows that taking the second dose in two-dose vaccine regimens provides optimum protection.
- Those fully vaccinated need to be aware that, even if they are well protected against infection and severe disease, there is still the possibility of breakthrough infections. This is to be expected, as no vaccine is 100% effective, though breakthrough infections do tend to produce milder illness. People with multiple comorbidities and/or low immunity are at highest risk of breakthrough infection and they may face more severe illness, and therefore they need to take additional precautions to further protect themselves.
- All citizens should also be reminded to continue to follow national recommendations regarding protective measures that are effective in reducing the spread of infection. These include respiratory and hand hygiene, as well as staying at home when having any symptoms of respiratory disease. Other measures can be considered, such as the use of face masks, improved ventilation indoors and physical distancing, as per national recommendations.

Key message for authorities

- Public health authorities need to stress the importance of vaccines as a powerful tool in helping to control the pandemic.
- The Delta variant is creating a rapidly evolving situation which requires additional measures to control community spread, even in well-vaccinated populations. Without these measures, there will be an inevitable increase in cases, which will also lead to an increase in hospitalisations and deaths. This may undermine, in the public eye, the perceived effectiveness of the vaccine, which in turn could adversely affect uptake.
- Uncertainty needs to be acknowledged. To maintain public trust, it is important to be transparent about the evolving evidence in relation to vaccine effectiveness, the impact of the dominant variant circulating and uncertainty regarding duration of protection from vaccines.
- In this context, people need to understand that vaccine recommendations as well as public health measures may need to be adapted to further control the pandemic. Providing a clear framework regarding which parameters are being used in order to adjust measures (e.g. vaccine coverage, hospital admissions, etc.) can be helpful to explain any changes that may be necessary.

Knowledge gaps

Much of the evidence presented here is based on unpublished data, which is evolving daily. Therefore, there are still many knowledge gaps and major uncertainties regarding the interpretation of the data. Knowledge gaps that are being, or still need to be, addressed, include:

SARS-CoV-2 virus and variant characterisation

- Incidence of variants in EU/EEA populations and elsewhere, where sufficient sequencing is not available
  - ECDC is supporting EU/EEA Member States to achieve sufficient sequencing of their samples
- Possible animal reservoir (species) being a risk for adaptive mutations and an ongoing source of infection for humans (e.g. mink).
- Competitive advantage of different variants, and consequences of co-circulation
- Unknown genetic markers related to receptor binding, infectivity, severity, etc.
- Antigenic characteristics of variant viruses
- Binding properties to human receptors, including ACE2 receptors
- Seasonality of transmission
  - ECDC is carrying out a systematic literature review on this subject.

Vaccine effectiveness

- Studies evaluating vaccine effectiveness by variant, age group, time since vaccination and different vaccine products and schedules, including with wide geographic representation and from multiple countries.
- The description of the characteristic of cases with breakthrough infections and of the associated virus (i.e., genetic variant) to complement the information on vaccine effectiveness. The monitoring and description of breakthrough infections should be routinely collected and assessed.
  - ECDC is implementing studies on COVID-19 vaccine effectiveness using a multi-country approach and a standardised protocol in a variety of settings (e.g., hospitals, primary care settings, healthcare worker cohort, etc.).

Natural infection

- Robust estimates of sero-prevalence of SARS-CoV-2 differentiated according to natural/vaccine induced immunity
- Clear extrapolation of seropositivity rates to the total population to determine levels of protection
- Under-ascertainment of cases
- Cross-protection
- Duration of protection following natural infection and the potential for waning immunity.

Clinical

- The severity and incidence of post-COVID condition
  - ECDC is planning a systematic literature review on this subject
- Impact of variants on possible treatment options (e.g., monoclonal antibodies).

Behaviour and social sciences

- In-depth understanding of what is driving low vaccination uptake in some populations
- High quality evaluations of interventions aimed at addressing vaccination misinformation
  - ECDC is currently developing a training on addressing online vaccination misinformation for public health experts and risk communicators, which will include a section on evaluation of interventions
- High quality evaluations of interventions aimed at facilitating vaccination uptake, including interventions based on incentivisation or mandates.

Limitations

This assessment is undertaken based on information known to ECDC at the time of publication and has several key limitations, hence it should be interpreted with caution, taking into account national and sub-national contexts.

The epidemiological data used in this assessment are dependent on availability from EU/EEA countries through surveillance reporting or publicly-available websites. The data not only reflect the epidemiological situation but are also dependent on local testing strategies and local surveillance systems.

Limitations regarding the modelling forecast are presented in the relevant section.

It is important to consider the time lag between infection, symptoms, diagnosis, case notification, death, and death notification, as well as the time lag for reporting at the EU level. Assessing the impact of response measures is complex due to the implementation of different components of NPIs and the pace of implementation for vaccination programmes.

The natural evolution of the virus (including the spread of variants of concern), compliance with measures, cultural, societal, environmental, and economic factors will all continue to play a role in the dynamics of disease transmission. There is still limited knowledge and uncertainty around VOCs. The assessment of the future trend of disease transmission is limited by the lack of knowledge from previous outbreaks.

Source and date of request

ECDC internal decision, 15 September 2021.

Consulted experts

ECDC experts (in alphabetic order):

Cornelia Adlhoch, Erik Alm, Xanthi Andrianou, Agoritsa Baka, Julien Beauté, Kim Brolin, Nick Bundle, Edoardo Colzani, Charlotte Deogan, Erika Duffell, Catherine Fleming, Luca Freschi, Rok Grah, Josep Jansa, Tommi Kärki, Maria Keramarou, Pete Kinross, John Kinsman, Anke Kohlenberg, Annette Kraus, Favelle Lamb, Angeliki Melidou, Rene Niehus, Kate Olsson, Ajibola Omokanye, Anastasia Pharris, Diamantis Plachouras, Giovanni Ravasi, Paul Riley, Emmanuel Robesyn, Gabrielle Schittecatte, Ettore Severi, Gianfranco Spiteri, Jonathan Suk, Therese Westrell, Andrea Würz.

External reviewers

European Medicines Agency: Marco Cavaleri

WHO Regional Office for Europe: Richard Pebody

All experts have submitted declarations of interest, and a review of these declarations did not reveal any conflict of interest.

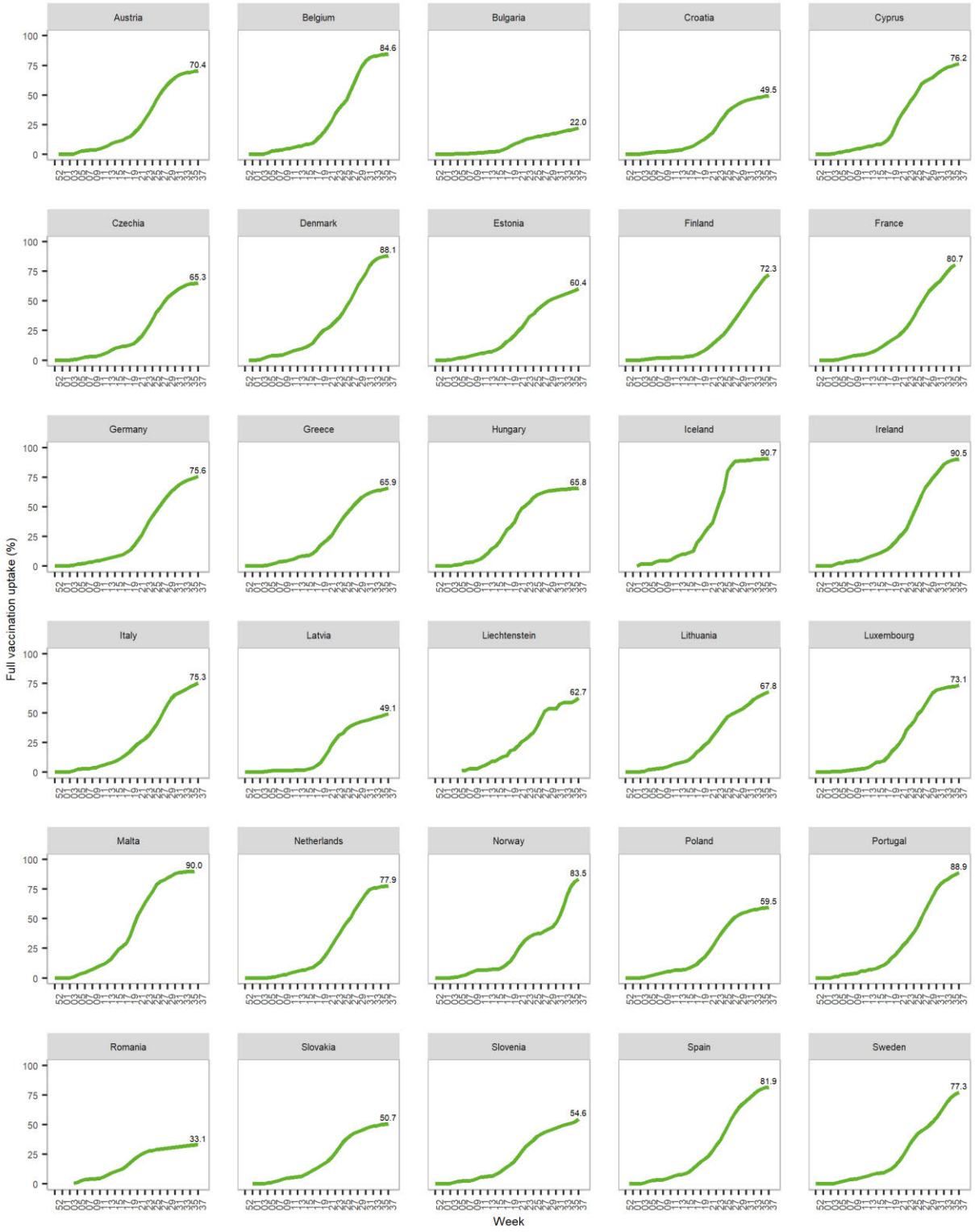
Disclaimer

ECDC issues this risk assessment document based on an internal decision and in accordance with Article 10 of Decision No 1082/13/EC and Article 7(1) of Regulation (EC) No 851/2004 establishing a European centre for disease prevention and control (ECDC). In the framework of ECDC's mandate, the specific purpose of an ECDC risk assessment is to present different options on a certain matter. The responsibility on the choice of which option to pursue and which actions to take, including the adoption of mandatory rules or guidelines, lies exclusively with the EU/EEA Member States. In its activities, ECDC strives to ensure its independence, high scientific quality, transparency and efficiency.

This report was written with the coordination and assistance of an Internal Response Team at the European Centre for Disease Prevention and Control. All data published in this risk assessment are correct to the best of our knowledge at the time of publication. Maps and figures published do not represent a statement on the part of ECDC or its partners on the legal or border status of the countries and territories shown.

Appendix 1

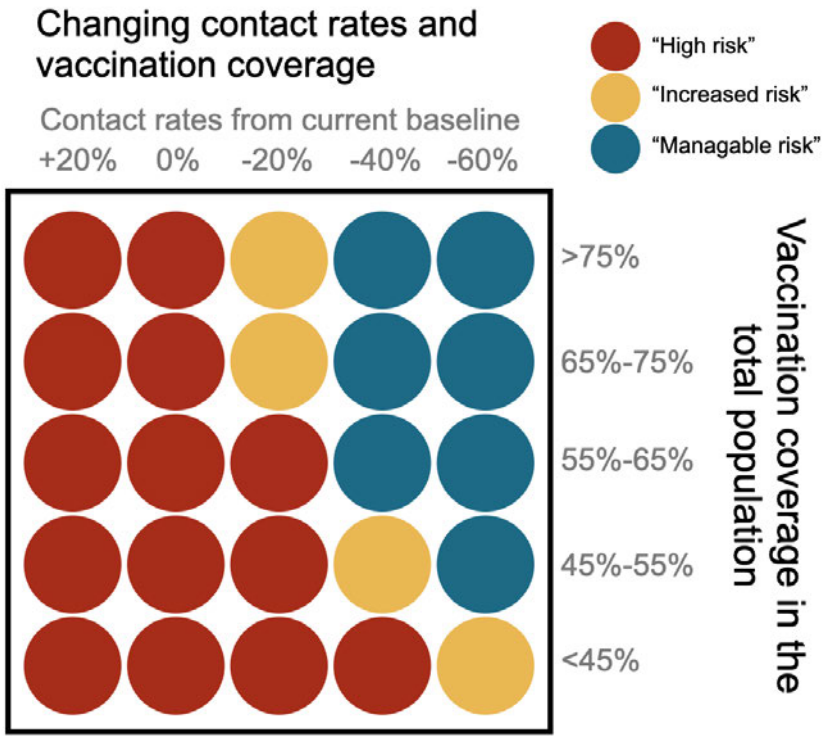
Cumulative uptake of full COVID-19 vaccination amongst adults in EU/EEA countries as a percentage (%) of the adult population as of week 37, 2021



Source: TESSy; data reported by 30 countries as of week 37, 2021. See the Notes on data in the ECDC Vaccine Tracker for country-specific disclaimers.

Appendix 2

Projected scenario outcomes across different COVID-19 vaccine coverages of the total population and contact rates relative to current baseline assuming waning of vaccine effectiveness against cases (mean of 57%, range 53%-61%)



All other parameters are as in Table 1.

Appendix 3

ECDC risk scoring matrix

The current assessment of the risk posed by the SARS-CoV-2 pandemic is stratified by four population groups: the vaccinated and the unvaccinated general population; the vaccinated and the unvaccinated vulnerable population. The assessment is based on the following principles: i) the vaccinated have a lower probability of infection and ii) a lower impact of such infection than the unvaccinated, while iii) whether vaccinated or not, the vulnerable population suffers a higher impact of such infection when compared with the general population. Following the current ECDC forecast, the risk to EU/EEA countries is assessed based on their current levels of full COVID-19 vaccination coverage in their total population, grouped into two categories (low/average and high). The assessment of risk, as outlined below, is at the population level and does not correspond to the individual risk for vaccinated persons.

	Vaccinated vulnerable population		**Unvaccinated** vulnerable population		**Vaccinated** general population		**Unvaccinated** general population	
EU/EEA countries with the highest levels of vaccination coverage in the total population	Probability: MODERATE Impact: HIGH	Risk **MODERATE**	Probability: HIGH Impact: VERY HIGH	Risk **HIGH - VERY HIGH**	Probability: MODERATE Impact: LOW	Risk **LOW**	Probability: HIGH Impact: MODERATE	Risk **MODERATE**
EU/EEA countries with vaccination coverage in the total population at or below the EU/EEA average	Probability: HIGH Impact: VERY HIGH *	Risk **HIGH - VERY HIGH**	Probability: VERY HIGH Impact: VERY HIGH	Risk **VERY HIGH**	Probability: HIGH Impact: LOW	Risk **LOW - MODERATE**	Probability: VERY HIGH Impact: HIGH **	Risk **HIGH - VERY HIGH**

** In the context of average and low vaccination coverage, we infer from modelling projections that in the absence of measures to effectively reduce population contact rates, then virus circulation and disease burden will be high. Impact is qualitatively assessed to be higher for the vaccinated vulnerable population, given the additional strain on healthcare systems.*
*** In the context of average and low vaccination coverage, we infer from modelling projections that in the absence of measures to effectively reduce population contact rates, then virus circulation and disease burden will be high. Impact is qualitatively assessed to be higher for the unvaccinated general population, given the additional strain on healthcare systems.*

Appendix 4

Interventions to address vaccine-hesitant populations

Diversity across EU/EEA countries – regarding the stage of vaccine campaigns as well as the wider social and political context – means that there can be no one-size-fits-all strategy to tackling vaccine hesitancy across the region. Adapted and context-specific strategies are needed. However, before such strategies are designed and deployed, it is necessary that countries diagnose the specific drivers of hesitancy in different populations [118]. Various scales and indexes have been developed for this purpose, including the Global Vaccine Confidence Index, which has been used regularly in the EU/EEA region [119,120], the Vaccine Confidence Scale [121], and the Vaccine Hesitancy Scale [122]. The WHO SAGE Working Group on Vaccine Hesitancy has also drafted a series of survey questions that can be used to support immunisation programs [123,124].

The interventions to address vaccine hesitancy detailed below are categorised using the '3Cs' model, as suggested by the WHO's SAGE Working Group on Vaccine Hesitancy. This model identifies Convenience, Complacency and Confidence as key components of vaccine hesitancy [83]. The strategies below may be selected, combined, and prioritised given a country's particular context and stage of vaccination.

Hesitancy due to *Convenience* may occur when people face barriers caused by geographical accessibility, cost, perceived poor quality of the vaccination services, and the suitability of time and place of the vaccination [83]. Belgium has sought to address access barriers facing socially-vulnerable populations by sending out mobile teams to key sites - such as homeless shelters, aid centres for migrants, transit homes, and shelters for victims of domestic abuse - and offering one-shot vaccines directly without requiring registration [125]. Key community locations, such as churches and mosques, have also been used by mobile teams in the Netherlands to reach under-vaccinated populations). Other countries have been addressing access issues by offering vaccination without appointments (Austria, Czechia, Liechtenstein) or at transportation hubs (Czechia, Estonia) and shopping centres (Czechia, Latvia), while others have been covering people's transport costs to the vaccination venue.

Hesitancy may be driven by *Complacency* when the risk presented by COVID-19 is perceived as low in an individual and/or group, and as such the perceived benefits of vaccination are perceived as marginal or irrelevant [83]. Addressing complacency requires clear, consistent, and transparent communication of the risks of COVID-19 for the specific groups in question, in easily understood language, along with explanations of the relative benefits of vaccination [115]. While messaging on risk shows variable outcomes dependent on the individual receiving the message [126,127], a 2021 study in the UK demonstrated that those who were strongly hesitant were most persuaded to vaccinate when messaging directly addressed personal benefit alongside a person's risk from the virus, rather than focusing on wider community benefits of vaccination [128]. Research from France and Spain suggests that chatbots can be used effectively to communicate with individuals on the risks and benefits of vaccination [129,130]. This interaction and dialogue is reportedly more likely to positively influence willingness to vaccinate than one-way messaging on risks vs. benefits.

Vaccine hesitancy can also be caused by a lack of *Confidence* in the vaccine, the health system, or those who make decisions about vaccination recommendations. Strategies to tackle issues of confidence should focus on building trust and community engagement. In Ireland, the Department of Health has created a network of young science communicators from across the country [131], who actively post content on social media to engage with, share experiences and answer the questions that young people across the country have concerning COVID-19 vaccination. Through this they aim to create a dialogue that will foster trust and thereby increase vaccine uptake in this group [132,133]. In Belgium, an innovative pilot programme involving community health workers runs to increase people's knowledge of the healthcare system and their trust in it, particularly in vulnerable populations [134]. Members of the communities themselves are informing individuals about the COVID-19 vaccine, linking them up with and accompanying them to their first vaccination, as well as doing follow-up activities [135].

Addressing misinformation

The term 'misinformation' refers to information that is false or incorrect according to current scientific knowledge. Misinformation includes disinformation, which is false or incorrect information that is knowingly and wilfully disseminated for economic or political purposes, as opposed to false and incorrect information that people disseminate, believing it to be correct.

Misinformation has the potential to undermine people's intentions to be vaccinated [136]. Within the context of the 3Cs model described above [83], misinformation could potentially have a strong influence on Confidence or on Complacency. Work conducted by ECDC has identified four core areas on which effective strategies for countering online vaccine misinformation should be built [136]:

- ***Monitoring misinformation on social media***. Social media sites are major outlets and amplifiers of vaccine misinformation, and they provide the venue for a large proportion of ongoing anti-vaccine debates. For health authorities, understanding this discourse is crucial if they are to design effective communication messages and strategies to stop misinformation from spreading. Monitoring of disinformation that targets the EU, its Member States, core institutions, and core values is conducted by the EU Disinfo Lab, using both traditional and social media platforms [137].
- ***Pre-emptive interventions***. These can include (i) pre-bunking or 'inoculation', which provides people knowledge in advance of how misinformation is spread, thereby giving them the ability to 'resist' such information should they be exposed to it; and (ii) interventions that promote digital, health and/or science literacy.
- ***Debunking misinformation***. Debunking refers to a technique of correcting erroneous claims by providing counter-arguments to messages containing misinformation. Efforts to debunk misinformation can be made even in settings without a substantial infrastructure for this sort of work, but care is needed as there is evidence that debunking exercises can backfire [138].
- ***Evaluation of the effectiveness of interventions***. This should include collection and analysis of both quantitative and qualitative evaluation data, as well as the perspectives and experiences of both the providers and recipients of services. Where possible, both process and impact should be included in any evaluation.

Interventions targeting healthcare workers

Results of a Flash Eurobarometer survey published in June 2021 confirm that EU citizens continue to see health professionals, doctors, nurses and pharmacists as their most trusted sources of information on COVID-19 vaccines [139]. Healthcare workers therefore play a key role in promoting COVID-19 vaccination and in addressing people's questions or concerns about the vaccines. They are also a key target group for tailored communication efforts to address any acceptance issues that they themselves face, both to avoid putting themselves, their families, their colleagues and patients at risk of SARS-CoV-2 infection, but also as any concerns they have may be amplified if they communicate these to their patients.

WHO identifies five key strategies to empower health workers to help ensure a successful public response to COVID-19 vaccination [140]: a) Understand health worker barriers and drivers of vaccination; b) Engage health workers as active partners in shaping vaccination efforts; c) Motivate, support and acknowledge health workers; d) Build health workers' knowledge, skills and confidence on COVID-19 vaccination and its communication; e) Value health workers as a target group and partners for information on any vaccine safety events; they are a key source of information both on any adverse reaction they witness and on public perceptions and concerns around the issue, and they also need to receive timely information regarding any safety events and how to respond to patients' concerns.

Considerations around incentives and mandates

Some EU/EEA countries have implemented incentives as part of their strategies to increase COVID-19 vaccine uptake [16]. For example, people who are vaccinated may participate in lotteries, receive vouchers or coupons to visit restaurants, or they may be granted access to recreational public venues and events. Literature on behavioural aspects of vaccination highlights some considerations and caveats in relation to past experiences with such programmes [141]. For example, whilst incentives may affirm the importance of vaccination, they can also signal that some people are not choosing to get vaccinated, which in turn gives a message that vaccination is not a normative behaviour. In addition, researchers have cautioned that even if financial incentives to 'get vaccinated' may seem appealing when focused on groups with persistently low vaccination rates, and they may produce a short-term increase in vaccination, they are not a panacea: broader, complementary strategies will still be needed [142].

A few EU/EEA countries have issued COVID-19 vaccination mandates, in particular for healthcare workers and personnel working in long-term care facilities. Other countries are also contemplating this strategy when, despite communication efforts, further increases in uptake have become difficult to achieve [16]. Even though mandatory requirements can be highly effective, researchers caution that depending on the reasons for under-vaccination, other strategies may be sufficient or more advisable [141]. Potential negative effects need to be carefully considered by policymakers. These include rejection of such measures by those who are ambivalent or unfavourable, anger from those who feel their freedom to act is being curtailed (making them even more susceptible to anti-vaccination messages), and motivation for people to seek ways to legally opt out of vaccination. Further, such decisions may have substantial practical, ethical and legal implications. Any such decision should be preceded by a thorough ethical analysis, conducted by experts in medical ethics, as highlighted by WHO [143].

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TAB 20

See Tab 19 at Pg. 12

TAB 21

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REVIEW | Free Access

Quantifying the risk of SARS-CoV-2 reinfection over time

Eamon O Murchu, Paula Byrne, Paul G. Carty, Cillian De Gascun, Mary Keogan, Michelle O'Neill, Patricia Harrington, Máirín Ryan

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Patricia Harrington and Máirín Ryan are co-senior authors.

Summary

Despite over 140 million SARS-CoV-2 infections worldwide since the beginning of the pandemic, relatively few confirmed cases of SARS-CoV-2 reinfection have been reported. While immunity from SARS-CoV-2 infection is probable, at least in the short term, few studies have quantified the reinfection risk. To our knowledge, this is the first systematic review to synthesise the evidence on the risk of SARS-CoV-2 reinfection over time. A standardised protocol was employed, based on Cochrane methodology. Electronic databases and preprint servers were searched from 1 January 2020 to 19 February 2021. Eleven large cohort studies were identified that estimated the risk of SARS-CoV-2 reinfection over time, including three that enrolled healthcare workers and two that enrolled residents and staff of elderly care homes. Across studies, the total number of PCR-positive or antibody-positive participants at baseline was 615,777, and the maximum duration of follow-up was more than 10 months in three studies. Reinfection was an uncommon event (absolute rate 0%–1.1%), with no study reporting an increase in the risk of reinfection over time. Only one study estimated the population-level risk of reinfection based on whole genome sequencing in a subset of patients; the estimated risk was low (0.1% [95% CI: 0.08–0.11%]) with no evidence of waning immunity for up to 7 months following primary infection. These data suggest that naturally acquired SARS-CoV-2 immunity does not wane for at least 10 months post-infection. However, the applicability of these studies to new variants or to vaccine-induced immunity remains uncertain.

Abbreviations

Covid-19
: coronavirus disease 2019

CI
: confidence interval

Ct
: cycle threshold

HIQA
: Health Information and Quality Authority

IgG
: immunoglobulin G

NAAT
: nucleic acid amplification technology

RNA
: ribonucleic Acid

RT-PCR
: reverse transcription polymerase chain reaction

SARS-CoV-2
: severe acute respiratory syndrome coronavirus type 2

WHO
: World Health Organization

1 INTRODUCTION

Following the emergence of a novel coronavirus (SARS-CoV-2) in China in December 2019 and the declaration by WHO of a public health emergency of international concern on 30 January 2020, countries worldwide have experienced epidemics of Covid-19. While much is yet unknown about the immune response following infection with SARS-CoV-2, evidence is emerging at a fast pace. The Health Information and Quality Authority (HIQA) of Ireland has conducted a series of rapid reviews on various public health topics relating to SARS-CoV-2 infection. These reviews arose directly from questions posed by policy makers and expert clinicians supporting the National Public Health Emergency Team to inform the national response to the pandemic in Ireland.

Our team at HIQA previously concluded that SARS-CoV-2 infection produces detectable immune responses in most cases.[1] However, the extent to which previously infected people are immune to reinfection is uncertain. In the short term, protection against reinfection is probable, as few confirmed SARS-CoV-2 reinfections have been reported despite over 140 million infections worldwide since the beginning of the pandemic.[2]

The objective of this systematic review was to evaluate the risk and relative risk of SARS-CoV-2 reinfection over time, comparing previously infected individuals to those without evidence of prior infection. The review informed a range of policy questions relating to the duration of protective immunity (as in, prevention of reinfection) following SARS-CoV-2 infection.

2 METHODS

A standardised protocol was employed[3] based on Cochrane methodology.[4] Electronic databases (PubMed, EMBASE and EuropePMC) were searched from 1 January 2020 to 19 February 2021 (Data S1). Table 1 outlines the Population, Outcome, Study design (POS) criteria for study selection.

TABLE 1. Population outcome Study design criteria for systematic search

Population	Individuals (of any age) with evidence of prior SARS-CoV-2 infection, who subsequently recovered [a] Evidence of prior infection includes diagnosis by RT-PCR or antigen testing, or evidence of an immune response through antibody detection (seropositivity)
Outcomes	1. Risk of RT-PCR or antigen-confirmed SARS-CoV-2 reinfection over time 2. Relative risk of RT-PCR or antigen-confirmed SARS-CoV-2 reinfection, comparing populations with evidence of prior infection with populations with no prior evidence of infection, at specified time points 3. RT-PCR cycle threshold results, if reported 4. Whole genome sequencing results of reinfected cases comparing first and second infections, if reported
Types of studies	Include: Observational cohort studies (prospective or retrospective) Exclude: Cohort studies that enrolled fewer than 100 participants unless the study reported comparative whole genome sequencing on all reinfection cases Studies with durations of follow-up of less than 3 months

Abbreviation: RT-PCR, reverse transcription polymerase chain reaction.

[a] 'Recovered' refers to molecular or clinical evidence of viral clearance following initial infection; definitions of recovery in primary studies were used. Common definitions include two consecutive negative respiratory RT-PCR tests 24 h apart and WHO clinical criteria of viral clearance (27 May 2020).[5]

Reinfection was defined as any reverse transcription polymerase chain reaction (RT-PCR) or antigen-confirmed SARS-CoV-2 infection in an individual with evidence of a prior SARS-CoV-2 infection. Evidence of prior infection included a previously documented immune response through antibody detection (seropositivity) and/or a prior SARS-CoV-2 diagnosis by RT-PCR or antigen testing followed by recovery (molecular or clinical evidence of viral clearance). No minimum time interval was defined between primary and secondary infections; however, cases within 90 days of initial infection were considered suggestive of prolonged viral shedding following the primary infection.

All potentially eligible papers, including preprints, were exported to Endnote x8.2 and screened for relevance by one reviewer. Following removal of irrelevant citations, two reviewers independently reviewed the full text of potentially relevant articles. For each included study, data on study design, participant demographics and relevant clinical and laboratory data were extracted by two reviewers. Quality appraisal was undertaken using the National Heart, Lung and Blood Institute (NIH) quality assessment tool for observational cohort studies.[6] The findings of the research question were synthesised narratively due to the heterogeneity of study designs and outcome data.

3 RESULTS

The collective database search resulted in 1893 citations, with four citations retrieved from other sources (grey literature search). Following removal of duplicates, 1771 citations were screened for relevance. This resulted in 105 studies eligible for full text review (Figure 1), where a further 94 studies were excluded (Table S1).

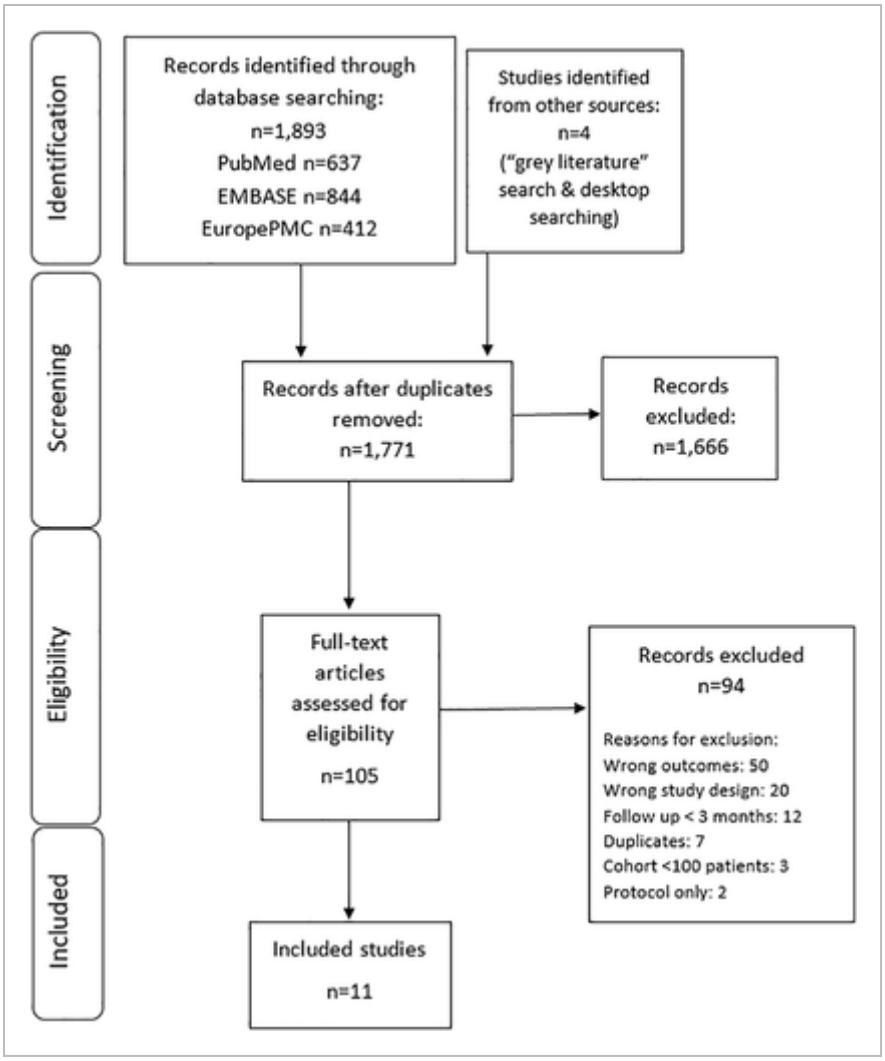

FIGURE 1

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PRISMA diagram of study selection

Eleven studies were identified that met the inclusion criteria.[7-17] Five studies were conducted in the United Kingdom,[8, 9, 11, 13, 14] of which three enrolled healthcare workers[8, 9, 11] and two enrolled the staff and residents of elderly care homes.[13, 14] The remaining six studies were all general population studies, conducted in Austria,[16] Denmark,[17] Israel,[12] Qatar [7] and the United States.[10, 15] Six studies were published as preprints at the time of submission.[7, 8, 10, 12, 14, 15] Across studies, the total number of PCR- or antibody-positive participants at baseline was 615,777 (median: 8845; range: 88–378,606). The median follow-up of individuals within studies was 131 days (4.4 months; range of medians: 54–210 days), with a maximum follow-up of ≥300 days (10 months) in three studies.[12, 14, 16]

Studies reported a range of primary endpoints (Table 2 and Table S2). Studies either determined evidence of prior infection based on a history of RT-PCR confirmed infection (*n* = 5

studies),[10, 12, 15-17] documented antibody detection (*n* = 4 studies)[7, 8, 11, 14] or a combination of both (*n* = 2 studies).[9, 13] Three studies separately reported the relative risks of symptomatic reinfections and 'all' reinfections (symptomatic/asymptomatic),[8, 11, 15] one study reported symptomatic reinfections only[9] and the remaining studies did not differentiate between symptomatic and asymptomatic reinfections.[7, 10, 12-17] In addition to quantifying the absolute risks of SARS-CoV-2 reinfection, the risks compared with PCR-negative or antibody-negative cohorts at baseline were expressed by a number of different measures, such as relative risks, odds ratios, risk ratios and hazard ratios. Due to heterogeneity in outcome measures and populations, meta-analysis of data were not considered appropriate. The following sections narratively report the findings of included studies by population group (general population, healthcare workers, and residents and staff of care homes).

TABLE 2. Summary of included studies and primary outcome results

First author; country; population	Participants[a] Follow-up	Author reported primary outcomes
Abu-Raddad 2021[7] (preprint); Qatar; General population	*N* = 43,044 antibody-positive at baseline **Median f/u:** 114 days (3.8 months) **Maximum f/u:** 242 days (8.1 months)	**Risk of reinfection (confirmed by WGS)**[b] : 0.10% (95% CI: 0.08%–0.11%) **Risk over time (any reinfection):** Incidence rate of reinfection by month of follow-up did not show any evidence of waning of immunity over seven months of follow-up
Hall 2021[8] (preprint); United Kingdom; HCWs	*N* = 6614 antibody-positive at baseline **Median f/u:** 202 days (6.7 months)	**Adjusted odds ratio of reinfection comparing antibody or PCR-positive group with negative group** • 'Probable' reinfection[c] : aOR: 0.01 (95% CI 0.00–0.03) • All 'possible' and 'probable' reinfections: aOR: 0.17 (95% CI: 0.13–0.24) • Symptomatic reinfection: aOR: 0.08 (95% CI 0.05–0.13)

Note: 'Any' reinfection—all reinfections, both symptomatic and asymptomatic. Numbers rounded to two decimal points. No cases were identified on the basis of antigen testing. The longest duration of follow-up was not stated in all studies or was provided only as an approximate estimate; when not stated, duration of follow-up was inferred from figures or tables within the study.

Abbreviations: aHR, adjusted hazard ratio; aOR, adjusted odds ratio (adjusted for week group); ARR, adjusted rate ratio; CI, confidence interval; f/u, follow-up; HCW, healthcare worker; IRR, incidence rate ratio; NAAT, nucleic acid amplification test; WGS, whole genome sequencing.

[a] In the baseline antibody and or PCR-positive group ('seropositive' or prior positive cohort).

[b] Based on cases with WGS confirming the first and second infections were from different viral strains (*N* = 16).

[c] 'Possible' reinfection was defined as a participant with two PCR-positive samples ≥90 days apart with available genomic data, or an antibody-positive participant with a new positive PCR at least 4 weeks after the first antibody-positive result. A 'probable' case additionally required supportive quantitative serological data and or supportive viral genomic data from confirmatory samples.

[d] NAAT used as proxy; includes all symptomatic reinfections and prolonged viral shedding, comparing patients who had a positive antibody test at index versus those with a negative antibody.

[e] Multivariate analysis of risk of PCR-positive infection by baseline antibody status, stratified by LTCF and adjusted for sex and age.

[f] IRR is the relative incidence of subsequent positive SARS-CoV-2 PCR tests and symptomatic infections comparing antibody-positive and antibody-negative groups at baseline.

[g] After adjustment for age, gender and month of testing or calendar time as a continuous variable.

[h] The midpoint of a range of follow-up dates was taken (300–349 days).

[i] Authors report effectiveness with the following calculation: 1−([56/8845]/[4163/141480]).

3.1 General population studies

3.1.1 Austria

In the study by Pilz et al.,[16] national SARS-CoV-2 infection data from the Austrian epidemiological reporting system were used to investigate potential reinfection events, with a maximum follow-up of 10 months. The primary outcome was the odds of PCR positivity in individuals who recovered from a confirmed SARS-CoV-2 infection during the first wave (22 February to 30 April 2020) compared with the odds of first infections in the remainder of the general population during the second wave (1 September to 30 November 2020). In total, 40 possible reinfections were recorded out of 14,840 individuals with a history of prior infection during the first wave (0.27%), compared with 253,581 infections out of 8,885,640 individuals of the remaining general population (2.85%). This translated into an odds ratio of 0.09 (95% CI: 0.07–0.13).

3.1.2 Denmark

In the study by Hansen et al.,[17] individual-level data were collected on patients who had been tested in Denmark in 2020 from the Danish Microbiology Database, with a maximum follow-up of 9.8 months. Infection rates were analysed during the second wave of the COVID-19 epidemic, from 1 September 2020 to 31 December 2020, comparing PCR-positive individuals with PCR-negative individuals during the first wave (March to May 2020). During the first wave (prior to June 2020), 533,381 people were tested, of whom 11,727 (2.2%) were PCR positive. Of these, 525,339 were eligible for follow-up in the second wave, of whom 11,068 (2.11%) had tested positive during the first wave. Among eligible PCR-positive individuals from the first wave, 72 (0.65%, 95% CI: 0.51%–0.82%) tested positive again during the second wave compared with 16,819 of 514,271 (3.27%, 95% CI: 3.22%–3.32%) who tested negative during the first wave. After adjusting for sex, age group and test frequency, the adjusted RR (aRR) of reinfection was 0.20 (95% CI: 0.16–0.25). Protection against repeat infection was estimated at 80.5% (95% CI: 75.4–84.5). In an alternative analysis, aRR by age category was reported. In individuals aged 65 years or more, the aRR was 0.53 (0.37–0.75), compared with 0.17, 0.20 and 0.19 in individuals aged 0–34 years, 35–49 years and 50–64 years, respectively.

3.1.3 Israel

In the study by Perez et al.,[12] published as a preprint, preliminary reinfection rates within the members of a large healthcare provider (Maccabi Healthcare Services) in Israel were reported, with a maximum follow-up of over 10 months. A total of 149,735 individuals had a recorded positive PCR test between March 2020 and January 2021. Among them, 154 members had two positive PCR tests at least 100 days apart and were included in this study. The reinfection rate was estimated at approximately 0.1%. In this cohort, 73 individuals (47.4%) had symptoms at both PCR-positive events.

3.1.4 Qatar

In the study by Abu-Raddad et al., published as a preprint, 43,044 anti-SARS-CoV-2 nucleocapsid antibody-positive participants were followed for up to 8 months for evidence of reinfection.[7] This retrospective cohort was identified from a database that covers all serological testing for SARS-CoV-2 conducted in Qatar.

There was evidence of a decreasing trend in the incidence rate of reinfection with each additional month of follow-up from the first month (incidence rate: 0.97 per 10,000; 52 cases per 167,149 person-weeks) to the sixth month (zero cases per 19,148 person-weeks) (Mantel-Haenszel trend analysis *p*-value: <0.001), noting that early reinfection cases (i.e., within 3 months) were likely due to persistent viral shedding following the primary infection. There was an increase at ≥7 months; however, this was based on only one case of reinfection (out of

3094 person-weeks). Applying a confirmation rate obtained through viral genome sequencing in a subset of patients with supporting clinical evidence for reinfection, the risk of documented reinfection was 0.1% (95% CI: 0.08%–0.11%).

These reinfections were compared to a cohort of 149,923 antibody-negative individuals followed for a median of 17 weeks (range: 0–45.6 weeks). Risk of infection was estimated at 2.15% (95% CI: 2.08%–2.22%). The efficacy of natural infection in protecting against reinfection was estimated at 95.2% (95% CI: 94.1%–96.0%).

3.1.5 United States

Two US studies were identified, both published as preprints. In the first, a retrospective database analysis of electronic health records was used to determine the risk of nucleic acid amplification technology (NAAT) test positivity, a proxy for reinfection, over a maximum follow-up of 3.1 months (Harvey et al.[10]). Of 3,257,478 unique patients with an index antibody test, 378,606 (11.6%) had a positive antibody result at baseline. The ratio of positive NAAT test results among patients who had a positive antibody test at index versus those with a negative antibody test at index declined from 2.85 (95% CI: 2.73–2.97) at 0–30 days; to 0.67 (95% CI: 0.6–0.74) at 31–60 days; to 0.29 (95% CI: 0.24–0.35) at 60–90 days and to 0.10 (95% CI: 0.05–0.19) at >90 days.

In the second, 150,325 patients were followed for a maximum of 10 months (Sheehan et al.[15]). In total, 56 reinfections were identified from the positive cohort of 8845 individuals, compared with 4163 infections from the negative cohort of 141,480 individuals. The protective effectiveness of prior infection against reinfection was estimated at 78.5% (95% CI: 72.0–83.5) and 83.1% (95% CI: 75.1–88.5) against symptomatic reinfection.

3.2 Healthcare workers

Three UK studies were identified that exclusively enrolled healthcare workers. In the first study, published as a preprint, 20,787 hospital staff were followed, of whom 32% (*n* = 6614) were assigned to the positive cohort (antibody or PCR positive) and 68% (*n* = 14,173) to the negative cohort (antibody negative, not previously known to be PCR or antibody positive) (Hall et al.[8]). In total, 1,339,078 days of follow-up data were analysed from the baseline positive cohort (maximum follow-up of 7.6 months). In total, 44 reinfections (2 probable and 42 possible) were detected in the baseline positive cohort (15 of which were symptomatic), compared with 318 new PCR-positive infections (249 of which were symptomatic) and 94 antibody seroconversions in the negative cohort. The adjusted odds ratio (aOR) was 0.17 for all reinfections ('possible' or 'probable'; 95% CI: 0.13–0.24). Restricting reinfections to probable reinfections only, participants in the positive cohort had a 99% lower odds of probable reinfection (aOR of 0.01,

95% CI: 0.00–0.03). Restricting reinfections to those who were symptomatic, investigators estimated that participants in the positive cohort had an aOR of 0.08 (95% CI 0.05–0.13).

In the second study, 1038 healthcare workers with evidence of previous infection (PCR and or antibody positive) and 10,137 without (negative antibody and PCR) were followed for a maximum of 7.6 months (Hanrath et al.[9]). A positive PCR test was returned in 0% (0/1038 [95% CI: 0%–0.4%]) of those with previous infection, compared to 2.9% (290/10,137 [95% CI: 2.6–3.2]) of those without ($p < 0.0001$, $\chi 2$ test).

In the third study, 12,541 UK healthcare workers were followed for up to 31 weeks to compare the incidence of SARS-CoV-2 infection in seropositive ($N = 1265$, including 88 who seroconverted during follow-up) versus seronegative ($N = 11,364$) groups at baseline (Lumley et al.[11]). A total of 223 anti-spike seronegative healthcare workers had a positive PCR test, 100 during screening while they were asymptomatic and 123 while symptomatic, whereas two anti-spike seropositive healthcare workers had a positive PCR test; both workers were asymptomatic when tested. Incidence varied by calendar time, reflecting the first (March through April) and second (October and November) waves of the pandemic in the United Kingdom and was consistently higher in seronegative healthcare workers. After adjustment for age, gender and month of testing or calendar time as a continuous variable, the incidence rate ratio in seropositive workers was 0.11 (95% CI: 0.03–0.44) compared with those who were seronegative at baseline.

3.3 Residents and staff of elderly care homes

Two studies were identified that enrolled both residents and staff at UK care homes.[13, 14]

In the first study (Jeffery-Smith et al.[13]), the risk of reinfection according to antibody seropositivity was investigated following outbreaks in two London care homes[13, 18] over 4 months. The median age of residents was 84 and 85 in each care home.

In total, 88 individuals with evidence of prior infection were investigated for evidence of reinfection (antibody positive $N = 87$; PCR positive $N = 1$). The reinfection rate in this cohort was 1/88 (1.1%), and this reinfection event was observed in a staff member. By comparison, infection risk in the seronegative cohort was 30.1% (22/73, including four people diagnosed by seroconversion). The RR was estimated at 0.038 (95% CI: 0.005–0.273). The protection against reinfection after four months in seropositive group was estimated at 96.2% (95% CI: 72.7%–99.5%).

In the second study, published as a preprint, staff and residents in 100 long-term care facilities (LTCFs) in England were followed between October 2020 and February 2021 (Krutikov et al.[14]). In total, 2111 individuals were enrolled (682 residents and 1429 staff). The median age of residents was 86 years (IQR: 79–91) and 47 years for staff (IQR range: 34–56). Blood sampling

was offered to all participants at three time points separated by 6–8 weeks intervals in June, August and October 2020. Samples were tested for IgG antibodies to nucleocapsid and spike protein. PCR testing for SARS-CoV-2 was undertaken weekly in staff and monthly in residents. The primary analysis estimated the adjusted hazard ratio (aHR) of a PCR-positive test by baseline antibody status (Cox regression adjusted for age and gender, and stratified by LTCF).

IgG antibodies to nucleocapsid were detected at baseline in 226 residents (33%) and 408 staff (29%). Staff and residents contributed 3749 and 1809 months of follow-up time, respectively. There were 93 PCR-positive tests in seronegative residents (0.054 per month at risk) compared with four in seropositive residents (0.007 per month at risk). There were 111 PCR-positive tests in seronegative staff (0.042 per month at risk) compared with 10 in seropositive staff (0.009 per month at risk). Controlling for the potential confounding effect of individual LTCFs, the relative aHRs for PCR-positive infection were 0.15 (95% CI: 0.05–0.44) and 0.39 (95% CI: 0.19–0.82) comparing seropositive versus seronegative residents and staff, respectively. Study authors concluded that the presence of IgG antibodies to nucleocapsid was associated with substantially reduced risk of reinfection in staff and residents for up to 10 months after primary infection, assuming that the earliest infections occurred in March 2020.

3.4 Quality of included studies

The NIH quality assessment tools was used for appraisal of observational cohort studies.[6] Ten studies were considered of 'good' or 'fair' methodological quality (Table S3), with one study[10] that used a proxy measure for outcomes (NAAT test positivity) considered to be of poor quality.

Each of the 10 studies of 'good' (*n* = 4) or 'fair' (*n* = 6) methodological quality was considered large enough to adequately capture reinfection events in their respective populations. A number of studies was downgraded due to lack of controlling for confounders (*n* = 7 studies). In these studies, potential confounding variables were either not assessed or not measured appropriately, or the statistical analysis was not adequately described. As all studies were observational in nature, they cannot be used to demonstrate causality. Therefore, only associations between prior infection and reinfection risk can be measured. While estimates of the effectiveness of natural infection to prevent reinfection were reported in a number of studies, such measures cannot be reliably estimated on the basis of these data.

Six studies are currently published as preprints,[7, 8, 10, 12, 14, 15] so have not yet been formally peer-reviewed, raising additional concerns about overall quality and the potential for results to change prior to formal publication.

4 DISCUSSION

4.1 Summary of findings

Eleven cohort studies estimated the risk or relative risk of SARS-CoV-2 reinfection in individuals who were either antibody-positive or who had a history of PCR-confirmed Covid-19 at baseline, compared with those who did not, for up to 10 months. Across studies, the total number of PCR- or antibody-positive participants at baseline was 615,777, with a maximum follow-up of over 10 months in three studies. Reinfection was a rare event (median PCR-confirmed reinfection rate: 0.27%, range: 0%–1.1%), with no study reporting an increase in the risk of reinfection over time.

Of the six general population studies, only one estimated the population-level risk of reinfection based on whole genome sequencing in a subset of patients with supporting evidence of reinfection.[7] The estimated risk was low (0.1% [95% CI: 0.08%–0.11%]) in this large cohort of 43,044 anti-SARS-CoV-2 nucleocapsid antibody-positive participants. Importantly, the incidence rate of reinfection by month did not show any evidence of waning of immunity over the seven months of follow-up. The remaining population-based studies (conducted in Austria, Denmark, Israel and the United States) also reported low absolute and relative risks of reinfection, and none reported an increased risk over time.

Only one study reported the relative risk of reinfection by age category, allowing comparisons across groups. In individuals aged 65 years or more, the aRR was 0.53 (0.37–0.75), compared with 0.17, 0.20 and 0.19 in individuals aged 0–34 years, 35–49 years and 50–64 years, respectively.[17] The lower protection in the over-65s group may be attributable to immunosenescence; however, little is known about this phenomenon in the context of COVID-19.

Two UK studies reported lower risks of reinfection in elderly individuals. Both studies enrolled residents of care homes (median age ≥84 years), a group that has been disproportionately affected by the COVID-19 pandemic, with high rates of infection and deaths among frail, elderly residents. In the first study, the relative risk of reinfection in staff and residents of two London care homes was very low (RR = 0.038; 95% CI: 0.005–0.273), and the protection against reinfection after four months in seropositive group was estimated at 96.2% (95% CI: 72.7%–99.5%).[13] This relative risk was based on a single reinfection event in a seropositive staff member, indicating the relative risk in the elderly resident cohort is even lower. The second study reported higher relative rates of reinfection[14] in a sample of staff and residents (*N* = 2111) across 100 LTCFs in England. The study, conducted between October 2020 and February 2021, coincided with a period of high community prevalence of SARS-CoV-2 in the United Kingdom, associated with the rapid emergence of the B.1.1.7 variant.[19] The estimated aHR for reinfection was 0.15 (95% CI: 0.05–0.44) in residents and 0.39 (95% CI: 0.19–0.82) in staff. The higher relative rates of infection compared with the earlier UK study raises concerns regarding the impact of new variants on the protective immunity of natural infection. Nonetheless, only four cases of possible reinfection were identified in residents, and although

all cases reported symptoms, none required hospital treatment. Taking into consideration that most residents were likely first infected during the first wave (up to 6 months prior), the risk of reinfection was substantially reduced in residents even in the context of high community transmission of the B.1.1.7 variant.

Three UK studies estimated the relative risk of reinfection specifically among healthcare workers.[8, 9, 11] The first study detected zero symptomatic infections in 1038 healthcare workers with evidence of a prior infection, compared with 290 in 10,137 without evidence of prior infection ($p < 0.0001$).[9] The second study detected two asymptomatic infections (and no symptomatic infections) out of 1265 seropositive individuals, compared with 223 infections (100 during screening while they were asymptomatic and 123 while symptomatic) out of 11,364 seronegative individuals.[11] After adjustment for age, gender and month of testing or calendar time, the incidence rate ratio in seropositive healthcare workers was 0.11 (95% CI: 0.03–0.44). The third study reported 44 reinfections in the baseline positive cohort of 6614 individuals (15 of which were symptomatic), compared with 318 new PCR-positive infections (249 of which were symptomatic) and 94 antibody seroconversions in the negative cohort of 14,173 individuals.[8] The aOR was 0.17 for all reinfections (95% CI: 0.13–0.24), and restricting reinfections to those who were symptomatic, the aOR was 0.08 (95% CI 0.05–0.13). This pattern of a lower relative risk of symptomatic reinfections in healthcare workers, compared with 'any' reinfection (symptomatic and asymptomatic), was also observed in the study by Sheehan et al. in general populations.[15] This finding suggests that not only is the risk of reinfection following natural infection low, when it does occur, it may represent a less severe form of disease.

4.2 Strengths and limitations

To our knowledge, this is the first systematic review to quantify the risk of SARS-CoV-2 reinfection over time. All studies were considered large enough to adequately capture reinfection events in their respective populations. Results across studies consistently demonstrated a substantially lower risk of reinfection in previously infected individuals without a waning of the protective response over time. However, despite these strengths, there are a number of limitations associated with this review.

First, as the studies are observational in nature, the prevention of reinfection cannot be causally confirmed, although longitudinal associations can be estimated. Additional concerns relating to observational studies include the greater potential for bias. It is possible that antibody test results affected individual behaviour. Individuals with evidence of prior infection may have believed that they possessed immunity to SARS-CoV-2, resulting in a reduction in health-seeking behaviour and testing (outcome ascertainment bias). Conversely, these individuals may have increased their engagement in social behaviour, placing them at greater

risk for infection. The overall direction of bias (whether over- or under-estimating reinfection) cannot be determined.

Second, studies included in this review could not determine whether past seroconversion, or current antibody levels, determine protection from infection. Furthermore, none could define which characteristics are associated with reinfection. For example, there is evidence to suggest immune responses are weaker following asymptomatic SARS-CoV-2 infections[20] and in immunocompromised patients,[21] which may increase susceptibility to repeat infection. Mucosal immunity and neutralising antibodies present in respiratory secretions may be more important for sterilising immunity than circulating IgG levels. The role of T-cell immunity was not assessed in any study; therefore, it is not possible to determine whether protection from reinfection is conferred through the measured antibodies or T-cell immunity. Future longitudinal serological cohorts may be able to determine protective correlates of immunity.

Third, only two studies undertook genomic sequencing of reinfected cases; consequently, the results of nine studies are only based on potential reinfections. The effect of this, however, is to overestimate the number of reinfections, thereby affirming the conclusion that reinfection is rare.

Fourth, due to the nature of a number of retrospective database analyses included in this review, many studies could not correlate symptomatic infections with protection against repeat infection or evaluate disease progression comparing first and second infections. This was true for studies that accessed large databases in Austria,[16] Denmark[17] and the United States.[10]

Finally, this review included a number of studies that were published as preprints (*n* = 6 studies[7, 8, 10, 12, 14, 15]). While preprints have been pivotal to guide policy and practice throughout this pandemic, these studies have not yet been formally peer-reviewed raising concerns over the quality and accuracy of presented data.

4.3 Generalisability of findings

There are a number of issues relating to the applicability and generalisability of the presented results. First, all but two studies preceded the widespread identification and spread of a number of new viral strains of international concern (e.g., variant 202012/01 [also known as 501Y.V1/B.1.1.7] from the United Kingdom and 501Y.V2 [B.1.351] from South Africa, both identified in December 2020[22]). In the first study that extended beyond December 2020, reinfection events between March 2020 and January 2021 in Israel were recorded.[12] A higher number of reinfections was recorded in January 2021 compared with previous months. However, genomic sequencing was not reported and statistical analysis of the recorded data (e.g., controlling for confounders and significance testing) was not undertaken. In the second study, elderly care home staff and residents in the United Kingdom were followed between

October 2020 and February 2021.[14] Sequencing data were not available for suspected reinfections, and study authors did not investigate the potential impact of new variants on the risk of reinfection. Nonetheless, the risk of reinfection was substantially reduced in elderly residents, most of whom were first infected up to 6 months previously. While these findings are reassuring, further research is needed on the role of natural immunity in populations that are experiencing the emergence and spread of new variants of concern.

Second, all presented data relate to unvaccinated cohorts as they preceded vaccine roll-out in 10 studies, and in the only study that was conducted during vaccine roll-out, all vaccinated individuals were excluded once 12 days had passed since their vaccination.[14] The applicability of the data to vaccinated populations is therefore unknown.

One preprint study (Lumley et al., 2021[23]), identified after our database search, reported reinfection rates among healthcare workers according to vaccination status and in relation to the B.1.1.7 variant. This study updates the 2020 study included in this review by the same authors[11] and presents data up to 28 February 2021. At this time point, 1456 of 13,109 participating healthcare workers had received two vaccine doses (Pfizer-BioNTech or Oxford-AstraZeneca). Compared to unvaccinated seronegative healthcare workers, natural immunity and two vaccination doses provided similar protection against symptomatic infection: no healthcare worker who had received two vaccine doses had a symptomatic infection, and incidence was 98% lower in seropositive healthcare workers (adjusted incidence rate ratio 0.02, 95% CI: <0.01–0.18). Two vaccine doses or seropositivity reduced the incidence of any PCR-positive result with or without symptoms by 90% (0.10, 95% CI: 0.02–0.38) and 85% (0.15 95% CI: 0.08–0.26) respectively. There was no evidence of differences in immunity induced by natural infection and vaccination for infections with the B.1.1.7 variant. These data suggest that both natural infection and vaccination both provide robust protection against SARS-CoV-2 infection, including against the B.1.1.7 variant. Future studies are expected to expand our understanding of the differences between natural and vaccine-acquired immunity and the impact of new variants.

Third, there is much uncertainty in relation to the risk of reinfection in younger and older age groups. Inconsistent data were identified relating to elderly populations, with one study reporting higher rates of reinfection compared with younger age groups[17] and two reporting low rates of reinfection in elderly residents of care homes (although these two studies did not compare risk across age groups).[13, 14]

4.4 Research in context and policy implications

This review was expected to inform a range of policy questions relating to the duration of protective immunity following infection with SARS-CoV-2, such as:

How long can asymptomatic individuals who have recovered from a prior SARS-CoV-2 infection be exempted from restriction of movement policies if they become a close contact of a confirmed COVID-19 case?

How long can asymptomatic individuals who have recovered from a prior SARS-CoV-2 infection be exempted from serial testing programmes?

How long can asymptomatic patients who have recovered from a prior SARS-CoV-2 infection be exempted from the requirement for testing prior to scheduled admission to hospital?

This review identified a large body of evidence that indicates the duration of presumptive protective immunity may last for at up to 10 months post-infection. However, given the uncertainty that exists relating to reinfection potential with emerging variants, any policy changes may not be applicable to possible exposure to emerging immune escape variants of concern. In addition, policies should be kept under review and informed by the international evidence and national surveillance data. In light of the findings of this review, policy was updated in Ireland to extend the period of presumptive immunity from 3 months to 6 months; therefore, a person who is an asymptomatic contact of a case and has had a positive test result within the previous 6 months is exempt from restriction of movements and serial testing. A period of 6 months was selected over 10 months due to the ongoing uncertainties relating to new variants.

Increasingly, reinfection cases are being investigated on a country level and are reported on websites of national public health agencies (e.g., Czechia now report a national reinfection rate of 0.1%, or 1400 cases out of 1,225,000 infections[24]). Future longitudinal studies should focus on the following issues that were not addressed in the aforementioned studies, including:

The durability of immunity beyond 10 months

Immune correlates of protection

Protective immunity in populations with comorbidities and the immunocompromised

The impact of new variants on protective immunity

5 CONCLUSIONS

Eleven large cohort studies were identified that estimated the risk of SARS-CoV-2 reinfection over time, including three that enrolled healthcare workers and two that enrolled elderly care home residents. All studies reported low relative SARS-CoV-2 reinfection rates in individuals with prior evidence of infection, compared with those without, for up to 10 months. The relative risk of reinfection was low across studies, although there was some inconsistent evidence of a

higher risk in older populations compared with younger populations. A limitation of this review was the uncertainty regarding the applicability of data to new variants of concern and to vaccinated populations.

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CONFLICT OF INTEREST

No conflict of interest declared.

AUTHOR CONTRIBUTIONS

Eamon O Murchu: Investigation, formal analysis and writing-original draft. **Paula Byrne:** Investigation and writing-original draft. **Paul G. Carty:** Investigation and writing-original draft. **Cillian De Gascun:** Writing-reviewing and editing. **Mary /Keogan:** Writing-reviewing and editing. **Michelle O'Neill:** Supervision, writing-reviewing and editing. **Patricia Harrington:** Supervision, writing-reviewing and editing. **Máirín Ryan:** Supervision, writing-reviewing and editing. All authors attest they meet the ICMJE criteria for authorship.

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DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

Supporting Information

Filename	Description
rmv2260-sup-0001-suppl-data.docx 57 KB	Supplementary Material 1

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TAB 22

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at Section 4.1

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TAB 26

COVID-19 natural immunity

Scientific brief

10 May 2021

World Health Organization

Key Messages:

- Within 4 weeks following infection, 90-99% of individuals infected with the SARS-CoV-2 virus develop detectable neutralizing antibodies.
- The strength and duration of the immune responses to SARS-CoV-2 are not completely understood and currently available data suggests that it varies by age and the severity of symptoms. Available scientific data suggests that in most people immune responses remain robust and protective against reinfection for at least 6-8 months after infection (the longest follow up with strong scientific evidence is currently approximately 8 months).
- Some variant SARS-CoV-2 viruses with key changes in the spike protein have a reduced susceptibility to neutralization by antibodies in the blood. While neutralizing antibodies mainly target the spike protein, cellular immunity elicited by natural infection also target other viral proteins, which tend to be more conserved across variants than the spike protein. The ability of emerging virus variants (variants of interest and variants of concern) to evade immune responses is under investigation by researchers around the world.
- There are many available serologic assays that measure the antibody response to SARS-CoV-2 infection, but at the present time, the correlates of protection are not well understood.

Objective of the scientific brief

This scientific brief replaces the WHO Scientific Brief entitled "'Immunity passports' in the context of COVID-19", published 24 April 2020.[1] This update is focused on what is currently understood about SARS-CoV-2 immunity from natural infection. More information about considerations on vaccine certificates or "passports"will be covered in an update of WHO interim guidance, as requested by the COVID-19 emergency committee.[2]

Methods

A rapid review on the subject was undertaken and scientific journals were regularly screened for articles on COVID-19 immunity to ensure to include all large and robust studies available in the literature at the time of writing.

COVID-19 immune responses to natural infection

Prior exposure to SARS-CoV-2 can be assessed by detecting the presence of virus-specific antibodies in serum. Functional neutralizing antibodies (NAb) are those able to neutralize the virus by blocking its entry into the cell.

Large cohort studies have reported that 90-99% of SARS-CoV-2 infected individuals develop neutralizing antibodies within 2-4 weeks after infection.[3–7] A small proportion of individuals do not develop NAb after SARS-CoV-2 infection for reasons that are unclear.[7] Individuals with mild or asymptomatic infection tend to have lower antibody levels than those with severe disease, and some studies have suggested that in some individuals waning of antibody levels occurs within several months after infection.[6–10] Studies aimed to detect immunological memory including the assessment of cellular immunity by testing for the presence of memory B cells, and $CD4^+$ and $CD8^+$ T cells, observed robust immunity at 6 months post-infection in 95% of subjects under study, which included individuals with asymptomatic, mild, moderate and severe infections.[11]

Correlates of protection against disease

How much cellular versus humoral immunity contributes to protection after natural infection is not fully understood. Studies point at NAb as a key element of immunoprotection, with cellular immunity likely to provide additional longer-term protection especially against severe disease and death.[12–15] How long overall protection may last remains unclear, and this may differ depending on the disease severity.[7] For other human coronaviruses (hCoV), hCoV-OC43, hCoV-229E, hCoV-NL63 and hCoV-HKU-1, which cause the common cold, antibodies last for at least a year after infection with significant inter-human variability,[16] while antibodies to more closely related MERS-CoV and SARS-CoV-1, which cause, respectively, middle east respiratory syndrome and severe acute respiratory syndrome, can be detected for years.[17–21]

Reinfection

Though rarely reported to date, reinfection with SARS-CoV-2 can occur. Four large studies from the United Kingdom, the United States of America and Denmark estimated that infection with SARS-CoV-2 provided 80-90% protection from reinfection up to 7 months, and up to 94% protection against symptomatic disease.[22–25] The level of protection against re-infection as assessed by PCR positivity was estimated to be 50% in people aged over 65 years old.[24]

SARS-CoV-2 variants and implications for immunity

The more the SARS-CoV-2 virus circulates, the more opportunities it has to change through natural evolution. The emergence of virus variants can pose new challenges. Currently, three virus variants, B.1.1.7, B.1.351 and P.1, with increased transmissibility or potential to partially escape immunity, are characterized as global Variants of Concern (VOC) by WHO and are circulating in many countries. Evidence of reduced susceptibility to neutralization by serum antibodies of some SARS-CoV-2 variants (*e.g.* P.1 and B.1.351) to natural (or vaccine-induced) neutralizing antibodies has been reported,[26–29] raising the concern that reinfection after natural infection (or breakthrough infection after vaccination) may increase in settings where these variants broadly circulate.[30] Of note, recent studies found that current global VOCs are unlikely to have an impact on $CD4^+$ and $CD8^+$ T cell reactivity in COVID-19 exposed donors and vaccinees, but how this observation applies to protection against reinfection or breakthrough infection after vaccination remains unclear.

Measuring immune responses

The immune response following infection with a virus can be measured by the detection of virus-specific antibodies such as IgA, IgM, IgG or total antibodies through immunoassays, as well as by the detection of sensitized memory B cells and/or CD4+ and CD8+ T cells, which require more complicated assays. The most commonly measured immune response is the presence of antibodies in serum. Serologic assays to detect the antibody response are usually based on enzyme immunoassays, which detect the presence of virus-specific antibodies in the blood or by live or pseudo-virus neutralization assays, which detect functional NAb. While serologic testing has limited use in clinical management because it does not capture active infection, it can be very useful in determining the extent of infection or estimating attack rates in given populations.

Interpreting the results of serologic testing, however, is complex: there are several antibody types and subtypes and multiple antigenic determinants/epitopes that can be used to target these antibodies, and the results may differ substantially depending on the combinations chosen. The results will also depend on the manufacturing specifics of the assay used. The most frequently used assays for detection of antibodies to SARS-CoV-2 are enzyme-linked immunosorbent tests, chemiluminescent tests, and lateral flow rapid diagnostic tests (RDTs). Advice on the use of RDTs for antibody detection is available on the WHO website.32

Conclusions

Current evidence points to most individuals developing strong protective immune responses following natural infection with SARS-CoV-2. However, inaccurate immunodiagnostic tests may falsely indicate infected individuals as naïve to the virus (not previously infected) or may falsely label non-infected people as positive for immune markers of recent infection.

To conclude, available tests and current knowledge do not tell us about the duration of immunity and protection against reinfection, but recent evidence suggests that natural infection may provide similar protection against symptomatic disease as vaccination, at least for the available follow up period.[33] The emergence of variants of concern poses challenges and their potential to evade immunity elicited by either natural infection or by vaccination, needs to be closely monitored.

Plans for updating

WHO continues to monitor the situation closely for any changes that may affect the information in this Scientific brief. Should any factors change, WHO will issue a further update. Otherwise, the validity of this brief will be reviewed 3 months after the date of publication.

Contributors

Lorenzo Subissi, Mick Mulders, Martin Friede, Maria Van Kerkhove, Mark Perkins.

Acknowledgments

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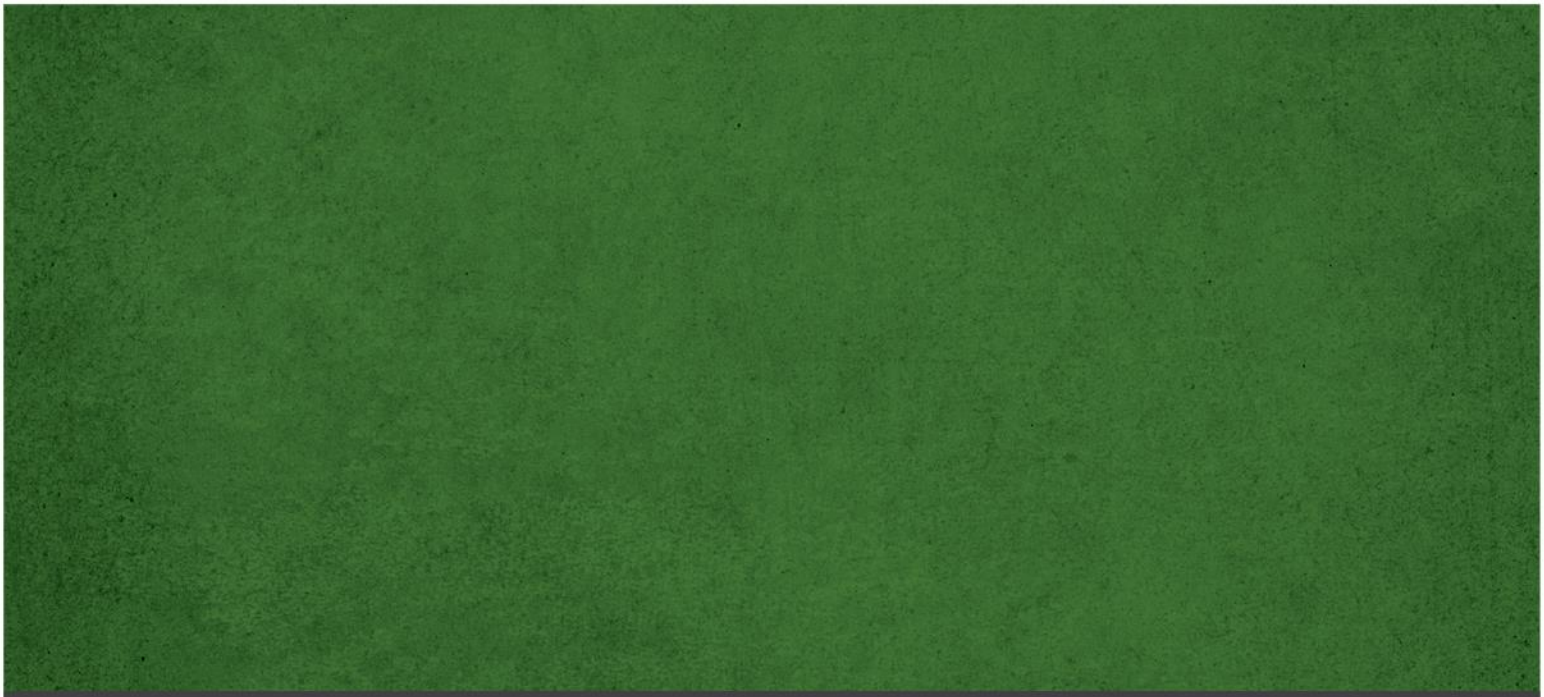
WHO reference number: WHO/2019-nCoV/Sci_Brief/Natural_immunity/2021.1

TAB 27

Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

Recommendations on the use of COVID-19 vaccines

Published: October 22, 2021



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Canada

PREAMBLE

The National Advisory Committee on Immunization (NACI) is an External Advisory Body that provides the Public Health Agency of Canada (PHAC) with independent, ongoing and timely medical, scientific, and public health advice in response to questions from PHAC relating to immunization.

In addition to burden of disease and vaccine characteristics, PHAC has expanded the mandate of NACI to include the systematic consideration of programmatic factors in developing evidence-based recommendations to facilitate timely decision-making for publicly funded vaccine programs at provincial and territorial levels.

The additional factors to be systematically considered by NACI include: economics, ethics, equity, feasibility, and acceptability. Not all NACI Statements will require in-depth analyses of all programmatic factors. While systematic consideration of programmatic factors will be conducted using evidence-informed tools to identify distinct issues that could impact decision-making for recommendation development, only distinct issues identified as being specific to the vaccine or vaccine-preventable disease will be included.

This statement contains NACI's independent advice and recommendations, which are based upon the best current available scientific knowledge. This document is being disseminated for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph. Recommendations for use and other information set out herein may differ from that set out in the product monographs of the Canadian manufacturers of the vaccines. Manufacturer(s) have sought approval of the vaccines and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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TABLE OF UPDATES

This evergreen document will be updated as COVID-19 vaccines are authorized and become available for use in Canada, as evidence on these vaccines and COVID-19 evolves, and as recommendations from NACI evolve based on this evidence. This table summarizes the updated information provided in the current version of this document since the publication of the last version of the document on September 28, 2021.

A complete list of changes to this document can be found in the Table of updates: Recommendations on the use of COVID-19 vaccines web page. Complete previous versions of this document are archived and are available through the National Advisory Committee on Immunization (NACI): Statements and publications web page under COVID-19.

Section	Update	Date
Vaccines: Schedule	Table 3 has been revised to reflect the optimal interval between the first and second dose for 2-dose COVID-19 vaccines. An additional section has been added below the table to provide evidence and rationale for the optimal intervals.	2021-10-22
Vaccine safety and adverse events following immunization	The section on "Myocarditis or pericarditis following vaccination with an mRNA vaccine" has been updated to include Canadian and international surveillance data.	2021-10-22
Vaccines: Precautions	Guidance on severe immediate allergic reactions (e.g., anaphylaxis) following vaccination with authorized COVID-19 vaccines has changed. Studies have shown that individuals with a severe immediate allergic reaction after a previous dose of mRNA vaccine can be re-vaccinated with the same vaccine or another mRNA COVID-19 vaccine.	2021-10-22
Recommendations	Recommendation #3 on extending the second dose of COVID-19 vaccine up to four months after the first dose has been removed. Vaccine supply for primary series is no longer an issue for eligible populations.	2021-10-22
Recommendations	NACI's recommendation on the use of COVID-19 vaccines has been updated to include the recommendation for a booster dose to long-term care residents and seniors living in other congregate settings who have already received a primary COVID-19 vaccine series.	2021-10-22

SUMMARY OF INFORMATION CONTAINED IN THIS NACI STATEMENT

The following highlights key, current information for immunization providers on COVID-19 vaccines. The evidence on COVID-19 disease and vaccines is evolving. Evidence from clinical trial data is limited due to limitations in the size and duration of follow-up of trial populations. However, clinical trials and studies in the real-world setting are ongoing. NACI will continue to monitor the evidence and update its recommendations as needed. Please refer to the remainder of the Statement for details.

What

Disease

- Novel coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
- Genetic mutations in the SARS-CoV-2 virus have been identified ("variants"), some of which make the virus more infectious and transmissible. They may also affect the severity of disease and the level of protection offered by vaccines against them.
- Anyone can be infected with SARS-CoV-2. However, some populations are at increased risk of exposure to the virus (e.g., due to living or work settings), and some populations are at increased risk of severe disease and death due to biological (e.g., advanced age, pre-existing medical conditions) and social (e.g., low socioeconomic status, belonging to a racialized population) factors that may intersect. Risk factors for exposure and severe disease may overlap, further increasing risk. Any combination of these factors, as well as varying access to health care services, has the potential for disproportionate consequences for specific populations.

Currently authorized vaccines
(Pfizer BioNTech Comirnaty COVID-19 vaccine, Moderna Spikevax COVID-19 vaccine, AstraZeneca Vaxzevria COVID-19 vaccine, Janssen COVID-19 vaccine)

- mRNA vaccines are authorized for use in Canada for individuals 12 years of age and older (Pfizer-BioNTech COVID-19 vaccine and Moderna COVID-19 vaccine)
- Non-replicating viral vector vaccines are authorized for use in Canada for individuals 18 years of age and older (AstraZeneca COVID-19 vaccine and Janssen COVID-19 vaccine).
- In clinical trials, all COVID-19 vaccines are efficacious in the short-term against symptomatic, confirmed COVID-19 disease; trials are ongoing. mRNA COVID-19 vaccines have demonstrated high efficacy (≥94%). The AstraZeneca COVID-19 vaccine has demonstrated an average efficacy of approximately 62% in those 18-64 years of age. In adults 65 years of age and older who received one dose of AstraZeneca, real-world observational data of vaccine effectiveness have shown a reduction in the risk of symptomatic disease and hospitalization. The Janssen COVID-19 vaccine has demonstrated efficacy of 67% against confirmed symptomatic moderate to severe/critical COVID-19 infection based on trials conducted in South Africa and Brazil while B.1.351 (Beta) variant of concern (VOC) and P.2 (Zeta) variant of interest (VOI) were circulating, respectively. There is currently limited evidence on the duration of protection and on the efficacy of these vaccines in reducing transmission of SARS-CoV-2, although studies are ongoing. Evidence of protection against asymptomatic SARS-CoV-2 infection is emerging for the mRNA and Janssen vaccines.
- Evidence of varying protection offered by COVID-19 vaccines against SARS-CoV-2 variants is evolving. To date, evidence has emerged that the Pfizer-BioNTech and

AstraZeneca vaccines offer protection against the B.1.1.7 (Alpha) VOC. Furthermore, there is emerging evidence that both vaccines also offer good protection against infection with the B.1.617.2 (Delta) VOC after the second dose and good protection against hospitalization after the first dose. There is evidence that the Janssen vaccine offers some protection against the B.1.351 (Beta) VOC as well as the P.2 (Zeta) VOI. There is evidence that the AstraZeneca vaccine does not offer protection against the B.1.351 (Beta) VOC.

- For all vaccines, some solicited adverse events are reported to be very common (defined as 10% or more) among vaccine recipients. However, they are mild or moderate and transient, resolving within a few days. These include pain at the injection site, fatigue, headache, muscle pain, chills, joint pain, and fever. In clinical trials of mRNA vaccines, some adverse events, including fever, are more frequent after the second dose; this was not the case with the AstraZeneca COVID-19 vaccine.
- Very rare cases of a specific syndrome that involves serious blood clots (at unusual sites such as cerebral venous sinus thrombosis) associated with thrombocytopenia have been reported after vaccination with viral vector vaccines. These cases often occur between 4 and 28 days after receipt of the vaccine. Early identification and appropriate treatment are critical. Investigations to better understand this syndrome, often referred to as Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT), are ongoing. Individuals who have experienced venous or arterial thrombosis with thrombocytopenia following vaccination with a viral vector COVID-19 vaccine should not receive a second dose of a viral vector COVID-19 vaccine.
- Very rare cases of myocarditis and pericarditis following vaccination with COVID-19 mRNA vaccines have been reported, most frequently in adolescents and younger adults under 30 years of age, more frequently in males compared to females, and more frequently after the second dose. The majority of reported cases were mild and the individuals tend to recover quickly. Investigations are ongoing. As a precautionary measure, individuals who have experienced myocarditis or pericarditis following vaccination with a first dose of an mRNA COVID-19 vaccine should defer the second dose in the vaccination series until more information is available. NACI will continue to monitor the evidence and update recommendations as needed.
- Very rare cases of capillary leak syndrome (CLS) have been reported following immunization with the AstraZeneca or Janssen COVID-19 vaccine [1-3]. Some affected patients had a previous diagnosis of CLS. CLS is a serious, potentially fatal condition characterized by acute episodes of limb edema, hypotension, hemoconcentration and hypoalbuminemia. Individuals with a history of CLS should not receive the AstraZeneca/COVISHIELD or Janssen COVID-19 vaccine.
- Very rare cases of Guillain Barre syndrome (GBS) have been reported following immunization with the authorized COVID-19 vaccines. Post-market safety surveillance has identified an increased risk of GBS following vaccination with viral vector COVID-19 vaccines but not with mRNA COVID-19 vaccines [4-8]. GBS is a rare but potentially serious immune-mediated neurologic disorder that results in pain or numbness, muscle weakness, and paralysis in severe cases. Most people fully recover from GBS but some have residual deficits or symptoms and rarely, fatal cases can occur. Individuals with past history of GBS should receive an authorized mRNA COVID-19 vaccine. When authorized mRNA COVID-19 vaccines are contraindicated or inaccessible, individuals may receive an authorized viral vector COVID-19 vaccine after consultation with their health care provider.
- There is currently minimal evidence to inform on differences in vaccine efficacy, effectiveness, or safety between individuals with and those without prior evidence of SARS-CoV-2 infection at the time of vaccination.

Who

NACI makes the following recommendations:

A complete series with an mRNA COVID-19 vaccine should be preferentially offered to individuals in the authorized age group without contraindications to the vaccine.

A viral vector COVID-19 vaccine may be offered to individuals in the authorized age group without contraindications to the vaccine to initiate a series when other authorized COVID-19 vaccines are contraindicated or inaccessible. Informed consent should include discussion about the risk and symptoms of VITT, as well as the need to seek immediate medical care should symptoms develop.

For those who are moderately to severely immunocompromised in the authorized age group who have not yet been immunized, a primary series of three doses of an authorized mRNA vaccine should be offered. For those who are moderately to severely immunocompromised in the authorized age group who have previously received a 1- or 2-dose COVID-19 vaccine series (with a homologous or heterologous schedule using mRNA or viral vector vaccines), an additional dose of an authorized mRNA COVID-19 vaccine should be offered.

A booster dose of an authorized mRNA COVID-19 should be offered to long-term care residents and seniors living in other congregate settings who have already received a primary COVID-19 vaccine series. This dose should be offered at a recommended interval of at least 6 months after the primary series has been completed.

A complete vaccine series with a currently authorized COVID-19 vaccine may be offered to:

- Individuals in the authorized age group without contraindications to the vaccine who have had previously polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection. Testing for previous SARS-CoV-2 infection is not needed prior to COVID-19 vaccination.

NACI also recommends that:

- Routine immunization programs and immunization with other vaccines recommended by NACI should continue during the COVID-19 pandemic with mitigation of risks of COVID-19 transmission during the immunization process as outlined in the Interim guidance on continuity of immunization programs during the COVID-19 pandemic.
- Clinical trials assessing COVID-19 vaccines should continue to be encouraged to include individuals with potential vulnerabilities to disease related to biological (e.g., pre-existing medical conditions, frailty, pregnancy and breastfeeding, immunocompromised), and social (e.g., residence in long term care facilities or crowded or remote locations, belonging to a racialized population, occupation) factors to ensure that vaccine options are informed by robust safety, immunogenicity, and efficacy data as outlined in NACI's guidance on Research Priorities for COVID-19 Vaccines to Support Public Health Decisions. Furthermore, NACI recommends the continuation of clinical trials and ongoing follow-up of participants for as long as it is ethically feasible to determine the level of immunity needed to prevent disease, duration of protection, efficacy in different sub-populations, and medium- and long-term safety.
- In addition to ongoing vaccine pharmacovigilance activities in Canada with Phase 4 clinical trials and post-marketing studies, additional research and surveillance of COVID-19

vaccination, particularly in populations not currently included in clinical trials (e.g., pregnant, breastfeeding, immunosuppressed, and seniors living in congregate care settings) is recommended.

NACI continues to recommend the following elements to guide ethical decision-making, as outlined in NACI's guidance on Key Populations for Early COVID-19 Immunization:

- Efforts should be made to increase access to immunization services to reduce health inequities without further stigmatization or discrimination, and to engage systemically marginalized populations and racialized populations in immunization program planning.
- Jurisdictions should ensure close and rapid monitoring of safety, coverage and effectiveness of the vaccines in different key populations, as well as effective and efficient immunization of populations in hardly reached, remote and isolated communities.
- Efforts should be made to improve knowledge about the benefits of vaccines in general and of COVID-19 vaccines as each becomes available, address misinformation, and communicate transparently about COVID-19 vaccine allocation decisions.

How

- Currently authorized COVID-19 vaccines are administered intramuscularly in a two-dose schedule (Pfizer-BioNTech, Moderna, and AstraZeneca) or in a one-dose schedule (Janssen) for the general population. For moderately to severely immunocompromised individuals, NACI recommends a three-dose primary series with an mRNA vaccine, or an additional dose of an mRNA vaccine if these individuals have already received an initial one-dose (with Janssen) or two-dose homologous or heterologous schedule (with mRNA or AstraZeneca vaccines).
- When the first dose in a COVID-19 vaccine series is an mRNA vaccine, the same mRNA vaccine product should be offered for the subsequent dose if readily available. When the same mRNA vaccine product is not readily available, or is unknown, another mRNA COVID-19 vaccine product recommended in that age group can be considered interchangeable and should be offered to complete the series.
- When the first dose in a COVID-19 vaccine series is the AstraZeneca/COVISHIELD vaccine, either the AstraZeneca/COVISHIELD vaccine or an mRNA vaccine product may be offered for the subsequent dose to complete the series; however, an mRNA vaccine product is preferred as a subsequent dose due to emerging evidence including the possibility of better immune response, and the safety of heterologous schedules. Individuals who have already received two doses of the AstraZeneca/COVISHIELD vaccine are considered protected and do not require further vaccination unless they are moderately to severely immunocompromised.
- Serologic testing is not needed before or after receipt of a COVID-19 vaccine to assess susceptibility to SARS-CoV-2 or immune response to the vaccine.
- COVID-19 vaccines may be given at the same time as, or any time before or after, other vaccines, including live, non-live, adjuvanted, and non-adjuvanted vaccines.
- COVID-19 vaccines should not be given simultaneously with monoclonal antibodies or convalescent plasma.

Why

- The COVID-19 pandemic has caused significant morbidity and mortality, as well as social and economic disruption in Canada and worldwide.
- The authorized COVID-19 vaccines that are recommended for use by NACI in this Statement have been shown to be safe (although very rare cases of VITT reported

following vaccination with the viral vector COVID-19 vaccines), efficacious against symptomatic laboratory confirmed COVID-19, and appear to protect against severe disease, hospitalization and death due to COVID-19.

I. INTRODUCTION

The overall goal of Canada's pandemic response is to minimize serious illness and death while minimizing societal disruption as a result of the COVID-19 pandemic. The goal of Canada's COVID-19 immunization response is: To enable as many Canadians as possible to be immunized against COVID-19 as quickly as possible, while ensuring that high risk populations are prioritized.

This guidance document will provide recommendations on the use of authorized COVID-19 vaccines as they are approved for use in Canada, and as evidence on these vaccines evolves.

There are four COVID-19 vaccines currently authorized for use in Canada:

1. The Pfizer-BioNTech COVID-19 vaccine was authorized for use in Canada on December 9, 2020, for ages 16 and up under Interim Order. On May 5, 2021, Health Canada expanded the Interim Order authorization for the Pfizer-BioNTech COVID-19 vaccine to include 12 to 15 year olds. On September 16, 2021, Health Canada authorized Pfizer-BioNTech Comirnaty COVID-19 vaccine for use in Canada under the Food and Drug Regulations.
2. The Moderna COVID-19 vaccine was authorized for use in Canada for those ages 18 and above on December 23, 2020 under Interim Order. On August 27, 2021, Health Canada expanded the Interim Order authorization for the Moderna COVID-19 vaccine to include 12 to 17 year olds. On September 16, 2021, Health Canada authorized Moderna Spikevax COVID-19 vaccine for use in Canada under the Food and Drug Regulations.
3. The AstraZeneca COVID-19 vaccine was authorized for use in Canada for those ages 18 and above on February 26, 2021 under an Interim Order.
    i. Health Canada authorized two manufacturers to produce this vaccine developed by AstraZeneca and Oxford University: AstraZeneca and Serum Institute of India (SII). NACI has not specifically reviewed evidence for the SII vaccine, but Health Canada has deemed SII and AstraZeneca vaccines to be comparable. Authorization of the SII COVID-19 vaccine (COVISHIELD) was based on its comparability to the AstraZeneca COVID-19 vaccine as determined by evaluation and direct comparison of manufacturing processes and controls and the quality characteristics of the two products. The results of this comparison by Health Canada determined that the two products were sufficiently similar and that the efficacy, immunogenicity and safety of COVISHIELD could be inferred from the non-clinical and clinical studies from the AstraZeneca COVID-19 vaccine.
4. The Janssen COVID-19 vaccine was authorized for use in Canada for those ages 18 and above on March 5, 2021 under an Interim Order.

The evidence on COVID-19 and COVID-19 vaccines has been rapidly evolving. To date, NACI has published the following evidence-informed guidance:

1. Research priorities for COVID-19 vaccines to support public health decisions (archived) to inform clinical trials of candidate COVID-19 vaccines to protect against infection, serious illness, and deaths caused by SARS-CoV-2.

2. Preliminary guidance on key populations for early COVID-19 immunization (archived) to plan for the efficient, effective, and equitable allocation of COVID-19 vaccine when limited initial vaccine supply will necessitate the immunization of some populations earlier than others.
3. Guidance on the prioritization of initial doses of COVID-19 vaccine(s) (archived) for the efficient and equitable prioritization of initial doses of COVID-19 vaccines to assist with the planning for allocation of the first COVID-19 immunization programs.
4. Guidance on the prioritization of key populations for COVID-19 immunization (archived) to provide guidance for the equitable, ethical, and efficient allocation of authorized COVID-19 vaccines in the context of staggered arrival of vaccine supply that will necessitate offering vaccines to some populations earlier than others.
5. Rapid response: Extended dose intervals for COVID-19 vaccines to optimize early vaccine rollout and population protection in Canada (archived) to maximize the number of individuals benefiting from the first dose of vaccine by extending the interval for the second dose up to four months after the first. This was followed by a more comprehensive NACI statement (archived) providing a detailed overview of the evidence and considerations leading to NACI's recommendation.
6. Rapid response: Recommended use of AstraZeneca COVID-19 vaccine in younger adults (archived) guidance developed in response to the investigation of Vaccine-Induced Prothrombotic Immune Thrombocytopenia (VIPIT) [hereafter referred to as Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)] following vaccination with AstraZeneca COVID-19 vaccine is investigated further.
7. Recommendation on the use of the Pfizer-BioNTech COVID-19 vaccine in adolescents 12 to 18 years of age (archived) recommending that a complete series with a Pfizer-BioNTech COVID-19 vaccine should be offered to individuals 12 to 18 years of age without contraindications to the vaccine; archived after issuance of updated guidance following authorization of the Moderna Spikevax vaccine in 12 to 17 year olds).
8. Rapid response: Interchangeability of authorized COVID-19 vaccines (archived) to provide advice on the interchangeability of authorized COVID-19 vaccines in a two-dose primary series schedule for COVID-19 immunization in Canada.
9. Recommendation on the use of mRNA COVID-19 vaccines in adolescents 12 to 17 years of age recommending that a complete series with an mRNA COVID-19 vaccine should be offered to adolescents 12 to 17 years of age without contraindications to the vaccine.
10. Rapid response: Additional dose of COVID-19 vaccine in immunocompromised individuals following a 1- or 2-dose primary series recommending that moderately to severely immunocompromised individuals who have not yet been immunized should be immunized with a primary series of 3 doses of an authorized COVID-19 mRNA vaccine, and moderately to severely immunocompromised individuals who have previously received a complete initial series should be offered an additional dose of an authorized COVID-19 mRNA vaccine.
11. Rapid Response: Booster dose in long-term care residents and seniors living in other congregate settings recommending that a booster dose of an authorized mRNA COVID-19 vaccine should be offered to long-term care residents and seniors living in other congregate settings who have already received a primary COVID-19 vaccine series. This dose should be offered at a recommended interval of at least 6 months after the primary series has been completed.
12. Recommendations on the use of COVID-19 vaccines (archived) initially published on December 12, 2020 and updated iteratively as new evidence becomes available and with the authorization of additional COVID-19 vaccines. This statement reflects the most up to date guidance.

Guidance Objective

The objective of this advisory committee statement is to provide evidence-informed guidance on the effective and equitable use of COVID-19 vaccines authorized for use in Canada. This evergreen document will be updated as COVID-19 vaccines are authorized for use in Canada, and as the evolution of evidence on these vaccines or the pandemic situation warrants changes in guidance. In this guidance document, the evidence and rationale for recommendations as well as current knowledge gaps will be summarized. Evidence summaries on vaccine characteristics for specific COVID-19 vaccines will be included in appendices.

II. METHODS

Details of NACI's recommendation development process can be found elsewhere [9, 10].

In brief, the broad stages in the preparation of this NACI advisory committee statement included:

1. Knowledge synthesis
2. Synthesis of the body of evidence of benefits and harms, considering the quality of the synthesized evidence and magnitude and certainty of effects observed across the studies
3. Translation of evidence into recommendations.

In order to develop comprehensive, appropriate immunization program recommendations, NACI considers a number of factors. In addition to critically appraising evidence on burden of disease and vaccine characteristics such as safety, efficacy, immunogenicity and effectiveness, NACI uses a published, peer-reviewed framework and evidence-informed tools to ensure that issues related to ethics, equity, feasibility, and acceptability (EEFA) are systematically assessed and integrated into its guidance [10]. The NACI Secretariat applied this framework with accompanying evidence-informed tools (Ethics Integrated Filters, Equity Matrix, Feasibility Matrix, and Acceptability Matrix) to systematically consider these programmatic factors for the development of clear, comprehensive, appropriate recommendations for timely, transparent decision-making. For details on the development and application of NACI's EEFA Framework and evidence-informed tools (including the Ethics Integrated Filters, Equity Matrix, Feasibility Matrix, and Acceptability Matrix), please see https://doi.org/10.1016/j.vaccine.2020.05.051.

For this advisory committee statement, NACI used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework to develop population-focused recommendations. Further information on this framework can be found in the GRADE handbook, available at: https://training.cochrane.org/resource/grade-handbook

NACI reviewed and approved the key policy questions used to guide recommendation development on November 25, 2020 and rated the outcomes for their importance for decision-making. With evolving evidence, NACI rated outcomes again on March 21, 2021. The Canadian Immunization Committee (CIC) provided feedback on the key policy questions to ensure alignment with program needs. Important ethical considerations relating to the key policy questions were presented on November 26, 2020, December 15, 2020, January 26, 2021, April 6, 2021, May 3, 2021 and July 6, 2021 to the PHAC Public Health Ethics Consultative Group, who provided an assessment of ethical considerations that are relevant to the development of recommendations. Knowledge synthesis and quality appraisal were performed by the NACI Secretariat for unpublished clinical trial evidence and were informed by NACI's rating of the outcomes. Unpublished data from Phase 1, 2, and 3 clinical trials were presented to the High

Consequence Infectious Disease Working Group and NACI for discussion. Proposed recommendations were then presented and approved at emergency NACI meetings. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in the text.

Key Dates

- Pfizer-BioNTech COVID-19 vaccine was discussed on December 4, 2020 and related recommendations were approved on December 7, 2020.
- The Moderna COVID-19 vaccine was discussed on December 14, 2020 and related recommendations were approved on December 17, 2020.
- The AstraZeneca COVID-19 vaccine was discussed on January 19, 28, February 5, and February 24, 2021 and related recommendations were approved on February 24, 2021.
- Considerations regarding an extended interval between authorized vaccine doses in the context of limited vaccine supplies, and clarifications to recommendations for populations who were either excluded from or were represented by small numbers of participants in clinical trials were discussed on January 7, 2021 and were approved on January 8, 2021.
- Additional evidence on an extended interval of 4 months between authorized vaccine doses in the context of limited vaccine supplies was reviewed on February 8, 19, and 24-25, 2021. Related recommendations were approved on March 1, 2021. Between March 25 and March 28, 2021, NACI members revisited these recommendations as they relate to specific population groups.
- Additional evidence from observational studies of effectiveness of the AstraZeneca vaccine in those 65 years of age and over was reviewed on March 10, 2021. Related recommendations were approved on March 13, 2021.
- Evolving evidence of VITT following the use of AstraZeneca COVID-19 vaccine was first reviewed on March 24, 2021 and related recommendations were approved on March 28, 2021. New evidence, including the Health Canada's safety assessment report issued on April 14, 2021, was formally reviewed on April 13, 15, 17 and 20, 2021. Updated recommendations were approved on April 20, 2021.
- The Janssen COVID-19 vaccine was discussed on March 16, 25 and April 13, 26, 2021, and recommendations were approved on April 30, 2021.
- Evolving evidence on extended intervals was reviewed on May 11 and 13, 2021. NACI updated the related recommendation on May 13, 2021 in the context of increasing COVID-19 vaccine supplies.
- Additional evidence in populations either excluded from, or included in small numbers, in clinical trials was reviewed on May 4 and 13, 2021. Related recommendations for COVID-19 vaccination in those who are immunosuppressed, have an autoimmune condition, are pregnant, or are breastfeeding were revised and approved on May 13, 2021.
- NACI reviewed the available evidence on the use of the Pfizer-BioNTech COVID-19 vaccine in adolescents 12 to 15 years of age on May 9, 2021 and approved the related recommendation on May 11, 2021. NACI reviewed the available evidence on the use of Moderna COVID-19 vaccine in adolescents 12 to 17 years of age on June 2, 9, 15, 21, 24 and July 8, 27 and August 3, 2021and approved the related recommendation on August 9, 2021.
- Evidence on mixed COVID-19 vaccine schedules was presented and reviewed by NACI on May 26, 2021 and related recommendations were approved on May 30, 2021. Emerging evidence was reviewed on June 9 and the related recommendation on interchangeability in a vaccine series when the first dose is an AstraZeneca/COVISHIELD COVID-19 vaccine was revised and approved on June 11, 2021.

- NACI reviewed the available evidence and its recommendation on simultaneous administration of COVID-19 vaccines with other vaccines and updated its recommendation on September 14, 2021.
- Evidence on myocarditis and pericarditis was presented and reviewed by NACI on May 18, June 1, June 15, June 21, and June 24, 2021. NACI approved updated information for inclusion in NACI's guidance on June 27, 2021.
- Evidence on an increased immune response after a third dose of an mRNA vaccine in moderately to severely immunocompromised individuals who had a reduced immune response to two doses of COVID-19 vaccines was reviewed by NACI on September 1, 2021. NACI approved the related recommendation for an additional dose of COVID-19 vaccine in immunocompromised individuals following a 1- or 2-dose primary series on September 1, 2021.
- Evidence on offering a booster dose of COVID-19 vaccine to long-term care residents and seniors living in other congregate settings was presented and reviewed by NACI on September 7, 2021 and September 14, 2021 and related recommendations were approved on September 28, 2021.

III. EPIDEMIOLOGY

Information on COVID-19 is continually evolving. The following section will describe the current basis of knowledge, with an emphasis on the best available Canadian data where possible. To access the most recent updates to specific elements, please refer to the links below.

Disease description

Infectious agent

COVID-19 is caused by the SARS-CoV-2, which was first recognized in Wuhan, China in December 2019.

Transmission

Current evidence suggests that SARS-CoV-2 is spread through respiratory droplets and aerosols created when an infected person coughs, sneezes, sings, shouts, or talks. A person may be infectious for up to three days before showing symptoms.

More information on the transmission of SARS-CoV-2 can be found on the PHAC webpages for COVID-19: Main modes of transmission and COVID-19 signs, symptoms and severity of disease: A clinician guide

Variants of concern

Genetic mutations in the SARS-CoV-2 virus have been identified, some of which make the virus more infectious and transmissible. They may also affect the severity of disease and the level of protection offered by vaccines against them.

More information on the variants of concern (VOC) reported in Canada is available in the COVID-19 epidemiology update. The COVID-19 Weekly Epidemiological Update by the World Health

Organization provides a summary on the global distribution and emerging evidence on VOC and variants of interest (VOI). Differences between VOC and VOI are available from SARS-CoV-2 variants: National definitions, classifications and public health actions.

NACI will continue to monitor the epidemiology and evidence pertaining to VOC and COVID-19 vaccines.

Risk factors

Anyone can be infected with SARS-CoV-2. However, some populations are at increased risk of exposure to the virus (e.g., due to living or occupational settings), and some populations are at increased risk of severe disease and outcomes (e.g., hospitalization and death) due to various biological (e.g., advanced age, pre-existing medical conditions) and social (e.g., socioeconomic status, belonging to a racialized population) factors that may intersect. Exposure and risk of severe disease factors may overlap, further increasing risk. Any combination of these factors, as well as varying access to health care services, has the potential for disproportionate consequences for specific populations characterized by increased rates of infection and disease, severe illness, hospitalizations, and/or deaths.

Please see NACI's Advisory Committee Statement on Key Populations for Early COVID-19 Immunization (archived) and the Equity Matrix [11] for a summary of inequities associated with COVID-19, potential reasons for and intersections between these inequities, and suggested interventions to reduce inequities and improve access to vaccines. NACI's Guidance on the prioritization of key populations for COVID-19 immunization (archived) builds on the foundational framework for the equitable, ethical and efficient allocation of authorized COVID-19 vaccines in the context of staggered arrival of vaccine supply that will necessitate offering vaccines to some populations earlier than others. This guidance was informed by evolving evidence on risk factors for COVID-19.

Table 1 summarizes populations at risk of severe outcomes from COVID-19 (hospitalization and/or mortality) based on the results of an updated rapid review of evidence [12] from studies in Organisation for Economic Co-operation and Development (OECD) countries, as well as populations at increased risk of exposure to COVID-19 (due to inability to physically distance and/or reduced access to infection prevention and control measures) identified, in part, through Canadian reports (epidemiological or analytic).

The review by the Alberta Research Centre for Health Evidence (ARCHE) found strong evidence (of moderate or high certainty) for at least a 2-fold increase in mortality from COVID-19 with age 60-69 years versus <60 years [12]. A previous review by ARCHE found a moderate certainty of evidence for at least a 5-fold increase in mortality and hospitalization with age over 70 years (versus 45 years and younger) [13]. Studies treating age on a continuum or across small increments consistently found that risks for hospitalization and mortality increased with increasing age (e.g., approximately 2-6% and 5-10% relative increase in risk per year) [12].

The ARCHE review found strong evidence (of moderate or high certainty) for at least a 2-fold increase in mortality from COVID-19 with a small number of medical conditions (classified as Level 1 in Table 1) [12]. The review found a low certainty of evidence for at least a 2-fold increase in mortality from COVID-19, and/or a low or moderate certainty of evidence for at least a 2-fold increase in hospitalization for a longer list of medical conditions (classified as Level 2). Individuals with two or more medical conditions were found to have at least a 2-fold increase in hospitalization

and mortality from COVID-19 (moderate certainty of evidence). Similarly, in populations 21 years of age and younger, individuals with two or more medical conditions were found to have at least a 2-fold increase in hospitalizations from COVID-19 (moderate certainty of evidence). However, there is no direct evidence on which combination of medical conditions increase this risk [12].

Caution should be taken when interpreting evidence of low certainty (e.g., for medical conditions listed as Level 2). As evidence accumulates, observed associations may change. For example, a previous rapid review by ARCHE [14] found low certainty evidence for at least a 2-fold increase in hospitalization or mortality for males, people with liver disease, and people with heart failure. As evidence has accumulated, there is now stronger evidence for little-to-no increased association of severe outcomes in these populations. The list of medical conditions included in Table 1 may not be comprehensive as it is based only on evidence from published studies included in the ARCHE review.

Table 1. Summary of risk factors for severe outcomes from COVID-19 and increased risk of exposure to COVID-19

Increased risk of severe outcomes from COVID-19 (hospitalization/mortality) [a]	Increased risk of exposure to COVID-19 [12] (e.g., due to inability to physically distance/reduced access to IPC) [b]
Increasing age (strong evidence) (based on moderate certainty of evidence of ≥2-fold increase in mortality) • ≥60 years (particularly ≥ 70 years) [12]	• Residents and staff of congregate living settings that provide care for seniors • Frontline healthcare workers • Adults in Indigenous communities • Residents and staff of other congregate living settings (e.g., quarters for migrant workers, shelters, correctional facilities, group homes) • Adults in racialized and marginalized communities • First responders (e.g., police, firefighters) • Frontline essential workers who cannot work virtually
Medical conditions – Level 1 (strong evidence) [12] (based on moderate or high certainty evidence of ≥2-fold increase in mortality) • Down syndrome • End-stage kidney disease • Epilepsy • Motor neuron disease, multiple sclerosis, myasthenia gravis, Huntington's disease [d] • Type 1 and 2 diabetes	
Medical conditions – Level 2 (limited evidence) [12] **Level 2a** (based on low certainty of evidence of ≥2-fold increase in mortality • Cerebral palsy • Major psychiatric disorder (schizophrenia, schizoaffective disorder, or bipolar disorder); in combination with prescription drug use for the condition in the past 6 months • Obesity class III (BMI ≥40 kg/m^2) • Parkinson's disease • Sickle cell disease or severe immunodeficiency, transplant (any type) • Solid organ transplant • Recent bone marrow or stem cell transplant • Metastatic cancer • Recent/current chemotherapy or radiotherapy **Level 2b** (based on low or moderate certainty of evidence of ≥2-fold increase in hospitalization)	

• Previous cerebrovascular accident • Pregnancy (any stage) • Frailty (among community and non-community dwelling people; measured on scales that include items such as weight loss, exhaustion, physical activity, walking speed, grip strength, overall health, disability, presence of disease, dementia, falls, mental wellbeing) • Vasculitis • Obesity – all classes (BMI >30 kg/m^2)	
Increased risk of severe outcomes (hospitalization/mortality)[c] and Increased risk of exposure [12]	
• Long-term care residents • Visible minority groups (includes mainly South Asian, Chinese, Black, Filipino, Latin American, Arab, Southeast Asian, West Asian, Korean, Japanese)	

[a] Identified through rapid review of evidence from OECD countries for an independent association with severe outcomes from COVID
[b] Identified, in part, through Canadian epidemiological reports
[c] Identified through rapid review of Canadian studies that may have an association with hospitalization and mortality from COVID-19. These studies may not have accounted for other covariates.
[d] These conditions were grouped within a single study; evidence for the individual conditions is either unavailable or of lower certainty.

The list of medical conditions in Table 1 may differ from those in other jurisdictions due to differences in local epidemiology and differing levels of evidence considered.

The evidence on risk factors for COVID-19 continues to evolve.

Spectrum of clinical illness

The median incubation period for non-variant SARS-CoV-2 has been estimated to be 5 to 6 days from exposure to symptom onset, with most individuals (97.5%) developing symptoms within 11.5 days of exposure. The incubation period ranges from 1 to 14 days.

Clinical presentation and symptoms of COVID-19 vary in frequency and severity. To date, there is no list of symptoms that has been validated to have high specificity or sensitivity for COVID-19.

More information on the spectrum of clinical illness is available on the PHAC webpage for COVID-19 signs, symptoms and severity of disease: A clinician guide.

Disease incidence

Global

Updated international data on COVID-19 cases and deaths is available at:
https://health-infobase.canada.ca/covid-19/international/

Weekly epidemiological updates highlighting key global, regional and country-level data on COVID-19 cases and deaths are available from the World Health Organization (WHO) at:
https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports

National
Updated national, provincial and territorial-level data on COVID-19 cases and deaths in Canada over time is available from the PHAC webpage on Coronavirus disease (COVID-19): Outbreak update.

IV. VACCINES

The following section summarizes information about COVID-19 vaccines authorized for use in Canada. More detailed vaccine-specific information is included in Appendices A through D. The current landscape of all candidate COVID-19 vaccines in clinical evaluation can be found on the WHO webpage Draft landscape of COVID-19 candidate vaccines. Under the Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19, Health Canada can make regulatory decisions for COVID-19 vaccines that have completed Phase 3 clinical trials for authorized use in Canada.

On September 16, 2021, Pfizer-BioNTech Comirnaty COVID-19 vaccine and Moderna Spikevax COVID-19 vaccine were authorized for use in Canada under the Food and Drug Regulations and are no longer under Interim Order. For ease and consistency, the brand names will not generally be used throughout the statement.

Most vaccine candidates in development that may become authorized for use in Canada use various technologies to deliver SARS-CoV-2 spike protein to vaccine recipients. This protein is expressed on the surface of the SARS-CoV-2 virus and is a major target for binding and neutralizing antibodies as well as cell-mediated immune responses.

mRNA vaccines
COVID-19 vaccines that use messenger RNA (mRNA) platforms contain modified nucleotides that code for the SARS-CoV-2 spike protein. A lipid nanoparticle formulation delivers the mRNA into the recipient's cells. Once inside the cytoplasm of a cell, the mRNA provides instructions to the cell's protein production machinery to produce the trans-membrane spike protein antigen that becomes anchored on the cell's external surface. The mRNA does not enter the nucleus of the cell and does not interact with, or alter, human DNA. The immune system is engaged by both the transmembrane spike protein and immune receptors carrying spike antigens to induce humoral and cellular immune responses. The mRNA, lipid nanoparticle, and spike protein are degraded or excreted within days to weeks from time of immunization. mRNA vaccines are not live vaccines and cannot cause infection in the host.

Canada has procured enough mRNA vaccines to fully vaccinate the currently eligible Canadian population.

Non-replicating viral vector vaccines
COVID-19 vaccines based on viral vector platforms use a modified virus to carry genes that encode SARS-CoV-2 spike proteins into the host cells. The vector virus is a type of adenovirus that has been modified to carry COVID-19 genes and to prevent replication. These modifications are intended to prevent the viral vector from causing disease (i.e., they are non-replicating). Once inside the cell, the SARS-CoV-2 spike protein genes are transcribed into mRNA in the nucleus and translated into proteins in the cytosol of the cell. The AstraZeneca vaccine uses a modified chimpanzee adenovirus vector (ChAd). The Janssen vaccine uses a modified human adenovirus serotype 26 vector (Ad26).

IV.1 Preparations of COVID-19 vaccines authorized for use in Canada

Table 2. COVID-19 vaccines authorized for use in Canada

Product Brand Name	Pfizer-BioNTech Comirnaty	Moderna Spikevax	AstraZeneca Vaxzevria / COVISHIELD	Janssen COVID-19 Vaccine
Type of vaccine	mRNA	mRNA	Non-replicating viral vector (ChAd)	Non-replicating viral vector (Ad26)
Date of Interim Order authorization in Canada	December 9, 2020 (16 years of age and older); May 5, 2021 (12 years of age and older)	December 23, 2020 (18 years of age and older); August 9, 2021 (12 years of age and older)	February 26, 2021	March 5, 2021
Authorized ages for use	12 years of age and older	12 years of age and older	18 years of age and older	18 years of age and older
Dose	0.3 mL (30 mcg of mRNA)[a]	0.5 mL (100 mcg of mRNA)	0.5 mL (5×10^{10} viral particles)	0.5 mL (5×10^{10} viral particles)
Authorized Schedule [b]	2 Doses, 3 weeks apart	2 Doses, 4 weeks apart	2 Doses, 4 to 12 weeks apart	1 Dose
Route of administration	IM	IM	IM	IM
Nature of the antigen	Transmembrane prefusion spike protein	Transmembrane prefusion spike protein	Transmembrane spike protein	Transmembrane prefusion spike protein
Adjuvant (if present)	None	None	None	None
Primary storage requirements pre-puncture[c]	-90°C to -60°C	-25°C to -15°C[d]	+2ºC to +8ºC	+2ºC to +8ºC
Additional storage options pre-puncture[c]	Frozen vials: -25°C to -15°C for up to 2 weeks[e] Thawed under frigeration: 1 month at +2°C to +8°C Thawed at room temperature: 2 hours up to +25°C	30 days at +2°C to +8°C AND/OR 24 hours at +8°C to +25°C	+2ºC to +8ºC	+2ºC to +8ºC
Diluent	Yes	No	No	No
Usage limit post-puncture	6 hours at +2°C to +25°C[f]	24 hours at +2°C to +25°C	6 hours at room temperature (up to +30ºC) OR 48 hours at +2ºC to +8ºC.	3 hours at room temperature (up to +25ºC) OR 6 hours at +2ºC to +8ºC
Formats available	Multi-dose vial (6 doses)[a], preservative-free	Multi-dose vial (10 doses), preservative-free	Multi-dose vial (8-and 10-dose presentations), preservative-free	Multi-dose vial (5 doses), preservative-free

Abbreviations: ChAd: Chimpanzee adenovirus; Ad26: modified human adenovirus 26; IM: Intramuscular; mRNA: Messenger ribonucleic acid

[a] After dilution, one vial contains 6 doses of 0.3 mL each. Low dead-volume syringes and/or needles can be used to extract 6 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract a 6th dose from a single vial. Refer to the product monograph available through Health Canada's Drug Product Database for choice of diluent, dilution instructions and type of syringes which can be used to extract 6 doses from a single vial.

[b] Authorized schedule per the product monograph. For NACI recommendations on intervals between doses, refer to Table 3.

[c] Protected from light during storage

[d] Do not store on dry ice or below -40ºC.

[e] Vials stored at -25°C to -15°C for up to 2 weeks may be returned one time to the recommended storage condition of -90°C to -60°C. Total cumulative time the vials are stored at -25°C to -15°C should be tracked and should not exceed 2 weeks.

[f] After dilution, vaccine must be used within 6 hours.

IV.2 Efficacy and Effectiveness

Due to the availability of only short-term clinical trial data, the duration of protection provided by COVID-19 vaccination is currently unknown. However, studies are ongoing.

The following section highlights key efficacy and effectiveness data for authorized mRNA COVID-19 vaccines (Pfizer-BioNTech COVID-19 vaccine, Moderna COVID-19 vaccine) and the authorized viral vector-based COVID-19 vaccines (AstraZeneca COVID-19 vaccine, Janssen COVID-19 vaccine) only. For additional details regarding trial design, including study population, length of follow-up, and efficacy for the authorized and available vaccines, refer to the evidence summaries in Appendix A (for the Pfizer-BioNTech COVID-19 vaccine), Appendix B (for the Moderna COVID-19 vaccine), Appendix C (for the AstraZeneca COVID-19 vaccine) and Appendix D (for the Janssen COVID-19 vaccine).

Efficacy against symptomatic COVID-19 disease

The currently authorized mRNA COVID-19 vaccines have been shown to be highly efficacious in the short term against confirmed symptomatic COVID-19 disease (presence of one or more symptoms plus laboratory confirmation of SARS-CoV-2 infection). The authorized two-dose mRNA vaccines schedules are similarly efficacious in adults with one or more comorbidities**,** as well as in adolescents, younger adults and older adults.

In clinical trials, AstraZeneca COVID-19 viral vector vaccine has shown moderate short-term efficacy against symptomatic COVID-19 disease (presence of at least one pre-defined COVID-19 symptom plus laboratory confirmation of SARS-CoV-2 infection) in adults 18–64 years of age, at least two weeks after receiving the full series of two standard doses of the vaccine. Clinical trial data show that efficacy increased as the interval between doses increased. At present, there are insufficient clinical trial data in adults ≥65 years of age to assess vaccine efficacy in this age group. The vaccine is similarly efficacious in adults ≥18 years of age with and without pre-defined comorbidities (presence of one or more mild to moderate and controlled cardiovascular disease, respiratory disease, diabetes or obesity). In the initial absence of sufficient data from clinical trials to date on the efficacy of the AstraZeneca COVID-19 vaccine in those 65 years of age and older, a review of three observational studies in the UK published as pre-prints on vaccine effectiveness in this age group has been conducted to inform NACI's recommendations in this age group. The findings of this review are summarized in Appendix C. These studies provide effectiveness estimates following the first dose of AstraZeneca vaccine and have shown a reduction in the risk of symptomatic disease and hospitalization that appears to reach a comparable level to that observed among persons of similar age who received one dose of mRNA vaccine.

The Janssen COVID-19 vaccine demonstrates moderate efficacy against symptomatic confirmed moderate to severe/critical COVID-19 infection from 14 days and 28 days post-vaccination, where the definition of moderate disease includes the presence of one to two or more of a relatively broad range of COVID-19 compatible signs and symptoms plus laboratory confirmation of SARS-CoV-2 infection. The point estimates of vaccine efficacy at these two time points across a variety of age groups are similar to the overall estimate, including among study participants ≥65 years of age who comprised approximately 20% of the study population. Point estimates of vaccine efficacy at 14 days post-vaccination are comparable in study participants with and without one or more comorbidities. In contrast, the point estimate of efficacy in participants with comorbidities is somewhat lower at 28 days post-vaccination. Efficacy for Janssen vaccine was based on clinical trials that were conducted in countries with widely circulating VOCs (South Africa and Brazil),

which may have impacted its overall efficacy. This is in contrast to the clinical trials for other authorized COVID-19 vaccines.

The clinical trial data demonstrates that the authorized mRNA COVID-19 vaccines are efficacious over the short-term in individuals with or without evidence of prior SARS-CoV-2 infection. However, participants with laboratory-confirmed (using a nucleic acid amplification test, such as RT-PCR) SARS-CoV-2 infection prior to enrollment were excluded from the trials and the number of trial participants with evidence of previous infection (as defined by trial protocol) who had confirmed symptomatic COVID-19 disease during the trials were small; therefore, the efficacy in this population and how it compares to those without evidence of previous infection is unknown at this time. The efficacy of the Janssen COVID-19 vaccine in those with evidence of prior infection is inconclusive at this time due to small sample size, and this outcome has not been assessed for AstraZeneca COVID-19 vaccine.

The first dose of the authorized COVID-19 vaccines has been shown to offer at least short-term protection against confirmed COVID-19 disease. For mRNA vaccines, the highest efficacy is seen after the second dose is administered. There is currently no available evidence on medium- and long-term efficacy of the authorized COVID-19 vaccines, however trials are ongoing, and this Statement will be updated as evidence emerges.

Efficacy and effectiveness against severe disease

The clinical trials of the authorized and available COVID-19 vaccines assessed efficacy against severe COVID-19 disease, but not all provided sufficient data to be able to assess the efficacy against hospitalizations or deaths.

The authorized mRNA and the Janssen COVID-19 vaccines appear efficacious against severe COVID-19 outcomes based on clinical trial data used for authorization (severe outcomes were defined as laboratory-confirmed COVID-19 with one of the following additional features: clinical signs at rest that are indicative of severe systemic illness; respiratory failure; evidence of shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death). However, the number of severe cases that have been observed to date was small in the Pfizer-BioNTech clinical trial in participants 16 years of age and older, and was too small in the AstraZeneca clinical trials to assess efficacy. There were no severe cases identified in adolescents 12 to 15 years of age in the Pfizer-BioNTech clinical trial, nor in adolescents 12 to 17 years of age in the Moderna clinical trial. Efficacy against hospitalization was not assessed in the clinical trials of the mRNA vaccines, but evidence from the clinical trials involving the viral vector vaccines is suggestive of a protective effect against hospitalization. To date there have been very few COVID-19 associated deaths identified in the clinical trials making it difficult to assess efficacy against this outcome. However, of the COVID-19 associated deaths identified in clinical trials, none have been in study participants receiving COVID-19 vaccines.

Emerging real world evidence from studies in the United Kingdom (UK) [15-17], Israel [18-20][21], the United States (US) [22], and Canada [23][24] suggests moderate to high vaccine effectiveness against severe COVID-19 outcomes after the first or second dose of mRNA COVID-19 vaccines in adults,[15-20, 22, 23][21], and after the first dose of AstraZeneca COVID-19 vaccine [15-17], including in older [15-17, 20] and frail [15] populations. COVID-19 related hospitalization was the most common severe COVID-19 outcome assessed [15-18, 22][21], while fewer studies provided estimates of effectiveness against severe disease [18, 19] and death [16, 18, 23]. Emerging evidence from Israeli studies suggest high vaccine effectiveness after the second dose of Pfizer-BioNTech COVID-19 vaccine against severe disease, [18, 19] COVID-19 related hospitalization [18][21] and death [21].

Studies for COVID-19 vaccines are ongoing and new effectiveness data against severe COVID-19 outcomes will be assessed as it emerges.

Efficacy and effectiveness against asymptomatic infection and transmission

Preliminary data from the ongoing Moderna COVID-19 vaccine trial showed a lower prevalence of SARS-CoV-2 positivity by PCR in asymptomatic participants at one particular time point (after Dose one but before Dose 2), and therefore viral shedding, in the group that received the vaccine compared to the placebo group. However, the current data are insufficient to draw conclusions. Exploratory analyses for the AstraZeneca viral vector vaccine have not demonstrated efficacy against confirmed SARS-CoV-2 asymptomatic infection, however the number of asymptomatic infections was small. The clinical trial of the Janssen COVID-19 vaccine found the vaccine to have moderate protection against asymptomatic and undetected COVID-19 infection. Studies are ongoing for these vaccines.

Evidence has begun to emerge from post-marketing studies conducted in Israel [18], the UK [25], and the US [26] on the effectiveness of COVID-19 vaccines against asymptomatic infection in adults. Estimates of vaccine effectiveness for the Pfizer-BioNTech COVID-19 vaccine against SARS-CoV-2 infection with no reported symptoms was moderate to high after the first dose [18, 25] (depending on time since vaccination) and high after the second dose [18, 25]. Similar results were reported for mRNA COVID-19 vaccines in general (i.e., Moderna and Pfizer-BioNTech) [26]. In one UK study, asymptomatic SARS-CoV-2 infections were significantly less likely to be identified in vaccinated participants compared to those who were unvaccinated [25]. There are no results specific to other COVID-19 vaccines yet, but studies are ongoing.

Efficacy and effectiveness against variants

Evidence of varying protection and effectiveness offered by authorized mRNA COVID-19 vaccines (Pfizer-BioNTech COVID-19 vaccine, Moderna COVID-19 vaccine) and viral vector-based COVID-19 vaccines (AstraZeneca COVID-19 vaccine, Janssen COVID-19 vaccine) against variants of SARS-CoV-2 is evolving. Please see Table 5 for a summary of this evidence.

The Janssen clinical trial was conducted during the time of emergence of SARS-CoV-2 VOC. As part of the testing conducted during the trial, a proportion of case isolates were genetically sequenced, and of the sequenced isolates, just over two-thirds of the isolates from Brazil were of the P.2 (Zeta) VOI lineage and nearly all isolates from South Africa were of the B.1.351 (Beta) VOC lineage. Point estimates of vaccine efficacy against confirmed symptomatic moderate to severe/critical COVID-19 infection with onset from 28 days post-vaccine are comparable to the overall estimate of efficacy against this outcome in Brazil and South Africa.

There is evidence that the Pfizer-BioNTech and AstraZeneca vaccines protect against the B.1.1.7 (Alpha) VOC. While there appears to be reduced protection against acquisition of B.1.617.2 (Delta) after the first dose for both Pfizer-BioNTech and AstraZeneca vaccines as compared with other strains, emerging data suggest that Pfizer-BioNTech offers very good protection and the AstraZeneca vaccine offers good protection against infection with the B.1.617.2 (Delta) VOC after the second dose. In addition, the vaccines offer good protection against hospitalization after the first doses. There are also emerging data on the efficacy or effectiveness of mRNA vaccines against B.1.351 (Beta) VOC. Evidence from the Janssen vaccine clinical trials indicate that it is protective against symptomatic moderate to severe/critical COVID-19 infection in areas where B.1.351 (Beta) VOC and P.2 (Zeta) VOI are circulating widely. The AstraZeneca clinical trial was conducted when the B.1.351 (Beta) lineage was the predominant strain in South Africa, and vaccine efficacy was not demonstrated against this strain.

NACI will continue to monitor the evidence and update recommendations as needed.

IV.3 Immunogenicity

No immunological correlate of protection has been determined for SARS-CoV-2; therefore, all immunological evidence in support of vaccine efficacy is indirect and cannot directly be used to estimate either vaccine efficacy or effectiveness.

There are several key knowledge gaps that affect the understanding of immune responses to COVID-19 vaccine:

- Which type of immune responses are important for protection from infection, severe disease, or transmission
- What level of humoral and cellular immune responses are necessary to confer protection
- The durability of immune responses and how they may change over time
- How immune responses to natural infection compare to responses elicited from a vaccine
- How immune responses differ across populations (e.g., children) or by SARS-CoV-2 serostatus (i.e., past COVID-19 infection)
- How immune responses differ based on previous infection with non-SARS-CoV-2 coronaviruses

Due to limitations in the number of participants evaluated for immunogenicity outcomes and duration of follow up from COVID-19 clinical trial data, long-term evidence on immunogenicity is unknown. However, studies are ongoing.

The following section highlights key immunogenicity data for the authorized mRNA COVID-19 vaccines (Pfizer-BioNTech COVID-19 vaccine and Moderna COVID-19 vaccine) and viral vector based COVID-19 vaccines (AstraZeneca COVID-19 vaccine and Janssen COVID-19 vaccine) only. For additional details regarding trial design, including study population and length of follow-up, and immunogenicity for these authorized vaccines, refer to the evidence summaries in Appendix A (for the Pfizer-BioNTech COVID-19 vaccine), Appendix B (for the Moderna COVID-19 vaccine), Appendix C (for the AstraZeneca COVID-19 vaccine) and Appendix D (for the Janssen COVID-19 vaccine).

Humoral immune responses

All authorized COVID-19 vaccines induce humoral immune responses, including binding and neutralizing antibody responses. Humoral responses peaked after the second dose of mRNA vaccine, and after the second dose of AstraZeneca COVID-19 vaccine in participants who were not previously infected. Humoral immune responses were elevated after the one dose of Janssen vaccine. Some vaccines induce higher immune responses in younger populations.

Viral vector-based vaccines may induce anti-vector immune responses, which may impact future vaccine efficacy and effectiveness and may vary by age, dose, and interval between doses.

Cellular immune responses

All authorized, available COVID-19 vaccines have been shown to produce cellular immune responses. Cellular immune responses increased after the second dose of mRNA COVID-19 vaccine, while responses for AstraZeneca COVID-19 vaccine were maintained or decreased after the second dose. Cellular immune responses were present following one dose of Janssen vaccine.

IV.4 Vaccine Administration

For additional vaccine product-specific information, consult the product leaflet or information contained within the product monograph available through Health Canada's Drug Product Database. Refer to Vaccine Administration Practices in the Canadian Immunization Guide (CIG), Part 1 - Key Immunization Information for additional general information.

As for the routine administration of all vaccines, COVID-19 vaccines should be administered in settings capable of managing anaphylaxis. Refer to Anaphylaxis and other Acute Reactions Following Vaccination in the CIG, Part 2 – Vaccine Safety for information on the management of anaphylaxis post-vaccination.

IV.4.1 Dose, route of administration, and schedule

Dose

Pfizer-BioNTech Comirnaty COVID-19 Vaccine

Each dose is 0.3 mL after dilution, containing 30 mcg of SARS-CoV-2 spike protein mRNA.

The dose for the Pfizer-BioNTech COVID-19 vaccine (0.3 mL) is unique compared to that of most routine vaccinations. Special precaution should be taken to ensure the correct dose is taken from the multi-dose vial.

Moderna Spikevax COVID-19 Vaccine

Each dose is 0.5 mL, containing 100 mcg of SARS-CoV-2 spike protein mRNA.

No dilution is required.

AstraZeneca Vaxzevria COVID-19 Vaccine

Each dose is 0.5 mL, containing 5×10^{10} particles of SARS-CoV-2 spike protein.

No dilution is required.

Janssen COVID-19 Vaccine

Each dose is 0.5 mL, containing 5×10^{10} particles of SARS-CoV-2 spike protein.

No dilution is required.

Route of administration

COVID-19 vaccines are given as an intramuscular (IM) injection into the deltoid muscle. The deltoid muscle of the arm is the preferred injection site in adolescents and adults (unless the muscle mass is not adequate or vaccination in that site is not possible, in which case the anterolateral thigh can be used).

Refer to Vaccine Administration Practices in the CIG, Part 1 - Key Immunization Information for additional general information.

Schedule

Refer to Table 3 for a summary of immunization schedules for authorized COVID-19 vaccines.

Table 3. Immunization schedule for primary series, by COVID-19 vaccine

Vaccine product	Immunization schedule[a]	Minimum interval	Authorized interval	Optimal interval[b]
Pfizer-BioNTech Comirnaty	2-dose schedule	19 days[c]	21 days	8 weeks
Moderna Spikevax	2-dose schedule	21 days[d]	28 days	8 weeks
AstraZeneca Vaxzevria	2-dose schedule	28 days	4 to 12 weeks	At least 8 weeks
Janssen COVID-19 vaccine	1-dose schedule	N/A	N/A	N/A

[a] Based on evidence of a reduced immune response to COVID-19 vaccination in moderately to severely immunocompromised individuals and an increased immune response after a third dose of an mRNA vaccine in immunocompromised individuals, NACI recommends that moderately to severely immunocompromised individuals who have not yet been immunized should be immunized with a primary series of 3 doses of an authorized COVID-19 mRNA vaccine, and moderately to severely immunocompromised individuals who have previously received a complete primary series should be offered an additional dose of an authorized COVID-19 mRNA vaccine. See the NACI Advisory Committee Rapid Response: Additional dose of COVID-19 vaccine in immunocompromised individuals following a 1- or 2-dose primary series.

[b] There is emerging evidence that longer intervals between the first and second doses of COVID-19 vaccines result in more robust and durable immune response and higher vaccine effectiveness. See **Optimal interval between the first and second dose for 2-dose COVID-19 vaccines below**. NACI will continue to monitor the evidence and update this interval as needed.

[c] The basis for this minimum interval is that the per-protocol design for the Pfizer-BioNTech COVID-19 vaccine clinical trial was 19-23 days.

[d] The basis for this minimum interval is that the majority of participants in the Moderna COVID-19 vaccine clinical trial received the second dose 21 to 42 days after the first, as per the pre-defined window.

For mixed COVID-19 vaccine schedules, the minimum interval between doses should be based on the minimum interval of the product used for the first dose (e.g., Pfizer-BioNTech COVID-19 vaccine should be offered a minimum of 28 days after AstraZeneca COVID-19 vaccine). Recommendations on extended intervals apply to mixed vaccine schedules.

Immunocompromised individuals who have a weakened immune system due to disease or treatment have been shown to have a lower immune response to COVID-19 vaccines compared to the general population. Recent studies demonstrate that individuals who are moderately to severely immunocompromised who did not respond to or who had a reduced immune response after COVID-19 vaccination can have an increased immune response after a third dose of an mRNA COVID-19 vaccine. Therefore, NACI recommends that moderately to severely immunocompromised individuals in the authorized age groups who have previously completed the authorized COVID-19 vaccine series should be offered an additional dose of an authorized mRNA COVID-19 vaccine. Please refer to the NACI Advisory Committee Rapid Response: Additional dose of COVID-19 vaccine in immunocompromised individuals following a 1- or 2-dose primary series.

Refer to Timing of Vaccine Administration in the CIG, Part 1 - Key Immunization Information for additional general information.

Optimal interval between the first and second dose for 2-dose COVID-19 vaccines.

The authorized intervals between the first and second dose of the currently available 2-dose COVID-19 vaccines were determined based on the interval chosen by the manufacturer for the initial clinical trials. However, the follow-up time in these COVID-19 vaccine clinical trials was short and the duration of protection after one or both doses was unknown when the vaccines were first authorized. Given the need to maximize vaccine supply and immunize the largest number of people as quickly as possible, and following principles of immunology which indicate that a longer interval between priming and booster doses of a vaccine results in a better and more durable response, and supported by preliminary evidence of 1-dose effectiveness and population modelling done by PHAC, NACI initially recommended extending the interval to the second dose of a COVID-19 vaccine up to 16 weeks (refer to the NACI Advisory Committee Statement: Extended dose intervals for COVID-19 vaccines to optimize early vaccine rollout and population protection in Canada in the context of limited vaccine supply (archived) for a summary of the evidence).

Following the initial authorizations for COVID-19 vaccines, data have become available that suggest that protection can be improved upon when the interval between the first and second doses are extended beyond the original manufacturer's recommended intervals. These data include immunogenicity and effectiveness of a first dose [27-32], data on waning immunity or effectiveness of the first dose prior to receipt of the second dose [27, 28] and data on immunogenicity and effectiveness following the second dose after a delayed interval [33-41]. Taken together, the interval between dose 1 and 2 for the current COVID-19 vaccines that appears to provide optimal protection while simultaneously minimizing the time at risk of infection due to having protection from only one dose is 8 weeks for mRNA vaccines [35, 42] and at least 8 weeks for AstraZeneca Vaxzevria [33]. These optimal intervals may change as further evidence on duration of protection accumulates.

The choice to use a longer interval to optimize protection should be made considering the local transmission of SARS-CoV-2 and the degree of individual risk of exposure, such as for front line health care or other high-risk occupation, and whether a second dose is needed for earlier protection, such as to protect against an emerging variant [29-32]. Canada has generally observed very good sustained protection against severe disease between the first and second dose during extended and authorized intervals.

In general, interruption of a vaccine series resulting in a greater interval between doses than that recommended by manufacturers does not require restarting the series, as delays between doses do not result in a reduction in final antibody concentrations for most multi-dose products. For many other multi-dose vaccines provided in adulthood using other vaccine technologies, the greatest proportion of short-term protection is achieved with the first dose with additional doses primarily intended to extend protection over the longer term.

NACI will continue to monitor the evidence and update recommendations as needed.

IV.4.2 Booster doses and re-immunization

NACI has determined that there is an immediate need to provide a recommendation for a booster dose of a COVID-19 vaccine in residents of long-term care and seniors living in other congregate settings as they are at increased risk of infection and severe disease and due to signs that protection might not persist as long in these individuals as in other populations in Canada. Based on ethical considerations, recent trends in COVID-19 epidemiology, and accumulating evidence on waning of COVID-19 vaccine immunogenicity and effectiveness over time (summarized in NACI's rapid response: Booster dose of a COVID-19 vaccine in long-term care residents and seniors living in other congregate settings), NACI recommends that:

For all long-term care residents and seniors living in other congregate settings who have received a primary COVID-19 vaccine series (with a homologous or heterologous schedule using mRNA or viral vector vaccines):

mRNA COVID-19 vaccine

A booster dose of an authorized mRNA COVID-19 vaccine should be offered. This dose should be offered at a recommended interval of at least 6 months after the primary series has been completed. Informed consent for a booster dose should include discussion about what is known and unknown about the risks and benefits, including the off-label status of NACI's recommendation.

(Strong NACI Recommendation)

AstraZeneca/COVISHIELD COVID-19 vaccine

A booster dose of an authorized viral vector vaccine should only be considered when other authorized COVID-19 vaccines are contraindicated or inaccessible. Informed consent should include discussion about the risk and symptoms of VITT, as well as the need to seek immediate medical care should symptoms develop.

(Discretionary NACI Recommendation)

Given the ongoing COVID-19 pandemic and emergence of VOC against which vaccine effectiveness may be decreased, additional vaccine doses may be necessary in other populations. NACI will continue to monitor the evidence and update recommendations as needed.

IV.4.3 Interchangeability

Interchangeability of authorized COVID-19 vaccines in a vaccines series when the first dose is:

mRNA COVID-19 vaccine

NACI recommends that, if readily available*, the same mRNA COVID-19 vaccine product should be offered for the subsequent dose in a vaccine series started with an mRNA COVID-19 vaccine. However, when the same mRNA COVID-19 vaccine product is not readily available*, or is unknown, another mRNA COVID-19 vaccine product recommended for use in that age group can be considered interchangeable and should be offered to

complete the vaccine series. The previous dose should be counted, and the series need not be restarted.

(Strong NACI Recommendation)

*readily available = easily available at the time of vaccination without delay or vaccine wastage

AstraZeneca/COVISHIELD COVID-19 vaccine

NACI recommends that while either an AstraZeneca/COVISHIELD COVID-19 vaccine or an mRNA COVID-19 vaccine product may be offered for the subsequent dose in a vaccine series started with an AstraZeneca/COVISHIELD COVID-19 vaccine, an mRNA COVID-19 product is preferred as a subsequent dose, due to emerging evidence, including the possibility of better immune response, and the safety of heterologous schedules. Regardless of which product is offered, a complete two-dose series is important for protection; the previous dose should be counted, and the series need not be restarted. Individuals who receive two doses of the AstraZeneca/COVISHIELD vaccine are considered protected and do not require further vaccination.

(Discretionary NACI Recommendation)

No data currently exist on the interchangeability of COVID-19 mRNA vaccines. However, there is no reason to believe that mRNA vaccine series completion with a different authorized mRNA vaccine product will result in any additional safety issues or deficiency in protection.

Emerging evidence indicates that mixed COVID-19 viral vector and mRNA vaccine schedules with dosing intervals between 4 and 12 weeks have acceptable safety profiles that may be associated with short-term increased systemic reactogenicity, which is potentially increased with shorter intervals between vaccines. Current evidence indicates that humoral and cellular immune responses (including responses against VOCs) increase when the Pfizer-BioNTech vaccine is administered as the second dose after AstraZeneca vaccine with an interval of 8 to 12 weeks [43], and are equivalent to or greater than immune responses following a homologous two-dose schedule of the AstraZeneca or Pfizer-BioNTech vaccine.

Due to the risk of VITT associated with the second dose of AstraZeneca/COVISHIELD COVID-19 vaccine, offering an alternative product with a more acceptable safety profile and expected comparable immunogenicity profile, while enabling individuals to make an informed choice is ethically justifiable. This is expected to lead to increased accessibility and acceptability for those who were initially offered a first dose of the AstraZeneca/COVISHIELD vaccine, including those who are most at risk of COVID-19. Given the risk of VITT associated with the Janssen vaccine, it should not be offered to individuals who received a first dose of AstraZeneca/COVISHIELD vaccine and prefer to receive an alternative product for their second dose. For more details on VITT, please see Thrombosis with Thrombocytopenia following vaccination with viral vector COVID-19 vaccines.

For mixed COVID-19 vaccine schedules, the minimum interval between doses should be based on the minimum interval of the product used for the first dose (e.g., Pfizer-BioNTech COVID-19 vaccine should be offered a minimum of 28 days after AstraZeneca COVID-19 vaccine).

Recommendations on extended intervals apply to mixed vaccine schedules. See Table 3 for information on recommended intervals for authorized COVID-19 vaccines.

Recommendations for the interchangeability of COVID-19 vaccines are consistent with the current NACI guidance on interchangeability for vaccines that are used for the same indication and contain comparable antigens. In line with basic principles of vaccinology [44], it is expected that combining different COVID-19 vaccines that induce an immune response against the SARS-CoV-2 spike protein will lead to a robust immune response. All currently authorized COVID-19 vaccines in Canada use the spike protein of the SARS-CoV-2 virus as the antigen. The spike protein produced by the mRNA (Pfizer-BioNTech, Moderna) and Janssen vaccines is stabilized in the prefusion conformation while the AstraZeneca vaccine produces a wild-type spike protein in various conformations, including prefusion.

Very rare cases of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining around the heart) following vaccination with COVID-19 mRNA vaccines have been reported in Canada and internationally, most frequently in adolescents and younger adults under 30 years of age, more frequently in males compared to females, and more frequently after the second dose in a two-dose homologous vaccination series compared to the first dose. The majority of cases are mild and individuals recover quickly. For more details on myocarditis/pericarditis, please see Myocarditis or pericarditis following vaccination with an mRNA COVID-19 vaccine.

Active surveillance of effectiveness and safety of a mixed schedule are important, and accurate recording of vaccines received will be critical. NACI will continue to monitor the evidence and update its recommendations as needed. For additional details on evidence related to mixed COVID-19 vaccine schedules, see NACI Rapid response: Interchangeability of authorized COVID-19 vaccines (archived).

IV.4.4 Post-vaccination counseling

NACI recommends that prophylactic oral analgesics or antipyretics (e.g., acetaminophen or ibuprofen) should not be routinely used before or at the time of vaccination, but their use is not a contraindication to vaccination. Oral analgesics or antipyretics may be considered for the management of adverse events (e.g., pain or fever, respectively), if they occur after vaccination.

Analgesics and antipyretics were used in clinical trials of COVID-19 vaccine for the management of pain and/or fever after vaccination. There is currently no evidence of benefit from administration of oral analgesics for the prevention of immunization injection pain or systemic reactions.

All vaccine recipients should be instructed to seek medical care if they develop signs or symptoms of an allergic reaction after their observation period ends and they have left the immunization clinic/venue.

All vaccine recipients who develop symptoms compatible with COVID-19 should be tested for SARS-CoV-2 to document breakthrough illness, particularly in the context of the emergence of VOC. Genetic sequencing should be strongly considered for those with SARS-CoV-2 infection after vaccination with either one or two doses of a COVID-19 vaccine.

Anyone receiving a viral vector COVID-19 vaccine should be informed of the recently recognized adverse event of thrombosis with thrombocytopenia syndrome and advised to seek immediate medical attention if they develop symptoms within 42 days of vaccination [45]. Symptoms to be vigilant for include: shortness of breath, chest pain, leg swelling, persistent abdominal pain, neurological symptoms including sudden onset of severe or persistent worsening headaches or blurred vision, skin bruising (other than at the site of vaccination) or petechiae. In addition, healthcare professionals should be aware of VITT including how to diagnose and treat the condition (see national guidance from Thrombosis Canada).

Refer to Vaccine Administration Practices in the CIG, Part 1 - Key Immunization Information for additional information on pre- and post-vaccination counseling.

IV.5 Serological testing

Serologic testing is not needed before or after immunization with COVID-19 vaccine.

IV.6 Storage requirements

Pfizer-BioNTech Comirnaty COVID-19 vaccine

Frozen vials prior to use
The Pfizer-BioNTech COVID-19 vaccine must be stored at ultra-low temperatures of -90°C to -60°C and protected from light, in the original packaging, until ready to use.

Refer to the re-icing guidelines (available at CVDVaccine.ca) for instructions regarding the use of the manufacturer's original thermal container for temporary storage.

Vials may also be stored at -25°C to -15°C for up to 2 weeks. Vials must be kept frozen and protected from light, in the original cartons, until ready to use. Vials stored at -25°C to -15°C for up to 2 weeks may be returned one time to the recommended storage condition of -90°C to -60°C. Total cumulative time the vials are stored at -25°C to -15°C should be tracked and should not exceed 2 weeks.

Thawed, unpunctured vials (prior to dilution)
The Pfizer-BioNTech COVID-19 vaccine may be thawed and stored at +2°C to +8°C for up to 1 month or at room temperature (up to +25°C) for no more than 2 hours. During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light. Thawed vials can be handled in room light conditions.

Do not refreeze thawed vials.

Thawed, punctured vials (after dilution)
The Pfizer-BioNTech COVID-19 vaccine must be stored between +2°C to +25°C and used within 6 hours from the time of dilution. During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light. After dilution, the vaccine vials can be handled in room light conditions.

Moderna Spikevax COVID-19 vaccine

Frozen vials prior to use
The Moderna COVID-19 vaccine should be stored at temperatures of -25°C to -15°C and protected from light in the original packaging. Do not store on dry ice or below -40°C.

Thawed, unpunctured vials
If not punctured, the Moderna COVID-19 vaccine can be thawed and stored at +2°C to +8°C for up to 30 days, or at +8°C to +25°C for up to 24 hours.

Do not refreeze thawed vials.

Thawed, punctured vials
The Moderna COVID-19 vaccine can be stored between +2°C to below +25°C but must be discarded after 24 hours from the time of first puncture.

AstraZeneca Vaxzevria COVID-19 vaccine

Unopened multidose vial
The AstraZeneca vaccine can be stored between +2ºC to +8ºC and protected from light in the original packaging. Do not freeze.

Opened multidose vial
After first opening, chemical and physical in-use stability has been demonstrated from the time of vial puncture to administration for no more than 6 hours at room temperature (up to +30ºC) or 48 hours in a refrigerator (+2ºC to +8ºC).

After the first puncture, the vial can be re-refrigerated, but the cumulative storage time at room temperature must not exceed 6 hours, and the total cumulative storage time must not exceed 48 hours. After this time, the vial must be discarded.

Janssen COVID-19 vaccine

Unopened multidose vial
The Janssen COVID-19 vaccine can be stored between +2ºC to +8ºC and protected from light in the original packaging. Do not freeze.

Punctured multidose vial
After the first dose has been withdrawn, the vial/filled syringe can be held at 2°C to 8°C for up to 6 hours or at room temperature (maximally 25°C) for up to 3 hours, after the first puncturing of the vial. Discard if vaccine is not used within this time.

For more information, consult the product leaflet or information contained within the product monograph available through Health Canada's Drug Product Database. Refer to Storage and Handling of Immunizing Agents in the CIG, Part 1 – Key Immunization Information for additional general information.

IV.7 CONCOMITANT ADMINISTRATION WITH OTHER VACCINES

NACI recommends that COVID-19 vaccines may be given concomitantly with, or at any time before or after, other vaccines*. (Discretionary NACI Recommendation)

*** including live, non-live, adjuvanted, or unadjuvanted vaccines**

Since each COVID-19 vaccine has been authorized in Canada, evidence on the efficacy/effectiveness, immunogenicity, and safety of these vaccines has been accumulating. Combined with the extensive data and experience on the concomitant administration of non-COVID-19 vaccines for routine immunizations, NACI has concluded that a precautionary approach of separating the time between administering COVID-19 and non-COVID-19 vaccines is now no longer necessary and recommends that COVID-19 vaccines may be administered concomitantly with (i.e. same day), or any time before or after, non-COVID-19 vaccines (including live, non-live, adjuvanted, or unadjuvanted). The concomitant administration of COVID-19 with non-COVID-19 vaccines will facilitate influenza vaccine programs in the fall and winter months and other routine vaccine programs that may have been delayed due to the COVID-19 pandemic.

Informed consent should include a discussion of the benefits and risks given the limited data available on administration of COVID-19 vaccines at the same time as, or shortly before or after, other vaccines. Studies to assess the safety and immunogenicity of concomitant administration of COVID-19 vaccines with other vaccines are ongoing.

It is currently not known if the reactogenicity of COVID-19 vaccines is increased with concomitant administration of other vaccines. While no specific safety concerns have been identified for various other vaccines with concomitant administration regimens, there is potential for increased reactogenicity with concomitant administration of COVID-19 vaccines with other vaccines, particularly those known to be more reactogenic, such as newer adjuvanted vaccines.

If more than one type of vaccine is administered at a single visit, they should be administered at different injection sites using separate injection equipment.

NACI will continue to monitor the evidence and update recommendations as needed.

Refer to Timing of Vaccine Administration in the CIG, Part 1 – Key Immunization Information for additional general information on simultaneous administration of other vaccines.

IV.8 Vaccine safety and adverse events following immunization (AEFI)

Due to limitations in the number of participants and duration of follow-up from COVID-19 clinical trials, medium- and long-term evidence on vaccine safety is limited. However, post-licensure vaccine pharmacovigilance is ongoing and safety signals around the world are detected and communicated globally. Clinical trials of the authorized COVID-19 vaccines excluded individuals with a history of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine. However, studies are ongoing.

The following section highlights key safety and AEFI data for the authorized COVID-19 vaccines. For additional details regarding trial design, including study population and length of follow-up, and safety for the vaccines authorized and available for use in Canada, refer to the evidence summaries in Appendix A (for the Pfizer-BioNTech COVID-19 vaccine), Appendix B (for the

Moderna COVID-19 vaccine), Appendix C (for the AstraZeneca COVID-19 vaccine) and Appendix D (for the Janssen COVID-19 vaccine). Refer to Appendix E for a summary of the frequency of AEFI for the different COVID-19 vaccine products.

Refer to Part 2 - Vaccine Safety in the CIG for definitions of AEFIs and additional general information.

IV.8.1 Very common and common adverse events

Common adverse events are defined as those that occur in 1% to less than 10% of vaccine recipients; very common adverse events occur in 10% or more of vaccine recipients. Please see Appendix E for a summary of adverse events identified in clinical trials of authorized, available COVID-19 vaccines.

Local

Pain at the injection site is very common after administration of the currently authorized COVID-19 vaccines. More than 40% of recipients experienced injection site pain. Redness and swelling are common or very common after administration. Localized axillary swelling and tenderness was a solicited adverse event in the Moderna COVID-19 clinical trial and was very common after administration with that vaccine. Local adverse events are usually mild or moderate and resolve within a few days of vaccination. For the authorized mRNA COVID-19 vaccines, pain at the injection site was slightly more frequent in younger authorized age groups including adolescents 12-15 years of age (Pfizer-BioNTech COVID-19 vaccine) and 12-17 years of age (Moderna COVID-19 vaccine) compared to older adults. For AstraZeneca COVID-19 vaccine, local reactions were milder and reported less frequently after the second vaccine dose in all age groups. Similar frequencies of local reactions were reported across age groups after administration of the Janssen vaccine.

Systemic

Fatigue, headache, muscle pain, chills, and joint pain are all either common or very common after the administration of the currently authorized COVID-19 vaccines. Fever was very common after administration of the second dose of the mRNA COVID-19 vaccines and common after any dose of viral vector vaccines. More than a quarter of vaccine recipients experienced headache and/or fatigue after any dose. Systemic adverse events are usually mild or moderate intensity and resolve within a few days of vaccination. For the mRNA COVID-19 vaccines, systemic reactions are more frequent after the second vaccine dose and in younger authorized age groups including adolescents 12-15 years of age (Pfizer-BioNTech COVID-19 vaccine). For AstraZeneca COVID-19 vaccine, systemic reactions are milder and reported less frequently after the second vaccine dose as compared with the first in all age groups. The frequencies of systemic reactions that were reported after administration of the Janssen vaccine were similar across age groups.

Adverse events following the second dose of COVID-19 in individuals previously infected with SARS-CoV-2

Evidence on the safety of vaccine booster doses is available from observational [46] and clinical studies [47][48][49]. Occurrence of solicited and unsolicited systemic adverse events in individuals with prior SARS-CoV-2 infection was slightly higher compared to the SARS-CoV-2 naïve

population, primarily in younger adults. However, there was no observed increase in the frequency of more severe adverse events in this population. Two observational studies included less than 100 patients with persistent symptoms from prior COVID-19 infections (long COVID). In this subgroup, receipt of COVID-19 vaccination with either an mRNA or viral vector vaccine was not associated with a worsening of long COVID symptoms or increased reactogenicity following immunization.

IV.8.2 Uncommon, rare, and very rare adverse events

Uncommon adverse events occur in 0.1% to less than 1% of vaccine recipients. Rare and very rare adverse events occur in 0.01% to less than 0.1% and less than 0.01% of vaccine recipients, respectively. The probability of detection of very rare adverse events in clinical trials is low given clinical trial population sizes; therefore, ongoing pharmacovigilance is essential.

To date, the available data does not indicate that vaccination of SARS-CoV-2 naïve individuals with authorized COVID-19 vaccines will elicit enhanced or altered disease upon subsequent infection by SARS-CoV-2 (e.g., vaccine-enhanced disease); however, further study is needed.

Lymphadenopathy was a solicited event in the Moderna clinical trials but not in other authorized COVID-19 vaccine trials see Appendix E). It was uncommonly reported after administration of the Pfizer-BioNTech, AstraZeneca and Janssen COVID-19 vaccines.

No other solicited uncommon, rare, or very rare adverse events were reported among vaccinated participants in the clinical trials at this time.

Thrombosis with Thrombocytopenia following vaccination with viral vector COVID-19 vaccines

Very rare cases of serious blood clots (at unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis) associated with thrombocytopenia have been reported globally following vaccination with viral vector COVID-19 vaccines. The terminology for this syndrome has been evolving since the safety signal was detected. The Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) uses the case definition for Thrombosis with Thrombocytopenia Syndrome (TTS) [(50)] to detect these rare events in Canada. Cases that test positive for a biomarker, anti-PF4 (antibodies to platelet factor 4-polyanion complexes), represent a subset of TTS events and are being referred to clinically as Vaccine-Induced Prothrombotic Immune Thrombocytopenia (VIPIT) or Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT).

International case reports and case series have raised the signal that those cases found to be positive for anti-PF4 could be associated with viral vector vaccines [(51)(52)(53)(54)(2)(55)]. Evidence on the association between TTS following vaccination with the viral vector COVID-19 vaccines is evolving; however, multiple international surveillance systems have early data that consistently point towards an association between adenovirus vector COVID-19 vaccines and TTS, including in the US, UK, and Europe. The exact mechanism by which the viral vector COVID-19 vaccines may trigger this syndrome is still under investigation but viral vector vaccines appear to trigger a presentation similar to spontaneous heparin-induced thrombosis (HIT) / autoimmune heparin-induced thrombosis, where antibodies to platelet factor 4 (PF4)-polyanion complexes induce platelet activation, which causes thrombosis and thrombocytopenia [(51)]. Clots related to VITT can

be very aggressive and challenging to treat [56]. Please refer to Thrombosis Canada guidance for clinical management of VITT. They cannot be managed the same way as clots related to oral contraceptives, immobility, or long-haul flights, and have an entirely different biologic mechanism of action.

Cases of VITT usually occur between 4 and 28 days after receipt of a viral vector COVID-19 vaccine, and patients should be monitored for symptoms up to 42 days [57]. The rate of VITT is estimated to be between 1 per 26,000 and 1 per 100,000 persons vaccinated with a first dose of AstraZeneca/COVISHIELD COVID-19 vaccine. As of June 1, 2021, PHAC has estimated the rate of VITT in Canada to be 1 in 73,000 doses administered. However, as investigations continue, this rate could be as high as 1 in 50,000. For updates to the numbers of cases of TTS and VITT in Canada, please see the "Serious and non-serious adverse events reported" section of Reported side effects following COVID-19 vaccination in Canada. The frequency of TTS following a second dose of AstraZeneca vaccine is currently reported to be approximately 1 per 520,000 in individuals vaccinated with a second dose, based on vaccine safety surveillance data from the United Kingdom, but this continues to evolve [2]. The case fatality rate of VITT also varies between countries, and ranges between 20 and 50%. Many cases have been reported to have serious long-term morbidity, including neurologic injury. Reports of TTS after administration of the Janssen vaccine are emerging from the United States. As of September 8, 2021, 46 cases have been confirmed after more than 14.5 million doses of Janssen vaccine administered in the United States, and others are under investigation [58]. For more information, see Appendix C, Appendix D, and NACI rapid response: Recommended use of AstraZeneca COVID-19 vaccine in younger adults.

Myocarditis or pericarditis following vaccination with an mRNA COVID-19 vaccine

Rare cases of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining around the heart) following vaccination with COVID-19 mRNA vaccines [59], have been reported in Canada and internationally including from Israel [60], the United States [61], Australia [55] and Europe [2, 62, 63].

Symptoms of myocarditis/pericarditis can include shortness of breath, chest pain, or the feeling of a rapid or abnormal heart rhythm. Symptoms can be accompanied by abnormal tests (e.g., electrocardiogram, serum troponins, echocardiogram).

International cases are consistently reported to have occurred::

- More often after the second dose
- Usually within a week after vaccination
- More often in adolescents and young adults (12 to 30 years of age)
- More often in males than females.

While follow-up is ongoing, available data indicate that the majority of individuals affected have responded well to conservative therapy, and tend to recover quickly.

Surveillance data from the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) in combination with Canada Vigilance Database (CVD) indicates a higher number of myocarditis/pericarditis cases following mRNA COVID-19 vaccines in younger age groups (primarily following the second dose) than would normally be expected [4]. Preliminary analyses suggest a higher unadjusted rate of myocarditis/pericarditis cases reported after vaccination with Moderna compared to Pfizer-BioNTech, however the analysis is ongoing.

Passive vaccine safety surveillance data from Ontario also suggests a product-specific difference in the risk of myocarditis/pericarditis following mRNA vaccines, in particular following the second dose [64]. The product-specific rate of myocarditis/pericarditis following the second dose was significantly higher for Moderna than Pfizer-BioNTech among 18-24 year old males. Additional analyses are ongoing.

Similarly, higher unadjusted rates of cases of myocarditis and/or pericarditis have been reported after the Moderna vaccine compared to Pfizer-BioNTech in other countries including Switzerland [63] and the UK [2]. A US analysis among individuals aged 12-39 years showed more than double the rate of chart confirmed myocarditis and/or pericarditis following the second dose of the Moderna vaccine compared to the Pfizer-BioNTech vaccine, however the reported rates were not statistically significantly different and investigations on ongoing [65].
Investigations into possible mechanisms of action that could explain the association between myocarditis and/or pericarditis and mRNA vaccines, identification of risk factors, including past history of myocarditis, and the potential impact of the interval between vaccine doses all continue in Canada and abroad [62, 65-67].
There are many potential causes for myocarditis and pericarditis, including both infectious and non-infectious causes, and disease severity can be variable. Myocarditis can also occur as a complication in people who are infected with SARS-CoV-2. A recent retrospective study from the US found myocarditis rates after confirmed COVID-19 infection to be as high as 450 cases per million infections in young males, aged 12-17 [68].

As part of ongoing COVID-19 vaccine safety efforts, PHAC and Health Canada are closely monitoring myocarditis and pericarditis through passive and active Canadian safety surveillance systems and collaboration with provincial and territorial health authorities, manufacturers and international regulators.

NACI continues to review information as it becomes available and will take appropriate action as needed.

Refer to the PHAC weekly AEFI report for information on numbers of cases reported in Canada. Refer to Reporting Adverse Events Following Immunization (AEFI) in Canada and to the recently developed Brighton Collaboration case definition of myocarditis/pericarditis for additional information on the completion and submission of AEFI reports.

Capillary leak syndrome following vaccination with AstraZeneca Vaxzevria COVID-19 vaccine

Very rare cases of capillary leak syndrome (CLS) have been reported following immunization with the AstraZeneca COVID-19 vaccine [2, 3, 62]. CLS is a very rare, serious condition that causes fluid leakage from small blood vessels (capillaries), resulting in swelling mainly in the arms and legs, low blood pressure, thickening of the blood and low blood levels of albumin (an important blood protein). Symptoms are often associated with feeling faint (due to low blood pressure).

In Canada, as of September 10, 2021, two cases of CLS had been confirmed [69] among more than 2,750,000 doses of AstraZeneca/COVISHIELD vaccines administered. As of May 27, 2021, six cases of CLS in individuals who had received the AstraZeneca COVID-19 vaccine had been reviewed by the European Medicine Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) among 78 million doses of AstraZeneca COVID-19 vaccine administered in the United Kingdom (UK) and European Economic Area/European Union (EU/EEA). Three of those affected had a previous history of CLS and one subsequently died. As of 21 June 2021, 3

cases of CLS in people who had received Janssen COVID-19 Vaccine had been reviewed by the EMA-PRAC among more than 18 million doses of Janssen COVID-19 Vaccine administered worldwide. One of those affected had a history of CLS and two subsequently died [70]. Following these reviews, the EMA's PRAC has concluded that individuals with a history of CLS should not be vaccinated with the AstraZeneca or Janssen COVID-19 vaccines.

PHAC and Health Canada are closely monitoring CLS in relation to the authorized viral vector COVID-19 vaccines. Health Canada has included information on CLS in the product monographs of the AstraZeneca, COVISHIELD and Janssen COVID-19 vaccines.

Cases of CLS following COVID-19 vaccination in Canada should be reported to assist with vaccine safety monitoring. Refer to Reporting Adverse Events Following Immunization (AEFI) in Canada for additional information on the completion and submission of AEFI reports.

Please see ***Section IV.10 Contraindications and Precautions*** for additional guidance on CLS as a contraindication for the Astra-Zeneca/COVISHIELD or Janssen COVID-19 vaccines.

Guillain-Barre Syndrome following vaccination with authorized COVID-19 vaccines

Guillain-Barre syndrome (GBS) is a rare but potentially serious immune-mediated neurologic disorder that results in pain or numbness, muscle weakness, and paralysis in severe cases. Most people fully recover from GBS but some have residual deficits or symptoms and rarely, fatal cases can occur. GBS can result from different causes, including infections, and occurs more frequently in males and persons aged 50 years or more. Cases have been rarely reported after receipt of some vaccines. To date, no increased risk of GBS has been identified following vaccination with the authorized mRNA COVID-19 vaccines (Pfizer-BioNTech and Moderna) [5, 6, 71]. Investigations have identified an increased risk of GBS following vaccination with the authorized viral vector COVID-19 vaccines (AstraZeneca/COVISHIELD and Janssen) [4-8]. In Canada, the number of cases of GBS following AstraZeneca/COVISHIELD vaccination is higher than would normally be expected based on rates in the general population. Up to and including September 10, 2021, PHAC had 30 reports of GBS among more than 2,750,000 doses of AstraZeneca/COVISHIELD vaccines administered (estimated rate of 1.08 cases per 100,000 doses). Symptoms occurred between 6 hours and 25 days after vaccination and the median age was 55 years (range 40 to 77 years old) and 22 (73%) were males. In the US, reports of adverse events suggest an increased risk of GBS during the 42 days following vaccination with the Janssen COVID-19 vaccine (note: AstraZeneca/COVISHIELD has not been used in the US). As of September 15, 2021, there were 201 preliminary cases of GBS reported in the US Vaccine Adverse Events Reporting System (VAERS) among more than 14.7 million doses of the Janssen vaccine administered (estimated rate of 1.37 cases per 100,000 doses) [58]. These cases have largely been reported about 2 weeks after vaccination and mostly in men, many 50 years and older.

The risk of GBS recurrence after COVID-19 vaccination amongst those with a past history of GBS appears to be very rare [72]. Only two cases have been described in the literature: one following Pfizer-BioNTech and one following a viral vector vaccine (product unknown). A causal association between these recurrences and COVID-19 vaccination has not been established. Both cases were recovering at the time of reporting.

As part of ongoing COVID-19 vaccine safety efforts, PHAC and Health Canada are closely monitoring GBS through passive and active Canadian safety surveillance systems and collaboration with Canadian provincial and territorial health authorities, manufacturers and

international regulators. Health Canada has included information on GBS in the product monographs of the AstraZeneca, COVISHIELD and Janssen COVID-19 vaccines.

NACI continues to review information as it becomes available and will take appropriate action as needed.

Refer to the PHAC weekly AEFI report for information on the number of cases of GBS reported in Canada.

Refer to Reporting Adverse Events Following Immunization (AEFI) in Canada and to the Brighton Collaboration case definition of Guillain-Barre syndrome for additional information on the completion and submission of AEFI reports.

Severe immediate allergic reactions (e.g., anaphylaxis) following vaccination with authorized COVID-19 vaccines.

Very rare cases of severe immediate allergic reactions (e.g., anaphylaxis) following vaccination with authorized mRNA COVID-19 vaccines have been reported in countries throughout the world with an incidence estimated between 2.0 to 7.9 cases per million doses of vaccine administered [61, 73-76]. Individuals tend to recover quickly with appropriate treatment and there have been no fatalities nor long-term morbidity observed with any of these severe immediate allergic reactions in Canada. In general, the majority of anaphylactic reactions following vaccination occur within 30 minutes of vaccination, although reactions can occur after this point [77]. Similarly, the majority of reactions to a COVID-19 vaccine occurred within 15 minutes (68%) to 30 minutes (86%) following vaccination [76]. They have been reported more frequently in females compared to males, and more frequently in those with prior allergic conditions [61, 73-76]. However, further studies on potential risk factors are needed given that the overall proportion of women who received the COVID-19 vaccines and the proportion of individuals with prior allergic conditions who received COVID-19 vaccines without severe immediate allergic reactions have not been reported consistently. Data in Canada are emerging, and surveillance data suggests similar patterns as observed in other countries [69]. Up to and including October 1, 2021; compared to rates following authorized mRNA COVID-19 vaccines (5.3 cases per million doses of vaccine administered), lower rates of anaphylaxis have been observed following authorized viral vector COVID-19 vaccines (4.7 cases per million doses of vaccine administered).

Studies have shown that individuals with a severe immediate allergic reaction after a previous dose of mRNA vaccine can be re-vaccinated with the same vaccine or another mRNA COVID-19 vaccine following an appropriate assessment [78-81]. In these studies, re-vaccination was safe and well tolerated with predominantly no, or mild, reactions after re-vaccination when provided in a controlled environment. Emerging evidence also suggests that most of the reported severe immediate allergic reactions following mRNA COVID-19 vaccines are likely not Immunoglobulin E (IgE)-mediated and therefore have a low risk of recurrence following future vaccine doses [81, 82]. Refer to the Contraindication and precautions section below for information on the re-vaccination of patients who had a severe immediate allergic reaction following a previous dose of COVID-19 vaccine.

PHAC and Health Canada are closely monitoring anaphylaxis through passive and active Canadian safety surveillance systems and collaboration with provincial and territorial health authorities, manufacturers and international regulators. Refer to the PHAC weekly AEFI report for information on the number of cases of anaphylaxis reported in Canada. Health Canada has

included information on anaphylaxis and hypersensitivity in the product monographs of the authorized COVID-19 vaccines.

NACI continues to review information as it becomes available and will take appropriate action as needed.

Refer to Anaphylaxis and other Acute Reactions Following Vaccination in the CIG, Part 2 – Vaccine Safety for information on the management of anaphylaxis post-vaccination.

IV.8.3 Guidance on reporting adverse events following immunization (AEFI)

Vaccine providers are asked to report AEFIs through local public health departments and to follow AEFI reporting requirements that are specific to their province or territory. In general, any serious (defined as resulting in hospitalization, permanent disability or death) or unexpected adverse event that is temporally related to vaccination should be reported.

In addition to provincial or territorial reporting requirements, the Brighton Collaboration has developed a list of Adverse Events of Special Interest (AESI) that are of particular interest and should be reported. Refer to https://brightoncollaboration.us/covid-19/ for the list with definitions.

There may be additional very rare AEFIs that have not been detected through clinical trials to date.

Refer to Adverse Events Following Immunization (AEFI) in the CIG, Part 2 – Vaccine Safety for additional information on definitions, reporting, investigating and managing, and causality assessments for AEFIs.

Refer to Reporting Adverse Events Following Immunization (AEFI) in Canada for additional information on the completion and submission of AEFI reports.

Refer to the PHAC weekly report for reported adverse events following COVID-19 vaccination in Canada.

IV.9 Special Populations

The following populations were either excluded from, or included in small numbers, in clinical trials for the COVID-19 vaccines. However, real-world data from the use of COVID-19 vaccines in these populations is accumulating. NACI will continue to monitor the evidence and update recommendations as needed.

Individuals previously infected with SARS-CoV-2

In studies looking at the immune response of individuals previously infected with SARS-CoV-2, binding and neutralizing antibodies have been shown to persist for at least 6 months post-infection [83], with only a small proportion of people becoming re-infected for potentially as long as 10 months [84]. Follow-up of cohorts of previously infected individuals have reported high levels of protection against reinfection and were more likely to be asymptomatic (~50%) than cases of primary infection (19%). The risk of re-infection due to VOCs is uncertain. Limited evidence assessing neutralizing activity against VOCs suggests that neutralizing activity is retained against

B.1.1.7 (Alpha); correspondingly, the risk of re-infection is similar to the original SARS-CoV-2 strain. There appears to be a reduction in neutralizing activity against B.1.351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta) compared to the original strain, and the risk of reinfection may be higher [85].

Evidence on the safety of COVID-19 vaccination of individuals with prior SARS-CoV-2 infection is available from observational [46][86][87] and clinical studies [47][48][49]. The occurrence of solicited and unsolicited systemic adverse events after the first or second dose in individuals with prior SARS-CoV-2 infection was slightly higher compared to the SARS-CoV-2 naïve population. However, there was no observed increase in the frequency of more severe adverse events in this population. Two observational studies included less than 100 patients with persistent symptoms from prior COVID-19 infections (long COVID). In this subgroup, receipt of COVID-19 vaccination with either an mRNA or viral vector vaccine was not associated with a worsening of long COVID symptoms or increased reactogenicity following immunization.

A number of large observational studies have compared the incidence of reinfection in individuals previously infected, with or without prior infection, to the incidence of infection in those without prior infection [88][89][90]. A retrospective cohort of 52,238 health care system employees (5% with prior infection) in the US found that after 5 months of follow-up, no cases of reinfection were identified (Shrestha et al.). The cumulative incidence of SARS-CoV-2 infection among previously infected unvaccinated employees did not differ from that of previously infected fully vaccinated employees or from that of previously uninfected fully vaccinated employees (63% of total study population received Moderna and 37% received Pfizer-BioNTech) [88].

A prospective observational study capturing the entire adult (≥16 years) Israeli population provided estimates of protection against subsequent infection, hospitalization, and severe illness in previously infected unvaccinated individuals over 3 months of follow-up, when the B.1.1.7 (alpha) variant was the most prevalent variant [90]. In this unvaccinated population, the estimates of protection due to prior SARS-CoV-2 infection were 95% against subsequent infection, 94% against hospitalization, and 96% against severe illness compared to unvaccinated individuals without prior infection. These estimates of protection were comparable to those provided by two doses of Pfizer-BioNTech vaccine in the previously uninfected vaccinated cohort [90].

In a prospective cohort of 23,324 staff working in National Health Service hospitals in the UK (35% with prior infection), after a follow-up of approximately two months, previously infected unvaccinated individuals had 90% protection against infection when compared to unvaccinated individuals without prior infection [89]. Although there was insufficient data to assess the vaccine effectiveness for previously infected individuals, the estimates of protection for vaccinated individuals without prior infection were 72% after the first dose and 86% after the second dose [89].

These observational studies suggest previous infection with SARS-CoV-2 induces good protection against subsequent infection and that the protective effect may be comparable to complete mRNA COVID-19 vaccination in individuals without prior infection. However, whether

the duration of protection generated from previous infection is similar to that elicited by mRNA COVID-19 vaccination remains unknown. The duration of protection provided by vaccination also remains unclear at this time.

In studies that reported immune responses after vaccination in individuals with previous SARS-CoV-2 infection [91][47][92][93][94][95][86], anti-spike binding and neutralizing antibody titres after Dose 1 were higher than those after Dose 1 in SARS-CoV-2 naïve individuals, and comparable to those observed after Dose 2 in SARS-CoV-2 naïve individuals. These trends were seen in both those who had previous symptomatic or asymptomatic infections; in some studies, antibody responses after Dose 1 were slightly higher in individuals with previous symptomatic infection compared to individuals with previous asymptomatic infection. In some studies of previously infected individuals, immune responses did not increase following Dose 2 and remained similar to those observed following Dose 1. Limited data on cellular immune responses were available. Two studies reported increased T cell responses in previously infected individuals compared to naïve individuals after Dose 1, but observed no differences in T cell responses between the two cohorts after Dose 2. However, in the absence of an established correlate of protection, it is not possible to determine the significance of differences in humoral and cellular immune responses in previously infected vaccinated individuals compared to SARS-CoV-2 naïve vaccinated individuals as they relate to the level and durability of protection against re-infection or breakthrough infections.

Individuals who are immunocompromised due to disease or treatment

Although the evidence is limited, observational studies show a reduction in vaccine effectiveness against SARS-CoV-2 infection and COVID-19 disease in immunocompromised adults when compared to the general population (based on use of the vaccines as per the manufacturers' schedules). The impact of immunocompromise on seroconversion after vaccination varies according to specific conditions and/or immunosuppressive therapy. Not all immunocompromised populations have been studied in detail. Some studies have shown that immunogenicity is substantially decreased in some immunocompromised adults when compared to healthy vaccine recipients. This notably included individuals with malignancy (solid and hematological), solid organ transplant recipients, and those with primary immune deficiency. Given the lack of a defined immunological correlate of protection against SARS-CoV-2 infection, the clinical significance of this difference in seroconversion and its impact on vaccine effectiveness is not known.

The safety profile of mRNA vaccines in real-world observational studies in adults who are immunocompromised has been comparable to what has been observed in the general population, with no unexpected or serious safety signals to date, including no worsening of an immunocompromising condition that has been attributed to the vaccine. Safety data in these populations following vaccination with a viral vector vaccine is not available.

<u>Summary of evidence on an additional dose of COVID-19 vaccine following a 2-dose series</u>

There are currently no data on the efficacy or effectiveness of an additional dose of a COVID-19 vaccine following a 1- or 2-dose primary series in individuals with immunocompromising conditions. Emerging evidence indicates that humoral immune responses increase after a third dose of mRNA COVID-19 vaccines is administered to adults with immunocompromising

conditions, although the degree of increase varies according to the type of immunocompromising condition or treatment. In the majority of studies, all three doses were mRNA vaccines. In some studies, although the increase in proportion of those who seroconverted was small, median antibody titers increased after the third dose compared to after the second dose. There was a significant amount of heterogeneity between studies due to differences in the populations that were studied. Given the limited size of the studies available to date and the lack of a defined immunological correlate of protection, there are limitations to interpreting the significance of these results.

Emerging evidence on safety of an additional dose in adults with immunocompromising conditions indicates that the reactogenicity of a third dose of COVID-19 vaccine was similar to that of prior doses. In the majority of studies, the third dose was an mRNA vaccine. No worsening of underlying disease was reported after immunization, however a few cases of graft versus host disease or organ rejection were reported. No serious adverse events were deemed to be associated with the vaccine. Due to the small size of these studies and limited follow-up times, the impact of additional doses on rare adverse events in these populations are unknown.

The risk of myocarditis and/or pericarditis following receipt of an mRNA COVID-19 vaccine is currently reported more commonly after second doses compared to first doses. The risk of myocarditis and/or pericarditis associated with an additional dose of an mRNA vaccine, including when given to immunocompromised individuals, is unknown at this time. NACI is continuing to monitor the evidence and will update recommendations as information becomes available.

Please see NACI's Rapid Response: Additional dose of COVID-19 vaccine in immunocompromised individuals following 1- or 2- dose primary series for a more detailed summary of the evidence on additional doses in this population.

Individuals who have an autoimmune condition

Emerging safety data from observational studies in individuals with autoimmune conditions indicates that the frequency and severity of adverse events in this population is comparable to that of individuals without autoimmune conditions and what was reported in clinical trials [96][97][98][99][100, 101][102]. The onset of new autoimmune disease or disease exacerbation following vaccination with mRNA COVID-19 vaccines was rare or comparable to the background incidence of these events in the general population. Safety data in this population following vaccination with a viral vector vaccine is not available.

The efficacy and effectiveness of COVID-19 vaccines in individuals with autoimmune conditions is unknown, but immunogenicity data is emerging. Data were available from observational studies in which participants received the mRNA or the AstraZeneca COVID-19 vaccines [103][98][104][100][105][101]. Immune responses were diminished only in participants who were also receiving immunosuppressive therapy. Given the limited number of participants and the lack of an immunological correlate of protection against SARS-CoV-2 infection, there are limitations in interpreting the significance of these results.

Individuals who are pregnant or breastfeeding

Evidence regarding the safety and immunogenicity of COVID-19 vaccines in individuals who are pregnant or breastfeeding are emerging. Pre-clinical studies on the safety of COVID-19 vaccines from animal developmental and reproductive toxicity studies did not identify concerns regarding

female reproduction, fetal/embryonal development, or postnatal development following the administration of the Moderna COVID-19 vaccine prior to or during gestation [106]. A report presented to the European Medicines Agency (EMA) also did not indicate adverse effects with respect to fertility, pregnancy, embryo/fetal development, or postnatal development (up to day 21) in studies in rats using a full dose of the Pfizer-BioNTech COVID-19 vaccine [107]. A US Food and Drug Administration (FDA) review of a study in rabbits that received the Janssen COVID-19 vaccine at two times the human dose prior to or during gestation similarly concluded there were no adverse effects on female reproduction, fetal/embryonal development, or postnatal development [108]. AstraZeneca performed a DART study in female mice given the vaccine prior to or during gestation and found no adverse effects on female fertility, embryofetal development or postnatal development in the mice [109].

Analysis of data collected through international COVID-19 immunization registries to date have not revealed any maternal or neonatal safety signals, and preliminary analyses of over 35,000 pregnant women in the United States who received an mRNA COVID-19 vaccine did not reveal any obvious safety signals [110]. In one small cohort study, mRNA from COVID-19 vaccines was undetectable in breastmilk 4-48 hours post-vaccination [111].

Emerging evidence suggests that COVID-19 mRNA vaccination during pregnancy is also immunogenic and results in comparable antibody titres to those generated in non-pregnant women [112][113][114]. Maternal IgG humoral response to mRNA COVID-19 vaccines transfers across the placenta to the fetus, leading to a significant and potentially protective, antibody titre in the neonatal bloodstream one week after the second dose [115][112][116, 117]. Observational studies consistently show that both anti-spike IgG and IgA are present in breastmilk for at least 6 weeks after maternal vaccination with mRNA vaccines [118][119][120][121].

IV.10 Contraindications and Precautions

Very rare cases of severe immediate allergic reactions (e.g., anaphylaxis) have been reported following immunization with mRNA COVID-19 vaccines. Recent studies have shown that most of the individuals who had these reactions after a previous dose of mRNA vaccine can be safely re-vaccinated with the same vaccine or another mRNA COVID-19 vaccine [78-81]. Re-vaccination in a controlled setting was safe and well tolerated with predominantly no, or mild, reactions after re-vaccination (see precautions below). Emerging evidence also suggests that many of these severe immediate allergic reactions following mRNA COVID-19 vaccines are likely not IgE-mediated and therefore have a low risk of recurrence after future vaccine doses [81, 82].

Table 4 lists potential non-medicinal ingredients in authorized COVID-19 vaccines that have been associated with allergic reactions in other products. These reactions have occurred rarely and ranged from mild cutaneous reactions to anaphylaxis. Anaphylaxis is typically a rare, severe, life-threatening allergic reaction usually with a rapid onset that involves multiple organ systems and can progress rapidly. Symptoms and signs of anaphylaxis may include but are not limited to generalized urticaria; wheezing; swelling of the mouth, tongue, and throat; difficulty breathing; vomiting; diarrhea; hypotension; decreased level of consciousness; and shock. It is important to note that other, less serious reactions may mimic allergic reactions (e.g., vasovagal syncope) and vaccination is not contraindicated in these cases.

Refer to Anaphylaxis and other Acute Reactions Following Vaccination in the CIG, Part 2 – Vaccine Safety for information on the management of anaphylaxis post-vaccination.

Table 4. Ingredients of authorized COVID-19 vaccines that have been associated with allergic reactions in other products

Vaccine product	Potential allergen included in the vaccine or its container	Other products where the potential allergen may be found
Pfizer-BioNTech Comirnaty	polyethylene glycol (PEG) [a,b,c]	Over the counter (e.g., cough syrup, laxatives), and prescription medications, medical bowel preparation products for colonoscopy, skin care products, dermal fillers, cosmetics, contact lens care solutions, products such as ultrasound gel[d].
Moderna Spikevax	PEG [a,b,c]	Over the counter (e.g., cough syrup, laxatives), and prescription medications, medical bowel preparation products for colonoscopy, skin care products, dermal fillers, cosmetics, contact lens care solutions, products such as ultrasound gel[d].
	tromethamine[e] (trometamol or Tris)	Component in contrast media, oral and parenteral medications.
AstraZeneca Vaxzevria	polysorbate 80[c]	medical preparations (e.g., vitamin oils, tablets, and anticancer agents), cosmetics[d,f]
Janssen COVID-19 vaccine	polysorbate 80[c]	medical preparations (e.g., vitamin oils, tablets, and anticancer agents), cosmetics[d,f]

*N.B. This is not a complete list of products.

[a] Medications that contain PEG are described in Stone CA, et al., DOI:10.1016/j.jaip.2018.12.003

[b] A review of immediate type hypersensitivity reactions to PEG is available in Wenande et al, DOI: 10.1111/cea.12760

[c] There is a potential of cross-reactive hypersensitivity between PEG and polysorbates

[d] PEG is an additive in some food and drinks but allergic reactions to PEG in food or drinks have not been documented.

[e] One case report of anaphylaxis to tromethamine has been described (Lukawska et al, DOI: 10.1016/j.jaip.2018.08.035).

[f] Case reports of anaphylaxis to polysorbate 80 have been described (Badiu et al, DOI: 10.1136/bcr.02.2012.5797, Palacios Castaño et al, DOI: 10.18176/jiaci.0109).

Rare cases of VITT have been reported following immunization with viral vector COVID-19 vaccines. Investigations are ongoing and the recommendations will be updated as evidence becomes available. For more information, refer to Appendix C and Appendix D

Contraindications

In general, an allergy to a component of a specific vaccine or its container is considered a contraindication, however for more details on the administration of COVID-19 vaccines to individuals with allergies to components of the COVID-19 vaccines or their container, please see the Precautions section.

Thrombosis and Thrombocytopenia following vaccination

Patients who have experienced venous or arterial thrombosis with thrombocytopenia following vaccination with a viral vector COVID-19 vaccine should not receive a second dose of a viral vector COVID-19 vaccine.

Capillary leak syndrome

As a precautionary measure following the international cases that have been reported, individuals with a history of capillary leak syndrome should not receive the AstraZeneca /COVISHIELD or the Janssen COVID-19 vaccine.

Precautions

Hypersensitivity and Allergies

Severe Immediate Allergic Reaction (e.g., anaphylaxis) to an authorized COVID-19 vaccine or a vaccine excipient

In individuals with a history of a severe, immediate (≤4h following vaccination) allergic reaction (e.g., anaphylaxis) after previous administration of an mRNA COVID-19 vaccine, re-vaccination (i.e. administration of a subsequent dose in the series when indicated) may be offered with the same vaccine or the same mRNA platform if a risk assessment deems that the benefits outweigh the potential risks for the individual and if informed consent is provided. The risk of a severe immediate allergic reaction after re-immunization appears to be low and no long-term morbidity has been associated with re-vaccination.

- Consultation with an allergist or other appropriate physician should be sought prior to re-vaccination.
- If re-vaccinated, vaccine administration should be done in a controlled setting with expertise and equipment to manage anaphylaxis. Individuals should be observed for **at least** 30 minutes after re-vaccination. For example, a longer period of observation is warranted for individuals exhibiting any symptom suggestive of an evolving AEFI at the end of the 30 minute observation period.

For those with a previous history of allergy to an mRNA vaccine, re-vaccination with an mRNA vaccine is preferred over a viral vector vaccine due to the better effectiveness and immunogenicity of mRNA vaccines and the possible adverse effects specifically associated with viral vector vaccines (e.g., Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT), capillary leak syndrome and Guillain-Barré Syndrome).

In individuals with a history of a severe, immediate (≤4h following vaccination) allergic reaction (e.g., anaphylaxis) after previous administration of a viral vector COVID-19 vaccine, re-vaccination may be offered with an mRNA platform if a risk assessment deems that the benefits outweigh the potential risks for the individual and if informed consent is provided. If re-vaccinated, individuals should be observed for at least 30 minutes after re-vaccination.

In individuals with a confirmed severe, immediate (≤4h following exposure) allergy (e.g., anaphylaxis) to a component of a specific COVID-19 vaccine or its container (e.g., PEG), consultation with an allergist is recommended before receiving the specific COVID-19 vaccine. Individuals who are allergic to tromethamine (found in the Moderna product) should be offered

the Pfizer-BioNTech vaccine which does not contain this excipient. Individuals who are allergic to polysorbates (found in viral vector vaccines), should be offered an mRNA vaccine.

Mild to Moderate Immediate Allergic Reactions Re-vaccination may be offered with the same vaccine or the same (mRNA) platform in individuals with mild to moderate immediate allergic reactions (defined as limited in the scope of symptoms and involvement of organ systems or even localized to the site of administration) after a previous dose of authorized mRNA COVID-19 vaccines or any of its components. Offering an mRNA vaccine is preferred over a viral vector vaccine (see above). Assessment by a physician or nurse with expertise in immunization may be warranted prior to re-immunization. Most instances of anaphylaxis to a vaccine begin within 30 minutes after administration of the vaccine. Therefore, if re-vaccination is chosen, an extended period of observation post-vaccination of at least 30 minutes should be provided for the aforementioned individuals.

Other Allergies or concerns relating to allergies

Individuals with proven severe allergic reaction (e.g., anaphylaxis) to injectable therapy not related to a component of authorized COVID-19 vaccines (e.g., other intramuscular, intravenous, or subcutaneous vaccines or therapies) may be routinely vaccinated and do not need to be assessed. Most instances of anaphylaxis to a vaccine begin within 30 minutes after administration of the vaccine. Therefore, an extended period of observation post-vaccination of 30 minutes should be provided for the aforementioned individuals.

Individuals with a history of allergy not related to a component of authorized COVID-19 vaccines or other injectable therapy (e.g., foods, oral drugs, insect venom or environmental allergens) can receive COVID-19 vaccines without any special precautions. Individuals should be observed for a minimum of 15 minutes following vaccination.

Individuals with suspected but unproven allergy to a vaccine component (e.g., PEG) may be routinely vaccinated and do not need a specific assessment regarding this suspected allergy. Most instances of anaphylaxis to a vaccine begin within 30 minutes after administration of the vaccine. Therefore, an extended period of observation post-vaccination of 30 minutes should be provided for the aforementioned individuals.

<u>Acute illness</u>

Vaccination of individuals who may be currently infected with SARS-CoV-2 is not known to have a detrimental effect on the illness. However, vaccination should be deferred in symptomatic individuals with confirmed or suspected SARS-CoV-2 infection, or those with respiratory symptoms, in order to avoid attributing any complications resulting from SARS-CoV-2 infection to vaccine-related AEFI and to minimize the risk of COVID-19 transmission at an immunization clinic/venue. If any persons are identified with symptoms on arrival at the venue, they should be instructed to follow current local public health measures.

As a precautionary measure and in light of the need to be able to monitor for COVID-19 vaccine adverse events without potential confounding from symptoms of COVID-19 or other co-existing illnesses, one should wait until all symptoms of an acute illness are resolved before vaccinating with an authorized COVID-19 vaccine.

<u>Hematologic</u>

In individuals with bleeding disorders, the condition should be managed prior to immunization to minimize the risk of bleeding. Individuals receiving long-term anticoagulation are not considered to be at higher risk of bleeding complications following immunization and may be safely immunized without discontinuation of their anticoagulation therapy.

Thrombosis and Thrombocytopenia

Individuals who have experienced a previous CVST with thrombocytopenia or heparin-induced thrombocytopenia (HIT) should only receive a viral vector COVID-19 vaccine if the potential benefits outweigh the potential risks. An alternate COVID-19 vaccine should be offered.

Anyone receiving any authorized viral vector COVID-19 vaccine should be informed of the risk of VITT and advised to seek immediate medical attention if they develop symptoms of VITT. These symptoms may include shortness of breath, chest pain, leg swelling or pain, or persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms after vaccination including sudden onset of severe headaches, persistent or worsening headaches, blurred vision, confusion or seizures, or who experiences unusual skin bruising or petechiae beyond the site of vaccination after a few days, should seek prompt medical attention.

Anyone receiving any authorized viral vector COVID-19 vaccine (AstraZeneca/COVISHIELD or Janssen) should be informed of the risks associated with viral vector vaccines (GBS, VITT/TTS, CLS) and be advised to seek medical attention if they develop signs and symptoms suggestive of these conditions.

Myocarditis and/or pericarditis

Post-market safety surveillance on mRNA COVID-19 vaccines has identified an increased frequency of myocarditis and pericarditis internationally, reported very rarely but most frequently in adolescents and young adults (12 to 30 years of age), more frequently in males compared to females, and more frequently after the second dose [60, 65]. The association of myocarditis and pericarditis with mRNA vaccination and a mechanism for inflammation remain under investigation.

As a precautionary measure, the second dose in the mRNA COVID-19 vaccination series should be deferred in individuals who experience myocarditis or pericarditis following the first dose of an mRNA COVID-19 vaccine until more information is available. Individuals who have a history of myocarditis unrelated to mRNA COVID-19 vaccination should consult their clinical team for individual considerations and recommendations. If the diagnosis is remote and they are no longer followed clinically for cardiac issues, they should receive the vaccine. NACI will continue to monitor the evidence and update recommendations as needed. NACI will continue to monitor the evidence and update recommendations as needed. Anyone receiving an authorized mRNA COVID-19 vaccine should be informed of the risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining around the heart) and advised to seek medical attention if they develop symptoms including chest pain, shortness of breath, or palpitations.

Healthcare providers should consider myocarditis and/or pericarditis in their evaluation if the patient presents with clinically compatible symptoms (chest pain, shortness of breath, palpitations) after the second dose of an mRNA COVID-19 vaccine but should be investigated regardless of timing from vaccination to onset. Investigations include electrocardiogram, serum troponins and echocardiogram with frequent abnormal electrocardiogram findings and elevated

troponin levels. Consultation with a cardiologist, infectious disease specialist, internal medicine specialist and/or rheumatologist may be advisable to assist in this evaluation, particularly to investigate the many potential causes of myocarditis and pericarditis. Investigations may include diagnostic testing for acute COVID-19 infection (e.g., PCR testing), prior SARS-CoV-2 infection (e.g., detection of SARS-CoV-2 nucleocapsid antibodies), and consideration of other potential infectious or non-infectious etiologies including auto-immune conditions.

Anyone receiving any authorized mRNA COVID-19 vaccine (Pfizer-BioNTech or Moderna) should be informed of the risks associated with mRNA COVID-19 vaccines (myocarditis and anaphylaxis) and be advised to seek medical attention if they develop signs and symptoms suggestive of these conditions.

Refer to Contraindications and Precautions in the CIG, Part 2 - Vaccine Safety for additional general information.

Guillain-Barré Syndrome

GBS is a rare but potentially serious immune-mediated neurologic disorder that can result from different causes, including infections, and occurs more frequently in males and persons aged 50 years or more.

GBS has been reported very rarely following COVID-19 vaccination [72]. Post-market safety surveillance has identified an increased risk of GBS following vaccination with viral vector COVID-19 vaccines but not with mRNA COVID-19 vaccines [4-8]. To date, the frequency of GBS recurrence among individuals with a past history of GBS has not been estimated.

Individuals with past history of GBS should receive an authorized mRNA COVID-19 vaccine. When authorized mRNA COVID-19 vaccines are contraindicated or inaccessible, individuals may receive an authorized viral vector COVID-19 vaccine after consultation with their health care provider.

If the benefits outweigh the risk and informed consent is provided, individuals who developed GBS after a previous dose of an authorized COVID-19 vaccine may receive an mRNA COVID-19 vaccine for their second dose after consultation with their health care provider.

NACI is monitoring the evidence and will update the recommendation as needed.

Anyone receiving any authorized viral vector COVID-19 vaccine (AstraZeneca/COVISHIELD or Janssen) should be informed of the risks associated with viral vector vaccines (GBS, VITT/TTS, CLS) and be advised to seek medical attention if they develop signs and symptoms suggestive of these conditions. Symptoms of GBS may include:

- weakness or tingling sensations, especially in the upper or lower limbs, that worsens and spreads to other parts of the body
- coordination problems and unsteadiness
- difficulty walking
- weakness in the limbs, chest or face
- difficulty with bladder control and bowel function
- double vision or difficulty moving eyes
- difficulty with facial movements, including swallowing, speaking, or chewing

Anyone receiving any authorized mRNA COVID-19 vaccine (Pfizer-BioNTech or Moderna) should be informed of the risks associated with mRNA COVID-19 vaccines (myocarditis/pericarditis and anaphylaxis) and be advised to seek medical attention if they develop signs and symptoms suggestive of these conditions.

IV.11 Drug Interactions

There have been no drug interactions studies performed to date.

For more information about potential interactions with products containing anti-SARS-CoV-2 antibodies, refer to section IV.11 Blood products, human immunoglobulin and timing of immunization, in this Statement.

Tuberculin skin testing (TST) or Interferon Gamma Release Assay (IGRA)

There is a theoretical risk that mRNA or viral vector vaccines may temporarily affect cell-mediated immunity, resulting in false-negative TST or IGRA test results. If tuberculin skin testing or an IGRA test is required, it should be administered and read before immunization or delayed for at least 4 weeks after vaccination. Vaccination with COVID-19 vaccines may take place at any time after all steps of tuberculin skin testing have been completed.

In cases where an opportunity to perform the TST or IGRA test might be missed, the testing should not be delayed since these are theoretical considerations. However, re-testing (at least 4 weeks post immunization) of individuals with negative results for whom there is high suspicion of tuberculosis infection may be prudent in order to avoid missing cases due to potentially false-negative results.

IV.12 Blood Products, Human Immunoglobulin and Timing of Immunization

NACI recommends that COVID-19 vaccines should not be given simultaneously with monoclonal antibodies or convalescent plasma.

To date, there is insufficient evidence on the receipt of both a COVID-19 vaccine and anti-SARS-CoV-2 monoclonal antibodies or convalescent plasma for treatment or prevention. Therefore, timing of administration and potential interference between these two products are currently unknown. Administration of these products close together may result in decreased effectiveness of a COVID-19 vaccine and/or anti-SARS-CoV-2 monoclonal antibodies because the monoclonal antibodies have high affinity for the spike protein expressed by the vaccines, which could prevent the production of antibodies stimulated by the vaccine.

In the post-exposure setting, expert clinical opinion should be sought on a case-by-case basis when deciding whether anti-SARS-CoV-2 monoclonal antibodies would be appropriate to administer after receipt of COVID-19 vaccine, taking into consideration the risk of exposure and the risk of severe COVID-19 disease in the individual.

To date, there is also insufficient evidence on the receipt of both a COVID-19 vaccine and any monoclonal antibodies or convalescent plasma for treatment or prevention of non-COVID-19 disease. Therefore, timing of administration and potential interference between these two products are currently unknown and expert clinical opinion should be sought on a case-by-case basis.

V. RECOMMENDATIONS

Following the thorough review of available evidence summarized above, as well as the systematic assessment of ethics, equity, feasibility and acceptability considerations with the EEFA Framework [10] as summarized in NACI's Guidance on Key Populations for Early COVID-19 Immunization, NACI makes the following evidence-informed recommendations for public health program level decision-making for the effective and equitable use of COVID-19 vaccines authorized for use in Canada.

NACI will continue to carefully monitor the scientific developments related to COVID-19 and COVID-19 vaccines, as well as ongoing vaccine pharmacovigilance, and will update recommendations as required.

Please note:

- A *strong recommendation* applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present.
- A *discretionary recommendation* may be offered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

Please see Table 6 for a more detailed explanation of the strength of NACI recommendations.

RECOMMENDATIONS ON AUTHORIZED COVID-19 VACCINES

These recommendations apply only to COVID-19 vaccines currently authorized for use in Canada (Pfizer-BioNTech COVID-19 vaccine; Moderna COVID-19 vaccine; AstraZeneca COVID-19 vaccine; and Janssen COVID-19 vaccine). In considering these recommendations and for the purposes of publicly funded program implementation, provinces and territories may consider local programmatic factors (e.g., logistical and operational contexts, resources) and local epidemiology (e.g., transmission of SARS-CoV-2 VOC).

1. **NACI preferentially recommends that a complete series with an mRNA COVID-19 vaccine should be offered to individuals in the authorized age group without contraindications to the vaccine.**
   (Strong NACI Recommendation)

2. **NACI recommends that a viral vector COVID-19 vaccine may be offered to individuals in the authorized age group without contraindications to the vaccine to initiate a series when other authorized COVID-19 vaccines are contraindicated or inaccessible. Informed consent should include discussion about the risk and symptoms of VITT, as well as the need to seek immediate medical care should symptoms develop.**
   (Discretionary NACI Recommendation)

Refer to the Table 5 for a summary of evidence and factors for jurisdictions to consider when implementing COVID-19 immunization programs.

Summary of evidence and rationale:

- The COVID-19 pandemic has caused significant morbidity and mortality, as well as social and economic disruption. The COVID-19 immunization program should be rolled out as efficiently, effectively and equitably as possible.
- mRNA COVID-19 vaccines are authorized in individuals 12 years of age and older (Pfizer-BioNTech COVID-19 vaccine, Moderna COVID-19 vaccine). Non-replicating viral vector vaccines are authorized for use in Canada for individuals 18 years of age and older (AstraZeneca COVID-19 vaccine, Janssen COVID-19 vaccine).
- A complete series for all currently authorized COVID-19 vaccines is two doses except for the Janssen COVID-19 vaccine which is authorized as a single dose in the general population. NACI recommends three doses of an authorized mRNA vaccine in moderately to severely immunocompromised individuals in the authorized age groups (see Recommendation #5).
- Some provinces/territories may decide to continue using only the Pfizer-BioNTech COVID-19 vaccine for adolescents 12 to 17 years of age, because there is more experience to date with Pfizer-BioNTech vaccine in this age group, and there is the possibility of a lower rate of myocarditis and/or pericarditis with this vaccine.
- See Table 1 for risk factors associated with increased risk of severe outcomes from COVID-19 and increased risk of exposure to COVID-19. Please refer to NACI's Guidance on the prioritization of key populations for COVID-19 immunization for additional details on sequencing of key populations, including a comprehensive analysis of ethical, equity, feasibility and acceptability considerations.

mRNA COVID-19 vaccines

- Clinical trial data available to date have shown that the currently authorized mRNA COVID-19 vaccines are highly efficacious (≥94%) in preventing confirmed symptomatic COVID-19 disease in the short term, starting at one to two weeks after receiving the full two-dose series.
- Highest efficacy and maximum immune response were observed after the second dose. Efficacy of a two-dose series was consistent across age groups.
- Estimates of vaccine effectiveness of the Pfizer-BioNTech vaccine were comparable in countries where the predominant circulating strain was the B.1.1.7 (Alpha) VOC. Emerging evidence suggests the Pfizer-BioNTech vaccine is 33.2% effective after the first dose and 87.9% effective after the second dose against the B.1.617.2 (Delta) VOC.
- Local and systemic adverse events were generally less frequent in older adults (≥56 in the Pfizer-BioNTech clinical trial and ≥65 in the Moderna clinical trial). There have been reports of myocarditis and/or pericarditis after immunization with mRNA COVID-19 vaccines in Canada and internationally. Cases of myocarditis and/or pericarditis occur more often in adolescents and adults under 30 years of age, more often in males than in females, and more often after a second dose of an mRNA vaccine than after a first dose.
- Post-market preliminary safety data reported by the US Vaccine Safety Datalink as well as Canadian post-market safety surveillance data suggest relatively higher rates of myocarditis/ pericarditis reported after Moderna vaccination compared to Pfizer-BioNTech, although verification of this potential difference is ongoing.
- The authorized mRNA vaccines are similarly safe and efficacious in those with one or more comorbidities (e.g., body mass index ≥30 kg/m2, chronic pulmonary disease, diabetes mellitus, cardiac disease).

Informed consent for-mRNA COVID-19 vaccines should include information about very rare reports of myocarditis or pericarditis in the week following an mRNA vaccine

- Post-market safety surveillance reports of myocarditis and pericarditis following mRNA vaccines have been reported most frequently in adolescents and younger adults 12 to 30 years of age, more frequently in males compared to females, and more frequently after the second dose [60, 65].
- The majority of cases are mild and individuals tend to recover quickly.
- Anyone receiving an mRNA COVID-19 vaccine should be informed of the risk of myocarditis and pericarditis and advised to seek medical attention if they develop symptoms, which include shortness of breath, chest pain, or the feeling of a rapid or abnormal heart rhythm.
- As a precautionary measure, the second dose in the mRNA COVID-19 vaccination series should be deferred in individuals who experience myocarditis or pericarditis as an adverse event following the first dose of an mRNA COVID-19 vaccine until more information is available. NACI will continue to monitor the evidence and update recommendations as needed.
- Informed consent should also include discussion about the individual's personal risk of severe COVID-19 disease (see Table 1), risk of infection and local epidemiology (including circulation of VOC), complications of COVID-19 (which may include myocarditis and pericarditis), and protection offered by COVID-19 vaccination.
    - Vaccination for adolescents and young adults is recommended as the benefits of vaccination to prevent COVID-19 including variants of concern, outweigh very rare cases of myocarditis/pericarditis.
    - Adolescents 12 to 17 years of age account for approximately 8% of the population [122], and this age group constitutes approximately 7% of COVID-19 cases reported nationally [123]. From January 1, 2020 to August 13, 2021, adolescents 12 to 17 years of age accounted for approximately 0.6% of COVID-19 cases resulting in hospitalization, approximately 0.4% of COVID-19 cases admitted to ICU, and approximately 0.01% of cases resulting in death [123].
    - Some individuals are at increased risk of hospitalization and mortality from COVID-19 (see Table 1). An updated rapid review of risk factors for severe illness conducted by the Alberta Research Centre for Health Evidence (ARCHE) found a moderate certainty of evidence of ≥2-fold increase in hospitalizations in individuals 21 years of age and younger with 2 or more chronic conditions (versus no chronic conditions) [12].
    - There is emerging evidence that mRNA vaccines offer good protection against infection with the B.1.617.2 (Delta) VOC after the second dose and very good protection against hospitalization after the first dose.
    - In clinical trials, mRNA COVID-19 vaccines have been shown to be immunogenic and efficacious in preventing symptomatic disease in adolescents and young adults. Clinical trials demonstrated a similar safety profile to that observed in older age groups.

AstraZeneca Vaxzevria COVID-19 vaccine

- Combined evidence from clinical trial and observational study data available to date have shown that the AstraZeneca COVID-19 vaccine offers protection against symptomatic

COVID-19 disease and hospitalization in adults ≥18 years of age after receiving at least one dose.

  - Clinical trial data available to date have shown that the AstraZeneca COVID-19 vaccine has demonstrated moderate efficacy against symptomatic, confirmed COVID-19 of approximately 62% in those 18-64 years of age. Efficacy of a two-dose series increased to approximately 82% when the interval between doses was 12 weeks or more. In adults 65 years of age and over, observational data from the UK of vaccine effectiveness after one dose have shown a reduction in the risk of symptomatic disease and hospitalization.
  - The highest efficacy with the authorized regimen of AstraZeneca COVID-19 vaccine was seen in clinical trial groups that had a longer interval between doses. Clinical trials suggest that vaccine efficacy increases with extended intervals between the first and second dose of vaccine, with a maximum reduction in risk of symptomatic disease observed at 12 weeks or more following the priming dose.

- Data suggest AstraZeneca COVID-19 vaccine has a vaccine efficacy of 74.6% against the B.1.1.7 (Alpha) VOC (compared to 84.1% against the non-B.1.1.7 (Alpha) strain). Published data suggests a vaccine efficacy of 10.4% against mild to moderate illness from the B.1.351 (Beta) VOC. Emerging data suggest the AstraZeneca vaccine is 32.9% effective after one dose and 59.8% effective after the second dose against the B.1.617.2 (Delta) VOC.
- In clinical trials, the majority of local and systemic adverse events with the AstraZeneca COVID-19 vaccine were mild and transient and did not differ by dose administered or age.
- Very rare but serious cases of blood clots, including cerebral venous sinus thrombosis, with concurrent thrombocytopenia have been reported globally following post-licensure use of viral vector COVID-19 vaccines. The exact mechanism by which these vaccines may trigger thrombosis with thrombocytopenia is still under investigation. The case fatality rate typically ranges between 20 and 50%.
- Very rare cases of CLS have been reported following immunization with the AstraZeneca COVID-19 vaccine. Of the six cases of CLS that occurred in Europe and the UK, three individuals had a previous history of CLS and one subsequently died.
- Very rare cases of GBS have been reported following vaccination with viral vector COVID-19 vaccines, at a higher rate that would normally be expected based on background rates in the general population.
- Anyone receiving the AstraZeneca COVID-19 vaccine should be informed of the risk of thrombosis with thrombocytopenia (also known as TTS or VITT), CLS and GBS and advised to seek medical attention if they develop signs and symptoms suggestive of these conditions.
- AstraZeneca COVID-19 vaccine is similarly efficacious in those with one or more mild to moderate and controlled medical conditions (e.g., cardiovascular disease, respiratory disease, diabetes, body mass index ≥30 kg/m^2).

Janssen COVID-19 vaccine

- Clinical trial data available to date have shown that the Janssen COVID-19 vaccine is 67% efficacious against moderate to severe/critical symptomatic COVID-19 disease at least two weeks after receiving one dose.
- Efficacy was consistent across age groups.
- Point estimates of vaccine efficacy against confirmed symptomatic moderate to severe/critical COVID-19 infection from 28 days post-vaccination were comparable in the

trial conducted in Brazil (68%), where two-thirds of the isolates were of the P.2 (Zeta) lineage and in the one conducted in South Africa (64%), where almost all isolates were of the B.1.351 (Beta) lineage.
- Local and systemic adverse events were typically mild and transient, and no safety signals were detected in clinical trials.
- As of September 8, 2021, 46 TTS cases were confirmed after more than 14.5 million doses of Janssen vaccine were administered in the United States.
- Very rare cases of GBS have been reported following vaccination with viral vector COVID-19 vaccines, at a higher rate that would normally be expected based on background rates in the general population. The vaccine is similarly safe and efficacious in those with one or more comorbidities 14 days after vaccination, although efficacy is somewhat lower in participants with comorbidities at 28 days post-vaccination.

mRNA COVID-19 vaccines versus viral vector COVID-19 vaccines

NACI reviewed the recent epidemiology of COVID-19 in Canada (including circulation of variants), vaccine characteristics (including efficacy, effectiveness, safety), evidence and international guidance on VITT, anticipated vaccine supplies, Health Canada's assessment of COVID-19 vaccines, as well as a comprehensive analysis of the implications on ethics, equity, feasibility and acceptability [10] of its recommendations for the use of COVID-19 vaccines in Canada.

NACI concluded that the advantages of safe, highly efficacious mRNA COVID-19 vaccines outweigh any possible disadvantages for eligible populations. Therefore, NACI made a strong recommendation for the preferential use of mRNA COVID-19 vaccines in all authorized age groups. NACI cautions that there is uncertainty in the evidence of advantages and disadvantages of the use of viral vector COVID-19 vaccines for eligible populations in Canada due to the risk of a rare but serious adverse event (Vaccine Induced Thrombotic Thrombocytopenia, VITT); the availability of other safe, highly efficacious mRNA COVID-19 vaccines; as well as some evidence of lower protection against asymptomatic transmission and the B.1.351 (Beta) and B.1.617.2 (Delta) VOC with the AstraZeneca vaccine. Therefore, NACI made a discretionary recommendation on the use of viral vector COVID-19 vaccines.

NACI previously made a discretionary recommendation on the use of viral vector COVID-19 vaccines for individuals who prefer an earlier vaccine rather than wait for an mRNA vaccine, only if certain conditions were met (including a benefit-risk analysis, informed consent, and substantial delay for receipt of an mRNA vaccine). This recommendation was based on a public health benefit-risk analysis using rates of VITT reported at that time (this analysis is available in archived versions of this statement). However, with increasing reported rates of VITT following vaccination with viral vector vaccines and increasing mRNA vaccine supplies in Canada, NACI now recommends that viral vector vaccines may be offered only if mRNA vaccines are contraindicated or inaccessible.

A summary of the evidence and rationale for NACI's preferential recommendation for the use of mRNA COVID-19 vaccines in population-level programs and discretionary recommendation for the use of a viral vector COVID-19 vaccine for individuals when other authorized COVID-19 vaccines are contraindicated or inaccessible is below:

- **Epidemiology**: The epidemiology and risk of COVID-19 vary across Canada and between populations. The proportion of COVID-19 cases classified as a VOC is increasing in Canada. Cases classified with a VOC are hospitalized more often relative

to those without a VOC in those aged 20 and over. NACI will continue to monitor the evolving epidemiology.

- **Efficacy and Effectiveness**: Emerging data suggest that all authorized vaccines offer protection against hospitalization and likely also death from COVID-19. In clinical trials, mRNA COVID-19 vaccines demonstrated higher efficacy than was shown for the viral vector COVID-19 vaccines. There is evidence that the mRNA COVID-19 vaccines and the AstraZeneca COVID-19 vaccine offer protection against the B.1.1.7 (Alpha) VOC. There is also emerging vaccine effectiveness evidence that suggests the Pfizer-BioNTech vaccine offers very good protection (87.9%) and the AstraZeneca vaccine provides good protection (59.8%) against the B.1.617.2 (Delta) VOC after the second dose. Effectiveness is much lower after only one dose of either the Pfizer-BioNTech and AstraZeneca vaccines (33.2% and 32.9% respectively). The mRNA COVID-19 vaccines and Janssen COVID-19 vaccines seem to offer protection against the B.1.351 (Beta) VOC, but the AstraZeneca COVID-19 vaccine does not. In studies in Brazil, the Janssen vaccine was shown to offer protection against the P.2 (Zeta) VOI. There is limited evidence on the protection of mRNA or viral vector COVID-19 vaccines against the P.1 (Gamma) VOC. New evidence, in particular from the US where they are both mRNA vaccines are extensively used, suggests slightly higher vaccine effectiveness against SARS-CoV-2 infection and/or COVID-19-related hospitalization with the Moderna vaccine compared to the Pfizer/BioNTech vaccine [22, 31, 124, 125]. Emerging evidence is also suggestive of a slightly more robust and durable immune response being mounted in recipients of the Moderna vaccine [126-131]. Studies investigating differences between these two COVID-19 vaccines are ongoing and new effectiveness and immunogenicity data will be assessed as they emerge.
- **Safety**:
  - Very rare cases of serious blood clots associated with thrombocytopenia have been reported globally following vaccination with viral vector COVID-19 vaccines. The case fatality rate of VITT also varies between countries, and ranges between 20 and 50%. Many cases have been reported to have serious long-term morbidity, including neurologic injury.
  - Very rare cases of a serious condition called capillary leak syndrome (CLS) have been reported following immunization with the AstraZeneca COVID-19 vaccine.
  - Post-market safety surveillance on mRNA COVID-19 vaccines has found an increased frequency of myocarditis and pericarditis following a second dose of a COVID-19 mRNA vaccine and in younger males and adolescents. However, the majority of cases reported were mild and individuals tended to recover quickly.
- **Ethics**: NACI consulted with the Public Health Ethics Consultative Group (PHECG) on the ethical considerations for restricting the use of a viral vector vaccine in the current and anticipated pandemic and vaccine supply context. The PHECG provided recommendations in the following areas: promoting well-being and minimizing risk of harm, maintaining trust, respect for persons and fostering autonomy, and promoting justice and equity. NACI integrated these recommendations into its guidance. NACI applied the precautionary principle in making its discretionary recommendation, and took into account the evolving evidence on VITT, the potential for harm, the availability of other effective vaccines without this safety signal, as well as evidence of the effectiveness of alternate infection prevention and control measures.
- **Equity**: NACI examined the implications of various recommendation options on the opportunity for all populations to have a fair opportunity to attain their full health potential [10]. Populations that received a viral vector COVID-19 vaccine when mRNA vaccine supplies were limited had protection against COVID-19 disease earlier than if they had

waited for mRNA vaccines to be available. However, these populations may ultimately have lower protection, as a larger proportion of the vaccinated population will remain susceptible. NACI considered the impact of the provision of a less efficacious vaccine with a safety signal of concern to marginalized and disadvantaged populations who have been disproportionately affected by the pandemic, and whose lived experience may have led to distrust of governments. Depending on vaccination strategies, this could potentially exacerbate health inequities if this potential harm is not considered when implementing the vaccine program in populations who experience intersecting risk factors for severe disease and exposure (e.g., racialized populations living in multigenerational housing with over-representation in jobs providing essential services such as food and healthcare). With increased supply of mRNA vaccines, inequities will be reduced if viral vector vaccines are offered only when mRNA vaccines are contraindicated or inaccessible.

- **Feasibility**: NACI considered the impact of its recommendations on the successful implementation of COVID-19 immunization programs in the local setting with available resources [10]. Canada has procured enough supply of mRNA vaccines to enable vaccination of currently eligible Canadian population. Expected supplies of viral vector COVID-19 vaccines for Canada are minimal in comparison to expected supplies of mRNA vaccines. The Janssen vaccine is authorized as a single dose vaccine; however, the duration of protection against COVID-19 is unknown.
- **Acceptability**: NACI reviewed recent Canadian data to consider the potential impact of its recommendations on intention and behaviours toward COVID-19 vaccination. The desire to be vaccinated continues to rise. However, various populations who have been disproportionately affected by the pandemic are also more hesitant or experience barriers in receiving a COVID-19 vaccine (e.g., racialized populations, migrant or undocumented workers). While public opinion research conducted in March 2021 suggested 44-60% of Canadians had no preference on which vaccine they received, surveys conducted in early April 2021 found that Canadians who are planning to get vaccinated are far more comfortable with the mRNA vaccines (90-92%) than the Janssen (70%) or AstraZeneca (41%) vaccines [132]. A follow up survey conducted in late April 2021 found that while comfort with mRNA vaccines remained high (90-92%), comfort receiving the Janssen vaccine decreased to 54% and was similar to comfort with receiving the AstraZeneca vaccine (52%) [133]. A survey of Canadians conducted in early May 2021 found that among unvaccinated respondents, 65% indicated they had a vaccine preference, with most willing to receive mRNA vaccines (58-82%) compared to viral vector vaccines (7-16%) [134]. Data collected over the course of the pandemic have consistently found that Canadians cite “ensuring the safety of the vaccine” as the main reason for delaying or not getting COVID-19 vaccination. NACI transparently summarized the best available evidence (including knowns and unknowns) to develop its evidence-informed expert guidance and enhance trust and confidence in its recommendations.

Long-term care (LTC) residents and seniors living in other congregate settings

3. **For all long-term care residents and seniors living in other congregate settings who have received a primary COVID-19 vaccine series (with a homologous or heterologous schedule using mRNA or viral vector vaccines) NACI recommends that a booster dose of an authorized mRNA COVID-19 vaccine should be offered. This dose should be offered at a recommended interval of at least 6 months after the primary series has been completed. Informed consent for a booster dose should include discussion about what is known and unknown about the risks and benefits, including the off-label status of NACI's recommendation. *(Strong NACI Recommendation)***

3a. A booster dose of an authorized viral vector vaccine should only be considered when other authorized COVID-19 vaccines are contraindicated or inaccessible. Informed consent should include discussion about the risk and symptoms of VITT, as well as the need to seek immediate medical care should symptoms develop. ***(Discretionary NACI Recommendation)***

Summary of evidence and rationale:

- Throughout the pandemic, LTC residents and seniors living in other congregate settings have faced a disproportionate burden of COVID-19-associated harms, including higher risk of sustained transmission and outbreaks, and high risk for severe COVID-19 outcomes. While over 50% of deaths in Canada to date are from LTC residents, this population only constituted approximately 3.6% of the confirmed cases nationally, with a cumulative case fatality rate estimated at 27% [135].
- Most LTC residents received an mRNA COVID-19 vaccine at the manufacturer-specified interval between dose 1 and dose 2. Evidence to date suggests that, compared to longer intervals, shorter intervals between the first and second dose in a primary series result in a lower immune response and more rapid waning of protection, including against variants of concern, is expected.
- Evidence from Canadian-led studies suggests that LTC residents produce a strong initial antibody response to a primary mRNA vaccine series (i.e., two doses) [136, 137]. However, studies also suggest the majority of residents did not have a detectable level of antibodies against the Delta variant six months following the primary series [138].
- Several studies are underway looking at mRNA booster doses. Early results are showing a favorable safety profile and evidence of an improved immune response, although data specific to LTC residents are limited. Two studies from Israel demonstrate the effectiveness of a booster dose in preventing SARS-CoV-2 infection [139, 140].
- There are currently limited data to determine the optimal interval between the completion of the primary series and administration of a booster dose. Immunogenicity data collected at 6 months following the primary series in LTC residents indicate waning immunity in this population. A longer interval between the primary series and a booster dose is likely to result in a better immune response. However, delaying the booster dose will increase the period during which individuals who may have reduced protection against SARS-CoV-2 infection are vulnerable to infection, although protection against severe outcomes will likely be more durable after the primary series.
- In addition to residents of congregate living settings, it is very important that healthcare workers, staff, visitors, and other close contacts of residents receive a primary COVID-19 vaccine series in order to prevent them from introducing the virus into the congregate living setting, infecting the residents and causing an outbreak.
- NACI will continue to monitor the evolving evidence on the need for and effectiveness of booster doses in other key populations and the general population and will update guidance as needed.

Individuals who had previously confirmed SARS-CoV-2 infection

4. NACI recommends that a complete series with a COVID-19 vaccine may be offered to individuals in the authorized age group without contraindications to the vaccine who have had previously PCR-confirmed SARS-CoV-2 infection. ***(Discretionary NACI Recommendation)***

Summary of evidence and rationale:

- Testing for previous SARS-CoV-2 infection is not needed prior to COVID-19 vaccination.
- On June 29, NACI reaffirmed its recommendation that those previously infected with SARS-CoV-2 may be offered a complete series with a COVID-19 vaccine, after considering evidence from rapid reviews that reported on the protective immunity of previous SARS-CoV-2 infection, the immunogenicity and safety of vaccination in previously infected individuals.
- In the absence of one-dose vaccine effectiveness data in previously infected individuals (particularly as it relates to the VOCs), no notable safety signals following a second-dose in this population, and the potential programmatic challenges associated with the implementation of a one-dose strategy, people with previous SARS-CoV-2 infection may continue to be offered a complete vaccine series at the recommended intervals, regardless of the severity of their previous infection. Based on current immunogenicity evidence, it is possible that one dose of COVID-19 vaccine for individuals who have had a previous SARS-CoV-2 infection may adequately protect against COVID-19.
- In COVID-19 vaccine clinical trials to date, individuals with PCR-confirmed SARS-CoV-2 were excluded and there were only a small number of trial participants with serologic evidence of previous infection (IgG+) who had confirmed symptomatic COVID-19 during the trials. Therefore, efficacy based on clinical trials in this population is uncertain.
- A number of large observational studies have found the incidence of reinfection in individuals with prior SARS-CoV-2 infection, with and without subsequent mRNA COVID-19 vaccination, to be comparable to individuals without prior infection who have received two doses of mRNA vaccine. In addition, a prospective observational study of the Israeli adult (≥16 years) population estimated prior SARS-CoV-2 infection provided very high (94 to 96%) protection against subsequent infection, hospitalization, and severe illness, which were comparable to the estimates of protection provided by two doses of vaccine in the previously uninfected vaccinated cohort. However, both the protective effect of immunity induced by previous infection and the durability of this protection against VOCs are unknown. Emerging evidence indicates that sera from convalescent patients may have reduced capacity to neutralize some VOCs and the risk of reinfection with these strains could be higher [(85)].
- There are currently limited data on potential differences in COVID-19 vaccine reactogenicity between those with and without prior evidence of SARS-CoV-2 infection. Due to the small sample sizes of the studies that report these data, the incidence of very rare adverse events such as myocarditis and pericarditis in previously infected individuals who receive one or two doses of COVID-19 vaccines is unknown. There is also a lack of evidence regarding the impact of the severity of the previous infection and the impact of the interval between a previous infection and the first dose of a COVID-19 vaccine on reactogenicity and rare adverse events.
- There is a growing body of evidence demonstrating that individuals with previous infection who receive a single dose of vaccine generate a comparable immune response compared to SARS-CoV-2 naïve individuals who receive two doses. Thus, it could be inferred that previously infected individuals who receive a single dose of vaccine may have similar levels of protection against infection as SARS-CoV-2 naïve individuals vaccinated with

two doses, although comparative vaccine effectiveness data between these two groups are lacking and protection against most VOCs in this scenario is unknown.

- There is also limited evidence that individuals with previous symptomatic infections may generate a greater immune response after vaccination compared to individuals with previous asymptomatic infections. Research on the immune response to SARS-CoV-2 and VOCs, including duration of immunity and cross-protection, is ongoing. There is a lack of evidence comparing the immune responses against VOCs in unvaccinated, previously infected persons to immune responses against VOCs in vaccinated individuals.
- While previously infected individuals may be able to obtain a similar level of protection from a single dose of vaccine compared to naïve individuals receiving two doses, previously infected individuals may choose to complete their vaccination series in order to meet vaccination-related requirements/guidelines to engage in activities, such as those related to travel.
- It was previously recommended in the context of limited supply that vaccination with a COVID-19 vaccine may be delayed for 3 months following a PCR-confirmed infection, due to available evidence on the risk of re-infection at the time. Research to establish the severity, frequency and risk factors for re-infection is ongoing. While binding and neutralizing antibodies have been shown in multiple studies to persist 6 months post-infection, and protection against re-infection could potentially be for as long as 10 months, the risk of re-infection over time in a given individual with previous infection is difficult to determine, as is the protection offered by previous infection against VOC. Therefore, if a delay in administering vaccination following infection is being considered, risk factors for exposure (including local epidemiology and circulation of VOCs) and risk of severe disease should also be taken into account.
- As a precautionary measure and in light of the need to be able to monitor for COVID-19 vaccine adverse events without potential confounding from symptoms of COVID-19 or other co-existing illnesses, and to minimize the risk of transmission of COVID-19 at an immunization venue, NACI recommends that, at a minimum, before vaccinating with COVID-19 vaccine, the person should no longer be considered infectious based on current criteria, and symptoms of an acute illness should be completely resolved.
- NACI will continue to monitor the evidence regarding vaccination in those previously infected with SARS-CoV-2 and will update recommendations as needed.

The following populations were either excluded from or were represented by small numbers of participants in the original pivotal clinical trials. NACI has updated recommendations for these populations as real-world evidence (mostly with mRNA vaccination) has become available. The recommendations above on the use of mRNA COVID-19 vaccines (Recommendation #1) and the use of viral vector COVID-19 vaccines (Recommendation #2), also apply to those who are immunosuppressed, have autoimmune conditions, are pregnant or are breastfeeding. However, NACI now recommends that individuals in the authorized age groups who are moderately to severely immunocompromised should be offered a primary series of three doses of an authorized mRNA vaccine (or an additional dose of an mRNA vaccine if they have previously received one dose of the Janssen COVID-19 vaccine or a 2-dose homologous or mixed schedule with the other COVID-19 vaccines authorized for use in Canada). Clarifications for informed

consent in these recommendations and a summary of the evidence and rationale for the recommendations in these populations is included below.

Immunosuppressed persons

5. **NACI preferentially recommends that a complete COVID-19 vaccine series with an mRNA COVID-19 vaccine should be offered to individuals in the authorized age group who are immunosuppressed due to disease or treatment. For those who are moderately to severely immunocompromised in the authorized age group who have not yet been immunized, NACI recommends that a primary series of three doses of an authorized mRNA vaccine should be offered. For those who are moderately to severely immunocompromised in the authorized age group who have previously received a 1- or 2-dose COVID-19 vaccine series (with a homologous or heterologous schedule using mRNA or viral vector vaccines), NACI recommends that an additional dose of an authorized mRNA COVID-19 vaccine should be offered. (*Strong NACI Recommendation*)**

   Moderately to severely immunosuppressed includes individuals with the following conditions:

   - Active treatment for solid tumour or hematologic malignancies
   - Receipt of solid-organ transplant and taking immunosuppressive therapy
   - Receipt of chimeric antigen receptor (CAR)-T-cell therapy or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)
   - Moderate to severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome)
   - Stage 3 or advanced untreated HIV infection and those with acquired immunodeficiency syndrome
   - Active treatment with the following categories of immunosuppressive therapies: anti-B cell therapies (monoclonal antibodies targeting CD19, CD20 and CD22), high-dose systemic corticosteroids (refer to the CIG for suggested definition of high dose steroids), alkylating agents, antimetabolites, or tumor-necrosis factor (TNF) inhibitors and other biologic agents that are significantly immunosuppressive.

6. **NACI recommends that a viral vector COVID-19 vaccine may be offered to individuals in the authorized age group who are immunosuppressed due to disease or treatment to initiate a series when other authorized COVID-19 vaccines are contraindicated or inaccessible. NACI recommends that the additional dose for those who are moderately to severely immunocompromised be a viral vector vaccine only when other authorized COVID-19 vaccines are contraindicated or inaccessible. Informed consent should include discussion about the risk and symptoms of VITT, the need to seek immediate medical care should symptoms develop, the limited evidence on the use of viral vector COVID-19 vaccines in this population, and the lack of evidence on the use of an additional dose of viral vector COVID-19 vaccines in this population. *(Discretionary NACI Recommendation)***

Summary of evidence and rationale

- Participants in the COVID-19 vaccine clinical trials only included individuals who were not immunosuppressed, such as those with stable infection with human immunodeficiency virus (HIV), and those not receiving immunosuppressive therapy during the trial. The efficacy of COVID-19 vaccines in immunocompromised individuals is currently unknown. However, real-world evidence (mostly with mRNA vaccination) has become available.
- Observational studies show a reduction in vaccine effectiveness against SARS-CoV-2 infection and COVID-19 disease in immunocompromised adults when compared to the general population. The criteria for being considered immunocompromised was not defined in these studies, and these analyses do not provide sufficient data to determine vaccine effectiveness for specific immunocompromising conditions or treatments.
- Some studies have shown that immunogenicity is substantially decreased in some immunocompromised adults when compared to healthy vaccine recipients. The clinical significance of this difference in seroconversion and its impact on vaccine effectiveness is not known.
- Emerging evidence indicates that humoral immune responses increase after a third dose of mRNA COVID-19 vaccine is administered to adults with immunocompromising conditions, although the degree of increase varies between studies and according to the type of immunocompromising condition or treatment. There was a significant amount of heterogeneity between studies due to differences in the populations that were studied.
- Studies assessing additional doses in immunocompromised individuals have primarily used mRNA vaccines, for both the initial primary series and additional dose. Moderna COVID-19 vaccine may produce a greater immune response in this population. Investigations are ongoing.
- **Individuals should continue to follow recommended public health measures for prevention and control of SARS-CoV-2 infection and transmission.**
- **A vaccine series should ideally be completed at least two weeks before initiation of immunosuppressive therapies where possible.**
- The **minimal interval between the 1- or 2- dose initial series and the additional dose should be 28 days**. An interval longer than the minimum 28 days between doses is likely to result in a better immune response. However, if a longer interval is being considered, then risk factors for exposure and risk of severe disease should also be taken into account.
- Safety data in immunocompromised individuals, including those receiving immunosuppressive therapy, were available from observational studies in solid organ transplant recipients, cancer patients and individuals with chronic inflammatory diseases who were taking immunosuppressive therapies [96][97][98][99][100][101][141][142][143][144][145][146][147][148]. The frequency and severity of adverse events following vaccination with an mRNA COVID-19 vaccine in these populations were comparable to that of non-immunosuppressed individuals in these studies and what was reported in clinical trials. Safety data in these populations following vaccination with a viral vector vaccine is not available. In studies with adults, the reactogenicity of a third dose of COVID-19 vaccine was similar to that of prior doses. No worsening of underlying disease was reported after immunization.
- People living with HIV who are considered immunocompetent should be vaccinated. In observational studies and clinical trials, humoral and cellular immune responses were similar between fully vaccinated people living with HIV and those who were HIV-negative [149][150][151].

- The relative degree of immunodeficiency in individuals who are immunocompromised is variable depending on the underlying condition, the progression of disease and use of medications that suppress immune function.
- Immunocompromised individuals, including those receiving immunosuppressive therapy, are at increased risk for prolonged infection and serious complications from SARS-CoV-2 infection. Canadian surveillance data collected since December 2020 indicates that the proportion of COVID-19 cases that are hospitalized or admitted into intensive care unit (ICU), without adjusting for age, is 4-5 times higher amongst individuals 12 years of age and older who are reporting either immunodeficiency or malignancy than amongst the general population. This was also observed when data was limited to Delta-specific cases reported since March 2021.
- Active surveillance in these vaccine recipients is strongly encouraged. NACI will monitor the evidence as it evolves, and update recommendations as needed.

Please see NACI's Rapid Response: Additional dose of COVID-19 vaccine in immunocompromised individuals following 1- or 2- dose primary series for a summary of the evidence and further rationale for this recommendation.

Refer to Immunization of Immunocompromised Persons in the CIG, Part 3 – Vaccination of Specific Populations for definitions and additional general information.

Persons with an autoimmune condition

7. **NACI preferentially recommends that a complete vaccine series with an mRNA COVID-19 vaccine should be offered to individuals in the authorized age group with an autoimmune condition. Informed consent should include discussion about the emerging evidence on the safety of mRNA COVID-19 vaccines in these populations. (*Strong NACI Recommendation*)**

8. **NACI recommends that a viral vector COVID-19 vaccine may be offered to individuals in the authorized age group with an autoimmune condition to initiate a series when other authorized COVID-19 vaccines are contraindicated or inaccessible. Informed consent should include discussion about the risk and symptoms of VITT, the need to seek immediate medical care should symptoms develop, as well as the limited evidence on the use of viral vector COVID-19 vaccines in this population.**
(Discretionary NACI Recommendation)

Summary of evidence and rationale

- Although participants with autoimmune conditions who were not immunosuppressed were not excluded from trials, they constitute a very small proportion of trial participants and represent a very narrow range of autoimmune conditions. However, real-world evidence (mostly with mRNA vaccination) has become available.
- Other applications of mRNA technologies have been for the treatment of cancer, which requires an immune response directed against an individual's cancer cells. This raised the theoretical concern that mRNA vaccines for infectious diseases would behave similarly, eliciting inflammation and possibly exacerbating existing autoimmune diseases. Current applications of mRNA technology for COVID-19 vaccines have been optimized to reduce this risk; however, further evaluation is needed. The theoretical concern is similar for viral vector vaccines. However, evidence on the safety of COVID-19 vaccination in individuals with an autoimmune condition is emerging.

- Observational studies in individuals with autoimmune conditions indicates that the frequency and severity of adverse events in this population is comparable to that of individuals without autoimmune conditions and what was reported in clinical trials [96][97][98][99][100][101][102]. The onset of new autoimmune disease or disease exacerbation following vaccination with mRNA COVID-19 vaccines was rare or comparable to the background incidence of these events in the general population. Safety data in these populations following vaccination with a viral vector vaccine is not available.
- Observational studies in individuals with autoimmune conditions who were taking immunosuppressive therapies showed diminished or delayed immune responses to the mRNA or AstraZeneca vaccines. Given the limited number of participants and the lack of an immunological correlate of protection against SARS-CoV-2 infection, there are limitations in interpreting the significance of these observational studies [103][98][104][100][105][101].
- The spectrum of autoimmune conditions is diverse. The relative degree of autoimmunity in individuals with autoimmune conditions is variable depending on the underlying condition, the severity and progression of disease, and use of medications that impact immune function.
- The evidence about autoimmune conditions as an independent risk factor for severe COVID-19 is evolving. A rapid review of evidence from OECD member countries found strong evidence (of moderate certainty) for at least a 2-fold increase in mortality from COVID-19 with type 1 diabetes, as well as with a group of neurological disorders including multiple sclerosis and myasthenia gravis. The review also found low certainty evidence for a large increase in hospitalization with vasculitis [12]. The review found a moderate certainty of evidence of little or no association with mortality or hospitalization from COVID-19 in those with rheumatoid arthritis, rheumatic or connective tissue disease, or systemic lupus erythematosus [12]. Caution should be taken when interpreting low certainty evidence. However, the review found a moderate certainty of evidence of at least a two-fold increase in hospitalization and mortality if an individual had two or more underlying medical conditions, compared to individuals with no comorbidities. No direct evidence on the combination of medical conditions associated with increased risk was found [12][14].
- Active surveillance in these vaccine recipients is strongly encouraged. NACI will monitor the evidence as it evolves, and update recommendations as needed.

Refer to Immunization in Persons with Chronic Diseases in the CIG, Part 3 – Vaccination of Specific Populations for additional general information on autoimmune conditions.

Pregnancy and Breastfeeding

9. **NACI preferentially recommends that a complete vaccine series with an mRNA COVID-19 vaccine should be offered to individuals in the authorized age group who are pregnant or breastfeeding. Informed consent should include discussion about emerging evidence on the safety of mRNA COVID-19 vaccines in these populations. (*Strong NACI Recommendation)***

10. **NACI recommends that a viral vector COVID-19 vaccine may be offered to individuals in the authorized age group who are pregnant or breastfeeding to initiate a series when other authorized COVID-19 vaccines are contraindicated or inaccessible. Informed consent should include discussion about the risk and symptoms of VITT, the need to seek immediate medical care should symptoms develop, as well as the limited evidence on the use of viral vector COVID-19 vaccines in these populations.**
***(Discretionary NACI Recommendation*)**

Summary of evidence and rationale

- Pregnant or breastfeeding individuals were excluded from the mRNA and viral vector COVID-19 clinical trials. However, outcomes in participants who became pregnant during the clinical trials and fetal outcomes are reported through registries, and real-world evidence (mostly with mRNA vaccination) has become available.
- An mRNA vaccine is preferred due to published safety data. Recently published preliminary analyses of 35,691 pregnant women in the United States who received an mRNA COVID-19 vaccine did not reveal any obvious safety signals [110]. If VITT were to occur after receipt of a viral vector vaccine in a pregnant person, there might be complexity in the medical care. The US safety data suggests mRNA vaccine administration within 30 days of conception is safe [110]. Those who are trying to become pregnant do not need to avoid pregnancy after vaccination with an mRNA vaccine.
- Analysis of data collected through international COVID-19 immunization registries to date have not revealed any maternal or neonatal safety signals.
- To date, no safety signals have been detected in Development and Reproductive Toxicity (DART) animal studies for Pfizer [107], Moderna [106], Janssen[152], and AstraZeneca vaccines [153].
- Emerging evidence suggests that COVID-19 mRNA vaccination during pregnancy results in comparable antibody titres to those generated in non-pregnant women [112][113][114]. Maternal IgG humoral response to mRNA COVID-19 vaccines transfers across the placenta to the fetus, leading to a significant and potentially protective, antibody titre in the neonatal bloodstream one week after the second dose [115][112][116][117].
- Observational studies consistently show that both anti-spike IgG and IgA are present in breastmilk at least for 6 weeks after maternal vaccination with mRNA vaccines [118][119][120][121][154][155][111][156].
- In one small cohort study, mRNA from COVID-19 vaccines was undetectable in breastmilk 4-48 hours post-vaccination. No safety signals have been detected with mRNA vaccination during breastfeeding and individuals should continue to breastfeed after vaccination [111].
- The evidence of pregnancy as an independent risk factor for severe COVID-19 is evolving. A rapid review of evidence from Organisation for Economic Co-operation and Development (OECD) member countries found a low certainty of evidence of at least a two-fold increase in hospitalization due to COVID-19 for pregnancy (any stage) and a low certainty of evidence for little to no increase in mortality. Caution should be taken when interpreting low certainty evidence. However, the review found a moderate certainty of evidence of at least a two-fold increase in hospitalization and mortality if an individual had two or more underlying medical conditions, compared to individuals with no comorbidities. No direct evidence on the combination of medical conditions associated with increased risk was found [12, 14].
- Compared to non-pregnant persons, SARS-CoV-2 infection in pregnancy may increase the risk of complications requiring hospitalization and intensive care, premature birth and caesarean delivery. A review of 438,548 pregnant individuals found pregnancy is a risk factor for poorer pregnancy outcomes, such as preeclampsia, pre-term birth, and stillbirth, and that these risks are much greater with severe infection [157]. Canadian-based surveillance of COVID-19 in pregnancy in five provinces from March 1st-December 21st, 2020 with a sample of 1880 pregnant positive cases, saw an increased risk of being hospitalized (RR=5.33, 95% CI: 4.51-6.20) and an increased risk of being admitted to the ICU (RR=5.88, 95% CI: 3.80 to 8.22) compared to non-pregnant counterparts [158].

Ventilatory support in pregnancy is more challenging and the risks are greater to both mother and child.

- Vaccine recipients and health care providers are encouraged to enroll patients who have received a COVID-19 vaccine during pregnancy in COVID-19 vaccine pregnancy registries (refer to Appendix F for a list of COVID-19 vaccine pregnancy registries). Timely reporting on adverse events following immunization to the local public health authority, as well as to the vaccine manufacturer, for follow up in these vaccine recipients is strongly encouraged.
- NACI encourages research on COVID-19 vaccination in pregnancy and during breastfeeding.
- NACI will monitor the evidence as it evolves, and update recommendations as needed.

Refer to Immunization in Pregnancy and Breastfeeding, Part 3 – Vaccination of Specific Populations of the CIG for additional general information.

Children and Adolescents

11. NACI recommends that a complete series with an mRNA COVID-19 vaccine should be offered to adolescents 12 to 17 years of age who do not have contraindications to the vaccine. Informed consent should include discussion about very rare reports of myocarditis and/or pericarditis following administration of mRNA vaccines. *(Strong NACI Recommendation)*

Summary of evidence and rationale

- Adolescents 12 to 17 years of age represent approximately 8% of the Canadian population [122] and constitute approximately 7% of COVID-19 cases reported in Canada [123]. Adolescents account for approximately 0.6% of COVID-19 associated hospitalizations, approximately 0.4% of COVID-19 cases admitted to ICU, and approximately 0.01% of deaths from COVID-19 [123].
- However, there have been recent reports of COVID-19 outbreaks affecting children, specifically related to the B.1.617.2 (Delta) variant, in areas of relatively high rates of vaccination in the adult population. Since May 2021 (coinciding with both the increasing prominence of the B.1.617.2 (Delta) variant and decreasing number of adult hospitalization events with increasing vaccination coverage in adults), the relative burden of disease for adolescents 12 to 17 years of age shifted upwards to approximately 8% of COVID-19 cases, 1.2% of COVID-19 cases resulting in hospitalization, 0.8% of COVID-19 cases admitted to ICU and 0.08% of cases resulting in death [123].
- Evidence from pivotal clinical trials of the Pfizer-BioNTech COVID-19 vaccine in adolescents 12-15 years of age, and the Moderna COVID-19 vaccine in adolescents 12-17 years of age, have demonstrated safety, immunogenicity and efficacy profiles similar to that previously reported in older individuals.
- Post-market safety surveillance of mRNA COVID-19 vaccines has found an increased frequency of myocarditis and pericarditis most frequently in adolescents and younger adults aged 12-30 years of age, more frequently in males compared to females, and more frequently after the second dose. However, the majority of cases have been mild and have resolved.
- Active surveillance in adolescent vaccine recipients is strongly encouraged. NACI will monitor the evidence as it evolves, and update recommendations as needed.

- Evidence on COVID-19 vaccination in those less than 12 years of age is not available at this time. NACI is monitoring the evidence and will update recommendations when results become available.

Please see NACI's Recommendation on the use of mRNA COVID-19 vaccines in adolescents 12 to 17 years of age for a summary of the evidence and further rationale for this recommendation.

NACI continues to recommend the following:

- Routine immunization programs and immunization with other vaccines recommended by NACI should continue during the COVID-19 pandemic with mitigation of risks of COVID-19 transmission during the immunization process as outlined in the Interim guidance on continuity of immunization programs during the COVID-19 pandemic.

- Clinical trials assessing COVID-19 vaccines should continue to be encouraged to include individuals with potential vulnerabilities to disease related to biological (e.g., pre-existing medical conditions, frailty, pregnancy and breastfeeding, immunocompromised), and social (e.g., residence in long term care facilities or crowded/remote locations, belonging to a racialized population, occupation) factors to ensure that vaccine options are informed by robust safety, immunogenicity, and efficacy data as outlined in NACI's guidance on Research Priorities for COVID-19 Vaccines to Support Public Health Decisions.

- In addition to ongoing vaccine pharmacovigilance activities in Canada with Phase 4 clinical trials and post-marketing studies, additional research and surveillance of COVID-19 vaccination, particularly in populations not currently included in clinical trials (e.g., pregnant, breastfeeding, immunosuppressed, seniors living in congregate care settings, children and adolescents) is recommended. Furthermore, NACI recommends the continuation of clinical trials and ongoing follow-up of participants for as long as it is ethically feasible to determine the level of immunity needed to prevent disease, duration of protection, efficacy in different sub-populations, and medium- and long-term safety.

NACI continues to recommend the following elements to guide ethical decision-making, as outlined in NACI's guidance on Key Populations for Early COVID-19 Immunization**:**

- Efforts should be made to increase access to immunization services to reduce health inequities without further stigmatization or discrimination, and to engage systemically marginalized populations and racialized populations in immunization program planning.

- Jurisdictions should ensure close and rapid monitoring of safety, effectiveness, and coverage of the vaccines in different key populations, as well as effective and efficient immunization of populations in hardly reached, remote and isolated communities.

- Efforts should be made to improve knowledge about the benefits of vaccines in general and of COVID-19 vaccines as each becomes available, address misinformation, and communicate transparently about COVID-19 vaccine allocation decisions.

V.I SUMMARY OF CONSIDERATIONS FOR COVID-19 VACCINES AUTHORIZED FOR USE IN CANADA

There are currently four authorized COVID-19 vaccines in Canada for the prevention of symptomatic COVID-19 that use two different vaccine platforms. The merits of both vaccine platforms have been summarized in Table 5 below.

Table 5. Vaccination considerations for types of COVID-19 vaccines authorized for use in Canada

Factor for consideration	Summary of available evidence and issues for consideration	
	mRNA COVID-19 Vaccines	**Non-replicating viral vector COVID-19 Vaccines**
Efficacy and Effectiveness	**Efficacy against symptomatic illness after a complete series** • Pfizer-BioNTech vaccine is overall 94% efficacious ≥14 days after dose 2 in study participants 16 years of age and older. Data suggest the Pfizer/BioNTech vaccine is 95% efficacious in participants ≥65 years of age, and 100% efficacious in participants 12-15 years of age, 7 or more days after dose 2. • Moderna vaccine is overall 94% efficacious in participants 18 years of age and older ≥14 days after dose 2. • Data suggest the Moderna vaccine is 86% efficacious in individuals ≥65 years of age ≥14 days after dose 2. **Effectiveness against severe disease, hospitalization and death from mRNA vaccines (with more data available for Pfizer-BioNTech than Moderna)** • Current data from real-world studies indicate that mRNA COVID-19 vaccines provide very good protection against COVID-19 hospitalization in adults following response to the first dose, including in older populations (≥65 years). • Data from real-world studies in adults provide some evidence that mRNA COVID-19 vaccines provide very good protection against COVID-19-related death following response to the first dose. • Real-world studies in adults indicate that mRNA COVID-19 vaccines provide excellent protection against severe disease, including COVID-19 related hospitalization and death following response to the second dose.	**Efficacy against symptomatic illness after a complete series** • AstraZeneca SD/SD vaccine is 62% efficacious in participants 18 to 64 years of age. • Current data from clinical trials are insufficient to determine the efficacy of the AstraZeneca vaccine in individuals ≥65 years of age. • The interval between the first and second dose of the AstraZeneca vaccine may impact efficacy of the vaccine, with lower efficacy if the interval is less than 12 weeks. • The Janssen COVID-19 vaccine (1 dose) is 66.9% and 66.1% efficacious against confirmed symptomatic moderate to severe/critical COVID-19 infection at ≥14 days and ≥28 days post-vaccination, respectively. • The Janssen COVID-19 vaccine is 76.7% and 85.4% efficacious against confirmed symptomatic severe/critical COVID-19 infection at ≥14 days and ≥28 days post-vaccination, respectively. **Effectiveness against symptomatic illness and hospitalization** • Observational data in individuals ≥65 years of age have shown a reduction in the risk of symptomatic disease and hospitalization with one dose of AstraZeneca vaccine. • Real-world effectiveness data on the Janssen COVID-19 vaccine indicate good protection against SARS-CoV-2 infection [159].

Factor for consideration	Summary of available evidence and issues for consideration	
	mRNA COVID-19 Vaccines	**Non-replicating viral vector COVID-19 Vaccines**
	• Effectiveness data in adolescents with either mRNA COVID-19 vaccine are not currently available.	
	Efficacy against asymptomatic infection • A preliminary analysis of limited data in an ongoing trial suggests the Moderna COVID-19 vaccine may be efficacious in preventing asymptomatic infection, however data is still being collected and the final analysis is not complete. **Effectiveness against asymptomatic infection** • Estimates of vaccine effectiveness for the Pfizer-BioNTech COVID-19 vaccine against SARS-CoV-2 infection with no reported symptoms was moderate to high after the first dose (depending on time since vaccination) and high after the second dose [18, 25] in adults. Similar results were reported for mRNA COVID-19 vaccines in general [26].	**Efficacy against asymptomatic infection** • An exploratory ad hoc analysis of limited data suggests the AstraZeneca vaccine may not be efficacious in preventing asymptomatic infection. • Preliminary analyses of limited data suggests that the Janssen COVID-19 vaccine has an estimated efficacy of 59.7% against asymptomatic or undetected SARS-CoV-2 infection with onset ≥28 days post-vaccination.
	Re-vaccination • It is not yet clear if booster doses (e.g., annual vaccination) will be required to provide long-term protection against symptomatic COVID-19 disease in the general population, in particular with the emergence of variants of concern. • Re-vaccinating those who initially received an mRNA vaccine with the same or another mRNA vaccine is currently being investigated. • The efficacy and safety of re-vaccinating those who initially received mRNA vaccine with a different COVID-19 vaccine are unknown at this time but are being investigated.	**Re-vaccination** • It is not yet clear if booster doses (e.g., annual vaccination) will be required to provide long-term protection against symptomatic COVID-19 disease in the general population, in particular with the emergence of variants of concern • Re-vaccination with a booster dose of viral vector vaccines may reduce vaccine effectiveness due to the possible development of immunity to the viral vector which may interfere with the immune response to subsequent doses. However, this is still being investigated. • The efficacy and safety of re-vaccinating those who initially received a viral vector vaccine with a different COVID-19 vaccine are unknown at this time.
Immunogenicity	**Humoral response** • Humoral responses for both mRNA COVID-19 vaccines in clinical trials peaked after a second dose, including elicitation of	**Humoral response** • For the AstraZeneca vaccine, humoral responses in clinical trials peaked after a second dose, including elicitation of neutralizing antibodies, for seronegative vaccine recipients. For seropositive

Factor for consideration	Summary of available evidence and issues for consideration	
	mRNA COVID-19 Vaccines	**Non-replicating viral vector COVID-19 Vaccines**
	neutralizing antibodies. However, as a correlate of protection is not known, these humoral responses cannot be interpreted as corresponding with protection. • Humoral responses in clinical trials had similar trends in individuals 18 to 55 years of age and individuals 65 to 85 years of age. • Humoral responses for the Pfizer-BioNTech and Moderna vaccines were similar in adolescents compared to young adults. • In observational studies, humoral responses in seropositive vaccine recipients after the first dose were comparable to those observed in SARS-COV-2 naïve individuals following administration of the second dose. However, as a correlate of protection is not known, the significance of these findings as they relate to the level of protection against reinfection is unknown [91][47][92, 93][94][95]. • Emerging evidence from observational studies indicate that humoral immune responses increase after a third dose of mRNA COVID-19 vaccine is administered to adults with immunocompromising conditions, although the degree of increase varies according to the type of immunocompromising condition or treatment. As a correlate of protection is not known, the significance of these findings as they relate to vaccine effectiveness against infection or severe COVID-19-related outcomes is unknown.	vaccine recipients, humoral responses peaked at the first dose and maintained or decreased at the second dose. • For the AstraZeneca vaccine, humoral responses in clinical trials were lower in individuals ≥65 years of age and older, compared to individuals 18 to 64 years of age in unpublished data presented to NACI. Conflicting results have been shown for other age groups in recently published data [160]. • For the Janssen vaccine, humoral responses in clinical trials, including binding antibodies, neutralizing antibodies and antibodies with Fc effector functions, were seen by day 29 after one dose. • For the Janssen vaccine, somewhat lower humoral immune responses were seen in older age cohorts (>65) compared to younger cohorts (18 to 55) in clinical trials. • However, as a correlate of protection is not known, these humoral responses cannot be interpreted as corresponding with vaccine protection.
	Cellular response • Both mRNA vaccines have been shown to produce a cellular immune response by one to two weeks after administration of a second dose. • Increases in cellular immune responses response were seen in both younger and older adults. No data exists on cellular immune responses in adolescents 12-17 years of age.	**Cellular response** • The AstraZeneca vaccine has been shown to produce cellular immune responses that did not appear to increase after the second dose. • Cellular immune responses do not appear to differ between age groups. • For the Janssen vaccine, cellular immune responses were elicited after one dose of vaccine.

Factor for consideration	Summary of available evidence and issues for consideration	
	mRNA COVID-19 Vaccines	**Non-replicating viral vector COVID-19 Vaccines**
	• As no immunological correlate of protection has been determined for SARS-CoV-2, these cellular responses cannot be interpreted as corresponding with vaccine protection.	• As no immunological correlate of protection has been determined for SARS-CoV-2, these cellular responses cannot be interpreted as corresponding with vaccine protection.
Protection against variants, including Variants of concern	**B.1.1.7 (Alpha)** • Data suggest comparable vaccine effectiveness of mRNA COVID-19 vaccines against symptomatic and severe illness due to the B.1.1.7 (Alpha) VOC. **B.1.351 (Beta)** • Emerging data suggest that mRNA COVID-19 vaccines are 43% effective against symptomatic illness due to the B.1.351 (Beta) VOC after one dose, and 88% effective after two doses [24]. **P.1 (Gamma) and P.2 (Zeta)** • There are limited data on the efficacy or effectiveness of mRNA vaccines against the P.1 (Gamma) VOC and P.2 (Zeta) VOI. **B.1.617.2 (Delta)** • Emerging data suggest the Pfizer-BioNTech vaccine is 33.2% effective against symptomatic illness due to B.1.617.2 (Delta) after one dose, and 87.9% effective after two doses [30]. • Against any infection (symptomatic or asymptomatic) due to B.1.617.2 (Delta) emerging data suggest the Pfizer-BioNTech vaccines is 30% effective after one dose, and 79% effective after two doses [161]. • Emerging data suggests the Pfizer-BioNTech vaccine is 94% effective against hospitalization due to B.1.617.2 (Delta) after one dose, and 96% effective after two doses [162].	**B.1.1.7 (Alpha)** • Data suggest AstraZeneca COVID-19 vaccine has a vaccine efficacy of 70.4% against the B.1.1.7 (Alpha) VOC first identified in the UK, compared to 81.5% against non-B.1.1.7 strains (where cases were predominantly due to B.1.177, a non-VOI/VOC strain). [163] **B.1.351 (Beta)** • Data suggest AstraZeneca **vaccine** has a vaccine efficacy of 10.4% against the B.1.351 (Beta) VOC against mild to moderate illness [164]. • In South Africa, where the B.1.351 (Beta) VOC was the dominant strain (approximately 95% of preliminary sequenced samples), the Janssen vaccine was 64% efficacious against moderate to severe/critical COVID-19 as of Day 29. **P.1 (Gamma) and P.2 (Zeta)** • There are limited data on the efficacy or effectiveness of viral vector vaccines against the P.1 (Gamma) VOC. • In Brazil, where P.2 (Zeta) was detected in approximately 70% of sequenced samples of COVID-19 cases, the Janssen vaccine was 68% efficacious against moderate to severe/critical COVID-19 as of Day 29. **B.1.617.2 (Delta)** • Emerging data suggest the AstraZeneca vaccine is 32.9% effective against symptomatic illness due to B.1.617.2 (Delta) after one dose, and 59.8% effective after two doses [30]. • Against any infection (symptomatic or asymptomatic) due to B.1.617.2 (Delta) emerging data suggest the AstraZeneca

Factor for consideration	Summary of available evidence and issues for consideration	
	mRNA COVID-19 Vaccines	**Non-replicating viral vector COVID-19 Vaccines**
		vaccine is 18% effective after one dose, and 60% effective after two doses [161]. • Emerging data suggests the AstraZeneca vaccine is 71% effective against hospitalization due to B.1.617.2 (Delta) after one dose, and 92% effective after two doses [162].
Safety	**Technology** • mRNA vaccines use a new technology (which has been studied in experimental vaccines); however, all COVID-19 vaccines undergo the same rigorous review and approval process as routine vaccines.	**Technology** • Viral vector vaccines use a relatively new technology (the authorized Ebola vaccine uses this technology); however, all COVID-19 vaccines undergo the same rigorous review and approval process as routine vaccines.
	Safety Signals • Rare anaphylactic reactions have been reported following immunization with mRNA COVID-19 vaccines. • For both vaccines, some solicited adverse events are reported to be very common (defined as 10% or more) among vaccine recipients; however, they are mild or moderate and transient, resolving within a few days. These include: pain at the injection site, fatigue, headache, muscle pain, chills, joint pain, and fever. Some adverse events, including fever, are more frequent after the second dose. • For the Pfizer-BioNTech COVID-19 vaccine, compared to individuals 16 to 55 years of age, adolescents 12 to 15 years of age demonstrated increased frequency of headache, chills, and fever. Up to 65% of adolescent participants had headaches, up to 42% of adolescent participants had chills, and up to 20% of adolescent participants had fever. Lymphadenopathy in adolescents occurred in 0.8% of vaccine recipients, (0.6% had vaccination-related lymphadenopathy), and no serious adverse events related to the vaccine and no deaths were reported. • For the Moderna vaccine, in adolescents 12-17 years of age, systemic events were predominantly fatigue, headaches, muscle pain, chills, joint pain, nausea/vomiting, and fever (in order of	**Safety Signals** • For both vaccines, some solicited adverse events are reported to be very common (defined as 10% or more) among vaccine recipients; however, they are mild or moderate and transient, resolving within a few days. These include: pain at the injection site, fatigue, headache, muscle pain, chills, joint pain, and fever. Some adverse events are less frequent after the second dose. • For the AstraZeneca vaccine, rare cases of thrombosis and thrombocytopenia have been reported during post-licensure use. The mechanism of action appears to be similar to spontaneous heparin-induced thrombocytopenia (called VITT-Vaccine-Induced Immune Thrombotic Thrombocytopenia). Internationally, the rate of this adverse event is still to be confirmed but had been most commonly estimated to be between 1/26,000 and 1/100,000 people vaccinated with AstraZeneca vaccine. Based on available evidence as of June 1, 2021, PHAC has estimated the rate of VITT in Canada as 1 in 73,000 doses administered. However, as investigations continue, this rate could be as high as 1 in 50,000 The case fatality rate typically ranges between 20 and 50%. Other predisposing factors for VITT are unclear. • For the Janssen vaccine, in the clinical trial, one case of cerebral venous thrombosis was reported among 21,895 vaccine

Factor for consideration	Summary of available evidence and issues for consideration	
	mRNA COVID-19 Vaccines	**Non-replicating viral vector COVID-19 Vaccines**
	descending frequency), and occurred more frequently after the second dose. Solicited adverse reactions were generally similar between participants aged 12 to 15 years and participants aged 16 to 17 years. Local reactogenicity was higher in adolescents compared with that observed in the adult Phase 3 study. In adolescents, there were no serious adverse events related to the vaccine and no deaths were reported. • Cases of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining around the heart) following vaccination with COVID-19 mRNA vaccines, have been reported in Canada and internationally. In Canada, we are seeing a higher number of myocarditis and/or pericarditis cases in younger age groups than would normally be expected. The evidence on this phenomenon is evolving and investigations into the association between myocarditis/ pericarditis and mRNA vaccines continue in Canada and abroad. Based on cases reported internationally, available information indicates that they occur more often after the second dose, usually within a week after vaccination, more often in adolescents and young adults and adolescents. Cases that have been reported after receipt of COVID-19 mRNA vaccines have been generally mild and resolved well with medical treatment.	recipients. As of September 8, 2021, 46 cases of TTS have been confirmed out of at least 14.5 million doses of Janssen vaccine administered in the United States. Investigations are ongoing. • Very rare cases of capillary leak syndrome (CLS) have been reported following immunization with the AstraZeneca COVID-19 vaccine. Some affected patients had a previous diagnosis of CLS. CLS is a serious, potentially fatal condition characterized by acute episodes of limb edema, hypotension, hemoconcentration and hypoalbuminemia. Individuals with a history of CLS should not receive the AstraZeneca/COVISHIELD COVID-19 vaccine. • Very rare cases of GBS have been reported following immunization with viral vector COVID-19 vaccines. The risk of recurrence of GBS after COVID-19 vaccination in individuals with a previous history of GBS is unknown. As a precautionary measure, individuals with a previous history of GBS should receive an mRNA vaccine.
Ethics and Equity	• mRNA vaccines have high short-term efficacy in all authorized age groups and Canada anticipates having enough doses of mRNA vaccines for every individual in Canada in 2021. • Vaccines that are more efficacious may be directed to those who are most at risk of severe disease and exposure to limit the exacerbation of existing inequities. • The impact of not offering a less efficacious vaccine earlier to populations who would otherwise have to wait to receive an mRNA vaccine in areas with a high risk of transmission and	• Offering any COVID-19 vaccine to those who would otherwise have to wait to receive one could enhance equity. • If protection against COVID-19 disease cannot be boosted for those that received a lower efficacy vaccine first, significant inequities could be created for those who receive a viral vector vaccine compared to an mRNA vaccine, depending on which population groups received the viral vector vaccine. • The viral vector vaccines may offer an option for individuals who are allergic to mRNA vaccine ingredients or their containers. The impact of offering a less efficacious vaccine earlier to some

Factor for consideration	Summary of available evidence and issues for consideration	
	mRNA COVID-19 Vaccines	**Non-replicating viral vector COVID-19 Vaccines**
	infection, should take into consideration trust, justice, and the risk of doing harm vs. good.	populations should take into consideration trust, justice and the risk of doing harm vs. good.

Feasibility	**Vaccine schedule**
	• Both mRNA vaccines are authorized as a two-dose series. NACI recommends a three-dose primary series for those who are moderately to severely immunocompromised.
	  • The mRNA vaccines have an authorized schedule of 21 (for the Pfizer vaccine) or 28 days (for the Moderna vaccine) between dose one and dose two. However, an interval of 8 weeks between doses provides more optimal protection based on current evidence.
		Vaccine schedule
		• The AstraZeneca vaccine is authorized as a two-dose series. NACI recommends an additional dose of an mRNA vaccine for those who are moderately to severely immunocompromised.
		• The interval between the first and second dose of the AstraZeneca vaccine seems to impact efficacy of the vaccine, with lower efficacy if the interval is less than 12 weeks. The Janssen vaccine is authorized as a single dose. This may increase the feasibility of the completion of a vaccine series. NACI recommends an additional dose of an mRNA vaccine for those who are moderately to severely immunocompromised.
		  • Vaccine recipients need to be advised of the VITT safety signal and the symptoms to watch for after vaccination.

	Storage requirements • The mRNA vaccines have more challenging transport and storage requirements, requiring frozen or ultra-frozen cold chains. Significant efforts have been undertaken to address these logistical complexities. The storage requirements for these vaccines increase the logistical complexity of offering these vaccines in some venues to increase access for various populations.	**Storage requirements** • The viral vector vaccines are easier to transport, store and handle than mRNA vaccines, and as a result, could be easier to use for wider distribution via pharmacies and primary healthcare providers. • The viral vector vaccines require storage and transport at +2 to +8°C, which uses standard cold chain infrastructure widely available in provinces and territories. • The storage requirements for these vaccines could increase access to the vaccine for various populations.
Acceptability	• It is possible that individuals will favor mRNA vaccines since they have higher proven efficacy. • Fewer cases of COVID-19 are expected after vaccination with a vaccine with high efficacy. The relatively low incidence of cases post-vaccination could positively affect acceptability of COVID-19 vaccines and vaccines in general.	• It is possible that individuals will favor the viral vector vaccines if it offers an earlier opportunity to receive a COVID-19 vaccine and is more convenient to access if they are available at more convenient locations due to ease of transport, storage and handling. • A greater number of COVID-19 cases are expected after vaccination with a vaccine that has lower efficacy. The relatively

<table>
<tr><th rowspan="2">Factor for consideration</th><th colspan="2">Summary of available evidence and issues for consideration</th></tr>
<tr><th>mRNA COVID-19 Vaccines</th><th>Non-replicating viral vector COVID-19 Vaccines</th></tr>
<tr><td></td><td></td><td>higher incidence of cases post-vaccination could negatively affect the public's acceptability of COVID-19 vaccines and vaccines in general.
• The Janssen vaccine is given as a single dose. This may increase acceptability of vaccination.
• Recent cases of VITT detected after administration with the viral vector vaccines have impacted their acceptability.</td></tr>
<tr><td></td><td colspan="2">Concerns about vaccine safety and effectiveness are the two most cited reasons for vaccine refusal [165]
• In a survey of Canadians conducted between February 9 and 16, 2021 [166], the following results were reported:
○ Of those who indicated they have not yet been vaccinated (n=1954), more respondents 'Agreed' or 'Strongly Agreed' with items stating intention to get a 'safe vaccine' (69%) and an 'effective vaccine' (67%) since Wave 4 of the survey (late May-early June 2020).
○ When respondents who were willing or neutral towards getting vaccinated were asked what is most important with respect to selecting a COVID-19 vaccine to receive (n=1595), 46% selected "Receiving the most effective vaccine", 15% selected "Receiving any vaccine as soon as possible" and 12% selected "Receiving the vaccine with the fewest reported side effects". The number of doses and type of vaccine technology were not important factors, and 14% of respondents indicated they have no preference on what COVID-19 vaccine they receive.
○ For those who will wait to get the vaccine once it is available: 80% will wait to ensure the safety of the vaccine, 64% will wait to ensure the effectiveness of the vaccine (n=691) [167]
• In a survey of health care providers conducted on Dec 4-13, 2020 [168], the most important factors reported to influence the decision to receive vaccine were vaccine safety (95.5%), followed by vaccine effectiveness (86.7%) (n=14,336)</td></tr>
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VI. RESEARCH PRIORITIES

COVID-19 disease and associated vaccines are novel; therefore, research is warranted in many areas. Research to address the following outstanding questions (not ordered in terms of importance) is encouraged, drawing from both short-term and long-term data, where available:

New and Emerging Research Priorities

Efficacy, Effectiveness, Immunogenicity and Safety

1. What is the population effectiveness (against infection/transmission, hospitalization and death) and medium and long-term durability of protection of a single dose or a complete series of each COVID-19 vaccine approved in Canada?
2. What is the efficacy, effectiveness, immunogenicity, and safety of COVID-19 vaccines across diverse population groups (e.g., adults of advanced age, those with high-risk medical conditions including autoimmune conditions and transplant recipients, individuals with social or occupational vulnerabilities, individuals who are pregnant or breastfeeding, children/adolescents, frailty)? Is a third booster dose of vaccine or a higher dose of vaccine needed to elicit an appropriate immune response in these individuals?
3. What is the efficacy, effectiveness, immunogenicity and safety of COVID-19 vaccines in individuals who have had a previous laboratory evidence of SARS-CoV-2 infection?
    a. Is there a discernable difference between seronegative and seropositive people in any of the above parameters?
    b. Does previous exposure to SARS-COV-2 impact efficacy, effectiveness, immunogenicity or safety of COVID-19 vaccines?
    c. Can a single-dose vaccine series be as effective and safe in individuals with previously proven COVID-19 disease?
    d. Are there any emerging safety signals with COVID-19 immunization that are not predicted by the current understanding of the safety profile of similar vaccines?
    e. Does vaccination following prior SARS-CoV-2 infection or vaccination of SARS-CoV-2 naïve individuals elicit enhanced or altered disease upon subsequent infection by SARS-CoV-2 or other endemic coronaviruses?
4. What is the efficacy, effectiveness, immunogenicity and safety of COVID-19 vaccines (including potential boosters) against SARS-CoV-2 VOC?
5. What is the efficacy and effectiveness of booster doses in LTC residents and seniors living in congregate living settings (and in other key populations and the general population), including against: symptomatic infection, severe disease, transmissibility, outbreaks, hospitalizations, death.
6. What are the risks associated with providing a booster dose earlier than necessary?
7. Will special adverse events that have been associated with the primary series (e.g., myocarditis, pericarditis) also be associated with additional/booster doses?
8. What is the correlate of protection for SARS-CoV-2? How are immune responses induced by natural infection similar or different from those induced by vaccines against COVID-19?

Is SARS-CoV-2 natural infection (symptomatic or asymptomatic) associated with protection against re-infection or severe disease?

9. Further immunological evidence is needed in the following areas to inform efficacy predictions:
    a. How do immune responses change over time; what is the durability of immune responses against SARS-COV-2 over the long-term? What is the impact of vaccine dose or interval on durability?
    b. Which immune responses are most important for protection from infection (adaptive or innate immunity), severe disease or transmissibility? What is the role of humoral vs. cellular immunity in preventing immune escape of viral variants? What is the minimum magnitude of antibody response needed for protection?
    c. Are immunoglobulin (Ig)A/IgG/IgM antibodies protective against SARS-CoV-2 and what is the correlate of protection?

10. What level of COVID-19 vaccination coverage is required to achieve various public health milestones, including: coverage to reduce the burden on the health care system to a manageable degree, achieve community immunity to protect non-vaccinated individuals, and remove public health measures (PHM) controls. What vaccine characteristics play the largest role on these milestones (i.e., efficacy, durability, uptake)?

11. What is the background level of Canadian vaccine-vector-specific responses (i.e., anti-Chimpanzee adenovirus)? Are these responses higher in some groups? Will these responses interfere with vaccine efficacy of these highly seropositive groups? What is the duration of anti-vector interference immunity following viral vector vaccines?

12. How will viral variants impact the efficacy, effectiveness, immunogenicity and safety of a vaccine with respect to death, severe disease, symptomatic disease, asymptomatic disease, infectivity and transmission? What is the effect of using booster vaccines containing heterologous antigens and what is the optimal timing for booster vaccination?

13. Are any components of the COVID-19 vaccine at high risk of inducing an anaphylactic reaction?

14. What is the incidence of rare, serious adverse events following immunization with COVID-19 vaccines?

    a. What is the incidence of thrombosis and thrombocytopenia including CVST and DIC after COVID-19 immunization and after infection with SARS-CoV-2? What is the trigger for the development of this adverse event following immunization and what can be done to mitigate its development?

    b. What is the exact biological mechanism by which viral vector vaccines may trigger VITT? Are VITTs a class effect of the adenovirus vector vaccines or are there separate mechanisms that are product-specific (e.g., due to differing dose and magnitude of immune response based on the nature of the vaccines)?

    c. How do age, sex, or other patient characteristics (e.g., pregnancy, health-seeking behaviours) affect the incidence of VITT and the complications of VITT?

15. Is there an association between myocarditis/pericarditis and mRNA COVID-19 vaccines? If so, what is the biological mechanism by which mRNA vaccines may trigger

myocarditis/pericarditis? How do age, sex, other patient characteristics, or vaccine schedule affect the incidence of myocarditis/pericarditis following immunization with COVID-19 vaccines?

16. Does endemic coronavirus infection history impact the course of SARS-CoV-2 disease? Is there cross-protection or interference from antibodies/exposure to human seasonal coronaviruses when exposed to SARS-CoV-2 or vaccinated against SARS-CoV-2?
17. Are there any negative interactions between COVID-19 vaccination and other medications? What is the recommended timing between COVID-19 vaccines and anti-SARS-CoV-2 prophylactic or therapeutic antibodies or convalescent plasma?
18. Does vaccination have an impact on the transmissibility of SARS-CoV-2 in individuals with asymptomatic infection?
19. What is the role of seasonal attenuation of SARS-CoV-2?
20. How does vaccination impact individual-level variation in transmission (e.g., superspreaders)?
21. What is the epidemiology of SARS-CoV-2 VOC over time and across the country and its regions? What are the transmissibility and virulence (including hospitalizations and deaths) of the VOC?
22. What are the epidemiological characteristics of breakthrough illness (e.g., vaccine recipient characteristics, SARS-CoV-2 VOC)?

Vaccine Administration

23. What is the optimal product, vaccine dose, interval between doses, interval between primary series and additional/booster dose, and potential need for (and frequency of) future booster doses for LTC residents and older adults in congregate living settings (and other key populations and the general population) to ensure protection against SARS-CoV-2 and VOCs?
24. What is the efficacy, effectiveness, immunogenicity and safety of a mixed dose schedule or a mixed dose booster series?
25. What are the minimum, maximum and optimal intervals between doses of a two-dose COVID-19 vaccine schedule that continue to provide protection against disease?
26. Are any other vaccines (e.g., Bacillus Calmette-Guérin) protective against COVID-19 through off-target effects?
27. Can COVID-19 vaccine be simultaneously administered with other non-COVID-19 vaccines? What is the minimum interval between administration of a COVID-19 vaccine and other, non-COVID-19 vaccines (either live or inactivated vaccines)? What are the immunological and clinical outcomes if COVID-19 vaccines were simultaneously administered with other, non-COVID-19 vaccines?
28. What is the minimum interval required for vaccine administration following receipt of convalescent plasma or anti-SARS-CoV-2 spike protein monoclonal antibodies?

Standing Research Priorities

COVID-19 infection and disease

1. What is the epidemiological profile of COVID-19 (e.g., communicable period, all risk groups)?

    a. What is the disease distribution and spectrum of clinical illness for COVID-19, including burden of illness and risk by age, sex and other demographic variables associated with higher risk?
    b. What are the transmission dynamics of COVID-19, including degree of asymptomatic transmission, role of children in transmission, vertical transmissibility, onset and duration of viral shedding and communicable period, impact of changing weather conditions, and trends over time?
    c. What are the rates of COVID-19 co-infections with other respiratory pathogens and what is the impact on pathogenesis and clinical outcomes?

2. Can COVID-19 vaccine be used to protect household contacts of a case from infection? Does COVID-19 vaccination decrease infectiousness and clinical illness in individuals that have already acquired infection? Is COVID-19 vaccination effective in interrupting transmission?

Ethics, Equity, Feasibility and Acceptability

3. What is the acceptability of (a) publicly funded COVID-19 vaccines and (b) other vaccines over time and over different epidemiological contexts among key populations, marginalized populations, providers and policy-makers in different epidemiological contexts across the country?
    a. What factors affect acceptability of immunization with a COVID-19 vaccine in these groups?
    b. What factors affect acceptability of immunization in general?
    c. How will acceptability of prioritized key populations for early immunization with COVID-19 vaccines evolve in different epidemiological contexts across the country?
    d. What strategies can improve acceptability of a COVID-19 vaccine in these groups?

4. How can vaccine allocation decisions be communicated to individuals and communities in order to maintain trust in public health authorities?

5. What COVID-19 vaccination strategies or implementation strategies can reduce health inequities in populations for whom the vaccination program is directly intended, and in populations for whom the vaccination program is not intended, but who are still impacted by it (e.g., impacted by the disease, spillover effects such as for caregivers, or externalities such as with community immunity)?

6. Can a different COVID-19 vaccine be used to complete a primary series or as a booster dose? How are returning travellers managed if they have initiated but not completed a COVID-19 vaccine series abroad?

Health-Related Quality of Life and Well-being

7. What is the health-related quality of life or well-being of COVID-19 patients and caregivers over time (e.g., health utilities, patient-reported outcomes, patient-reported experiences measures)?

8. What is the impact of COVID-19 vaccination on health-related quality of life or well-being on individuals?

VII. SURVEILLANCE ISSUES

Ongoing and systematic data collection, analysis, interpretation and timely dissemination is fundamental to planning, implementation, evaluation, and evidence-informed decision-making. To support such efforts, NACI encourages surveillance improvements in the following areas:

1. Epidemiology

- Enhance social and socioeconomic data collected and made available to understand and address health inequities related to COVID-19
- Systematic examination of the Canadian burden and epidemiology of COVID-19 outbreaks by setting and severity, identifying high-risk activities, settings and populations
- Evaluation of the success of public health interventions to minimize or prevent COVID-19 outbreak events, especially in vulnerable or high-risk communities

2. Laboratory (e.g., strain characterization)

- Enhance laboratory surveillance in order to provide early warning of increasing or decreasing activity by age, sex, and presence of symptoms, and help interpret case data based on changes to testing algorithms
- Conduct genomic surveillance to identify international and inter-provincial transmission and new strains/variants with differing severity, transmissibility, or vaccine comparability
- Explore other SARS-CoV-2 detection kits at point of care with immediate results

3. Vaccine (coverage, effectiveness, safety)

- Reliably monitor coverage rates for each authorized COVID-19 vaccine in different key populations, ensuring data on series completion
- Ensure existing mechanisms for the evaluation of adverse events are positioned to generate data for each authorized COVID-19 vaccine

TABLES

Table 6. Strength of NACI Recommendations

Strength of NACI Recommendation *based on factors not isolated to strength of evidence* (e.g., public health need)	**STRONG**	**DISCRETIONARY**
Wording	"*should/should not be* offered"	"*may/may not be* offered"
Rationale	Known/anticipated advantages outweigh known/anticipated disadvantages ("should"), OR Known/anticipated disadvantages outweigh known/anticipated advantages ("should not")	Known/anticipated advantages are closely balanced with known/anticipated disadvantages, OR uncertainty in the evidence of advantages and disadvantages exists
Implication	A strong recommendation applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present.	A discretionary recommendation may/may not be offered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

LIST OF ABBREVIATIONS

Abbreviation	***Term***
Ad26	Modified human adenovirus 26
AE	Adverse event
AEFI	Adverse event following immunization
ARCHE	Alberta Research Center for Health Evidence
CDC	Centres for Disease Control and Prevention (United States)
ChAd	Chimpanzee Adenovirus
CI	Confidence interval
CIC	Canadian Immunization Committee
CIG	Canadian Immunization Guide
CLS	Capillary leak syndrome
COVID-19	Coronavirus disease 2019
CVST	Cerebral venous sinus thrombosis
DART	Developmental and Reproductive Toxicity
DIC	Disseminated intravascular coagulation
EEFA	Ethics, Equity, Feasibility, and Acceptability
EMA	European Medicines Agency
FDA	Food and Drug Administration (US)
GBS	Guillain Barre syndrome
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HIV	Human immunodeficiency virus
ICU	Intensive care unit
IM	Intramuscular
Ig	Immunoglobulin
IGRA	Interferon gamma release assay
JCVI	Joint Committee on Vaccination and Immunisation (UK)
MAAE	Medically attended adverse event
MenACWY	Quadrivalent meningococcal vaccine
mRNA	messenger ribonucleic acid
OECD	Organisation for Economic Co-operation and Development
PF4	Platelet Factor 4
NACI	National Advisory Committee on Immunization
NITAG	National Immunization Technical Advisory Group
PCR	Polymerase chain reaction

PHAC	Public Health Agency of Canada
SAE	Serious adverse events
SAGE	Strategic Advisory Group of Experts on Immunization (WHO)
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard dose
SII	Serum Institute of India
SOC	System organ class
TST	Tuberculin skin test
TTS	Thrombosis with Thrombocytopenia Syndrome
UK	United Kingdom
US	United States
VIPIT	Vaccine-Induced Prothrombotic Immune Thrombocytopenia
VITT	Vaccine-Induced Thrombotic Thrombocytopenia
VOC	Variant of concern
VOI	Variant of interest
VPD	Vaccine preventable disease
WHO	World Health Organization

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NACI Members: S Deeks (Chair), R Harrison (Vice-Chair), J Bettinger, N Brousseau, P De Wals, E Dubé, V Dubey, K Hildebrand, K Klein, J Papenburg, C Rotstein, B Sander, S Smith, and S Wilson.
Former member: C Quach (Chair)

Liaison representatives: LM Bucci (Canadian Public Health Association), E Castillo (Society of Obstetricians and Gynaecologists of Canada), A Cohn (Centers for Disease Control and Prevention, United States), L Dupuis (Canadian Nurses Association), J Emili (College of Family Physicians of Canada), D Fell (Canadian Association for Immunization Research and Evaluation), M Lavoie (Council of Chief Medical Officers of Health), D Moore (Canadian Paediatric Society), Dr. M Naus (Canadian Immunization Committee), A Pham-Huy (Association of Medical Microbiology and Infectious Disease Canada), P Emberley (Canadian Pharmacists Association), L Bill (Canadian Indigenous Nurses Association), and Dr. S Funnel (Indigenous Physicians Association of Canada).

Ex-officio representatives: K Robinson (Marketed Health Products Directorate, HC), E Henry (Centre for Immunization and Respiratory Infectious Diseases [CIRID], PHAC), M Lacroix (Public Health Ethics Consultative Group, PHAC), S Ogunnaike-Cooke (CIRID, PHAC), C Lourenco (Biologic and Radiopharmaceutical Drugs Directorate, Health Canada), G Poliquin (National Microbiology Laboratory, PHAC), V Beswick-Escanlar (National Defence and the Canadian Armed Forces), and T Wong (First Nations and Inuit Health Branch, Indigenous Services Canada).

NACI High Consequence Infectious Disease Working Group

Members: S Deeks (Chair), R Harrison (Vice-Chair), Y-G Bui, K Dooling, K Hildebrand, M Miller, M Murti, J Papenburg, R Pless, S Ramanathan, N Stall, and S Vaughan.

PHAC Participants: NK Abraham, E Abrams, K Farrah, V Ferrante, N Forbes, SJ Ismail, C Jensen, R Krishnan, A Killikelly, A Nam, M Patel, K Ramotar, A Sinilaite, E Tice, MC Tunis, MW Yeung, and K Young.

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APPENDIX A: CLINICAL TRIAL EVIDENCE SUMMARY FOR PFIZER-BIONTECH COMIRNATY COVID-19 VACCINE

Study C4591001 is the pivotal Phase 1/2/3 trial for the Pfizer-BioNTech COVID-19 vaccine. Evidence on immunogenicity is available for participants aged 12 to 15, 16 to 55, and 65 to 85. Evidence on the safety and efficacy of the vaccine is available for adolescents 12-15 years of age and adults 16 years of age and older. Studies did not include participants from long term care facilities. The Phase 2/3 portion of the trial involved approximately 46,000 study participants randomized (1:1) to receive either the vaccine or placebo. The data presented below are for an interim analysis, therefore the time of follow-up is not consistent but was less than four months after the second dose (maximum of 14 weeks) for all participants.

Evidence from the ongoing Phase 2/3 trial (participants 16 years of age and older [169] and in adolescents 12 to 15 years of age [170]) were published in December 2020 and May 2021, respectively, after NACI's review of the evidence. Evidence from post-marketing surveillance and studies is found in the main body of this statement.

Efficacy

Severe outcomes due to COVID-19
There are no efficacy data for hospitalizations and deaths specifically, however data exists for efficacy against severe COVID-19 outcomes, defined as laboratory-confirmed COVID-19 with one of the following additional features: clinical signs at rest that are indicative of severe systemic illness; respiratory failure; evidence of shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death [171].

There may be a protective effect against severe COVID-19 outcomes for individuals 16 years of age and older when receiving at least one dose of vaccine (overall vaccine efficacy of 88.9%, 95% CI: 20.1 to 99.7%), based on one case identified in the vaccine group (N=21,669) and nine cases in the placebo group (N=21,686). Vaccine efficacy against severe COVID-19 disease was also examined after receipt of Dose 2 (from 7 days and 14 days after Dose 2), but there were an insufficient number of events reported (one severe outcome in the vaccine group and three in the placebo group for each outcome) to determine whether the vaccine was efficacious in reducing severe outcomes with any precision (i.e., the resulting point estimates had wide confidence intervals that included zero).

In adolescents 12 to 15 years of age, vaccine efficacy could not be assessed against severe outcomes as there were no confirmed cases of severe COVID-19 identified as of the date of data cut-off for the efficacy analysis. There were also no deaths identified in adolescent study participants during the clinical trial [170].

Symptomatic COVID-19 disease

In adults 16 years of age and older:
The estimated vaccine efficacy at least 7 days after Dose 2 was 94.6% (95% CI: 89.9 to 97.3%), with 9 confirmed symptomatic COVID-19 cases, as defined in trial protocol [169] identified among vaccine recipients (N=19,965) compared to 169 cases among placebo recipients (N=20,172). The vaccine efficacy at least 14 days after Dose 2 in this population was comparable (94.4%,

95% CI: 89.1 to 97.3%). Results were similar when estimating the efficacy specifically in individuals without evidence of prior SARS-CoV-2 infection at 95.0% (95% CI: 90.3 to 97.6%) with 8 confirmed cases among vaccine recipients (N=18,198) compared to 162 cases among placebo recipients (N=18,325).

When adult study participants without evidence of prior SARS-CoV-2 infection were stratified by age, vaccine efficacy against COVID-19 from 7 days after Dose 2 was between 93.7% (>55 years) and 95.6% (16 to 55 years). In individuals ≥65 years of age, vaccine efficacy was 94.7% (95% CI: 66.7 to 99.9%), while in participants ≥75 years of age, the observed vaccine efficacy was 100% compared to placebo, but with a wide confidence interval including zero which resulted from an insufficient number of events reported (0 vs 5 cases, 95% CI: –13.1 to 100.0%). The estimated vaccine efficacy against confirmed COVID-19 from 7 days after Dose 2 was greater than 91% (between 91.7% and 100.0%) in all subgroups stratified by "at risk" status (e.g., presence of a 1 or more comorbidities). The estimated vaccine efficacy against confirmed COVID-19 from 7 days after Dose 2 was greater than 89% for all races (89.3 to 100%) and 94% for all ethnicities included in the sub-analysis (94.4 to 95.4%).

After Dose 1, but prior to administration of Dose 2, 39 COVID-19 cases were identified in the vaccine group (n=21,669) compared to 82 in the placebo group (n=21,686) for an overall estimated vaccine efficacy in participants 16 years of age and older of 52.4% (95% CI: 29.5 to 68.4%). If the analysis was restricted to cases identified only in the time period >14 days after Dose 1 to before Dose 2 the estimated vaccine efficacy increased to 92.3% (95% CI: 69 to 98%).

Table 7. Pfizer-BioNTech vaccine efficacy against the first occurrence of symptomatic COVID-19 disease after dose 1 and before dose 2 in participants 16 years of age and older[a]

Time period of interest	Events in vaccine group (N=21,669)	Events in placebo group (N=21,686)	Estimate of vaccine efficacy (95% confidence interval)
After dose 1 to before dose 2	39	82	52.4% (29.5 to 68.4%)
>14 days after dose 1 to before dose 2[b]	2	27	92.3% (69 to 98%)

[a] In the all-available efficacy population consisting of randomized study participants who received at least one dose of the study intervention (i.e., vaccine or placebo)

[b] Comité sur l'immunisation du Québec. Stratégie de vaccination contre la COVID-19 : report de la 2e dose en contexte de pénurie. Institut national de Santé Publique du Québec, 18 décembre 2020

In adolescents 12 to 15 years of age:
In study participants without prior evidence of SARS-CoV-2 infection, there were no confirmed COVID-19 cases occurring at least 7 days after Dose 2 among vaccine recipients (n=1,005) compared to 16 cases among placebo recipients (n=978) for an estimated vaccine efficacy against confirmed COVID-19 of 100.0% (95% CI: 75.3 to 100%) [170].

After Dose 1, but prior to administration of Dose 2, 3 COVID-19 cases were identified in the vaccine group (n=1,131) compared to 12 in the placebo group (n=1,129) for an overall estimated vaccine efficacy in adolescents 12 to 15 years of age of 75.0% (95% CI: 7.4 to 95.5%). If the analysis was restricted to case identified only in the time period ≥11 days after Dose 1 to before Dose 2, the estimated vaccine efficacy increased to 100% (95% CI: 41.4 to 100%).

Table 8. Pfizer-BioNTech vaccine efficacy against the first occurrence of symptomatic COVID-19 disease after dose 1 and before dose 2 in adolescents 12 to 15 years of age[a]

Time period of interest	Events in vaccine group (N=1,131)	Events in placebo group (N=1,129)	Estimate of vaccine efficacy (95% confidence interval)
After dose 1 to before dose 2	3	12	75% (7.4 to 95.5%)
≥11 days after dose 1 to before dose 2	0	8	100% (41.4 to 100%)

[a] In the all-available efficacy population consisting of randomized study participants who received at least one dose of the study intervention (i.e., vaccine or placebo)

There is no analysis provided for efficacy specifically in individuals (any age range) with prior evidence of SARS-CoV-2 infection.

Asymptomatic infection and transmission
There are no efficacy data for these outcomes at this time.

Immunogenicity

Humoral immune responses
Both SARS-CoV-2 binding and neutralizing antibodies induced by this vaccine had similar trends across both adult age groups (18 to 55 and 65 to 85 years of age N=195). In adults, maximal immune responses were seen on day 28, 7 days after the second dose. Binding and neutralizing antibodies were both induced by one dose of vaccine and boosted by the second dose of vaccine. The immune response elicited by one dose accounted for 10-20% of the maximal immune response. Up to day 35, older adults (65-85 years of age) had a lower immune response compared to younger adults (18-55 years of age). After the peak on day 28, immune responses decreased until the final evaluation point on day 52, 30 days after dose 2 in younger adults, while no decrease was observed in older adults. SARS-CoV-2 neutralizing antibody responses one month following dose 2 were consistent, if not slightly higher, in adolescents 12-15 years of age compared to young adults 16-25 years of age. At every time point tested and across all included age groups, immune responses were higher than placebo.

Cellular immune responses
Cellular immune responses were assessed in the adult age groups (18 to 55 and 65 to 85 years of age). Both CD4+ and CD8+ T-cells specific to SARS-CoV-2 were induced by the vaccine, as demonstrated by the increase in these cell population percentages from day 1 to day 28. Increases were seen in both younger adults (18-55 years of age) and older adults (65-85 years of age). The characterization of these cells indicates a Th-1 biased cellular immune response. Intermediate time points were not reported.

Vaccine Safety and Adverse Events Following Immunization

Safety evidence for participants 16 years and older is based on interim analyses of 37,586 participants with a median of two months of follow-up (range: <2 weeks to <14 weeks) after Dose 2. About 19,000 participants had at least 2 months of follow-up, including about 9,500 who received the vaccine. Participants who inadvertently received the vaccine (n=12) or placebo (n=11) while pregnant are being followed. Safety evidence for adolescent participants 12 to 15

years of age is based on interim analyses of 2,260 participants. Approximately 1,300 participants had at least 2 months of follow-up after Dose 2, of which 660 in this group received the vaccine.

Local Reactions
In vaccine recipients 12 years of age and older, the frequency of local reactions was similar after Dose 1 and Dose 2. Pain at the injection site was very common (occurring in up to 86% of adolescents 12 to 15 years of age after dose 1). Most local reactions among vaccine recipients were mild or moderate in severity, with any severe reactions being reported by ≤1% of participants. No Grade 4 local reactions were reported. Across all adolescent and adult age groups, local reactions after either dose had a median onset between zero and 2 days post-vaccination and a median duration of 1 to 3 days.

Systemic Reactions
Systemic events were generally increased in frequency and severity in vaccine recipients compared to placebo recipients, and in younger adults (16-55 years old) compared to older adults (≥56 years old), with frequencies and severity increasing with the number of doses (Dose 2 compared to Dose 1). Fatigue (34.1 to 59.4%), headache (25.2 to 51.7%), and muscle pain (13.9 to 37.3%) were very common in both younger and older adults and after Dose 1 and Dose 2, respectively. Fever was common after the first dose (3.7% of 16-55 year olds, 1.4% of >55 year olds) but was very common after the second dose (15.8% of 16-55 year olds, 10.9% of >55 year olds). Joint pain was very common or common in both younger and older adults (11.0 to 21.9% of 16-55 year olds, 8.6 to 18.9% of >55 year olds). Diarrhea was very common or common in both younger and older adults (10.0 to 11.0% of 16-55 year olds, 8.0% of >55 year olds), but was similar to rates seen in the placebo group and did not appear to differ between Dose 1 and Dose 2.

Systemic events were more frequent in adolescents compared to adults. In the adolescent group, fatigue (60.1 to 66.0%), headache (55.3% to 64.5%), chills (27.6 to 41.5%), muscle pain (24.1 to 32.4%) and fever (10.1 to 19.6%) were very common after Dose 1 and Dose 2, respectively. Joint pain was common after Dose 1 (9.7%) and very common after Dose 2 (15.8%). Vomiting (2.8 to 2.6%) and diarrhea (8.0 to 5.9%) were common after both Dose 1 and Dose 2, respectively.

For adolescents and adults, the median onset day for most systemic events after either dose of vaccine was 1 to 3 days post-vaccination, with a median duration of 1 day, except for fatigue and chills, which had median durations of 1 to 2 days. The majority of systemic events were mild or moderate in severity.

Overall, the frequency of any severe systemic event after Dose 1 was ≤0.9% in individuals 16 years of age and older. After Dose 2, severe systemic events had frequencies of <2% with the exception of fatigue (3.8%) and headache (2.0%). The proportion of participants that experience severe fever (>38.9°C to 40.0°C) increased between Dose 1 (0.2%) and Dose 2 (0.8%). Grade 4 fever (>40.0°C) was reported for 2 participants in each of the vaccine and placebo groups. In adolescents 12 to 15 years of age, the frequency of severe systemic events was ≤3.5%. Grade 4 fever (40.4 °C) was reported for 1 participant in the vaccine group.

Severe or Serious Adverse Events
Among adult participants 16 years of age and older in the vaccine group, 1.1% and 0.1% of participants experienced at least one severe AE and one life-threatening adverse events (AE), respectively, compared to 0.7% and 0.1% of participants in the placebo group. Among non-

serious unsolicited adverse events, there was a numerical imbalance of four reports of Bell's palsy in the vaccine group compared with no report in the placebo group. These cases of Bell's palsy occurred 3, 9, 37, and 48 days following vaccination. Among adolescents 12 to 15 years of age in the vaccine group, 0.8% and 0.1% of participants experienced at least one severe AE and one life-threatening AE, compared to 0.3% and 0.1% of participants in the placebo group. In adolescents, no clinically meaningful differences were observed in AEs by age, sex, or race/ethnicity.

The proportions of adult participants 16 years of age and older who reported at least 1 serious adverse event (SAE) were similar in the vaccine group (0.5%) and in the placebo group (0.4%), and was lower in adolescents 12 to 15 years of age (0.4% in the vaccine group and 0.2% in the placebo group). In adults 16 years of age and older, three of the SAEs in the vaccine group and none in the placebo group were assessed by the investigator as related to the study intervention: 1 SAE each of shoulder injury related to vaccine administration, ventricular arrhythmia, and lymphadenopathy. No SAEs reported in adolescents 12 to 15 years of age were assessed by the investigator as related to the study intervention. No clinically meaningful differences in SAEs were observed by age, sex, or race/ethnicity. After either vaccine dose, no participant reported an immediate allergic reaction to vaccine.

Other serious adverse events

Lymphadenopathy

Lymphadenopathy was not a solicited AE. Among adult participants 16 years of age and older (n=37,586) who were followed for <2 weeks to <14 weeks after Dose 2, AEs of lymphadenopathy were reported in 0.3% (n=64) participants (0.5% [n=54] in the younger age group and 0.1% [n=10] in the older age group) in the vaccine group and 6 participants (0.0%) in the placebo group. Most lymphadenopathy events were reported within 2 to 4 days after vaccination. The average duration of these events was approximately 10 days, with 11 events ongoing at the time of the data cut-off. Vaccination-related lymphadenopathy in adolescents 12 to 15 years of age occurred in 0.6% of vaccine recipients (0.8% related and not related), and in 0.1% of placebo recipients (0.2% related and not related). Most cases were reported within 2 to 10 days after vaccination and approximately half resolved within 1 to 10 days, with others ongoing at the time of the data cut-off.

Appendicitis

Among adult participants 16 years of age and older who were followed <2 weeks to <14 weeks after Dose 2, there were a total of 12 participants with SAEs of appendicitis; 8 of which were in the vaccine group. Six of those 8 occurred in younger adults and 2 occurred in older adults. None of the cases were assessed as related to the vaccine by the investigators. The rate in either age group was not estimated to be greater than expected compared to baseline rates. Among adolescents 12 to 15 years of age, 1 participant in the vaccine group and 2 participants in the placebo group reported appendicitis. None were assessed as related to the vaccine by investigators.

Death

There were 6 adult participants (16 years of age and older) who died as of 14 November 2020, the data cut-off date for the interim analysis. This included 2 participants in the vaccine group and 4 participants in the placebo group. None of these deaths in the vaccinated group were assessed by the investigator as related to the vaccine. No deaths were reported in adolescents aged 12 to 15.

APPENDIX B: CLINICAL TRIAL EVIDENCE SUMMARY FOR MODERNA SPIKEVAX COVID-19 VACCINE

Pivotal Phase 1, 2, and 3 trials are being conducted for the Moderna COVID-19 vaccine. Evidence on efficacy, immunogenicity, and safety is available for adults ≥18 years of age. Studies did not include participants from long term care facilities. The Phase 3 portion of the trial involved 30,413 study participants randomized (1:1) to receive either the vaccine (2 doses of 100 mcg) or placebo. The data presented below are for an interim analysis, therefore the time of follow-up is not consistent but was a median of two months after the second dose (maximum of 14 weeks) for all participants. Evidence from post-marketing surveillance and studies is found in the main body of this statement.

Evidence from the ongoing Phase 2/3 trial (participants 12-17 years of age) was published on August 11, 2021 [172], after NACI's review of the evidence. Evidence from post-marketing surveillance and studies is found in the main body of this statement.

Efficacy

Severe outcomes due to COVID-19
There are no efficacy data for hospitalizations and deaths specifically, however data exists for efficacy against severe COVID-19 outcomes, as defined in the trial protocol [173].

The efficacy of the Moderna COVID-19 vaccine to protect against severe COVID-19 cases occurring at least 14 days after the second injection was in 28,207 adult study participants (14,073 participants in the placebo group and 14,134 participants in the Moderna COVID-19 vaccine group). There were 30 confirmed severe COVID-19 cases in the placebo group compared to 0 cases in mRNA-1273 vaccine recipients, for an estimated vaccine efficacy of 100.0% (95% CI: not evaluable to 100.0%).

Symptomatic COVID-19 disease
The primary efficacy outcome examined the efficacy of Moderna COVID-19 vaccine to protect against confirmed symptomatic COVID-19 starting 14 days after Dose 2 in study participants 18 years of age or older without prior evidence of SARS-CoV-2 infection at baseline. This analysis included 28,207 study participants (14,073 participants in the placebo group and 14,134 participants in the Moderna COVID-19 vaccine group), with a median time of follow-up after receiving the second injection of 63 days. There were 185 confirmed COVID-19 cases [174] occurring at least 14 days after the second injection among placebo recipients compared to 11 cases among Moderna COVID-19 vaccine recipients, for an estimated vaccine efficacy of 94.1% (95% confidence interval, CI: 89.3 to 96.8%).

A subgroup analysis of the interim primary efficacy outcome was conducted in three age groups: 18 to <65 years of age (10,521 participants in the placebo group and 10,551 participants in the Moderna COVID-19 vaccine group), ≥65 years of age (3,552 participants in the placebo group and 3,583 participants in the Moderna COVID-19 vaccine group), and a further subgroup of study participants ≥75 years of age (688 participants in the placebo group and 630 participants in the Moderna COVID-19 vaccine group).

In study participants 18 to <65 years, there were 156 confirmed COVID-19 cases occurring at least 14 days after the second injection among placebo recipients compared to 7 cases among mRNA-1273 vaccine recipients, for an estimated vaccine efficacy of 95.6% (95% CI: 90.6 to 97.9%). The corresponding incidence rate per 1,000 person-years (total time at risk in each treatment group) was 64.63 in the placebo group and 2.88 in the Moderna COVID-19 vaccine group. In study participants ≥65 years of age there were 29 confirmed COVID-19 cases among placebo recipients compared to 4 cases among Moderna COVID-19 vaccine recipients, corresponding to a somewhat lower point estimate of vaccine efficacy of 86.4% (95% CI: 61.4 to 95.2%). The corresponding incidence rate per 1,000 person-years was 33.73 in the placebo group and 4.60 in the Moderna COVID-19 vaccine group. In the subgroup of study participants ≥75 years of age there were 7 confirmed COVID-19 cases among placebo recipients compared to 0 cases among Moderna COVID-19 vaccine recipients, for a corresponding vaccine efficacy of 100.0% (95% CI: not evaluable to 100.0%), but this must be interpreted with caution as there were few events identified in this age group.

The efficacy of the Moderna COVID-19 vaccine to protect against confirmed COVID-19 cases occurring at least 14 days after the second injection was also assessed in participants most at risk for severe complications of COVID-19. In study participants 18 to <65 years of age and at risk for severe complications of COVID-19 (2,118 participants in the placebo group and 2,155 participants in the Moderna COVID-19 vaccine group) there were 35 confirmed COVID-19 cases in the placebo group compared to 2 cases among Moderna COVID-19 vaccine recipients, for an estimated vaccine efficacy of 94.4% (95% CI: 76.9 to 98.7%). In study participants 18 to <65 years of age, but not at risk for severe complications of COVID-19 (8,403 participants in the placebo group and 8,396 participants in the Moderna COVID-19 vaccine group) the estimated vaccine efficacy was 95.9% (95% CI: 90.0 to 98.3%) based on 121 confirmed COVID-19 cases in the placebo group and 5 cases among Moderna COVID-19 vaccine recipients. Vaccine efficacy estimates were also calculated for select individual co-morbid conditions; however, as of November 7, 2020 the number of identified events in these subgroups (n=0 to 11) were too small for meaningful analysis.

A secondary analysis of vaccine efficacy to protect against the first occurrence of confirmed COVID-19 starting 14 days after Dose 2 regardless of prior SARS-CoV-2 infection, as determined by serologic titre, involved the full analysis set (randomly assigned study participants who received at least one injection). There were 30,351 study participants 18 years of age or older (15,170 participants in the placebo group and 15,181 participants in the Moderna COVID-19 vaccine group). There were 187 confirmed COVID-19 cases among placebo recipients compared to 12 cases among Moderna COVID-19 vaccine recipients, for an estimated vaccine efficacy of 93.6% (95% CI: 88.6 to 96.5%). However, there was a small proportion of study participants enrolled (n=679/29,148; 2.3%) with positive SARS-CoV-2 infection status at baseline.

In participants who had only received one dose of vaccine at the time of data analysis (placebo group: n=1,079; vaccine group: n=996), vaccine efficacy was 80.2% (95% CI: 55.2 to 92.5%). Limiting the analysis to 14 or more days after Dose 1, efficacy rose to 92.1% (95% CI: 68.8 to 99.1%). However, there are limited data on the efficacy of Dose 1 alone beyond 28 days post-vaccination.

Table 9. Moderna vaccine efficacy against the first occurrence of symptomatic COVID-19 disease after dose 1[a]

Time period of interest	Events in vaccine group (N=996)	Events in placebo group (N=1,079)	Estimate of vaccine efficacy (95% confidence interval)
After dose 1	7	39	80.2% (55.2 to 92.5%)
>14 days after dose 1	2	28	92.1% (68.8 to 99.1%)

[a] In the modified intention-to-treat population consisting of randomized study participants who had received only one dose of their assigned intervention (i.e., vaccine or placebo) at the time of analysis

Asymptomatic infection and transmission

Nasopharyngeal swabs for SARS-CoV-2 virus were collected for all participants at specified intervals before Dose 1 and before Dose 2. There were 14 participants in the vaccine arm who were previously seronegative before administration of Dose 1 who had asymptomatic infection at the second time point, compared to 38 participants in the placebo arm. No formal efficacy data are available; however, assessment of this outcome is ongoing.

Immunogenicity

Humoral immune responses

Antibodies that bind the spike protein were induced in vaccine recipients by day 15 (15 days after dose 1) and reach maximum levels on day 43 (15 days after dose 2). Maximal binding antibody responses approximate the levels of the highest affinity samples of convalescent sera. Binding antibodies reached elevated levels on day 36 (7 days after dose 2) and persisted but decreased through day 119 (90 days after dose 2), the last day for which data is available.

Binding antibodies induced by 1 dose of the vaccine (i.e., on day 29) were 10-20% of the elevated responses seen on day 36. It is unknown how binding antibody responses change over time. Binding antibody responses through day 36 seems to be approximately equivalent across age groups. The data may suggest an age-dependent binding antibody durability. Antibody responses for age 70 or below decreased more slowly than for those above 70.

Neutralizing antibodies were not induced to the level of convalescent sera until day 36, 7 days after dose 2 for all age groups. Neutralizing antibody responses through day 36 seems to be approximately equivalent across age groups. Neutralizing antibody responses on Day 119 represent a larger proportion of the maximum on day 43, compared to binding antibody responses. This may indicate increased durability of neutralizing antibody responses compared to binding antibody responses. These neutralizing data may also suggest an age-dependent neutralizing antibody durability as antibody responses on day 119 for each cohort were inversely proportional to the age of the cohort.

Immunogenicity data from the Phase 1 trial of the Moderna COVID-19 vaccine in a small number of subjects (n=33) demonstrate antibody persistence for 6 months [(175)].

Cellular immune responses

Both CD4+ and CD8+ T-cells specific to SARS-CoV-2 were induced by the vaccine. Maximal induction of both CD4+ and CD8+ T cells was observed on day 43, 14 days after dose 2. The percentage of CD8+T cells was lower for all age groups compared to CD4+ T cells. By comparing the percentage of cells that express Th-1 (IFN gamma, IL-2, TNF) vs. Th-2 (IL-4 and IL-13), it was demonstrated that this vaccine induces a Th1-biased cellular immune response.

Vaccine Safety and Adverse Events Following Immunization

Safety evidence is based on interim analyses of 30,351 participants with a median follow-up time of 63 days after Dose 2 (92 days after Dose 1). 23,276 participants had at least one month of follow-up after Dose 2 (12,021 individuals received the vaccine) and 7,667 individuals had at least 2 months of follow-up after Dose 2 (3894 individuals received the vaccine) [174]. Participants who inadvertently received the vaccine (n=6) or placebo (n=7) while pregnant are being followed.

Solicited Local Reactions

In vaccine recipients, frequency of local reactions increased from Dose 1 to Dose 2. Pain at the injection site was very common (occurred in 83.7% of vaccine recipients after Dose 1 and in 88.2% of vaccine recipients after Dose 2). Redness was common (2.8 to 8.6%) and swelling was common to very common (6.1 to 12.2%). Grade 3 (severe) reactions were reported by 3.5% and 7.0% of vaccine recipients after Dose 1 and Dose 2, respectively [174]. No Grade 4 local reactions were reported. The majority of local reactions after either dose occurred within the first 1 to 2 days post-vaccination and had a median duration of 1 to 3 days. Delayed injection-site reactions (i.e., with onset on day 8 or after) were noted in 0.8% of participants after the first dose and in 0.2% of participants after the second dose. Reactions were characterized by erythema, induration, and tenderness, and they resolved within 4 to 5 days.

Localized axillary swelling and tenderness was solicited and occurred in less than 5% of placebo recipients after any dose, and 10.2% and 14.2% of vaccine recipients after Dose 1 and 2, respectively. Among vaccine recipients, the incidence of severe (Grade 3) axillary swelling and tenderness increased from Dose 1 to Dose 2 (0.3 to 0.5%), whereas in the placebo group it decreased from Dose 1 to Dose 2 (0.2 to 0.1%) [174].

Solicited Systemic Reactions

Systemic events generally had a higher frequency and severity in vaccine recipients compared to placebo recipients, with frequency and severity increasing with the number of doses (Dose 1 compared to Dose 2). In vaccine recipients, fatigue (37.2 to 65.3%), headache (32.6 to 58.6%), muscle pain (22.7 to 58.0%), and arthralgia (16.6 to 42.8%) were very common in all age groups and after Dose 1 and Dose 2, respectively. Chills and nausea/vomiting were very common or common (8.3 to 44.2% and 8.3 to 19.0%, respectively). Fever was uncommon after the first dose (0.8%) but was very common after the second dose (15.5%).

Grade 3 reactions were reported by 2.9% and 15.7% of vaccine recipients after Dose 1 and Dose 2, respectively [174]. After Dose 2, Grade 3 fever (1.3%), headache (4.3%), fatigue (9.4%), myalgia (8.7%), arthralgia (5.1%), and chills (1.3%) were common. The proportion of vaccine recipients that experience Grade 3 fever (>38.9°C to 40.0°C) increased between Dose 1 (<0.1%; n=11) and Dose 2 (1.3%; n=202). Among placebo recipients only 2.7% reported Grade 3 adverse events after either dose.

The incidence of any Grade 4 events was <0.1% after both doses in both vaccine (6 to 12 events) and placebo (2 to 4 events) recipients. Grade 4 fever (>40.0°C) was reported for 4 placebo recipients and 4 vaccine recipients after Dose 1, and 2 placebo recipients and 12

vaccine recipients after Dose 2. The majority of systemic reactions after either dose occurred within the first 1 to 2 days post-vaccination and had a median duration of 1 to 2 days.

Unsolicited Severe or Serious Adverse Events

During the first 28 days after any dose, 1.5% and 0.5% of participants in the vaccine group (Dose 1 and Dose 2, respectively) reported unsolicited severe and serious AEs (SAEs), compared to 1.3% and 0.6% of participants in the placebo group. There was no apparent effect of age on the relative incidence of SAEs in the vaccinated or placebo group. There were three reports of Bell's palsy in the vaccine group which occurred 22, 29, and 32 days after the second dose and one in the placebo group which occurred 17 days post injection. One case of Bell's palsy in the vaccine group was considered a SAE (67-year-old female with diabetes who was hospitalized for stroke due to new facial paralysis 32 days after vaccination).

Three SAEs in vaccinated individuals were considered by the study sponsor to be related to the trial intervention: two cases of facial swelling and one case of nausea and vomiting with headaches and fever.

Four additional SAEs in vaccine recipients and five SAEs in placebo recipients were considered to be related to the trial intervention by trial investigators [174]. Of the SAEs considered related to the Moderna vaccine, 2 cases of autoimmune diseases were reported: one rheumatoid arthritis in a participant known with hypothyroidism, that was unresolved at the time of the report and one autonomic dysfunction in a participant known with hypothyroidism, also unresolved at the time of the report. In the placebo group, one participant (known to have chronic back pain) developed polymyalgia rheumatica, which was resolving.

No clinically meaningful differences in SAEs were observed by age. Sex and race/ethnicity were not assessed. After either vaccine dose, no participant in the Phase 3 study reported an immediate allergic reaction to vaccine.

Other serious adverse events

<u>Facial swelling</u>

Two female participants with a history of dermal filler injection in the cheeks experienced facial swelling 1 to 2 days following immunization. Both were treated and the swelling resolved after a duration of about 5 days. A third female participant with a history of dermal filler injection in the lips had lip angioedema 2 days after vaccination which was classified as medically significant but not considered as an SAE. The management and duration of this third event were not specified.

<u>Death</u>

A total of 13 deaths were reported, 6 in the vaccine group and 7 in the placebo group. None of these deaths were assessed to be related to any study intervention or COVID-19.

APPENDIX C: CLINICAL TRIAL EVIDENCE SUMMARY FOR ASTRAZENECA VAXZEVRIA COVID-19 VACCINE

Results from four clinical trials (two Phase 1/2, one Phase 2/3, and one Phase 3) were available at time of authorization for the AstraZeneca COVID-19 vaccine. Results from an ongoing Phase 3 trial in the United States (US) were not available at time of writing. Evidence on efficacy, immunogenicity, and safety is available for adults ≥18 years of age. The Phase 2/3 trial (COV002) trial and Phase 3 trial (COV003) assessed efficacy, safety and immunogenicity of the vaccine. The Phase 2/3 trial was based in the United Kingdom, (UK) while the Phase 3 trial was based in Brazil. These two studies underwent a series of protocol amendments and logistical challenges during the conduct of the trials that resulted in significant changes to the trials' methodology. There were changes from a single to a two-dose vaccine regimen, the use of both a low dose/standard dose (LD/SD) (in COV002 only, due to dosing error) and standard dose/standard dose (SD/SD) vaccine regimen, and the recruitment of progressively older study participants (56–69 and then ≥70 years of age) after the initial focus on adults 18–55 years of age. In the SD/SD vaccine regimen, study participants were randomized (1:1) to receive either the AstraZeneca COVID-19 vaccine, AZD1222 (5×10^{10} viral particles per 0.5 mL dose) or control injection. The participants randomized to the control group were administered two doses of quadrivalent meningococcal vaccine (MenACWY) (COV002) or MenACWY for Dose 1 and placebo for Dose 2 (COV003).

There were significant differences in the baseline characteristics of participants in the Phase 2/3 and Phase 3 trials. In addition, the clinical trials prioritized the recruitment of health care professionals and other adults with high potential for exposure to SARS-CoV-2, including health care and social setting workers.

Evidence from the AstraZeneca COVID-19 vaccine trials has been published [33]. Evidence from post-marketing surveillance and studies is found in the main body of this statement.

Efficacy

The estimates of vaccine efficacy for the AstraZeneca COVID-19 vaccine (AZD1222) come from the Phase 2/3 and Phase 3 trials. As of a data cut-off date of November 4, 2020 the primary analysis population (study participants who received either the LD/SD or SD/SD regimens) for the primary outcome included 11,636 participants seronegative at baseline (5,807 in the vaccine group, 5,829 in the control group). Of this population, 8,895 study participants (4,440 vaccine recipients and 4,455 controls) received the SD/SD regimen. As of a data cut-off date of December 7, 2020, the SD/SD population had increased to include 12,158 study participants (6,085 vaccine recipients and 6,073 controls). Unless otherwise noted, all data presented in this summary is based on the SD/SD vaccine regimen and as of a data cut-off date of December 7, 2020.

Symptomatic COVID-19 disease

The primary efficacy outcome assessed in the two trials was prevention of the first occurrence of confirmed COVID-19 beginning ≥15 days after Dose 2, based on assessments of cases by an Adjudication Committee blinded to participant group assignment, and analysed in the combined LD/SD and SD/SD regimen population. Assessment in the subgroup that only received SD/SD was a pre-specified secondary analysis in the clinical trial. Symptomatic

COVID-19 was defined as having at least one of the following symptoms (objective fever ≥37.8 C, cough, shortness of breath, and anosmia or ageusia) AND a swab positive for SARS-CoV-2 by RT-PCR AND confirmed by an Adjudication Committee.

Based on data as of December 7, 2020, there were 12,158 study participants 18 years of age or older without prior evidence of SARS-CoV-2 infection at baseline (6,085 vaccine recipients and 6,073 controls) included as part of the SD/SD regimen analysis. The estimated vaccine efficacy against confirmed COVID-19 cases occurring at ≥15 days after Dose 2 in study participants receiving the SD/SD vaccine regimen was 62.5% (95% CI: 50.7 to 71.4%), based on identification of 71/6,085 (1.2%) cases in vaccine recipients and 186/6,073 (3.1%) in controls. The estimated vaccine efficacy by age was 63.1% (51.1 to 72.1%) in study participants 18-64 years of age and 50.7% (-65.8 to 85.4%) in participants ≥65 years of age. An ad-hoc subgroup analysis performed to examine the potential confounding effect of age and dosing interval on estimates of vaccine efficacy in the COV002 (UK) clinical trial generated an estimate of vaccine efficacy in study participants 18–55 years of age who received the SD/SD dosing regimen. Based on the interim data as of November 4, 2020, this subgroup analysis found an estimated vaccine efficacy of 59.3% (95% CI: 25.1 to 77.9%) in this age group. This analysis included study participants with any interval duration between doses.

Symptomatic COVID-19 by interval

As of December 7, 2020, the majority of study participants in the COV002 (UK) and COV003 (Brazil) clinical trials received the two doses of the SD/SD regimen within a 4–8 week (UK: 45.6%, Brazil: 87.2%) or a 9–12-week interval (UK: 34.4%; Brazil: 10.5%). About 1 in 5 study participants in the UK clinical trial (18.9%) received the SD/SD regimen with a >12-week interval between vaccine doses, and in the Brazil trial it was less than 1 in 50 study participants (1.8%). A very small proportion of study participants received the SD/SD regimen with a <4-week interval between doses (UK: 1.0%, Brazil: 0.4%).

An exploratory analysis examined the potential effect of the interval between the administration of the first and second vaccine doses on vaccine efficacy in study participants receiving the SD/SD vaccine regimen. Table 10 summarizes the estimates of vaccine efficacy against confirmed COVID-19 cases occurring at ≥15 days after dose 2 by dosing interval. There is a suggestion of an increase in the point estimate of vaccine efficacy with increasing intervals between the first and second dose of vaccine. However, it is important to note that the confidence intervals around these point estimates overlap.

Table 10. Estimates of vaccine efficacy against the first occurrence of confirmed COVID-19 beginning ≥15 days after Dose 2 in all participants, by dosing interval (SD/SD seronegative baseline efficacy set[a])

Dosing interval	Event in vaccine group (AZD1222) n/N (%)	Events in control group (MenACWY) n/N (%)	Vaccine efficacy (95% CI)
4–12 weeks	67/5,473 (1.2)	162/5,422 (3.0)	59.6% (46.4 to 69.6%)
4 – 8 weeks	52/4,188 (1.2)	113/4,098 (2.8)	55.7% (38.5 to 68.1%)
9–12 weeks	15/1,285 (1.2)	49/1,324 (3.7)	69.0% (44.8 to 82.6%)
>12 weeks	4/571 (0.7)	22/599 (3.7)	81.6% (47.0 to 93.6%)

[a] Participants without prior evidence of SARS-CoV-2 infection at baseline; all SD/SD vaccine recipients (or respective controls)

In a subgroup analysis in study participants who received the SD/SD vaccine regimen, vaccine efficacy against confirmed COVID-19 cases occurring at ≥15 days after dose 2 was estimated by dosing interval and age group. These ad-hoc subgroup analyses were performed in participants 18-55 years of age from the COV002 (UK) clinical trial and in all study participants

who received the SD/SD regimen (from COV002 and COV003), dichotomized into groups 18–64 years and ≥65 years of age.

The ad-hoc subgroup analysis performed to examine the potential confounding effect of age and dosing interval on estimates of vaccine efficacy in the COV002 (UK) clinical trial generated an estimate of vaccine efficacy in study participants 18-55 years of age who received the SD/SD regimen at an interval of >8 weeks between doses. Based on the interim data as of November 4, 2020, this subgroup analysis found an estimated vaccine efficacy of 65.6% (95% CI: 24.5 to 84.4%). In the updated dataset as of December 7, 2020, there were 1,375 study participants ≥65 years of age (699 in the vaccine group and 676 in the control group). Efficacy estimates for participants ≥65 years for the overall 4–12-week dosing interval and the 4–8-week interval have wide confidence intervals that include zero. Estimates of vaccine efficacy could not be calculated for participants ≥65 years for the 9–12-week and >12-week dosing intervals due to a lack of older study participants who received the SD/SD regimen during these dosing intervals (Table 11).

Table 11. Estimates of vaccine efficacy against the first occurrence of confirmed COVID-19 beginning ≥15 days after dose 2, by dosing interval and age group (SD/SD seronegative baseline efficacy set[a])

Dosing interval and age group	Event in vaccine group (AZD1222) n/N (%)	Events in control group (MenACWY) n/N (%)	Vaccine efficacy (95% CI)
4–12 weeks			
18–64 years	63/4,790 (1.2)	156/4,760 (3.0)	60.5% (47.1 to 70.5%)
≥65 years	4/683 (0.6)	6/662 (0.9)	43.2% (-99.3 to 83.8%)
4 – 8 weeks			
18–64 years	48/3,506 (1.4)	107/3,439 (3.1)	56.6% (39.1 to 69.1%)
≥65 years	4/682 (0.6)	6/659 (0.9)	43.4% (-98.5 to 83.9%)
9–12 weeks			
18–64 years	15/1,284 (1.2)	49/1,321 (3.7)	69.0% (44.8 to 82.6%)
≥65 years	0/1 (0)	0/3 (0)	No estimate
>12 weeks			
18–64 years	4/571 (0.7)	22/599 (3.7)	81.6% (47.0 to 93.6%)
≥65 years	0/0 (0)	0/0 (0)	No estimate

[a]Participants without prior evidence of SARS-CoV-2 infection at baseline; all SD/SD vaccine recipients (or respective controls)

Symptomatic COVID-19 by presence of co-morbidity

Efficacy was also assessed based on the presence of comorbidity, which was defined as the presence of one or more of the following mild to moderate and controlled medical conditions at baseline: cardiovascular disease, respiratory disease, diabetes, or obesity (BMI ≥30 kg/m^2) based on a data cut-off date of November 4, 2020. For this exploratory analysis, included study participants who were SARS-CoV-2 seronegative at baseline and received the SD/SD regimen. The estimated vaccine efficacy against confirmed COVID-19 cases occurring at ≥15 days after Dose 2 in study participants without comorbidities was 58.0% (95% CI: 25.8 to 76.2%), based on 17/2,825 (0.6%) cases identified in the vaccine group compared to 39/2,774 (1.4%) cases in the control group. The corresponding estimate of vaccine efficacy in study participants with comorbidities was 67.1% (95% CI: 33.2 to 83.8%), based on the identification of 10/1,611 (0.6%) cases in the vaccine group compared to 32/1,670 (1.9%) cases in the control group.

Symptomatic COVID-19 after one dose

Efficacy at various time points after one dose of AstraZeneca COVID-19 vaccine was assessed as a secondary/exploratory analysis based on data as of the interim analysis cut-off date of November 4, 2020 (Table 12). The analysis involved study participants who were SARS-CoV-2 seronegative at baseline and received SD vaccine as their initial vaccine dose. The median duration of follow-up after Dose 1 was 115 days (range: 41–149 days). Note that approximately 80% of study participants in the vaccine arm received the second dose of the vaccine; therefore, several estimates of vaccine efficacy are not solely due to the one dose of SD vaccine.

Table 12. Estimates of vaccine efficacy against the first occurrence of confirmed COVID-19 beginning after Dose 1, (SD/SD seronegative baseline efficacy set[a])

Time period of interest	Events in vaccine group (AZD1222)	Events in control group (MenACWY)	Estimate of vaccine efficacy (95% CI)
After Dose 1	92 (N=8,008)	185 (N=8,013)	50.5% (36.5 to 61.5%)
≥22 days after Dose 1	51 (N=6,307)	141 (N=6,297)	64.1% (50.5 to 73.9%).
≥22 after Dose 1 but before Dose 2	15 (N=6,310)	52 (N=6,296)	71.3% (49.0 to 83.8%)

[a] Participants without prior evidence of SARS-CoV-2 infection at baseline; all SD/SD vaccine recipients (or respective controls)

Severe outcomes due to COVID-19

Severe COVID-19 disease

Severe COVID-19 disease, defined as study participants who met the confirmed COVID-19 case definition and were assigned a severity score of ≥6 on the World Health Organization Clinical Progression Scale (e.g., clinical severity requiring hospitalization, and may include intubation and mechanical ventilation, and death), was assessed as a secondary analysis of vaccine efficacy. Analysis included study participants who had been followed for ≥15 days since Dose 2, who were seronegative for SARS-CoV-2 at baseline, and received both doses of the SD/SD regimen. As of December 7, 2020, there were 6,085 study participants in the vaccine group and 6,073 participants in the control group. There was 1 case of severe COVID-19 disease identified in a study participant in the control group who received the control intervention within the 4–12-week dosing interval. This participant also required ICU admission and eventually died. An additional severe case occurred >21 days after the first dose and ≤14 days after the second dose in a study participant in the control group.

Hospitalizations

Vaccine efficacy against COVID-19 associated hospitalizations was assessed at multiple time points (Table 13). Assessment included study participants who were seronegative for SARS-CoV-2 at baseline and received both doses of the SD/SD regimen. After Dose 2 (median follow-up duration: 36 days, range: 1–79 days, based on data as of November 4, 2020), there were 7 hospitalizations due to COVID-19 identified in study participants who received the SD/SD regimen within the 4–12-week dosing interval, all in participants in the control group. There were no hospitalizations in the vaccine group ≥22 days after Dose 1; however, there were 2 cases hospitalized due to COVID-19 identified in the vaccine group and 16 in the control group ≥15 days after Dose 1, resulting in an estimate of vaccine efficacy of 87.6% (95% CI: 46.0 to 97.2%).

The 2 hospitalizations in the vaccine group were 1 and 10 days post vaccination (median follow up: 115 days, range: 41–149).

Table 13. Estimates of vaccine efficacy against hospitalization, by dosing interval (SD/SD seronegative baseline efficacy set[a])

Time period of interest	Event in vaccine group (AZD1222) n/N (%)	Events in control group (MenACWY) n/N (%)	Vaccine efficacy (95% CI)
≥22 days after Dose 1[b]	0/6,307 (0.0)	9/6,297 (0.1)	100% (95% CI: 49.6 to NE)
≥15 days after Dose 2[c]	0/6,085 (0.0)	7/6,073 (0.1)	N/A

[a] Participants without prior evidence of SARS-CoV-2 infection at baseline; all SD/SD vaccine recipients (or respective controls)
[b] Based on data as of November 4, 2020
[c] Based on data as of December 7, 2020

Deaths

As of the updated data cut-off date of December 7, 2020, there has been a single death due to COVID-19 identified in a study participant in the control group.

Asymptomatic infection and transmission

This was an exploratory analysis conducted only in clinical trial COV002 (UK). As part of the study protocol, beginning one week after receipt of Dose 1, study participants were asked to provide weekly self-administered nose or throat swabs for RT-PCR testing. Participants were asked to report symptoms when they appeared; however, the presence or absence of symptoms at the time of sample collection was not routinely collected. An asymptomatic infection was defined as a study participant with a swab virologically confirmed for SARS-CoV-2 and who reported no clinical trial–defined symptoms of confirmed COVID-19. Study participants with virologically confirmed SARS-CoV-2 infection, but who did not report whether or not they had symptoms were classified as "unknown symptoms".

Table 14. Estimates of vaccine efficacy against asymptomatic infection, by dosing interval (SD/SD seronegative baseline efficacy set[a])

Dosing interval	Event in vaccine group (AZD1222) n/N (%)	Events in control group (MenACWY) n/N (%)	Vaccine efficacy (95% CI)
≥22 days after Dose 1[b]			
	14/3,060 (0.5%)	15/3,064 (0.5%)	6.6% (-93.5 to 54.9%)
≥15 days after Dose 2[c]			
Any interval	8/2,377 (0.3%)	11/2,340 (0.5%)	26.9% (-81.5 to 70.6%)
4–12 weeks	N/A	N/A	37.7% (-90.1 to 79.6%)
>12 weeks	N/A	N/A	-4.3% (-416.5 to 79.0%)

[a] Participants without prior evidence of SARS-CoV-2 infection at baseline; all SD/SD vaccine recipients (or respective controls)
[b] Based on data as of November 4, 2020
[c] Based on data as of December 7, 2020

An additional ad-hoc analysis combining study participants with SARS-CoV-2 asymptomatic infection or associated with unknown symptoms also failed to demonstrate the efficacy of the SD/SD regimen (3.9%, 95% CI: -72.1 to 46.4%), based on the identification of 22 cases in the vaccine group and 23 cases in the control group ≥15 days after Dose 2.

Immunogenicity

Approximately 15% of the overall safety analysis set was targeted for inclusion in the immunogenicity analysis set. These analyses combined evidence from SD/SD and LD/SD dosing regimens, and may not completely align with the data from individual studies.

Humoral immune responses
Antibody responses, both binding and neutralizing, differed for seronegative and seropositive vaccine recipients. Vaccine recipients who were seropositive at baseline demonstrated high antibody titres 28 days after Dose 1 compared to seronegative recipients. Seronegative recipients demonstrated an increase in their immune responses 28 days after Dose 2. By contrast, seropositive recipients had decreased immune responses after Dose 2 compared to responses after Dose 1. However, immune responses for seropositive recipients at all time points were higher than those for seronegative recipients. The mechanism behind these differences, and their potential impact on vaccine efficacy and effectiveness remains unclear. A recently published article contains additional evidence on humoral responses [160].

Antibody responses, both binding and neutralizing, were lower in older adults (65+) than in younger adults after both the first and second dose of vaccine. Without a correlate of protection, the significance of these difference in antibody responses is unclear.

Cellular immune responses
Cellular immune responses were elicited by this vaccine. The first dose elicited Th-1 biased CD4+ T cells in both younger and older age groups. Younger vaccine recipients exhibited higher cellular immune responses than older age groups. Notably, the second vaccine dose did not augment cellular immune responses. The mechanism and the impact on vaccine efficacy and effectiveness remains unclear.

Anti-Vector immune responses
It is unclear to what extent pre-existing immunity to any adenovirus-based vaccine vector exists in the Canadian population and what impact that could have on adenovirus-based vaccine safety and efficacy. It is also unclear as to what extent immunization with adenovirus-based vaccines elicits anti-vector immune responses and what impact that could have on homologous or heterologous booster doses with adenovirus-based vaccines. Evidence for a viral vector vaccine based on human adenovirus 5 (not authorized in Canada) indicated that vaccine recipients with high pre-existing immunity to the adenovirus vector had lower anti-SARS-CoV-2 immune responses [176]. The AstraZeneca COVID-19 vaccine uses a modified chimpanzee adenovirus vector (ChAd). AstraZeneca found no correlation between anti-ChAd neutralizing antibody responses and anti-SARS-CoV-2 immune responses. It also found that neutralizing antibody levels were not boosted after receiving the second dose. However, neutralization is not the only anti-vector immune response that could impact vaccine-induced immunity. It remains unclear if immune responses to the ChAd vector will impact the efficacy or effectiveness of this vaccine.

Vaccine Safety and Adverse Events Following Immunization

Safety evidence is based on interim analyses of 23,745 participants of which 12,021 received at least one dose of the AZ COVID-19 vaccine and 11,724 received a control. The safety analyses were conducted in different analysis sets. Solicited adverse events occurring within 7 days after any dose were assessed among 2648 vaccine recipients who received at least one

dose (SD) and 2497 control recipients. Approximately one third of study participants received their second vaccine dose within 6 weeks of receiving Dose 1. The majority (~90%) of study participants in the safety cohort were less than 65 years of age. The median duration of follow-up was 105 days post-Dose 1 and 62 days post-Dose 2.

Solicited Local Reactions
Solicited local injection site AEs were reported by 74.7% of evaluated participants within the first 7 days following any vaccine dose. Pain and tenderness were most frequently reported (54.2% and 63.7%, respectively) followed by warmth (17.7%), bruising (17.3%), redness (14.0%), pruritus (12.7%), and swelling (10.0%). The majority of solicited local reactions among vaccine recipients were mild or moderate in severity, with any grade 3 or 4 reactions being reported by ≤9.5% of participants. No Grade 4 AEs were reported. Local reactions were generally milder and reported less frequently after the second dose of the vaccine. By dose interval, the reactogenicity of the vaccine was lower in participants who received the second dose within 6 weeks following Dose 1 (38.0% versus 58.3% to 74.3% when Dose 2 was provided after ≥6 weeks).

Solicited Systemic Reactions
Solicited systemic AEs were reported by 73.0% of evaluated participants within the first 7 days following any vaccine dose. The most common systemic solicited systemic AEs were fatigue (53.1%) and headache (52.6%). Other frequently reported systemic solicited AEs were muscle pain (44.0%), malaise (44.2%), feverishness (33.6%), chills (31.9%), joint pain (26.4%), nausea (21.9%) and fever ≥38.0°C (7.9%). Overall, the frequency of any grade 3 or 4 reaction was ≤8.3%. The single reported Grade 4 event was fever > 40°C. Across study groups, AEs were milder and reported less frequently after the second vaccine dose. By dose interval, the reactogenicity of the vaccine was lower in participants who received the second dose at <6 weeks following Dose 1 (37.6% versus. 49.2% to 67.1% when Dose 2 was provided after at ≥6 weeks).

Unsolicited Serious Adverse Events
SAE were reported by less than 1% of study participants and was similar between the vaccine and control groups (0.7% and 0.8%, respectively). There were no clear imbalances by System Organ Class (SOC). The most frequently reported SAEs by SOC were 'Infections and Infestations' (0.1% vs 0.2%) and 'Injury, poisoning and procedural complications' (<0.1% vs 0.1%).

Two SAEs (pyrexia, transverse myelitis) in the vaccine recipients were considered related to the vaccine by the study investigators. The case of pyrexia (40.5° C) occurred 2 days after dose 1 and resolved the same day following the administration of acetaminophen. The event of transverse myelitis occurred in a 37-year-old female with a family history of Charcot-Marie-Tooth type 1a (mother and brother). The participant received two doses of study intervention 77 days apart. Two weeks after the second dose, the participant developed sensory changes and clumsiness. Magnetic resonance imaging showed a lesion consistent with transverse myelitis or anterior spinal infarction. A third SAE was originally identified (C-reactive protein increase); However, after the cut-off date, causality for the SAE of C-reactive protein increase was updated by the investigator to be not treatment related.

Other serious adverse events

Demyelinating events
An event of multiple sclerosis occurred in a 37-year-old female who developed sensory symptoms about 10 days after first (and only) vaccination. The clinical episode had a duration of 3 weeks. Further follow up with MRI of spine and brain showed an acute spinal lesion and older cerebral lesions, revealing pre-existing, but previously unrecognized, multiple sclerosis.

Death
A total of 6 deaths were reported among study participants (2 in the vaccine group and 4 in the control group). The cause of death among vaccine recipients included malignant neoplasm and fungal pneumonia, with neither considered to be related to the study intervention by the investigators.

Vaccine-Induced Immune Thrombotic Thrombocytopenia
Rare cases of serious blood clots, including cerebral venous sinus thrombosis, associated with thrombocytopenia have been reported in Canada and globally following post-licensure use of AstraZeneca COVID-19 vaccine. Cases have usually occurred between 4 and 28 days after receipt of vaccine. This adverse event is being referred to as Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT). The mechanism of action is similar to heparin-induced thrombocytopenia (HIT). The exact mechanism by which the viral vector COVID-19 vaccines may trigger VITT is still under investigation. At this time, no other predisposing factors have consistently been identified in patients who develop VITT. The rate of this adverse event is still to be confirmed but had been most commonly estimated to be between 1 in 26,000 and 1 in 100,000 persons vaccinated with a first dose of AstraZeneca COVID-19 vaccine although this continues to evolve and may increase. Based on available evidence as of June 1st, 2021, PHAC has estimated the rate of VITT in Canada to be 1 in 73,000 doses administered. However, as investigations continue, this rate could be as high as 1 in 50,000 persons vaccinated with the COVISHIELD COVID-19 vaccine. The frequency of TTS following a second dose of AstraZeneca vaccine is currently reported to be approximately 1 per 520,000 in individuals vaccinated with a second dose, based on vaccine safety surveillance data from the United Kingdom but this continues to evolve [(2)]. Additional information is currently being gathered to characterize the rate of VITT more accurately. Based on available information, the case fatality of VITT typically ranges between 20 and 50%. Case fatality may vary with increased awareness of the adverse event and appropriate early treatment.

Effectiveness in individuals ≥65 years of age

In the absence of sufficient data from clinical trials to date on the efficacy of the AstraZeneca COVID-19 vaccine in those 65 years of age and older, a review of three observational studies in the UK published as pre-prints on real-world vaccine effectiveness in this age group has been conducted to inform NACI's recommendations in this age group. The findings of this review are summarized below.

All three observational studies assessed one dose of either the Pfizer-BioNTech or the AstraZeneca vaccines in the United Kingdom. The results below pertain only to the AstraZeneca portion of the studies. The studies were conducted during the period when the B.1.1.7 (Alpha) variant was rapidly becoming the dominant circulating strain in their respective geographic regions. Approximately 50% of laboratory samples were found to have a profile consistent with the B.1.1.7 (Alpha) variant in early December, 2020 in England, and 43% in

Scotland in early January, 2021. By mid to late February, the B.1.1.7 (Alpha) variant represented almost 100% of circulating strains in England, and was considered the dominant strain in Scotland.

Overall summary of evidence:

In adults 65 years of age and over, observational data available from pre-prints from the United Kingdom have shown a reduction in the risk of symptomatic disease and hospitalization starting from two weeks following one dose of AstraZeneca vaccine.

Detailed summary of each study:

1. Hyams et al., Assessing the Effectiveness of BNT162b2 and ChAdOx1nCoV-19 COVID-19 Vaccination in Prevention of Hospitalisations in Elderly and Frail Adults: A Single Centre Test Negative Case-Control Study. SSRN-Lancet **preprint.** March 3, 2021. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3796835

Description: Test-negative case control study of hospitalized people ≥80 years of age (many of whom were frail with comorbidities) in two hospitals in Bristol, United Kingdom. Vaccination was determined by record linkage and adjustment was conducted for a number of factors. Vaccine effectiveness against hospitalization was assessed in those who had been vaccinated ≥14 days before symptom onset.

Results: One-dose vaccine effectiveness of 80.4% (95% CI: 36.4 – 94.5%) against hospitalization occurring within 14 or more days (maximum 53 days) after one dose of AstraZeneca COVID-19 vaccine among patients ≥80 years of age.

Review:

- Vaccination was determined by record linkage and clinical information was obtained from records by individuals who are blinded to the participants SARS-CoV-2 results. These are methodological strengths of this study.
- The authors performed a sensitivity analysis of those with symptom onset < 14 days after vaccination and did not find an effect, which is expected as this is too early for the vaccine to work, and adds strength to differences they note 14 days or more after vaccination.
- Eligible cases and controls were selected from the medical admission list, and it is unclear how this was done.
- Separate analyses seemed to have been conducted for AstraZeneca and Pfizer-BioNTech but it is unclear how the study subjects for each analysis were assigned.

2. Lopez Bernal et al., Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England. medRxiv. **Preprint** March 2, 2021. https://www.medrxiv.org/content/10.1101/2021.03.01.21252652v1

Description: Test negative-case control study using linked surveillance data in the United Kingdom among patients ≥70 years of age. PCR tests were within 10 days of onset of symptoms. For those who were vaccinated, cases and controls were assessed by time since vaccination to onset of symptoms, controlling for a number of factors. The impact of vaccination on hospitalization in individuals ≥80 years of age was also assessed in those who tested positive.

Results: One-dose vaccine effectiveness against symptomatic PCR confirmed SARS-CoV-2 infection in the adjusted analysis was 22% (95% CI: 11 – 32) 14 to 20 days after vaccination and gradually rose up to 73% (95% CI: 27 – 90) 35 or more days (maximum 48 days) after vaccination. As well as the effect against symptomatic disease, in individuals who were ≥80 years of age there was an additional 37% protection against hospitalization within 14 days of a positive test in those 14 or more days from their first dose of vaccine compared to those who were unvaccinated.

Review:

- Record linkage using large data sets is a strength of this study.
- A relatively small number of subjects were included in the AstraZeneca COVID-19 vaccine analysis at later time periods, particularly in the time period of 35 or more days after vaccination when the vaccine effectiveness was the highest.
- The unadjusted and adjusted odds ratio are considerably different in the AstraZeneca COVID-19 analysis reflecting differences between study groups.
- Demographic and clinical information for cases and controls and vaccinated and unvaccinated individuals were not provided.

3. Vasileiou et al. Effectiveness of first dose COVID-19 vaccines against hospital admissions in Scotland effectiveness findings from Scotland: national prospective cohort study of 5.4 million people. SSRN-Lancet **preprint.** February 19, 2021. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3789264

Description: A prospective observational cohort study using record linkage between databases, including vaccination, hospitalization and laboratory records for the population in Scotland, with adjustment for a number of factors. Although the study included those ≥18 years of age, the AstraZeneca vaccine was mostly administered to participants aged 65 years and older. Age-specific vaccine effectiveness is provided but did not distinguish between the Pfizer-BioNTech and AstraZeneca vaccines, which were both studied, although those ≥80 years of age mainly received the AstraZeneca vaccine.

Results: The effectiveness of one dose of the AstraZeneca vaccine against hospitalization was 74% (95% CI: 66 – 81) 14 to 20 days after vaccination and rose up to 94% (95% CI: 73 – 99) 28 to 34 days after vaccination. In patients ≥80 years of age, the authors found a peak vaccine effectiveness (VE) of 81% (95% CI: 65 – 90) against hospitalization within 28 to 34 days after one dose of vaccine that was mainly the AstraZeneca vaccine.

Review:

Due to concerns with methodological weaknesses in this study, NACI did not use these results to inform its recommendations. Methodological weaknesses include:

- AstraZeneca COVID-19 vaccine effectiveness against hospitalization was high (70%) 7 to 13 days after vaccination, which is biologically implausible, as 7 to 13 days would be too early to expect protection from infection or hospitalization as a result of vaccination, suggesting methodological concerns and making the high vaccine effectiveness results at later time periods (94% at 28 to 34 days) challenging to interpret.
- The number of people vaccinated with the AstraZeneca COVID-19 vaccine is small in the period 28 days and more from vaccination.

- As vaccine roll out was initially tailored to priority groups at higher risk of severe disease or exposure, adjustments for potential confounding factors conducted during the statistical analyses might not have adequately controlled for all the differences between vaccinated and unvaccinated individuals. Demographic and risk factor comparisons between vaccinated and unvaccinated groups were not provided separately for each vaccine.
- Hospital admission was defined as: COVID-19 as the main cause of admission or hospitalization within 28 days of a positive PCR SARS-CoV-2 test. Hospital admission for COVID-19 is a less specific criteria for determining COVID-19 hospitalization and the proportion of cases defined using that criteria are not provided.
- Although product specific vaccine effectiveness and age specific vaccine effectiveness are both provided separately, product specific vaccine effectiveness by age was not provided.
- Record linkage using large data sets is a strength of this study.

APPENDIX D: CLINICAL TRIAL EVIDENCE SUMMARY FOR JANSSEN COVID-19 VACCINE

Data from Phase 1, 2, and 3 trials were available at the time of authorization for the Janssen vaccine. Evidence on efficacy, immunogenicity, and safety is available for adults ≥18 years of age. The Phase 3 trial involved 44,325 study participants randomized (1:1) to receive either the vaccine (1 dose of 5×10^{10} viral particles) or placebo. The data presented below was a median of two months after the completion of the series (one dose). Evidence from post-marketing surveillance and studies is found in the main body of this statement.

Efficacy

Symptomatic COVID-19 disease
Estimates of efficacy against moderate to severe/critical COVID-19 disease was the primary outcome for the Phase 3 trial. Due to the relatively broad definition of moderate COVID-19 disease adopted for the clinical trial, less than 1% of identified cases met the mild COVID-19 case definition. Therefore, nearly all observed symptomatic COVID-19 cases are captured by the definition of moderate to severe/critical COVID-19.

The co-primary endpoints for the efficacy analysis of the vaccine are the prevention of the first occurrence of confirmed symptomatic moderate to severe/critical COVID-19 infection with onset ≥14 post-vaccination and with onset ≥28 days post-vaccination. The primary analysis is supported by subgroup analyses of the primary endpoints stratified by study country, age group, the presence of comorbidities associated with an increased risk of progression to severe COVID-19 disease, sex, and by race/ethnicity. Efficacy against confirmed symptomatic severe/critical COVID-19 infection with onset ≥14 and ≥28 days post-vaccination are secondary endpoints, also supported by analyses stratified by the same subgroups as the primary endpoint. Additional analyses of efficacy in cases with severe/critical COVID-19 include examinations by cases requiring medical intervention, hospitalizations and deaths. For both the primary and secondary endpoints, cumulative incidence curves are used to examine the potential onset and duration of vaccine efficacy. Exploratory analyses of vaccine efficacy against asymptomatic or undetected SARS-CoV-2 infection, symptom severity and viral load are also investigated. Select outcomes from these analyses are presented in this Appendix.

A number of the analyses are conducted in the full analysis set, defined as study participants who were randomized and received the study intervention (vaccine or placebo), regardless of the occurrence of protocol deviations or serostatus at baseline. However, most primary efficacy analyses are conducted in the per-protocol set, defined as study participants who were randomized, received the study intervention (vaccine or placebo), were seronegative at the time of vaccination, and had no major protocol deviations that were judged to possibly impact the efficacy of the vaccine. Many of the subgroup analyses are conducted in the per-protocol set using centrally confirmed COVID-19 cases, but repeated using a larger dataset consisting of both centrally confirmed cases and cases with a positive PCR result from a local testing site that had not yet been confirmed by the central clinical trial testing facility at the date of data cut-off for the analysis. The use of the locally confirmed cases is supported by the demonstration of a high concordance (90.3%) in PCR results between local and central clinical trial testing facilities. **Unless otherwise specified, all efficacy analyses presented in this summary are**

in the per-protocol set of study participants based on a January 22, 2021 data cut-off date.

Confirmed symptomatic moderate to severe/critical COVID-19 infection

The definition of moderate COVID-19 disease used in the clinical trial was very broad and so cases meeting the moderate to severe/critical case definition constituted >99% of all identified symptomatic COVID-19 in the trial. The estimates of vaccine efficacy against confirmed symptomatic moderate to severe/critical COVID-19 infection with onsets ≥14 days and ≥28 days post-vaccination are 66.9% and 66.1%, respectively (Table 15).

Table 15. Efficacy against confirmed symptomatic moderate to severe/critical COVID-19 infection with onset ≥14 days and ≥28 days post-vaccination, per-protocol set

Co-Primary outcomes	Vaccine group		Placebo group		Vaccine efficacy (95% CI)
	Cases (n/N)	Person years	Cases (n/N)	Person years	
≥14 days post-vaccination					
Moderate and severe/critical COVID-19 infection	116/19,514	3,116.6	348/19,544	3,096.1	66.9% (59.0 to 73.4)
≥28 days post-vaccination					
Moderate and severe/critical COVID-19 infection	66/19,306	3,102.0	193/19,178	3,070.7	66.1% (55.0 to 74.8)

Source: Janssen manufacturer submission to Health Canada, Module 2.5: Clinical overview, Tables 5 and 6

Confirmed symptomatic severe/critical COVID-19 infection

The estimates of vaccine efficacy against confirmed symptomatic severe/critical COVID-19 infection are 76.7% with onset ≥14 days post-vaccination and 85.4% with onset ≥28 days post-vaccination (Table 16).

Table 16. Efficacy against confirmed symptomatic severe/critical COVID-19 infection with onset ≥14 days and ≥28 days post-vaccination, per-protocol set

Co-Primary outcomes	Vaccine group		Placebo group		Vaccine efficacy (95% CI)
	Cases (n/N)	Person years	Cases (n/N)	Person years	
≥14 days post-vaccination					
Severe/critical COVID-19 infection	14/19,514	3,125.1	60/19,544	3,122.0	76.7% (54.6 to 89.1)
≥28 days post-vaccination					
Severe/critical COVID-19 infection	5/19,306	3,106.2	34/19,178	3,082.6	85.4% (54.2 to 96.9)

Source: Janssen manufacturer submission to Health Canada, Module 2.5: Clinical overview, Tables 5 and 6

Subgroup analyses

By study country

The time period of the clinical trial was associated with the emergence of new SARS-CoV-2 VOC in some study countries. At the time of data cut-off for the primary analysis, preliminary genetic sequencing data were available for a proportion of case isolates from Brazil, South Africa and the US (Table 17). No SARS-CoV-2 variants from the B.1.1.7 (Alpha) or P.1 (Gamma) lineages were detected in any of the sequenced isolates.

Table 17. Genetic sequencing results for VOC, September–December, 2020

Country	Cases identified N	Cases sequenced n (%)	Sequencing Results
Brazil	179	124 (69.2)	86/124 (69.4%) – variant 20J/501Y.V3 of the of the P.2 (Zeta) lineage 38/124 (30.6%) – Wuhan-Hu1 reference sequence+D614G
South Africa	136	91 (66.9)	86/91 (94.5%) – variant 20H/501Y.V2 of the B.1.351 (Beta) lineage
United States	268	197 (73.5)	190/197 (96.4%) – Wuhan-Hu1 reference sequence+D614G

Source: Janssen manufacturer submission to Health Canada, Module 2.5: Clinical overview, Section 4.1.3.1. Epidemiologic Setting of the Study

Analyses of vaccine efficacy by country were conducted in countries with >100 identified cases (US, 247; Brazil, 153; and South Africa, 133) using a dataset consisting of both centrally PCR-confirmed COVID-19 cases and cases with a positive PCR result from in-country testing not yet confirmed by the central clinical trial testing facility at the data cut-off date for the analysis. The rationale for inclusion of the locally confirmed cases was demonstration of a high concordance (90.3%) in PCR results between local and central clinical trial testing facilities. The point estimates of vaccine efficacy by country against both confirmed symptomatic moderate to severe/critical COVID-19 and severe/critical COVID-19 with onset ≥14 days and ≥28 days post-vaccination are comparable to or greater than the overall estimates of efficacy at these time points (Table 18). The one exception is the point estimate of efficacy for South Africa at ≥14 days post-vaccination.

Table 18. Efficacy against confirmed symptomatic moderate to severe/critical and severe/critical COVID-19, by country for countries with greater than 100 moderate to severe/critical cases, centrally and in-country PCR-confirmed cases

Country	Onset post-vaccination	COVID-19 severity	
		Moderate to severe/critical Efficacy (95% CI)	Severe/critical Efficacy (95% CI)
US	≥14 days	74.4% (65.0 to 81.6)	78.0% (33.1 to 94.6)
	≥28 days	72.0% (58.2 to 81.7)	85.9% (-9.4 to 99.7)
Brazil	≥14 days	66.2% (51.0 to 77.1)	81.9% (17.0 to 98.1)
	≥28 days	68.1% (48.8 to 80.7)	87.6% (7.8 to 99.7)
South Africa	≥14 days	52.0% (30.3 to 67.4)	73.1% (40.0 to 89.4)
	≥28 days	64.0% (41.2 to 78.7)	81.7% (46.2 to 95.4)

Source: Janssen manufacturer submission to Health Canada, Module 2.5: Clinical overview, Table 11

By age group

Efficacy against confirmed symptomatic moderate to severe/critical COVID-19 infection with onset ≥14 days and ≥28 days post-vaccination was assessed in a variety of age groups (Table 19).

Table 19. Efficacy against confirmed symptomatic moderate to severe/critical COVID-19 infection with onset ≥14 days and ≥28 days post-vaccination, by age group, per-protocol set

Age group (years)	Vaccine group		Placebo group		Vaccine efficacy (95% CI)
	Cases (n/N)	Person years	Cases (n/N)	Person years	
≥14 days post-vaccination					
18–39	47/4,356	775.3	122/4,330	762.1	62.1% (46.6 to 73.6)
40–59	48/8,394	1,331.5	138/8,452	1,332.9	65.2% (51.3 to 75.5)
60–69	19/4,800	722.9	65/4,907	732.2	70.4% (50.0 to 83.2)
70–79	2/1,768	259.5	23/1,650	239.2	92.0% (67.6 to 99.1)
≥80	0/196	27.42	0/205	29.8	N/A*
<60 (i.e., 18–59)	95/12,750	2,106.8	260/12,782	2,095.0	63.7% (53.9 to 71.6)
<65 (i.e., 18–64)	107/15,544	2,530.3	297/15,552	2,511.2	64.2% (55.3 to 71.6)
≥60	21/6,764	1,009.8	88/6,762	1,001.2	76.3% (61.6 to 86.0)
≥65	9/3,970	586.3	51/3,992	584.9	82.4% (63.9 to 92.4)
≥75	0/751	88.4	8/690	99.2	100.0% (45.9 to 100.0)
≥28 days post-vaccination					
18–39	29/4,316	772.4	84/4,254	756.6	66.2% (47.9 to 78.6)
40–59	23/8,301	1,325.2	68/8,273	1,320.4	66.3% (45.2 to 80.0)
60–69	12/4,749	719.3	32/4,833	727.1	62.1% (24.4 to 82.2)
70–79	2/1,746	257.8	9/1,620	237.2	79.6% (1.2 to 97.9)
≥80	0/194	27.3	0/198	29.3	N/A
<60 (i.e., 18–59)	52/12,617	2,097.6	152/12,527	2,077.0	66.1% (53.3 to 75.8)
<65 (i.e., 18–64)	60/15,378	2,518.7	170/15,253	2,490.1	65.1% (52.9 to 74.5)
≥60	14/6,689	1,004.4	41/6,651	993.6	66.2% (36.7 to 83.0)
≥65	6/3,928	583.3	23/3,925	580.5	74.0% (34.4 to 91.4)
≥75	0/740	106.4	3/673	98.1	N/A

*N/A = Not available; estimates of vaccine efficacy not calculated when there were fewer than 6 events identified.
Source: Janssen manufacturer submission to Health Canada, Module 2.5: Clinical overview, Figures 30 and 31

The efficacy against confirmed symptomatic severe/critical COVID-19 infection with onset ≥14 days and ≥28 days post-vaccination was calculated for four age groups: 18–59, 18–64, ≥60, and ≥65 years of age (Table 20).

The analysis was repeated using the larger dataset of both confirmed COVID-19 cases and cases with a positive PCR result from a local, in-country testing site. The estimates of vaccine efficacy in participants ≥65 years of age at ≥14 days and ≥28 days post-vaccination increased to 71.4% and 70.1%, respectively.

Table 20. Efficacy against confirmed symptomatic severe/critical COVID-19 infection with onset ≥14 days and ≥28 days post-vaccination, by age group, per-protocol set

Age group (years)	Vaccine group		Placebo group		Vaccine efficacy (95% CI)
	Cases (n/N)	Person years	Cases (n/N)	Person years	
≥14 days post-vaccination					
18–59	8/12,750	2,114.3	41/12,782	2,115.1	80.5% (57.8 to 92.1)
18–64	11/15,544	2,538.5	50/15,552	2,533.8	78.0% (57.3 to 89.7)
≥60	6/6,764	1,010.7	19/6,762	1,006.9	68.5% (18.1 to 89.7)
≥65	3/3,970	586.6	10/3,992	588.3	69.9% (-16.8 to 94.7)
≥28 days post-vaccination					
18–59	2/12,617	2,101.0	24/12,527	2,086.7	91.7% (66.7 to 99.1)
18–64	2/15,378	2,522.8	28/15,253	2,500.9	92.9% (71.9 to 99.2)
≥60	3/6,689	1,005.1	10/6,651	995.9	70.3% (-15.5 to 94.7)
≥65	3/3,928	583.4	6/3,925	581.7	50.1% (-133.4 to 91.9)

Source: Janssen manufacturer submission to Health Canada, Module 2.5: Clinical overview, Figures 32 and 33

By comorbidity

In the clinical trial, the presence of comorbidities was defined as a study participant with one or more medical conditions at baseline that were associated with an increased risk of progression to severe COVID-19 disease (e.g., asthma, cerebrovascular disease, hypertension, respiratory disease, liver disease, and obesity). In participants with and without comorbidities, efficacy was assessed against confirmed symptomatic moderate to severe/critical and against severe/critical COVID-19 infection with onset ≥14 days and ≥28 days post-vaccination (Table 21).

A repeat of the analysis using the larger dataset of both centrally and locally in-country confirmed COVID-19 cases estimated vaccine efficacy against (a) moderate to severe/critical COVID-19 infection and (b) against severe/critical COVID-19 infection in participants with comorbidities of 58.6% (95% CI: 40.6 to 71.6%) and 75.2% (95% CI: 32.0 to 92.7%) with onset ≥28 days post-vaccination.

Table 21. Efficacy against confirmed symptomatic (a) moderate to severe/critical and (b) severe/critical COVID-19 infection with onset ≥14 days and ≥28 days post-vaccination, by presence or absence of comorbidities, per-protocol set

Presence of comorbidities (yes/no)	Vaccine group		Placebo group		Vaccine efficacy (95% CI)
	Cases (n/N)	Person years	Cases (n/N)	Person years	
(a) Moderate to severe/critical COVID-19 infection					
≥14 days post-vaccination					
Yes	47/7,777	1,140.0	126/7,798	1,133.7	62.9% (47.8 to 74.1)
No	69/11,737	1976.6	222/11,746	1,962.5	69.1% (59.4 to 76.8)
≥28 days post-vaccination					
Yes	27/7,684	1,133.6	52/7,626	1,121.7	48.6% (16.7 to 69.0)
No	39/11,622	1,968.4	141/11,552	1,949.0	72.6% (60.7 to 81.3)
(b) Severe/critical COVID-19 infection					
≥14 days post-vaccination					
Yes	8/7,777	1,142.9	29/7,798	1,141.7	72.4% (38.2 to 89.1)
No	6/11,737	1,982.1	31/11,746	1,980.3	80.7% (53.0 to 93.4)
≥28 days post-vaccination					
Yes	4/7,684	1,135.0	12/7,626	1,124.2	67.0% (-8.9 to 92.2)
No	1/11,622	1,971.1	22/11,552	1,958.3	95.5% (72.1 to 99.9)

Source: Janssen manufacturer submission to Health Canada, Module 2.5: Clinical overview, Figures 30, 31, 32 and 33

By serostatus

This analysis was conducted using the expanded dataset of both centrally and locally confirmed COVID-19 cases and estimated vaccine efficacy against confirmed symptomatic moderate to severe/critical COVID-19 infection in study participants based on serostatus at baseline (Table 22).

Table 22. Efficacy against confirmed symptomatic moderate to severe/critical COVID-19 infection with onset ≥14 days and ≥28 days post-vaccination, including confirmed and non-centrally confirmed cases, by serostatus, per-protocol set

Baseline SARS-CoV-2 serostatus	Vaccine group		Placebo group		Vaccine efficacy (95% CI)
	Cases (n/N)	Person years	Cases (n/N)	Person years	
≥14 days post-vaccination					
Regardless of baseline status	176/21,636	3,450.2	513/21,574	3,409.8	66.1% (59.7 to 71.6%)
Positive	3/2,122	336.3	4/2,030	320.8	28.5% (-322.8 to 89.5)
Negative	173/19,514	3,113.9	509/19,544	3,089.1	66.3% (59.9 to 71.8)
≥28 days post-vaccination					
Regardless of baseline status	114/21,424	3,436.3	326/21,199	3,385.9	65.5% (57.2 to 72.4)
Positive	1/2,118	336.1	2/2,021	320.0	N/A*
Negative	113/19,306	3,100.3	324/19,178	3,065.9	65.5% (57.2 to 72.4)

*N/A = Not available; estimates of vaccine efficacy not calculated when there were fewer than 6 events identified.
Source: Table 14, FDA Briefing document for Vaccines and Related Biological Products Advisory Committee meeting (February 26, 2021)

Hospitalizations

A post-hoc analysis assessed vaccine efficacy against COVID-19 associated hospitalizations. The analysis was performed for cases with onset ≥1 day, ≥14 days and ≥28 days post-vaccination in study participants seronegative at baseline (Table 23). At each time point, the analysis was performed using (a) centrally confirmed COVID-19 cases only, and (b) both centrally and locally confirmed cases ("Any positive PCR result").

Table 23. Efficacy against COVID-19 associated hospitalizations with onset ≥1, ≥14 and ≥28 days post-vaccination

Analysis population	Vaccine group		Placebo group		Vaccine efficacy (95% CI)
	Cases (n/N)	Person years	Cases (n/N)	Person years	
≥1 day post-vaccination (in FAS-SN)					
Confirmed cases	6	3,202.8	18	3,213.1	66.6% (12.1 to 89.1)
Any positive PCR result	6	3,202.8	42	3,211.6	85.7% (66.1 to 95.0)
≥14 days post-vaccination (PP)					
Confirmed cases	2	3,125.8	11	3,125.9	81.8% (16.7 to 98.0)
Any positive PCR result	2	3,125.8	29	3,125.1	93.1% (72.7 to 99.2)
≥28 days post-vaccination (PP)					
Confirmed cases	0	3,106.3	6	3,084.4	100.0% (15.7 to 100.0)
Any positive PCR result	0	3,106.3	16	3,083.9	100.0% (74.3 to 100.0)

FAS-SN = Full analysis set, all randomized study participants with documented study vaccine administration, seronegative at baseline; PP = per-protocol set
Source: Janssen manufacturer submission to Health Canada, Module 2.5: Clinical overview, Table 10

Deaths

There were 19 deaths reported during the clinical trial: 3 in the vaccine group and 16 in the placebo group. Of the 19 deaths, zero in the vaccine group were determined to be associated with COVID-19, based on WHO COVID-19 case classifications combined with a positive RT-PCR result, compared to 5 COVID-19 associated deaths in the placebo group. All 5 deaths in the placebo group were in South African study participants with one or more comorbidities with an increased risk for progression to severe COVID-19 disease.

Asymptomatic or undetected SARS-CoV-2 infection

Analysis of vaccine efficacy against asymptomatic or undetected COVID-19 infection (study participants not meeting one of the case definitions for symptomatic COVID-19 and with a positive PCR or serology result) and against seroconversion were conducted at two time points: with onset 1 to 29 days and ≥28 days post-vaccination. A sensitivity analysis was also performed for each of these outcomes by removing participants with symptoms at any time since screening and prior to the positive PCR or serology result ("without previous symptoms").

The point estimate of vaccine efficacy against asymptomatic or undetected COVID-19 infection with onset ≥28 days post-vaccination is 59.7% (and 74.0% after removal of participants with prior symptoms) and against seroconversion it is 66.5% (74.2% with removal of participants with prior symptoms) (Table 24). The seroconversion results should be interpreted with caution as this is a preliminary analysis based on a limited duration of follow-up in approximately 29% of study participants planned for the final analysis based on Day 71 serology.

Table 24. Efficacy against asymptomatic and undetected COVID-19 infection, and against seroconversion, with onset ≥28 days post-vaccination

Outcomes	Vaccine group		Placebo group		Vaccine efficacy (95% CI)
	Cases (n/N)	Person years	Cases (n/N)	Person years	
Full analysis set, seronegative at baseline					
Asymptomatic or undetected SARS-CoV-2 infection	22/19,301	3,099.7	54/19,162	3,064.2	59.7% (32.8 to 76.6)
Asymptomatic or undetected SARS-CoV-2 infection *without previous symptoms*	10/19,301	3,098.0	38/19,162	3,061.5	74.0% (46.8 to 88.4)
Serology risk set*					
Seroconverted	18/1,346	312.2	50/1,304	298.2	65.5% (39.9 to 81.1)
Seroconverted *without previous symptoms*	10/1,346	310.9	37/1,304	296.6	74.2% (47.1 to 88.6)

*Serology risk set = study participants with a serology result available at Day 71 post-vaccination
Source: Janssen manufacturer submission to Health Canada, Module 2.5: Clinical overview, Table 12

Immunogenicity

The majority of the immunogenicity analysis is based on data from a Phase 1 trial that included 2 cohorts of healthy adults aged 18 to 55 and ≥65 years of age. Within each cohort, there were two dose levels given as one or two doses. The analysis below is from one dose of the lower dose, $5x10^{10}$ viral particles.

Humoral immune responses
Antibody responses were elicited by one dose of the Janssen vaccine. Binding and neutralizing antibodies reached a maximum by day 29 and maintained through day 85 (last time point of evaluation) in the younger cohort. In the older cohort, binding antibody responses were slightly lower than those in the younger cohort and were elicited more slowly, increasing from day 15 through day 57 (last time point of evaluation). Neutralizing antibody responses were similar levels to those in the younger cohort, elicited by day 15 and maintained an approximate plateau through day 57. Functional antibody responses as determined through Fc effector function were maximally elicited by day 29 (the last day of evaluation), at similar levels in both age cohorts.

Minimal data are available for seropositive vaccine recipients that may suggest that they respond strongly to one dose of vaccine.

Minimal data are also available demonstrating decreased neutralizing antibody responses to viral variant B.1.1.7 (Alpha).

Without a correlate of protection, the significance of these difference in antibody responses is unclear.

Cellular immune responses
Cellular immune responses were elicited by one dose of this vaccine and were similar in both age cohorts. Spike protein-specific CD4+ T cells responses were detected in 76% of younger vaccine recipients and 60% of older vaccine recipients. Th-1 biased CD4+ T cell responses were observed by day 15 post-vaccination and remained elevated until day 29 (last time point of evaluation). Spike protein-specific CD8+ T cells responses were detected in 51% of younger vaccine recipients and 36% of older vaccine recipients by day 15 post vaccination and remained elevated until day 29.

Anti-vector immune responses
It is unclear to what extent pre-existing immunity to any adenovirus-based vaccine vector exists in the Canadian population and what impact that could have on adenovirus based vaccine safety and efficacy. It is also unclear as to what extent immunization with adenovirus-based vaccines elicits anti-vector immune responses and what impact that could have on homologous or heterologous booster doses with adenovirus-based vaccines. Evidence for a COVID-19 viral vector vaccine based on human adenovirus 5 (not authorized in Canada) indicated that vaccine recipients with high pre-existing immunity to the adenovirus vector had lower anti-SARS-CoV-2 immune responses [(176)]. The Janssen COVID-19 vaccine uses a modified Ad26. Janssen found no correlation between anti-Ad26 neutralizing antibody responses and anti-SARS-CoV-2 immune responses. However, neutralization is not the only anti-vector immune response that could impact vaccine-induced immunity. It remains unclear if immune responses to the Ad26 vector will impact the efficacy or effectiveness of this vaccine.

Vaccine safety and adverse events following immunization

Safety evidence is based on interim analyses of 21,895 participants (of whom 7,331 were ≥60 years of age) who received at least one dose of the vaccine. A safety subset included 3,356 participants in the vaccine group who were followed for solicited reactions within 7 days following vaccination and unsolicited reactions within 28 days following vaccination. Medically attended adverse events (MAAEs), SAEs and AEs leading to discontinuation from study participation were assessed in all participants. Overall, the median duration of follow-up was 58 days after vaccination.

Solicited local reactions
Solicited local injection site AEs were reported by 50.3% of evaluated participants within the first 7 days following any vaccine dose. Injection site pain was the most frequently reported local AE (48.7%) followed by warmth (7.3%) and swelling (5.3%). In the vaccine group, the frequency of solicited local AEs was lower in participants aged ≥60 years compared to participants aged ≥18 to <60 years. The frequency of solicited local AEs was also similar in participants who were seronegative for SARS-CoV-2 at baseline compared to participants who were seropositive for SARS-CoV-2 at baseline (50.1% and 54.5%, respectively). The majority of solicited local reactions among vaccine recipients were mild or moderate in severity, with any Grade 3 reactions being reported by ≤0.7% of participants. No Grade 4 solicited local AEs were reported.

Solicited systemic reactions
Solicited systemic AEs were reported by 55.2% of evaluated participants within the first 7 days following vaccine administration. The most common systemic solicited AEs were headache (39.0%) and fatigue (38.3%). Other frequently reported systemic solicited AEs were muscle pain (33.2%), nausea (14.2%) and fever ≥38.0°C (9.0%). While AEs were lower in participants aged ≥60 years compared to participants aged ≥18 to <60 years, there were no clinically relevant differences in the frequency of solicited systemic AEs. AEs were similarly observed in participants who were seronegative for SARS-CoV-2 at baseline (55.4%) compared to participants who were seropositive for SARS-CoV-2 at baseline (50.6%). Overall, the frequency of any Grade 3 reactions was <2%, and no Grade 4 solicited systemic AEs were reported. Antipyretics were recommended post-vaccination for symptom relief as needed. Analgesics or antipyretics were used by 26.4% of vaccinated 18 to 59 year olds and 9.8% of vaccinated individuals 60 years of age and older up to 7 days post vaccination in the full analysis. The majority of solicited systemic AEs were transient in nature and had a median duration of 1 to 2 days after vaccination.

Unsolicited serious adverse events
During the 28-day period post-vaccination, there were 19 (0.6%) participants with unsolicited AEs of at least Grade 3 in the vaccine group compared to 18 (0.6%) participants in the placebo group. Of these unsolicited AEs of at least Grade 3, 5 (0.1%) were considered to be related to the study vaccine. There were no clear imbalances by System Organ Class (SOC). No cases of anaphylaxis were identified in the clinical trials. However, the manufacturer announced receipt of preliminary reports of two cases of severe allergic reactions, including one case of anaphylaxis, in participants who had received the vaccine. Details on the reports have not been provided to date.
In total there were 7 (<0.1%) participants who reported SAEs that were considered to be related to the study vaccine by the investigator and lead to discontinuation from the study. These included:

- Grade 4 Guillain-Barré syndrome in a participant 16 days after vaccination. The case was considered indeterminate as per WHO AEFI criteria; however, due to close temporal association and lack of other explanatory factors, it was considered as possibly related to the vaccine for reporting purposes.
- Grade 4 pericarditis in a participant approximately 17 days following vaccination and resulted in hospitalization. The event was assessed as indeterminate as per WHO AEFI criteria; however, due to close temporal association and a lack of other explanatory factors it was assessed as possibly related to the vaccine for reporting purposes.
- Grade 3 brachial radiculitis in a participant with immediate onset following vaccination.
- Grade 3 post-vaccination syndrome 2 days following vaccination. Based on the symptoms, the event was assessed as vaccine reactogenicity (asthenia).
- Grade 3 Type IV hypersensitivity in a participant 3 days following vaccination. The case was considered likely related to vaccination due to close temporal association.
- Grade 2 facial paralysis (Bell's Palsy) in two participants 3 and 16 days after vaccination. Both events were assessed to have an inconsistent causal association with immunization, per the WHO AEFI criteria.

Other serious adverse events

Tinnitus

Six cases of tinnitus were reported in the vaccine group and none in the placebo group. All cases were considered non-serious, and two cases were considered related by the investigator. All participants had underlying medical conditions (such as history of tinnitus and migraine, history of hypertension, seasonal allergies and hypothyroidism) or used medications that offered a more plausible alternative cause for the event compared to the vaccine.

Convulsions/seizures

Four cases were reported in the vaccine group (1 serious) and one case (non-serious) in the placebo group, all of which were considered not related to the study vaccine by the investigator. The serious case of convulsion/seizure was reported in a participant with a history of epilepsy and obsessive-compulsive disorder.

Thrombotic and thromboembolic events

The overall incidence of thrombotic and thromboembolic events (arterial and venous) was similar across the vaccine (n=15, 0.1%) and placebo groups (n=10, <0.1%). A numerical imbalance was observed for the deep vein thrombosis deep/ pulmonary embolism subtypes, with a total of 9 cases in the vaccine group (4 serious) and 3 cases in the placebo group (2 serious). One case of transverse sinus thrombosis occurred on Day 21 following vaccination in a 25-year-old male participant with no past medical history. The participant also presented a seizure reported to be a consequence of a secondary bleed caused by elevated venous pressure from the venous flow obstruction. Two thrombectomy procedures were performed because of the participant's hypercoagulable state. No clear cause of the event was identified and it was deemed unrelated to the vaccine as there were possible contributing factors (preceding infection and anatomical anomaly). One non-serious case with onset 27 days after vaccination in a participant with a medical history of obesity and cholecystectomy was considered to be related to the vaccine.

Vaccine-Induced Immune Thrombotic Thrombocytopenia

Rare cases of serious blood clots, including cerebral venous sinus thrombosis, associated with thrombocytopenia have been recently reported in the United States following post-licensure use

of Janssen COVID-19 vaccine. This adverse event is being referred to as Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) and has been associated with both the AstraZeneca and Janssen COVID-19 viral vector vaccines. The mechanism of action is similar to heparin-induced thrombocytopenia (HIT). The exact mechanism by which the viral vector COVID-19 vaccines may trigger VITT is still under investigation. As of May 24, 2021, 32 cases of TTS out of about 10.2 million doses of Janssen administered in the United States have been confirmed. Most of the cases to date have occurred in females between the ages of 18 and 49 years; however, investigations are ongoing and additional cases may be identified with increased awareness and current emphasis on the clinical recognition of this event. Reports indicated symptom onset between 6 and 15 days after vaccination. Investigations are ongoing.

Demyelinating disorders

In total there were four cases of demyelinating disorders that were reported in the vaccine group (2 cases peripheral neuropathy, 1 benign monoclonal hypergammaglobulinemia, 1 Guillain-Barré syndrome) compared with 5 cases in the placebo group (2 cases peripheral neuropathy, 1 Guillain-Barré syndrome and 2 sensory loss.

Death

A total of 19 deaths were reported among study participants (3 in the vaccine group and 16 in the control group). In the vaccine group, causes of death by preferred term were lung abscess, non-COVID-19 pneumonia, and 1 of unknown cause at the time of data cut-off. None of these deaths were considered to be related to the study intervention by the investigators.

Pregnancies

Eight pregnancies were reported through January 22, 2021 (4 vaccine, 4 placebo). Vaccination was within 30 days after last menstrual period in 7 participants (3 vaccine, 4 placebo) while in 1 vaccine recipient vaccination was prior to last menstrual period. Unsolicited AEs related to pregnancy included spontaneous abortion (1 vaccine, 0 placebo), incomplete abortion (0 vaccine, 1 placebo), elective abortion (0 vaccine, 2 placebo) and ectopic pregnancy (1 vaccine, 0 placebo). Two pregnancies are ongoing among participants in the vaccine group, with unknown outcomes at this time.

APPENDIX E: FREQUENCY OF SOLICITED ADVERSE EVENTS FOLLOWING IMMUNIZATION FOR COVID-19 VACCINES IN CLINICAL TRIALS

Table 25. Frequency of solicited local adverse events in authorized populations for mRNA COVID-19 vaccines[a]

AEFI	Pfizer-BioNTech Comirnaty COVID-19 Vaccine								Moderna Spikevax COVID-19 Vaccine							
	Adults (≥16 years old)				Adolescents (12 to 15 years old)				Adults				Adolescents (12 to 17 years old)			
	Vaccine		Placebo control		Vaccine		Placebo control		Vaccine		Placebo control		Vaccine		Placebo control	
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2
Pain at injection site	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common
Tenderness	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Redness/erythema	Common	Common	Uncommon	Uncommon	Common	Common	Common	Uncommon	Common	Common	Uncommon	Uncommon	Very Common	Very Common	Uncommon	Uncommon
Swelling	Common	Common	Uncommon	Uncommon	Common	Common	Common	Uncommon	Common	Very Common	Uncommon	Uncommon	Very Common	Very Common	Common	Common
Lymphadenopathy[b]/ Axillary swelling and tenderness	NS	NS	NS	NS	NS	NS	NS	NS	Very Common	Very Common	Common	Common	Very Common	Very Common	Common	Common
Warmth	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Pruritis	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Induration	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

Abbreviations: AEFI: adverse event following immunization; MenACWY: Quadrivalent meningococcal vaccine; NS: not solicited

[a] Very common = occur in 10% or more of vaccine recipients, common = occur in 1 to less than 10% of vaccine recipients, uncommon= occur in 0.1% to less than 1% of vaccine recipients

[b] Lymphadenopathy was not a solicited adverse event for the Pfizer BioNTech COVID-19 vaccine and was reported as an unsolicited adverse event. Please see Appendix A for more details.

Table 26. Frequency of solicited local adverse events in authorized populations for viral vector COVID-19 vaccines[a]

AEFI	AstraZeneca Vaxzevria COVID-19 Vaccine				Janssen COVID-19 Vaccine[b]	
	Vaccine		MenACWY control		Vaccine	Placebo control
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 1
Pain at injection site	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common
Tenderness	Very Common	Very Common	Very Common	Very Common	NS	NS
Redness/erythema	Very Common	Common	Common	Uncommon	Common	Common
Swelling	Common	Common	Common	Common	Common	Common
Lymphadenopathy[c]/ Axillary swelling and tenderness	NS	NS	NS	NS	NS	NS
Warmth	Very Common	Common	Very Common	Common	NS	NS
Pruritis	Very Common	Common	Common	Common	NS	NS
Induration	Common	Common	Common	Common	NS	NS

Abbreviations: AEFI: adverse event following immunization; MenACWY: Quadrivalent meningococcal vaccine; NS: not solicited

[a] Very common = occur in 10% or more of vaccine recipients, common = occur in 1 to less than 10% of vaccine recipients, uncommon= occur in 0.1% to less than 1% of vaccine recipients

[b] Single dose vaccine (dose 2 not applicable)

[c] Lymphadenopathy was not a solicited adverse event for the AstraZeneca or Janssen COVID-19 vaccine and was reported as an unsolicited adverse event. Please see Appendix C for more details.

Table 27. Frequency of solicited systemic adverse events in authorized populations for mRNA COVID-19 vaccines[a]

AEFI	Pfizer-BioNTech Comirnaty COVID-19 Vaccine								Moderna Spikevax COVID-19 Vaccine							
	Adults (≥16 years old)				Adolescents (12 to 15 years old)				Adults				Adolescents (12 to 17 years old)			
	Vaccine		Placebo control		Vaccine		Placebo control		Vaccine		Placebo control		Vaccine		Placebo control	
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2
Fatigue	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common
Headache	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common
Muscle Pain	Very Common	Very Common	Very Common	Common	Very Common	Very Common	Very Common	Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common
Chills	Very Common	Very Common	Common	Common	Very Common	Very Common	Common	Common	Common	Very Common	Common	Common	Very Common	Very Common	Very Common	Common
Joint Pain	Common	Very Common	Common	Common	Common	Very Common	Common	Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Common
Fever[b]	Common	Very Common	Uncommon	Uncommon	Very Common	Very Common	Common	Uncommon	Uncommon	Very Common	Uncommon	Uncommon	Common	Very Common	Common	Common
Feverishness[b]	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Diarrhea	Common	Common	Common	Common	Common	Common	Common	Common	NS	NS	NS	NS	NS	NS	NS	NS
Nausea and/or Vomiting[c]	Uncommon	Common	Uncommon	Uncommon	Common	Common	Uncommon	Common	Common	Very Common	Common	Common	Very Common	Very Common	Common	Common

Abbreviations: AEFI: adverse event following immunization; MenACWY: Quadrivalent meningococcal vaccine; NS: not solicited

[a] Very common = occur in 10% or more of vaccine recipients, common = occur in 1 to less than 10% of vaccine recipients, uncommon= occur in 0.1% to less than 1% of vaccine recipients

[b] Fever was objectively reported as having a temperature ≥38°C/100.4°F. Feverishness was a subjective, self-reported feeling of having fever.

[c] If two frequencies are reported the first reflects frequency of nausea and the second reflects the frequency of vomiting.

Table 28. Frequency of solicited systemic adverse events in authorized populations for viral vector COVID-19 vaccines[a]

AEFI	AstraZeneca Vaxzevria COVID-19 Vaccine				Janssen COVID-19 Vaccine[b]	
	Vaccine		MenACWY control		Vaccine	Placebo control
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 1
Fatigue	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common
Headache	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common
Muscle Pain	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common
Chills	Very Common	Common	Common	Common	NS	NS
Joint Pain	Very Common	Very Common	Common	Common	NS	NS
Fever[c]	Common	Common	Uncommon	Uncommon	Common	Uncommon
Feverishness[c]	Very Common	Common	Common	Common	NS	NS
Diarrhea	NS	NS	NS	NS	NS	NS
Nausea and/or Vomiting[d]	Very Common/ Common	Common/ Uncommon	Very Common/ Uncommon	Common/ Uncommon	Very Common	Common

Abbreviations: AEFI: adverse event following immunization; MenACWY: Quadrivalent meningococcal vaccine; NS: not solicited

[a] Very common = occur in 10% or more of vaccine recipients, common = occur in 1 to less than 10% of vaccine recipients, uncommon= occur in 0.1% to less than 1% of vaccine recipients

[b] Single dose vaccine (dose 2 not applicable)

[c] Fever was objectively reported as having a temperature ≥38°C/100.4°F. Feverishness was a subjective, self-reported feeling of having fever.

[d] If two frequencies are reported the first reflects frequency of nausea and the second reflects the frequency of vomiting.

APPENDIX F: PREGNANCY, BREASTFEEDING AND COVID-19 VACCINE REGISTRIES

There is a Canadian COVID-19 vaccine registry for pregnant and breastfeeding individuals:

- Canadian COVID-19 Vaccine Registry for Pregnant and Lactating Individuals

Table 29: Pregnancy registry information by vaccine product

Vaccine product	Registry information
Pfizer-BioNTech Comirnaty COVID-19 vaccine	Pfizer does not have a pregnancy exposure registry. Pfizer COVID-19 vaccine recipients and health care providers are encouraged to report any exposure to COVID-19 vaccine during pregnancy or breastfeeding to the vaccine manufacturer (1-866-723-7111).
Moderna Spikevax COVID-19 vaccine	There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to the Moderna COVID-19 vaccine during pregnancy. Women who are vaccinated with the Moderna COVID-19 vaccine during pregnancy are encouraged to enroll in the registry by calling 1-866-MODERNA (1-866- 663-3762).
AstraZeneca Vaxzevria COVID-19 vaccine	There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to AstraZeneca COVID-19 vaccine during pregnancy. Women who are vaccinated with AstraZeneca COVID-19 Vaccine during pregnancy are encouraged to enroll in the registry by visiting https://c-viper.pregistry.com or calling 1-800-616-3791.
Janssen COVID-19 vaccine	There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Janssen COVID-19 vaccine during pregnancy. Women who are vaccinated with Janssen COVID-19 vaccine during pregnancy are encouraged to enroll in the registry by visiting https://c-viper.pregistry.com

TAB 28

See Tab 27 at Pg. 61

TAB 29

Protection of previous SARS-CoV-2 infection is similar to that of BNT162b2 vaccine protection: A three-month nationwide experience from Israel

Yair Goldberg[1]*, Micha Mandel[2], Yonatan Woodbridge[3], Ronen Fluss[3], Ilya Novikov[3], Rami Yaari[3], Arnona Ziv[3], Laurence Freedman[3], Amit Huppert[3,4]

[1]Technion - Israel Institute of Technology, Israel

[2]The Hebrew University of Jerusalem, Israel

[3]The Gertner Institute for Epidemiology & Health Policy Research, Sheba Medical Center, Israel

[4]Tel Aviv University, Israel

Contributed equally

*corresponding author

email: yairgo@technion.ac.il

Abstract

Worldwide shortage of vaccination against SARS-CoV-2 infection while the pandemic is still uncontrolled leads many states to the dilemma whether or not to vaccinate previously infected persons. Understanding the level of protection of previous infection compared to that of vaccination is critical for policy making. We analyze an updated individual-level database of the entire population of Israel to assess the protection efficacy of both prior infection and vaccination in preventing subsequent SARS-CoV-2 infection, hospitalization with COVID-19, severe disease, and death due to COVID-19. Vaccination was highly effective with overall estimated efficacy for documented infection of 92·8% (CI:[92·6, 93·0]); hospitalization 94·2% (CI:[93·6, 94·7]); severe illness 94·4% (CI:[93·6, 95·0]); and death 93·7% (CI:[92·5, 94·7]). Similarly, the overall estimated level of protection from prior SARS-CoV-2 infection for documented infection is 94·8% (CI:[94·4, 95·1]); hospitalization 94·1% (CI:[91·9, 95·7]); and severe illness 96·4% (CI:[92·5, 98·3]). Our results question the need to vaccinate previously-infected individuals.

Keywords: vaccine efficacy, COVID-19, SARS-CoV-2, previous infection, protection from reinfection

Introduction

Israel is currently in the later stages of a vaccination campaign to reduce both SARS-CoV-2 infection and the number of COVID-19 cases. Israel is administering the BNT162b2 vaccine, developed by BioNTech in cooperation with Pfizer,[1] for which an Emergency Use Authorization (EUA) was issued by the Food and Drug Administration (FDA).[2] The vaccine is administered in two doses, with a 21-day interval between doses. Israel launched its COVID-19 vaccination program on December 20, 2020. The vaccine became available, free of charge, to different risk groups in stages: first to those older than 60 years old, nursing home residents, healthcare workers, and patients with severe comorbidities, and then gradually to younger age groups. As of February 6, 2021, the vaccine was made available to all individuals aged 16 or older not previously infected by SARS-CoV-2. As of March 20, 2021, 77% of the eligible population is vaccinated. Due to the high caseload and the local detection of viral mutants such as B.1.1.7, Israel went into a third nationwide lockdown during the vaccination campaign. A light lockdown began on December 24, 2020, and was tightened on January 5, 2021. Restrictions were eased in stages starting February 7, 2021. The dynamics of the epidemic as well as the vaccination campaign appear in Figure 1.

SARS-CoV-2 testing in Israel is carried out according to the following policy: individuals may request testing due to either symptoms or contact with an individual who tested positive. These PCR tests are given free of charge. Individuals who have come into contact with an individual who tested positive are required to self-quarantine for 14 days. This quarantine period may be shortened to 10 days if the individual is tested twice during the first 10 days, and both test results are negative. Individuals who have received both vaccine doses, and had the second dose seven days or more before a contact with a positive individual, and do not have symptoms, are not required to self-quarantine, and thus have

less motivation to get tested. In addition to voluntary testing, Israel conducts routine testing of all nursing-home workers.

Recent results based on aggregated data[3–5] and individual level data[6–10] have shown that the vaccine substantially reduces the number of severe COVID-19 cases. Two studies also indicate that the viral load of vaccinated individuals is significantly reduced.[11,12] These encouraging initial results are based on a short follow-up of vaccinated individuals. Results on previous COVID-19 infection[13–16] suggest protection against reinfection compared to uninfected unvaccinated individuals.

In this study, we estimate the efficacy of the vaccine in the reduction of documented SARS-CoV-2 infection and severe COVID-19 disease. We focus on four cohorts: unvaccinated individuals; vaccinated individuals followed from first dose to a week after the second dose; vaccinated individuals followed from a week after the second dose onwards, and the Recovered Cohort of unvaccinated individuals previously infected with SARS-CoV-2. For more details, see the Methods section. All efficacies, of vaccine or previous infection, are compared to the unvaccinated cohort.

The prospective observational analysis that we present faced several challenges. The first challenge was self-selection of treatment, which implies differences in potential risk factors between vaccinated and non-vaccinated individuals. These include age, sex, socio-demographic level,[17] level of infection in the immediate environment, and possibly other behavioral variables that could affect level of exposure to the virus. The second challenge was detection bias: willingness to undergo vaccination can be associated with trust in the healthcare system, which may also imply a tendency to comply with testing regulations. On the other hand, vaccinated individuals may feel more protected and may ignore mild symptoms indicative of the disease, and have less motivation to get tested as they are not required to self-quarantine after a contact with a positive individual. The third challenge was the variation in infection risk throughout the vaccination campaign, mainly due to varying lockdown levels, relative prevalence of viral mutants, and local outbreaks. Lastly, the status of individuals (i.e., unvaccinated, partially vaccinated, or fully vaccinated) was

dynamic: with time, individuals move from one cohort to another, and between risk groups. In the Methods Section we explain how we designed the analysis to address these challenges.

Methods

Data

The database included two main tables. The first table was of all 1373 municipalities in Israel, with data on the number of residents, the daily count of PCR tests, and the daily positive results. This table was constructed based on data from the Israel Ministry of Health and the Israel Central Bureau of Statistics.

The second table was an individual-level table on persons aged 16 and above collected by the Israeli Ministry of Health based on data received routinely from all HMOs and hospitals and linked using the person's identity number. This table contained basic demographic data and information on dates of first and second vaccinations, if received, and dates and results of all PCR tests performed from March 1, 2020, up to March 20, 2021. For individuals with a positive PCR test, the table contained information on symptoms, as well as the maximum severity status throughout the course of the disease (hospitalization, severe disease, death). The definition of hospitalization, severe disease, and death due to COVID-19 is based on international recommendations.[18] Specifically, hospitalization is defined as being admitted due to COVID-19. Disease is considered severe when a patient has >30 breaths per minute, oxygen saturation on room air <94%, or ratio of arterial 148 partial pressure of oxygen to fraction of inspired oxygen <300mm mercury. Data on symptoms were also available but we found them less reliable and thus did not include symptomatic COVID-19 as an outcome.

Thus, the table contained an entry for every adult (age $\geq$ 16) in Israel who had at least one PCR test or had received at least the first dose of the vaccine (with a total of 5,682,928 entries). Adults with no PCR test and no vaccination (668,975) were added to the table using data from the Israel Central Bureau of Statistics. Thus, this second table included

6,351,903 entries with basic demographic data of the total adult population in Israel, as well as their PCR tests and vaccination dates. Individuals under age 16 are not eligible for vaccination and were excluded from this study. A summary of the data appears in Table 1.

To account for environmental risk, we calculated a municipality daily risk index by the number of cases newly confirmed in the past seven days per 10,000 residents. We used a 7-day moving average since the number of PCR tests typically drops at weekends. The index was categorized into four risk levels (up to one , one to four, four to ten, and more than ten daily cases per 10,000) to yield the municipality daily risk category, and was used as a covariate in the risk model.

Behavioral differences among people may result in different levels of exposure to infection and compliance with PCR testing guidelines. We partially accounted for this by counting the number of PCR-test clusters that an individual underwent from March 1, 2020, to December 20, 2020 (i.e., prior to the vaccination program). Here, a PCR-test cluster comprised all consecutive test performed within 10 days of each other. We then defined three individualized background risk levels: no PCR tests, one cluster, and two or more clusters, and this covariate was also included in the risk model. For previously-infected individuals, we set the level to one cluster and checked sensitivity to this value. Note that the time interval for defining this variable (up to December 20, 2020) did not overlap with the follow-up period.

In addition to estimating vaccine efficacy, we estimated the protection of prior SARS-CoV-2 infection against a recurrent infection. Thus, we also included in the dataset individuals who had recovered from COVID-19. Recovery from SARS-CoV-2 infection is not well-defined, and individuals may continue to show traces of the virus weeks and sometimes even months after the infection.[14] We defined as a recurrent infection only cases occurring three months or more after the first diagnosis. We also considered only individuals for whom the first infection was diagnosed between June 1 and September 30, 2020, as the PCR results before June 1 are considered less reliable. Hence, individuals infected before

June 1, 2020 or between October 1, 2020 and December 20, 2020 were excluded from the analysis.

Statistical Modeling

To estimate the efficacy of the Pfizer BNT162b2 vaccine in reducing documented SARS-CoV-2 infection and other COVID-19 events, we considered four dynamic sub-populations or cohorts:

- Cohort 0: Unvaccinated and not previously infected with SARS-CoV-2;
- Cohort 1: Vaccinated and followed from the day of first vaccination to 6 days after the second dose;
- Cohort 2: Vaccinated and followed from a week after the second dose onwards;
- Recovered: Unvaccinated and previously diagnosed with SARS-CoV-2 between June 1 and September 30, 2020.

On any given calendar day, each individual included in the analysis belongs to a single cohort, but cohort membership is dynamic. Moreover, individuals may not only move between cohorts over time (for example, from cohort 0 to cohort 1 after first vaccination, or from cohort 1 to cohort 2 at 7 days after the second vaccination), but also exit from the follow-up (for example, on infection with SARS-CoV-2 or death). The outcomes hospitalization, severe disease, and death, were attributed to the date on which COVID-19 was documented.

We modeled the daily risk of each individual from December 20, 2020 to March 20, 2021, as a function of calendar time, the cohort to which the individual currently belonged, and the individual's current risk factors, which included fixed covariates: age group (16-39, 40-49, 50-59, 60-69, 70-79, and 80+), sex, and background risk level (0,1, and 2+ past PCR tests), and the time-dependent variable: municipality risk level(low, medium, medium-high,

and high). We refer to each combination of possible covariate values (age group, sex, background risk level, and municipality risk level) as the risk profile.

Our analysis model falls within the framework of multi-state survival models, where each cohort represents a separate state;[19] see Figure S1. Similar to the study of mRNA-1273, the vaccine developed by Moderna,[20] we defined the efficacy of the vaccine in terms of hazard ratios, where the main interest is in comparing the hazard of a non-vaccinated individual (Cohort 0) to that of an individual who had completed the recommended protocol (Cohort 2). Hazard ratios between cohorts and for each adjusting covariate were estimated via a generalized linear model with a Poisson distribution and logarithmic link function, and an offset for each risk profile.[21]

Our model assumes that for a given cohort and risk profile, the hazard was constant and did not depend on the time from the second dose (Cohort 2). Obviously, the hazard of individuals who have never received the first dose (Cohort 0) cannot depend on the time of the first dose, but we also assumed that the time elapsed from the second vaccination did not affect the hazard in Cohort 2. In other words, we assumed that the protection level did not change with time after the "completion" of the vaccination protocol. While protection by vaccination is expected to decrease in the long run, our assumption is reasonable given the time frame of only three months after first vaccination, where waning immunity is not expected to play a role. We split Cohort 1 into two sub-cohorts: Cohort 1A from the first dose to two weeks after the first dose, and Cohort 1B from 15 days after the first dose to six days after the second dose. Following Skowronski and De Serres,[22] we considered, as a crude approximation, a constant hazard for each of these two sub-cohorts for every risk profile. To estimate the level of protection among the Recovered Cohort, we made a similar assumption, that the time elapsed from SARS-CoV-2 infection did not affect the hazard ratio.

The formal definition of vaccine efficacy adopted was as follows. Consider any particular risk profile. Let h_i denote the hazard of an individual in one of the vaccinated cohorts 1A, 1B, 2, or Recovered, and let h_0 be the hazard of an individual having the identical risk

profile in the unvaccinated group. Efficacy of the vaccine in that cohort for that risk profile is defined as $1 - h_i/h_0$. Note that the calendar time affects the hazards of the different cohorts only via the time-dependence of the municipality risk level. From the model assumptions, the ratio h_i/h_0 is the same for each risk profile, so the estimate of vaccine efficacy may be combined over all the risk profiles. For more details about the model, see Appendix. We analyzed efficacy separately for each of the following outcomes: documented infection, hospitalization, severe disease, and death.

Results

The data are based on follow-up of the four cohorts from December 20, 2020 up to March 20, 2021, with over 573 million person-days of follow-up. The lengths of follow-up for the fully vaccinated and the recovered cohorts appear in Figures S2 and S3, respectively. During this time 4,606,247 PCR tests were performed (8,040 per million person-days), and 306,712 individuals tested positive (5·4 infections per 10,000 person-days). Of those testing positive, 14,019 (4·6%) required hospitalization, 8,463 (2·8%) were defined as severe cases, and 2,727 (0·9%) died. Table 2 presents these numbers by cohort and age group. The numbers of PCR tests performed per million person-days appear in Table 3. There is a decrease in the rate of PCR testing in both Cohort 2 and the Recovered Cohort compared to the other cohorts. This is likely since fully vaccinated or recovered individuals (Cohorts 2 & Recovered) are more protected against SARS-CoV-2 infection. Additionally, people in Israel need to self-quarantine for 14 days after contacting SARS-CoV-2 infected persons, which can be shortened to ten days if they present two negative PCR tests. This is not required for fully vaccinated and recovered persons unless they develop symptoms.

We first investigated the dynamics of the vaccination program, disease outcomes, PCR testing, and municipality risk as a function of calendar time. Figures S4 and S5 present the proportion of vaccinated over time among different age and municipality risk groups, respectively. As can be seen from Figure S4, the Israeli vaccination policy was initially to immunize the older population, and as time progressed, younger age groups. Figure S5 shows the association between environmental risk and vaccination. Figure S6 shows the

rates over time of the different age groups among those tested, infected, hospitalized, having severe disease, and dying. Table 4 shows, by age group, the estimated vaccine efficacy for the main outcomes for Cohort 2 (fully vaccinated) adjusted for sex, municipality risk, and past PCR. Note that for age groups below 60 years, there were, fortunately, none or very few events of severe illness and death, and thus estimates were omitted for these groups. The table shows that vaccine efficacy was quite similar in all age groups with some decrease in efficacy for the 80+ age category. Fitting a model without age-group/cohort interaction yielded overall vaccine efficacy for documented infection of 92·8% (CI: [92·6, 93·0]); hospitalization 94·2% (CI: [93·6, 94·7]); severe illness 94·4% (CI: [93·6, 95·0]); and death 93·7% (CI: [92·5, 94·7]). We repeated the analysis with full vaccination defined as 15 days or more after the second dose. The results are similar (not shown).

Table 5 presents the results for the Recovered Cohort when the past PCR-based individualized risk was set to one PCR cluster. Again, the protection was quite similar in all age groups with some decrease in efficacy for the 80+ age category, and quite similar to the results in Table 4. The overall estimated protection of prior SARS-CoV-2 infection for documented recurrent infection was 94·8% (CI: [94·4, 95·1]); hospitalization 94·1% (CI: [91·9, 95·7]); and severe illness 96·4% (CI: [92·5, 98·3]). As there were only 1 death cases in the Recovered Cohort, protection against death was not estimated.

As described above, we assigned the recovered individuals to the middle PCR risk group, so that the estimated protection of a prior infection is compared to unvaccinated individuals having a single PCR cluster in the past. The protection levels afforded by a prior infection compared to unvaccinated persons who had no or 2+ past PCR tests are given in a sensitivity analysis shown in Table S1. In addition, Table S1 presents results of a model without PCR, which can be interpreted as the overall protection of a prior infection. As expected, the protection of a prior infection compared to unvaccinated persons who did not have past PCR tests is estimated to be smaller and compared to those who had 2+ tests is larger. The results when omitting the PCR variable are very similar to the figures in Table 5.

The results for Cohorts 1A and 1B appear in Tables S2 and S3, respectively. The results up to two weeks after the first dose (Cohort 1A) suggest low but statistically significant efficacy. For Cohort 1B that comprises individuals at more than two weeks after the first dose, the efficacy is higher, being 57·7% (CI: [57·1, 58·4]) for documented infection; 69·4% (CI: [67·5, 71·2]) for hospitalization; 65·9% (CI: [63·1, 68·5]) for severe illness; and 62·7% (CI: [58·0, 66·8]) for death. The coefficients of all four models used for analyzing the data appear in Tables S4-S7.

Discussion

This population-based observational study demonstrates the high efficacy of the BNT162b2 vaccine and prior SARS-CoV-2 infection against both subsequent SARS-CoV-2 infection and other COVID-19–related outcomes. There are a few characteristics that make this study unique. First, it was a nationwide study and thus represented the real-world effectiveness of vaccination and prior infection on the full population. Second, it used individual-level data that enabled, at least to some degree, to mitigate biases caused by selection to get vaccinated, selection to undergo PCR testing, and time-changing level of risk, via adjustment for between-cohort differences in individuals' characteristics and municipality risk level. Third, the study included follow-up of the population for a period of three months, allowing follow-up of the fully vaccinated cohort over an extended duration. Fourth, this is the first large-scale study that has explored the protection due to prior SARS-CoV-2 infection compared to the Pfizer BNT162b2 vaccine.

There are some limitations to this observational study. One major source of confounding is related to possible population differences between individuals who were vaccinated compare to those who were not. This confounding is partially addressed by controlling for risk factors. Specifically, for each individual we adjusted for sex, age group, number of past PCR tests and the time-dependent environmental exposure. Another major source of potential bias is related to detection of SARS-CoV-2 infection. As apparent from the PCR test counts in Table 3, individuals who are fully vaccinated or were previously infected get tested less often than the unvaccinated cohort. Our results for the outcomes of

hospitalization, severe disease, and death do not suffer from this bias and thus are more reliable. The vaccine protection against infection might be biased upward as explained above, nevertheless the remarkable curtailing of the outbreak in Israel which followed the high vaccine uptake by the Israeli population further suggest that the vaccine is efficient in blocking transmission, see Figure 1.

The efficacy estimates of the BNT162b2 vaccine in this study are similar to those reported by previous large-scale studies. For the severe disease outcome, the randomized trial of BNT162b2[1] reported 89% efficacy for severe disease. A study by the Israeli Ministry of Health using aggregated data[5] reported 96% efficacy for people as defined in our Cohort 2. A study on data from Israel's largest HMO[6] split people as defined in our Cohort 1B and reported an efficacy of 62% and 80% for the third and fourth weeks after the first vaccine, respectively, and of 92% for their Cohort 2. In comparison, our analysis showed efficacy of 66% for Cohort 1B and 94% for Cohort 2. For other outcomes, the estimated vaccine efficacy for Cohort 2 in our study were 93% and 94%, for documented infection and hospitalization, respectively. These estimates are similar to previous studies[5,6] that estimated efficacy of 92% and 96% for documented infection, and of 87% and 96% for hospitalization. Our findings are based on a longer follow-up and a larger number of event than in the previous individual-level data reports. For example, the analysis of severe cases in the randomized clinical trial is based on only 10 cases, and that of Israel's largest HMO on 229.[6] In comparison, the analysis in our study is based on 8,463 cases, including 2,240 cases from Cohort 1 and 319 cases from Cohort 2. On the other hand, the other two studies[1,6] have the respective advantages of randomization and a detailed matching process which help in bias reduction.

The estimated protection against reinfection in this study is similar to that of the BNT162b2 vaccine. For documented SARS-CoV-2 reinfection, these results are similar to the results obtained in a large study from Qatar of 95% protection,[13] and suggest higher protection than reported by other previous studies. A large study from Denmark[14] suggested 80% protection against reinfection. A study on healthcare workers in the United Kingdom[16] reported that previous infection was associated with an 83% lower risk of infection. These

two studies are based on 11,727 and 6,614 previously infected individuals, with 72 and 44 reinfections, respectively. In comparison, the Recovered cohort in our study comprised 187,549 individuals, with 894 reinfections. One possible reason for the differences in the estimated protection against reinfection could be related to detection bias of SARS-CoV-2 infection. However, our estimated high levels of protection against hospitalization and serious disease after reinfection are unlikely to be affected by detection bias, and are reassuring.

An important assumption made here is that rates of infection or hazards are independent of time from vaccination. However, the rate of infection is expected to depend on time from vaccination or on time from first infection. Studying the hazard as a function of time is crucial for understanding waning immunity and for the need for additional booster vaccinations. Follow-up is currently too short to answer time-dependent questions, but this is a crucial and required next step that can be answered using the national Israeli data in the future. The hazard may also depend on calendar time, not only via environmental exposure, but also because of new variants appearing, against which, the vaccine may have different efficacy. During the period over which the data were collected, the COVID-19 variant B.1.1.7 was by far the most prevalent variant, and accounted for most of the documented cases, hence the approximation of a constant hazard is justified. Yet, it is of great importance to repeat this study in other populations in order to estimate the efficacy for other variants and vaccines.

This study suggests that both the BNT162b2 vaccine and prior SARS-CoV-2 infection are effective against both subsequent SARS-CoV-2 infection and other COVID-19–related outcomes. Moreover, the effectiveness seems similar for both cohorts. This puts into question the need to vaccinate recent (up to six month) previously-infected individuals.

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Contributors

LF, YG, AH and MM were responsible for study design and for writing of the manuscript. RF, YG, MM, IN, YW, RY, and AZ analyzed the data. YW and AZ were responsible for collecting the data and for data management. LF, YG, AH and MM did the literature survey. LF, RF, YG, MM, and IN developed the mathematical model. YG and YW developed the software for analyzing the data. All authors interpreted the data and reviewed the draft and final versions of the manuscript.

Ethics statement

The study was approved by the Institutional Review Board of the Sheba Medical Center. Helsinki approval number: SMC-8228-21

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Competing interests statement

All authors declare no competing interests.

Data sharing

The data used in this study are sensitive and will not be made publicly available.

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Table 1: Population level data. Columns Male, Female, and Total are in thousands. Columns PCR tests, Positive tests, Hospitalized, Severe, and Death, are the counts during the period December 20, 2020 to March 20, 2021.

Age	Male	Female	Total	PCR	Positive	Hospitalization	Severe	Death
16-39	1,513	1,484	2,997	2,414,803	183,617	2,722	684	44
40-49	531	542	1,073	810,988	49,373	1,614	814	64
50-59	404	423	827	575,853	34,411	1,978	1,252	153
60-69	345	386	731	399,149	21,073	2,242	1,528	406
70-79	207	249	456	207,538	10,410	2,358	1,757	674
80+	106	161	267	197,916	7,828	3,105	2,428	1,386
Total	3,107	3,245	6,352	4,606,247	306,712	14,019	8,463	2,727

Table 2: Person-day event counts. Person-day counts and event counts for the different cohorts during the period December 20, 2020 to March 20, 2021. Person-day counts are in millions. PCR, Positive, Hospitalized, Severe, and Death, are the actual counts.

Cohort	Age	Person Days	PCR	Positive	Hospitalization	Severe	Death
0	16-39	170.5	1,609,352	156,104	2,413	602	38
0	40-49	49.4	449,371	37,075	1,331	683	56
0	50-59	31.3	268,892	23,383	1,541	1,011	122
0	60-69	20.5	143,320	12,130	1,528	1,051	261
0	70-79	9.7	70,430	5,483	1,455	1,116	431
0	80+	7.1	64,035	3,908	1,789	1,425	841
1A	16-39	27.3	287,539	19,707	231	63	5
1A	40-49	11.4	107,441	7,619	201	99	6
1A	50-59	9.6	85,134	6,355	290	165	17
1A	60-69	8.8	61,433	4,638	400	269	74
1A	70-79	6.5	30,853	2,247	418	304	113
1A	80+	3.6	32,731	1,759	643	490	262
1B	16-39	25.5	265,444	6,185	54	11	1
1B	40-49	11.2	103,730	3,651	52	20	2
1B	50-59	9.6	84,936	3,655	96	52	11
1B	60-69	9.0	64,055	3,238	240	160	52
1B	70-79	6.7	32,475	1,904	339	244	94
1B	80+	3.7	32,244	1,440	467	363	204
2	16-39	32.9	224,106	1,002	12	2	0
2	40-49	21.7	142,540	903	26	12	0
2	50-59	22.5	130,718	931	44	21	3
2	60-69	27.0	126,381	1,030	69	45	19
2	70-79	21.3	72,091	764	140	92	36
2	80+	11.4	67,345	707	202	147	78
Recovered	16-39	9.0	28,362	619	12	6	0

Recovered	40-49	2.4	7,906	125	4	0	0
Recovered	50-59	1.8	6,173	87	7	3	0
Recovered	60-69	1.1	3,960	37	5	3	0
Recovered	70-79	0.5	1,689	12	6	1	0
Recovered	80+	0.2	1,561	14	4	3	1

Table 3: PCR tests per million person days.

Cohort	16-39	40-49	50-59	60-69	70-79	80+
0	9,439	9,097	8,591	6,991	7,261	9,019
1A	10,533	9,425	8,868	6,981	4,747	9,092
1B	10,410	9,262	8,848	7,117	4,847	8,715
2	6,812	6,569	5,810	4,681	3,385	5,908
Recovered	3,151	3,294	3,429	3,600	3,378	7,805

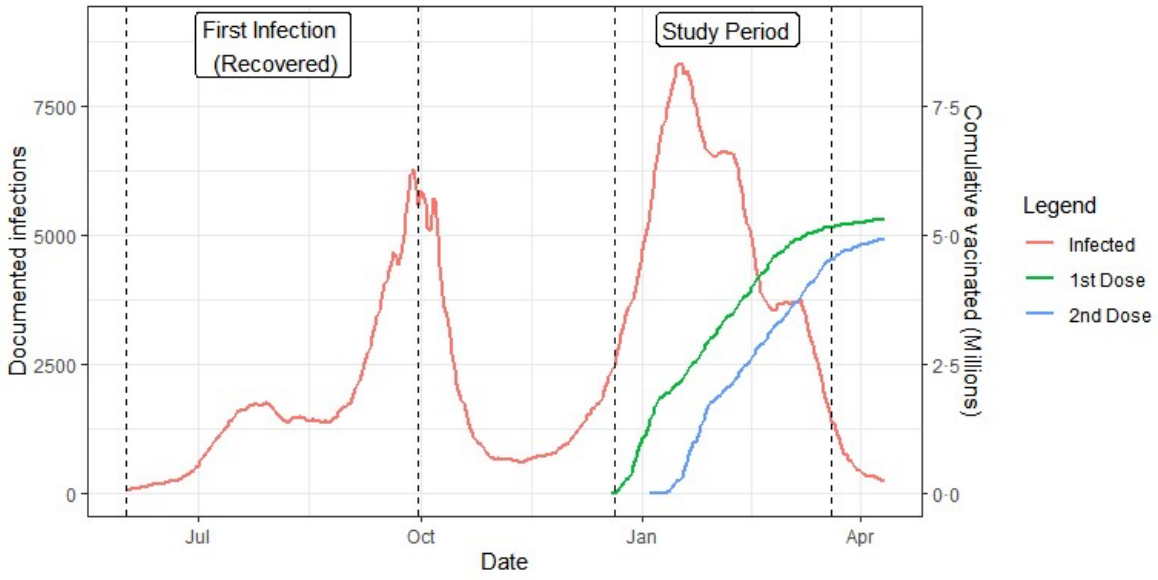
Table 4: Vaccination efficacy. Vaccination efficacy for the different age groups adjusted for sex, municipality risk, and past PCR. The overall estimates are based on models without cohort-age interaction. Estimates are not provided for Severe and Death outcomes for the lowest age groups due to very low case numbers in the vaccinated cohorts.

Age	Positive	Hospitalized	Severe	Death
16-39	95·1% [94·8, 95·4]	96·5% [93·8, 98·0]	—	—
40-49	92·5% [92·0, 93·0]	94·4% [91·7, 96·2]	—	—
50-59	92·7% [92·2, 93·1]	95·0% [93·3, 96·3]	—	—
60-69	92·4% [91·9, 92·9]	96·1% [95·1, 97·0]	96·4% [95·1, 97·3]	94·0% [90·4, 96·2]
70-79	92·2% [91·6, 92·8]	94·8% [93·8, 95·6]	95·5% [94·5, 96·4]	95·4% [93·5, 96·7]
80+	85·6% [84·3, 86·7]	91·2% [89·8, 92·4]	91·9% [90·4, 93·2]	92·6% [90·6, 94·1]
Overall	92·8% [92·6, 93·0]	94·2% [93·6, 94·7]	94·4% [93·6, 95·0]	93·7% [92·5, 94·7]

Table 5: Protection of prior SARS-CoV-2 infection. Protection of prior SARS-CoV-2 infection for the different age groups adjusted for sex, municipality risk, and past PCR. The overall estimates are based on models without cohort-age interaction. Estimates are not provided for Severe outcomes for the lowest age groups and for Death for all age groups due to very low case numbers in the previously-infected cohorts.

Age	Positive	Hospitalized	Severe
16-39	94·5% [94·1, 94·9]	92·8% [87·3, 95·9]	—
40-49	95·1% [94·2, 95·9]	95·4% [87·7, 98·3]	—
50-59	95·2% [94·1, 96·1]	93·9% [87·1, 97·1]	—
60-69	96·1% [94·6, 97·2]	95·7% [89·6, 98·2]	96·1% [87·8, 98·7]
70-79	97·0% [94·7, 98·3]	94·1% [86·8, 97·3]	98·7% [90·5, 99·8]
80+	91·4% [85·5, 94·9]	94·2% [84·5, 97·8]	94·2% [81·9, 98·1]
Overall	94·8% [94·4, 95·1]	94·1% [91·9, 95·7]	96·4% [92·5, 98·3]

Figure 1: Population dynamics. Documented new infections and cumulative vaccinated persons by date. The study period and the infection period of the recovered cohorts are marked by vertical lines.



Web Appendix: The Statistical Model

We define the efficacy of the vaccine in terms of hazard ratios. We use the following constant hazard models to describe the dynamics of an uninfected individual risk over time (calendar time and time from vaccination), where, in the most general model, each cohort has different coefficients:

$$h_i(x) = \exp\{\alpha_i + \beta_i^T x\} \quad i = 0,\ 1A,\ 1B,\ 2,\ \text{Recovered}.$$

Here x indicates a set of risk factors of an individual, including time dependent variables (municipality risk). While the model above is quite general, enabling different coefficients for the different cohorts, our basic model restricts the coefficients of sex, past PCR tests and municipality risk to be equal among the cohorts. Specifically, let

$$\beta_i^T x = \beta_{i,age} \times \text{Age} + \beta_{i,sex} \times \text{Sex} + \beta_{i,ppcr} \times \text{Past PCR} + \beta_{i,risk} \times \text{Municipal risk},$$

We assume that for $i = 0,\ 1A,\ 1B,\ 2,\ \text{Recovered},$

$$\beta_{i,sex} = \beta_{sex},\ \ \beta_{i,ppcr} = \beta_{ppcr},\ \ \text{and}\ \ \beta_{i,risk} = \beta_{risk}.$$

Thus, the effect of sex, past PCR test, and municipal risk on efficacy is multiplicative and identical among cohorts. However, efficacy may vary between different age groups.

The constant hazard assumption implies underlying exponential event-free models for these cohorts, with time-dependent covariates. The analysis can be carried out by performing Poisson regression with offsets for each risk profile. Specifically, consider a group of individuals' days in Cohort i with a certain risk profile x_0 (here the profile also includes time-dependent covariates, so only days satisfying x_0 count). The response variable is 'case count' – the number of cases among these individuals' days, and the exposure is the sum of all at-risk days for individuals with cohort and risk-profile combination (i, x_0). Thus, the model implies

$$\frac{\text{E(case count} \mid x_0, \text{at-risk days)}}{\text{at-risk days}} = \exp\{\beta_i^T x_0\}.$$

In other words, the daily hazard for an event for an individual in Cohort i and risk profile x, denoted by $h_{i,x}$, is $e^{\beta_i^T x}$. The relative risk for Cohort $i = 2$ with risk profile x is defined as $h_{2,x}/h_{0,x}$, and the efficacy is defined as $1 - h_{2,x}/h_{0,x}$. Under the assumption of equal coefficients for sex, past PCR tests and municipality risk, the relative efficacy depends only on the age group.

Technically, in order to estimate the coefficients in the model, we create a working dataset as follows. For each combination of cohort, age group, sex, municipality risk level, and individualized risk level, we count the number of COVID-19 events and the number of at-risk days. Consider, for example, a 56-year-old male who lives in Tel Aviv, had 1 negative PCR test before December 20, 2020, received his first dose on January 1, 2021, and his second dose on January 23, 2020, and tested positive on February 8, 2021. Assume that the Tel Aviv risk level was category 1 during the period December 20, 2020 to January 20, 2021, category 2 from January 21, 2021 until the end of follow-up on February 8, 2021. This person contributes:

1. 11 days (Dec-20 to Dec-31) and 0 events to the group:
   cohort_0/50-60/male/mun_risk=1/past_pcr=1

2. 14 days (Jan-1 to Jan-14) and 0 events to the group:
   cohort_1A/50-60/male/mun_risk=1/past_pcr=1

3. 6 days (Jan-15 to Jan-20) and 0 events to the group:
   cohort_1B/50-60/male/mun_risk=1/past_pcr=1

4. 9 days (Jan-21 to Jan-29) and 0 events to the group:
   cohort_1B/50-60/male/mun_risk=2/past_pcr=1

5. 10 days (Jan-30 to Feb-8) and 1 event to the group:
   cohort_2/50-60/male/mun_risk=2/past_pcr=1

Figure S1: The dynamics of the cohort model. Solid arrows indicate possible transitions between cohorts. Dashed arrows indicate possible disease outcomes.

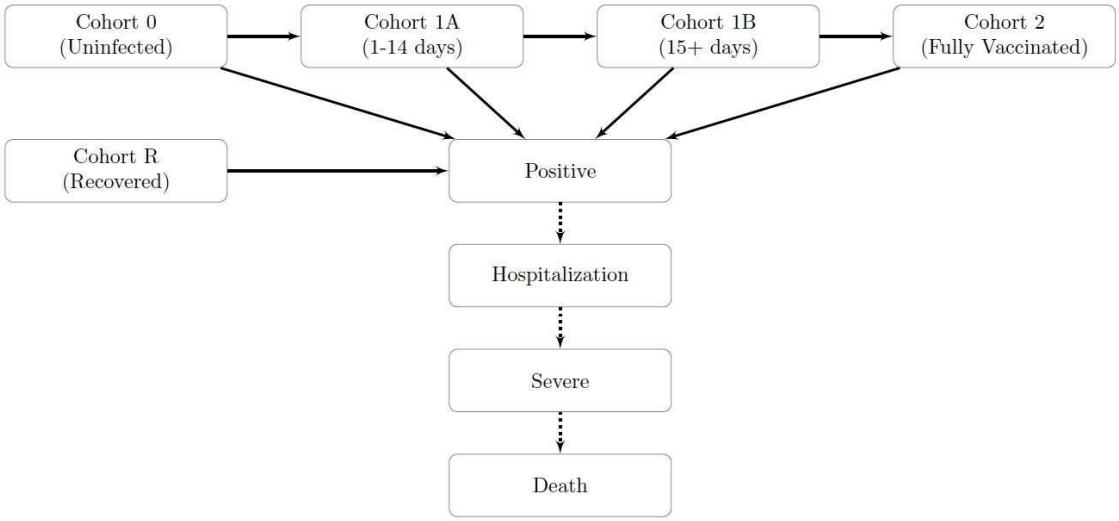


Figure S2: Length of follow-up for Cohort 2. Length of follow-up for Cohort 2 of the fully vaccinated, according to age group. Vaccination became available first to the 60+ age groups and then gradually to younger age groups as can be seen from the follow-up counts.

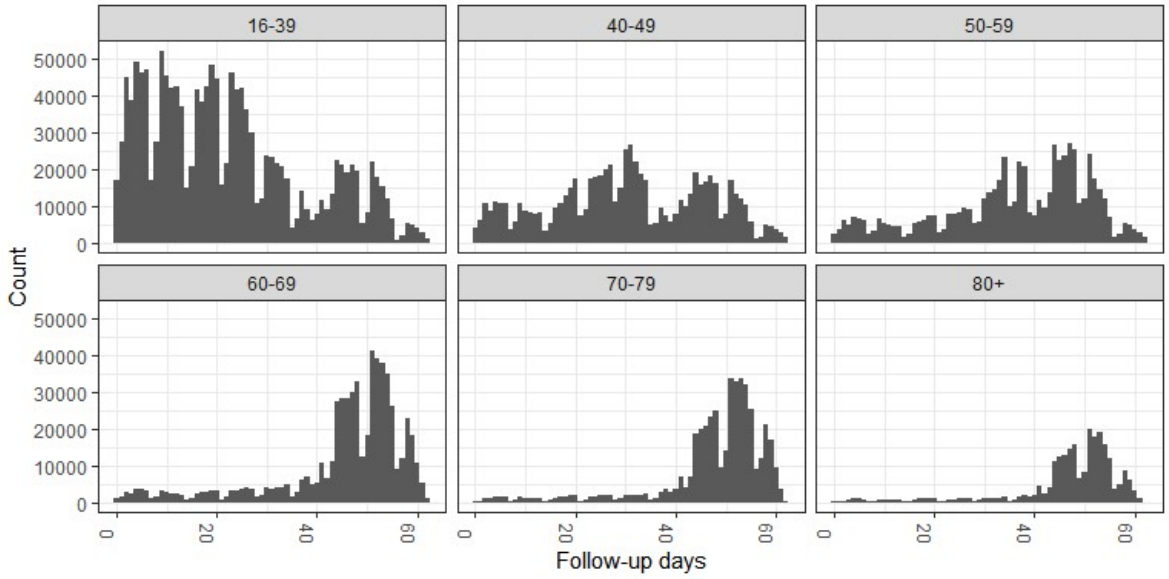


Figure S3: Length of follow-up for the Recovered Cohort. Length of follow-up from first positive PCR test for the Recovered Cohort, according to age group. This cohort included individuals that had a positive PCR test between June 1 and September 30, 2020. Note the sharp decrease in counts as a function of the follow-up. Note that each subfigure has a different scale.

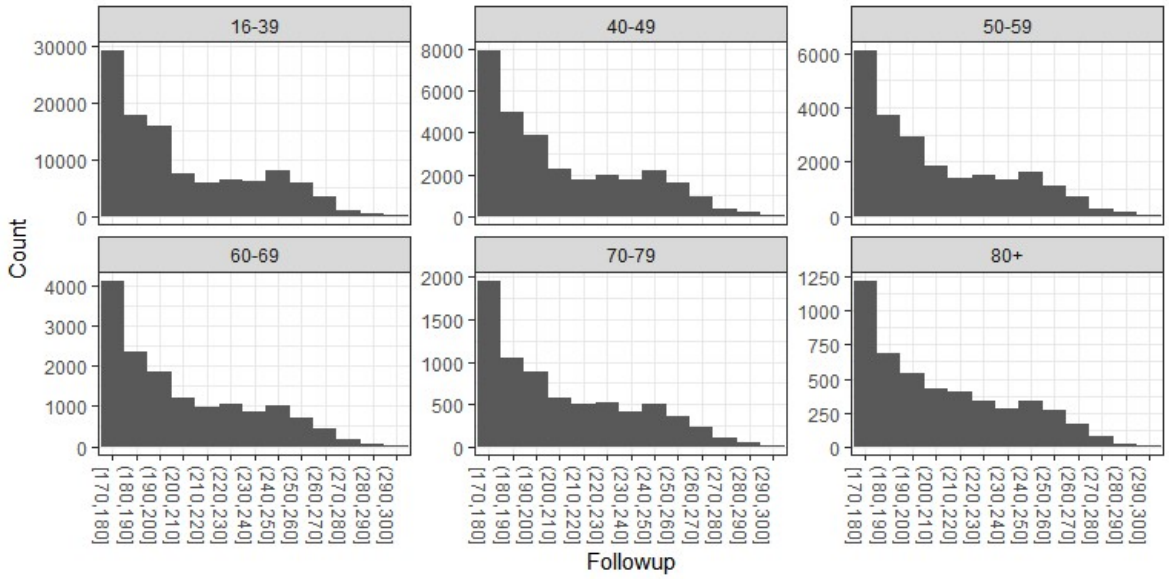


Figure S4: Vaccination by age. Percent of individuals vaccinated with the first and the second dose, by age group. The vaccination initiated in the 60+ age group. See text for details.

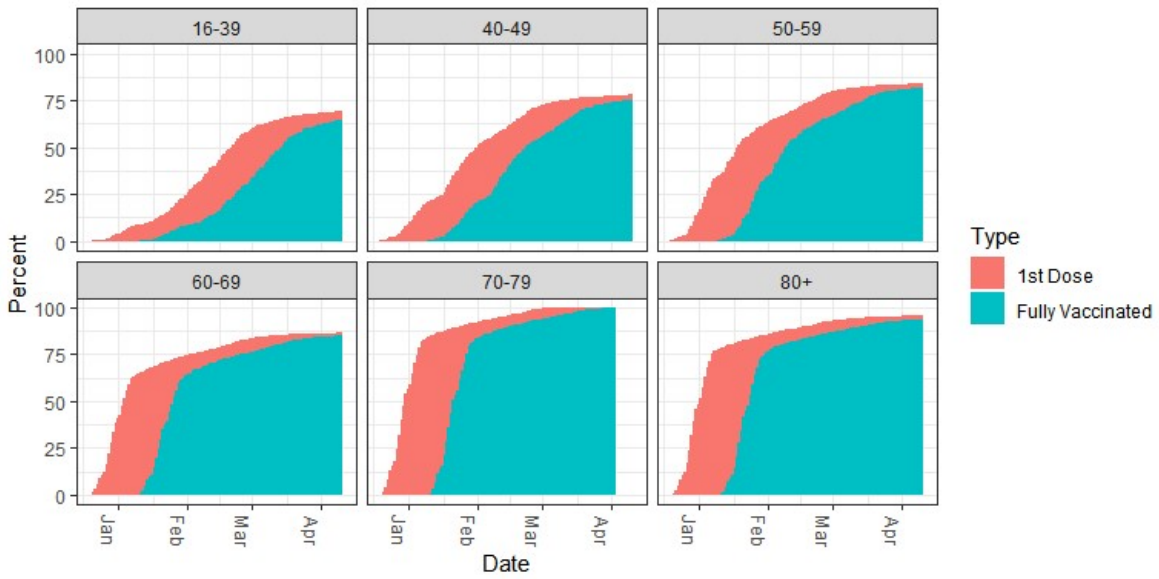


Figure S5: Vaccination by municipality risk. Percent of individuals vaccinated with the first and the second dose, by municipality risk group. The municipality risk was calculated as the median of the daily risk over the research period . Note that there is a negative correlation between vaccine coverage and risk group.

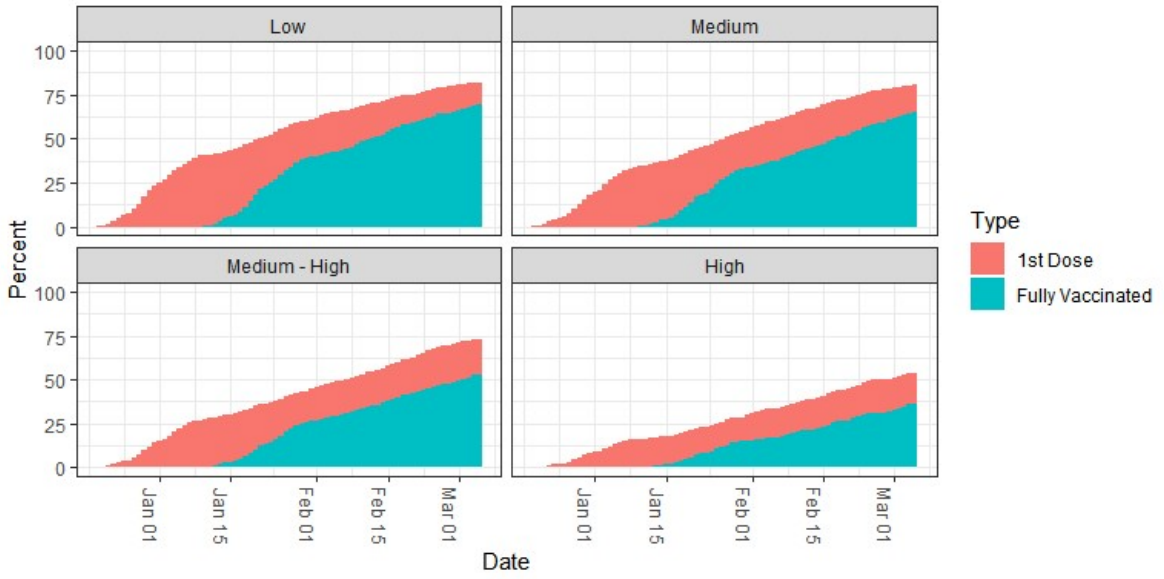


Figure S6: Events over time. Cases per 100,000, smoothed using seven-day moving average for the different age groups and the outcomes: PCR tests, documented infection cases, hospitalized cases, severe cases, and deaths.

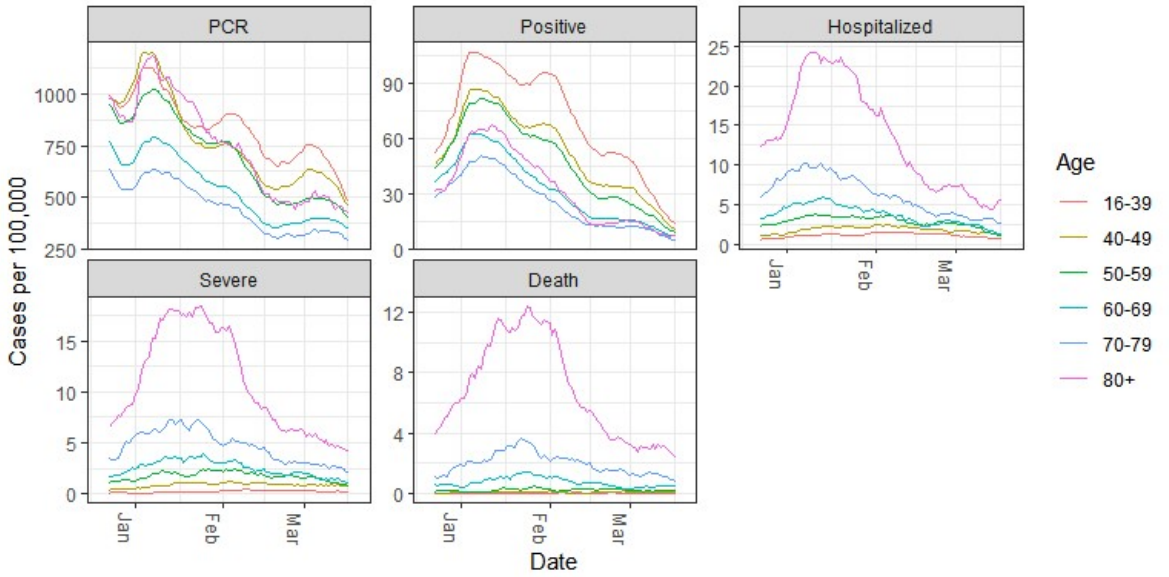


Table S1: Sensitivity analysis of past PCR on prior SARS-CoV-2 infection. Protection of prior SARS-CoV-2 infection for the different age groups. The model was fitted when the number of PCR clusters is assigned to be 0, 1, 2+, and omitted.

Analysis	Age	Positive	Hospitalized	Severe
PCR 0	16-39	91·9% [91·3, 92·6]	89·5% [81·5, 94·1]	—
PCR 0	40-49	92·8% [91·4, 93·9]	93·3% [82·0, 97·5]	—
PCR 0	50-59	92·9% [91·3, 94·3]	91·0% [81·2, 95·7]	—
PCR 0	60-69	94·2% [92·1, 95·8]	93·7% [84·8, 97·4]	94·6% [83·2, 98·3]
PCR 0	70-79	95·6% [92·2, 97·5]	91·4% [80·7, 96·1]	98·2% [86·9, 99·7]
PCR 0	80+	87·4% [78·7, 92·5]	91·6% [77·5, 96·8]	92·0% [75·1, 97·4]
PCR 1	16-39	94·5% [94·1, 94·9]	92·8% [87·3, 95·9]	—
PCR 1	40-49	95·1% [94·2, 95·9]	95·4% [87·7, 98·3]	—
PCR 1	50-59	95·2% [94·1, 96·1]	93·9% [87·1, 97·1]	—
PCR 1	60-69	96·1% [94·6, 97·2]	95·7% [89·6, 98·2]	96·1% [87·8, 98·7]
PCR 1	70-79	97·0% [94·7, 98·3]	94·1% [86·8, 97·3]	98·7% [90·5, 99·8]
PCR 1	80+	91·4% [85·5, 94·9]	94·2% [84·5, 97·8]	94·2% [81·9, 98·1]
PCR 2+	16-39	95·7% [95·4, 96·1]	95·4% [91·8, 97·4]	—
PCR 2+	40-49	96·2% [95·5, 96·8]	97·0% [92·0, 98·9]	—
PCR 2+	50-59	96·3% [95·4, 97·0]	96·0% [91·7, 98·1]	—
PCR 2+	60-69	97·0% [95·8, 97·8]	97·2% [93·3, 98·8]	97·9% [93·3, 99·3]
PCR 2+	70-79	97·7% [95·9, 98·7]	96·2% [91·5, 98·3]	99·3% [94·8, 99·9]
PCR 2+	80+	93·3% [88·7, 96·1]	96·3% [90·0, 98·6]	96·8% [90·2, 99·0]
No PCR	16-39	93·4% [92·9, 93·9]	91·7% [85·3, 95·3]	—
No PCR	40-49	94·0% [92·8, 95·0]	94·5% [85·4, 98·0]	—
No PCR	50-59	94·0% [92·6, 95·2]	92·6% [84·5, 96·5]	—
No PCR	60-69	95·1% [93·2, 96·4]	94·7% [87·3, 97·8]	95·5% [86·1, 98·6]
No PCR	70-79	96·4% [93·6, 97·9]	93·2% [84·8, 96·9]	98·6% [89·8, 99·8]
No PCR	80+	90·5% [84·0, 94·4]	94·0% [84·1, 97·8]	94·5% [83·0, 98·2]

Table S2: Vaccination efficacy for Cohort 1A. Vaccination efficacy for Cohort 1A adjusted for sex, municipality risk, and past PCR. The overall estimates are based on models without cohort-age interaction. Estimates are not provided for Severe and Death outcomes for the lowest age groups due to very low case numbers in the vaccinated cohorts.

Age	Positive	Hospitalized	Severe	Death
16-39	17·7% [16·4, 18·9]	39·7% [31·0, 47·4]	—	—
40-49	17·6% [15·5, 19·6]	40·7% [31·2, 48·9]	—	—
50-59	18·6% [16·3, 20·9]	44·6% [37·2, 51·1]	—	—
60-69	22·4% [19·7, 25·0]	47·3% [41·2, 52·8]	49·2% [42·0, 55·6]	44·7% [28·3, 57·3]
70-79	44·0% [41·2, 46·7]	60·5% [55·9, 64·6]	62·9% [57·8, 67·3]	63·6% [55·2, 70·4]
80+	17·2% [12·4, 21·7]	32·6% [26·3, 38·5]	36·2% [29·2, 42·4]	40·3% [31·3, 48·1]
Overall	20·6% [19·7, 21·4]	45·7% [43·1, 48·2]	49·3% [45·7, 52·7]	48·5% [42·8, 53·7]

Table S3: Vaccination efficacy for Cohort 1B. Vaccination efficacy for Cohort 1B adjusted for sex, municipality risk, and past PCR. The overall estimates are based on models without cohort-age interaction. Estimates are not provided for Severe and Death outcomes for the lowest age groups due to very low case numbers in the vaccinated cohorts.

Age	Positive	Hospitalized	Severe	Death
16-39	67·3% [66·4, 68·1]	82·4% [77·0, 86·6]	—	—
40-49	55·1% [53·6, 56·6]	82·8% [77·3, 87·0]	—	—
50-59	50·3% [48·5, 52·0]	80·7% [76·3, 84·3]	—	—
60-69	48·6% [46·6, 50·6]	70·0% [65·6, 73·8]	71·4% [66·3, 75·8]	63·3% [50·5, 72·7]
70-79	56·2% [53·9, 58·5]	70·4% [66·6, 73·7]	72·6% [68·5, 76·1]	72·1% [65·1, 77·7]
80+	36·6% [32·6, 40·3]	54·1% [49·2, 58·6]	55·8% [50·4, 60·6]	56·6% [49·3, 62·8]
Overall	57·7% [57·1, 58·4]	69·4% [67·5, 71·2]	65·9% [63·1, 68·5]	62·7% [58·0, 66·8]

Table S4: Model coefficients for the documented infection outcome.

term	estimate	std.error	statistic	p.value
Female	-9.760	0.030	-330.81	<0.001
Male	-9.847	0.030	-333.72	<0.001
Age 40-49	-0.104	0.006	-18.04	<0.001
Age 50-59	-0.118	0.007	-16.77	<0.001
Age 60-69	-0.270	0.009	-28.55	<0.001
Age 70-79	-0.309	0.014	-22.48	<0.001
Age 80+	-0.421	0.016	-25.91	<0.001
Municipal Risk 2	1.911	0.030	64.50	<0.001
Municipal Risk 4	3.490	0.030	118.21	<0.001
Municipal Risk 3	2.622	0.029	89.00	<0.001
Past PCR 1	0.388	0.004	91.55	<0.001
Past PCR 2+	0.639	0.005	132.02	<0.001
Age 16-39:Cohort 1A	-0.194	0.008	-25.61	<0.001
Age 40-49:Cohort 1A	-0.193	0.013	-15.36	<0.001
Age 50-59:Cohort 1A	-0.206	0.014	-14.56	<0.001
Age 60-69:Cohort 1A	-0.254	0.017	-14.69	<0.001
Age 70-79:Cohort 1A	-0.580	0.025	-23.16	<0.001
Age 80+:Cohort 1A	-0.188	0.029	-6.56	<0.001
Age 16-39:Cohort 1B	-1.117	0.013	-85.90	<0.001
Age 40-49:Cohort 1B	-0.802	0.017	-46.18	<0.001
Age 50-59:Cohort 1B	-0.699	0.018	-39.30	<0.001
Age 60-69:Cohort 1B	-0.666	0.020	-33.67	<0.001
Age 70-79:Cohort 1B	-0.826	0.027	-31.05	<0.001
Age 80+:Cohort 1B	-0.455	0.031	-14.75	<0.001
Age 16-39:Cohort 2	-3.014	0.032	-94.98	<0.001
Age 40-49:Cohort 2	-2.596	0.034	-77.00	<0.001
Age 50-59:Cohort 2	-2.612	0.033	-78.11	<0.001

Age 60-69:Cohort 2	-2.578	0.032	-79.42	<0.001
Age 70-79:Cohort 2	-2.551	0.039	-66.04	<0.001
Age 80+:Cohort 2	-1.935	0.041	-47.33	<0.001
Age 16-39:Cohort Recovered	-2.906	0.040	-71.98	<0.001
Age 40-49:Cohort Recovered	-3.016	0.090	-33.65	<0.001
Age 50-59:Cohort Recovered	-3.036	0.107	-28.25	<0.001
Age 60-69:Cohort Recovered	-3.243	0.165	-19.69	<0.001
Age 70-79:Cohort Recovered	-3.508	0.289	-12.14	<0.001
Age 80+:Cohort Recovered	-2.458	0.268	-9.18	<0.001

Table S5: Model coefficients for the hospitalization outcome.

term	estimate	std.error	statistic	p.value
Female	-13.605	0.114	-119.280	<0.001
Male	-13.469	0.114	-118.210	<0.001
Age 40-49	0.733	0.034	21.451	<0.001
Age 50-59	1.332	0.033	40.784	<0.001
Age 60-69	1.829	0.033	55.740	<0.001
Age 70-79	2.525	0.033	75.708	<0.001
Age 80+	2.940	0.032	92.933	<0.001
Municipal Risk 2	1.488	0.113	13.140	<0.001
Municipal Risk 4	2.902	0.113	25.636	<0.001
Municipal Risk 3	2.219	0.112	19.726	<0.001
Past PCR 1	0.377	0.021	18.111	<0.001
Past PCR 2+	0.815	0.021	38.294	<0.001
Age 16-39:Cohort 1A	-0.507	0.069	-7.349	<0.001
Age 40-49:Cohort 1A	-0.522	0.076	-6.901	<0.001
Age 50-59:Cohort 1A	-0.590	0.064	-9.219	<0.001
Age 60-69:Cohort 1A	-0.641	0.056	-11.402	<0.001
Age 70-79:Cohort 1A	-0.928	0.056	-16.705	<0.001
Age 80+:Cohort 1A	-0.395	0.046	-8.559	<0.001
Age 16-39:Cohort 1B	-1.740	0.138	-12.638	<0.001
Age 40-49:Cohort 1B	-1.760	0.141	-12.451	<0.001
Age 50-59:Cohort 1B	-1.645	0.105	-15.637	<0.001
Age 60-69:Cohort 1B	-1.204	0.069	-17.328	<0.001
Age 70-79:Cohort 1B	-1.216	0.060	-20.128	<0.001
Age 80+:Cohort 1B	-0.779	0.052	-14.943	<0.001
Age 16-39:Cohort 2	-3.353	0.289	-11.582	<0.001
Age 40-49:Cohort 2	-2.882	0.198	-14.546	<0.001
Age 50-59:Cohort 2	-3.005	0.153	-19.641	<0.001

Age 60-69:Cohort 2	-3.254	0.123	-26.432	<0.001
Age 70-79:Cohort 2	-2.949	0.089	-33.302	<0.001
Age 80+:Cohort 2	-2.425	0.074	-32.629	<0.001
Age 16-39:Cohort Recovered	-2.635	0.290	-9.093	<0.001
Age 40-49:Cohort Recovered	-3.074	0.501	-6.137	<0.001
Age 50-59:Cohort Recovered	-2.790	0.379	-7.359	<0.001
Age 60-69:Cohort Recovered	-3.138	0.448	-7.000	<0.001
Age 70-79:Cohort Recovered	-2.826	0.409	-6.903	<0.001
Age 80+:Cohort Recovered	-2.849	0.501	-5.689	<0.001

Table S6: Model coefficients for the severe disease outcome. Estimates are not provided for the lowest age groups due to very low event counts in the vaccinated cohorts.

term	estimate	std.error	statistic	p.value
Female	-12.258	0.177	-69.170	<0.001
Male	-11.829	0.177	-66.859	<0.001
Age 70-79	0.807	0.043	18.716	<0.001
Age 80+	1.261	0.041	30.411	<0.001
Municipal Risk 2	1.400	0.176	7.944	<0.001
Municipal Risk 4	2.902	0.176	16.445	<0.001
Municipal Risk 3	2.158	0.175	12.321	<0.001
Past PCR 1	0.321	0.035	9.285	<0.001
Past PCR 2+	0.929	0.032	29.362	<0.001
Age 60-69:Cohort 1A	-0.678	0.068	-9.914	<0.001
Age 70-79:Cohort 1A	-0.991	0.065	-15.281	<0.001
Age 80+:Cohort 1A	-0.449	0.053	-8.513	<0.001
Age 60-69:Cohort 1B	-1.253	0.085	-14.751	<0.001
Age 70-79:Cohort 1B	-1.293	0.071	-18.248	<0.001
Age 80+:Cohort 1B	-0.817	0.059	-13.808	<0.001
Age 60-69:Cohort 2	-3.313	0.152	-21.748	<0.001
Age 70-79:Cohort 2	-3.104	0.109	-28.587	<0.001
Age 80+:Cohort 2	-2.515	0.087	-28.962	<0.001
Age 60-69:Cohort Recovered	-3.237	0.579	-5.593	<0.001
Age 70-79:Cohort Recovered	-4.314	1.001	-4.311	<0.001
Age 80+:Cohort Recovered	-2.845	0.579	-4.918	<0.001

Table S7: Model coefficients for the death outcome. Estimates are not provided for the lowest age groups and the Recovered cohort due to very low event counts.

term	estimate	std.error	statistic	p.value
Female	-13.685	0.259	-52.938	<0.001
Male	-13.096	0.258	-50.798	<0.001
Age 70-79	1.227	0.079	15.612	<0.001
Age 80+	2.072	0.072	28.798	<0.001
Municipal Risk 2	1.284	0.253	5.066	<0.001
Municipal Risk 4	2.760	0.254	10.864	<0.001
Municipal Risk 3	2.023	0.252	8.038	<0.001
Past PCR 1	0.393	0.055	7.198	<0.001
Past PCR 2+	1.202	0.046	25.975	<0.001
Age 60-69:Cohort 1A	-0.592	0.132	-4.489	<0.001
Age 70-79:Cohort 1A	-1.010	0.106	-9.534	<0.001
Age 80+:Cohort 1A	-0.515	0.071	-7.218	<0.001
Age 60-69:Cohort 1B	-1.002	0.152	-6.593	<0.001
Age 70-79:Cohort 1B	-1.277	0.114	-11.191	<0.001
Age 80+:Cohort 1B	-0.834	0.079	-10.606	<0.001
Age 60-69:Cohort 2	-2.811	0.238	-11.823	<0.001
Age 70-79:Cohort 2	-3.081	0.174	-17.743	<0.001
Age 80+:Cohort 2	-2.599	0.119	-21.889	<0.001

TAB 30

See Tab 27 at Pg. 39

TAB 31

Necessity of COVID-19 vaccination in previously infected individuals

Nabin K. Shrestha,[1] Patrick C. Burke,[2] Amy S. Nowacki,[3] Paul Terpeluk,[4] Steven M. Gordon[1]

From the Departments of [1]Infectious Diseases, [2]Infection Prevention, [3]Quantitative Health Sciences, and [4]Occupational Health, Cleveland Clinic, Cleveland, Ohio.

Keywords: SARS-CoV-2; COVID-19; Incidence; Vaccines; Immunity;

Running Title: COVID-19 vaccination if already infected

Corresponding author:

Nabin K. Shrestha, MD, MPH

9500 Euclid Avenue / G-21

Cleveland, OH 44195

Phone: 216-636-1873 / Fax: 216-445-9446 / Email: shrestn@ccf.org

Summary: Cumulative incidence of COVID-19 was examined among 52238 employees in an American healthcare system. COVID-19 did not occur in anyone over the five months of the study among 2579 individuals previously infected with COVID-19, including 1359 who did not take the vaccine.

ABSTRACT

Background. The purpose of this study was to evaluate the necessity of COVID-19 vaccination in persons previously infected with SARS-CoV-2.

Methods. Employees of the Cleveland Clinic Health System working in Ohio on Dec 16, 2020, the day COVID-19 vaccination was started, were included. Any subject who tested positive for SARS-CoV-2 at least 42 days earlier was considered previously infected. One was considered vaccinated 14 days after receipt of the second dose of a SARS-CoV-2 mRNA vaccine. The cumulative incidence of SARS-CoV-2 infection over the next five months, among previously infected subjects who received the vaccine, was compared with those of previously infected subjects who remained unvaccinated, previously uninfected subjects who received the vaccine, and previously uninfected subjects who remained unvaccinated.

Results. Among the 52238 included employees, 1359 (53%) of 2579 previously infected subjects remained unvaccinated, compared with 22777 (41%) of 49659 not previously infected. The cumulative incidence of SARS-CoV-2 infection remained almost zero among previously infected unvaccinated subjects, previously infected subjects who were vaccinated, and previously uninfected subjects who were vaccinated, compared with a steady increase in cumulative incidence among previously uninfected subjects who remained unvaccinated. Not one of the 1359 previously infected subjects who remained unvaccinated had a SARS-CoV-2 infection over the duration of the study. In a Cox proportional hazards regression model, after adjusting for the phase of the epidemic, vaccination was associated with a significantly lower risk of SARS-CoV-2 infection among those not previously infected (HR 0.031, 95% CI 0.015 to 0.061) but not among those previously infected (HR 0.313, 95% CI 0 to Infinity).

Conclusions. Individuals who have had SARS-CoV-2 infection are unlikely to benefit from COVID-19 vaccination, and vaccines can be safely prioritized to those who have not been infected before.

INTRODUCTION

The two FDA-approved (BNT162b2 mRNA [Pfizer-BioNTech] and mRNA-1273 [Moderna]) mRNA vaccines have been shown to be very efficacious in protecting against Severe Acute Respiratory Syndrome (SARS) – associated Coronavirus-2 (SARS-CoV-2) infection [1,2]. The effectiveness of the Pfizer-BioNTech vaccine in a real-world setting has also been shown to be comparable to the efficacy demonstrated in clinical trials [3,4]. Given these, there has been an understandable desire to vaccinate as many people as possible.

The ability to vaccinate a large part of the population is limited by the supply of vaccine. As of March 21, 2021, 78% of 447 million doses of the coronavirus disease 2019 (COVID-19) vaccines that had been deployed had gone to only ten countries [5]. The COVAX initiative was borne out of the recognition that equitable distribution of vaccines worldwide was essential for effective control of the COVID-19 pandemic. However, the reality is that there is great disparity in the availability of vaccines across countries. Countries with limited supplies of vaccine have to prioritize how their supply of vaccines will be allocated within their populations. Criteria used for such prioritization have included profession, age, and comorbid conditions. Data that inform prioritization criteria with help maximize the benefits of whatever vaccine is available.

Observational studies have found very low rates of reinfection among individuals with prior SARS-CoV-2 infection [6–8]. This brings up the question about whether it is necessary to vaccinate previously infected individuals. These studies notwithstanding, there remains a theoretical possibility that the vaccine may still provide some benefit in previously infected persons. A prior large observational study concluded that immunity from natural infection cannot be relied on to provide adequate protection and advocated for vaccination of previously infected individuals [9]. The CDC website recommends that persons previously infected with SARS-CoV-2 still get the vaccine [10]. Despite these recommendations, credible reports of previously infected persons getting COVID-19 are rare. The rationale often provided for getting the COVID-19 vaccine is that it is safer to get vaccinated than to get the disease. This is

certainly true, but it is not an explanation for why people who have already had the disease need to be vaccinated. A strong case for vaccinating previously infected persons can be made if it can be shown that previously infected persons who are vaccinated have a lower incidence of COVID-19 than previously infected persons who did not receive the vaccine.

The purpose of this study was to attempt to do just that, and thereby evaluate the necessity of the COVID-19 vaccine in persons who were previously infected with SARS-CoV-2.

METHODS

Study design

This was a retrospective cohort study conducted at the Cleveland Clinic Health System in Ohio, USA. The study was approved by the Cleveland Clinic Institutional Review Board. A waiver of informed consent and waiver of HIPAA authorization were approved to allow access to personal health information by the research team, with the understanding that sharing or releasing identifiable data to anyone other than the study team was not permitted without additional IRB approval.

Setting

PCR testing for SARS-CoV-2 at Cleveland Clinic began on March 12, 2020, and a streamlined process dedicated to the testing of health care personnel (HCP) was begun shortly thereafter. All employees with a positive SARS-CoV-2 test were interviewed by Occupational Health, with date of onset of symptoms of COVID-19 being one of the questions asked. Vaccination for COVID-19 began at Cleveland Clinic on December 16, 2020. When initially started it was the Pfizer-BioNTech vaccine that was administered, until the Moderna vaccine became available, from which time employees received one or the other. All employees were scheduled to receive their second vaccine dose 28 days after the first one, regardless of which vaccine was given. The employee cohort was chosen for this study because of documentation of their COVID-19 vaccination and of any SARS-CoV-2 infection in the Occupational Health database.

Participants

All employees of the Cleveland Clinic Health System, working in Ohio, on Dec 16, 2020, were screened for inclusion in the study. Those who were in employment on December 16, 2020, were included.

Variables

SARS-CoV-2 infection was defined as a positive nucleic acid amplification test. The date of infection was taken to be the date of onset of symptoms when available, and the date of specimen collection when not. A person was considered vaccinated 14 days after receipt of the second dose of the vaccine (which would have been 42 days after receipt of the first dose of the vaccine for most subjects). For the sake of consistency in the duration assumed for development of natural and vaccine immunity, any person who tested positive for SARS-CoV-2 at least 42 days before the vaccine rollout date, was considered previously infected. Other covariates collected were age, job location, job type (patient-facing or non-patient facing), and job category. The job location variable could be one of the following: Cleveland Clinic Main Campus, regional hospital (within Ohio), ambulatory center, administrative center, or remote location. The job category was one of the following: professional staff, residents/fellows, advance practice practitioners, nursing, pharmacy, clinical support, research, administration, and administration support.

Outcome

The study outcome was time to SARS-CoV-2 infection, the latter defined as a positive nucleic acid amplification test for SARS-CoV-2 on or after December 16, 2020. Time to SARS-CoV-2 infection was calculated as number of days from December 16, 2020 (vaccine rollout date) to SARS-CoV-2 infection. Employees that had not developed a SARS-CoV-2 infection were censored at the end of the study follow-up period (May 15, 2021). Those who received the Johnson & Johnson vaccine (81 subjects) without having had a SARS-CoV-2 infection were censored on the day of receipt of the vaccine, and those whose employment was terminated during the study period before they had SARS-CoV-2 infection (2245 subjects) were censored on the date of termination of employment. The health system never had a requirement for asymptomatic employee test screening. Most of the positive tests, therefore, would have

been tests done to evaluate suspicious symptoms. A small proportion would have been tests done as part of pre-operative or pre-procedural screening.

Statistical analysis

A Simon-Makuch hazard plot [11] was created to compare the cumulative incidence of SARS-CoV-2 infection among previously infected subjects who were vaccinated, with those of previously infected subjects who remained unvaccinated, previously uninfected subjects who were vaccinated, and previously uninfected subjects who remained unvaccinated. Previous infection was treated as a time-independent covariate (SARS-CoV-2 infection at least 42 days before Dec 16, 2020), and vaccination (14 days after receipt of the second dose of the vaccine) was treated as a time-dependent covariate (Figure 1). Curves for the unvaccinated were based on data for those who did not receive the vaccine over the duration of the study, and for those who did until the date they were considered vaccinated, from which point onwards their data were recorded into the corresponding vaccinated set. A Cox proportional hazards regression model was fitted with time to SARS-CoV-2 infection as the outcome variable against vaccination (as a time-dependent covariate whose value changed on the date a subject was considered vaccinated)[12]. Previous infection (as a time-independent covariate) and an interaction term for previous infection and vaccination were included as covariates. The phase of the epidemic was adjusted for by including the slope of the epidemic curve as a time-dependent covariate whose value changed continuously with the slope of the epidemic curve. The analysis was performed by NKS and ASN using the *survival* package and R version 4.0.5 [12–14].

RESULTS

Of 52238 employees included in the study, 2579 (5%) were previously infected with SARS-CoV-2.

Baseline characteristics

Those previously infected with SARS-CoV-2 were significantly younger (mean ± SD age; 39 ± 13 vs. 42 ± 13, $p<0.001$), and included a significantly higher proportion with patient-facing jobs (65% vs. 51%, $p<0.001$). Table 1 shows the characteristics of subjects grouped by whether or not they were previously infected. A significantly lower proportion of those previously infected (47%, 1220 subjects) were vaccinated by the end of the study compared to 59% (29461) of those not previously infected ($p<0.001$). Of those vaccinated, 63% received the Moderna vaccine. Twelve percent of subjects with previous SARS-CoV-2 infection did not have a symptom onset date, suggesting they may possibly have been identified on pre-operative or pre-procedural screening, and may not have had symptomatic infection. When vaccination was begun, the epidemic in Ohio was at the peak of its third wave (Figure 2).

Cumulative incidence of COVID-19

Figure 3 is a Simon-Makuch plot showing that SARS-CoV-2 infections occurred almost exclusively in subjects who were not previously infected with SARS-CoV-2 and who remained unvaccinated. The cumulative incidence of SARS-CoV-2 infection among previously infected unvaccinated subjects did not differ from that of previously infected subjects who were vaccinated, and that of previously uninfected subjects who were vaccinated. For all three of these groups, the cumulative incidence of SARS-CoV-2 infection was much lower than that of subjects who were not previously infected and who remained unvaccinated. Of the 2154 SARS-CoV-2 infections during the study period, 2139 (99.3%) occurred among those not previously infected who remained unvaccinated or were waiting

to get vaccinated, and15 (0.7%) occurred among those not previously infected who were vaccinated. Not one of the 2579 previously infected subjects had a SARS-CoV-2 infection, including 1359 who remained unvaccinated throughout the duration of the study.

Association of vaccination with occurrence of COVID-19

In a Cox proportional hazards regression model, after adjusting for the phase of the epidemic, vaccination was associated with a significantly lower risk of SARS-CoV-2 infection among those not previously infected (HR 0.031, 95% CI 0.015 – 0.061) but not among those previously infected (HR 0.313, 95% CI 0 – Infinity). The absence of events among those who were previously infected, whether they received the vaccine or not, precluded accurate or precise estimates for the latter effect size.

Duration of protection

This study was not specifically designed to determine the duration of protection afforded by natural infection, but for the previously infected subjects the median duration since prior infection was 143 days (IQR 76 – 179 days), and no one had SARS-CoV-2 infection over the following five months, suggesting that SARS-CoV-2 infection may provide protection against reinfection for 10 months or longer.

DISCUSSION

This study shows that subjects previously infected with SARS-CoV-2 are unlikely to get COVID-19 reinfection whether or not they receive the vaccine. This finding calls into question the necessity to vaccinate those who have already had SARS-CoV-2 infection.

It is reasonable to expect that immunity acquired by natural infection provides effective protection against future infection with SARS-CoV-2. Observational studies have indeed found very low rates of reinfection over the following months among survivors of COVID-19 [6–8]. Reports of true reinfections are extremely rare in the absence of emergence of new variants. When such reinfections occur, it would be purely speculative to suggest that a vaccine might have prevented them. Duration of protective immunity from natural infection is not known. However, the same also can be said about duration of protective immunity from vaccination. Uncertainty about the duration of protective immunity afforded by natural infection is not by itself a valid argument for vaccinating previously infected individuals. This study provides direct evidence that vaccination with the best available vaccines does not provide additional protection in previously infected individuals.

A prior study concluded that natural infection cannot be relied on to protect against COVID-19 [9]. That study was based on comparison of PCR-positivity rates during a second COVID-19 surge in Denmark between those who tested positive and negative during the first COVID-19 surge, and indirectly calculated that prior infection provided 80.5% protection against repeat infection, and that protection against those older than 65 years was only 47.1%. The study did not compare vaccinated and unvaccinated people, and it is therefore an assumption to consider that a vaccine would have provided better protection in that particular population. Furthermore, there was a gap of only seven weeks between the end of the first surge and the beginning of the second in that study. It is now well-known that a small number of people can continue to have positive PCR test results for several weeks to a few months after infection, one study finding that 5.3% remained positive at 90 days [15]. It is possible that some of the positives picked up in the early part of the second surge were not necessarily new infections but residual

virus from the tail end of the first surge. Since the actual number of infections was small, a few such misclassifications could change the rates substantially. Our study examined rates of SARS-CoV-2 infection in vaccinated and unvaccinated individuals and showed that those previously infected who did not receive the vaccine did not have higher rates of SARS-CoV-2 infection than those previously infected who did, thereby providing direct evidence that vaccination does not add protection to those who were previously infected.

There are several strengths to our study. Its large sample size and follow-up of up to 5 months provide us with an ample degree of confidence in its findings. A major strength of our study is that we adjusted the analyses for the phase of the epidemic at all time points. The risk of acquisition of infection is strongly influenced by the phase of the epidemic at any given time, and it is important to adjust for this for accurate risk analyses. Given that was this a study among employees of a health system, and that the health system had policies and procedures in recognition of the critical importance of keeping track of the pandemic among its employees, we had an accurate accounting of who had COVID-19, when they were diagnosed with COVID-19, who received a COVID-19 vaccine, and when they received it.

The study has its limitations. Because we did not have a policy of asymptomatic employee screening, previously infected subjects who remained asymptomatic might have been misclassified as previously uninfected. Given this limitation, one should be cautious about drawing conclusions about the protective effect of prior asymptomatic SARS-CoV-2 infection. It should be noted though, that 12% of the subjects classified as previously infected did not have a symptom onset date recorded, suggesting that at least some of those classified as previously infected might have been asymptomatic infections. It is reassuring that none of these possibly asymptomatically infected individuals developed COVID-19 during the duration of the study. The study follow-up duration was short, being only five months, but this was longer than published mRNA vaccine efficacy studies [1,2], and longer than the follow-up duration of the largest published vaccine effectiveness studies to date [3,4]. Median freedom from reinfection (time from initial infection until end of follow-up) in this study, for those previously infected, of almost 10 months, is consistent with findings in an earlier study that immunoglobulin G (IgG) to the spike protein remained

stable over more than six months after an episode of infection [16]. Our study included no children and few elderly subjects, and the majority would not have been immunosuppressed. Data governance policies in our institution precluded us from obtaining detailed clinical information on employees. While one cannot generalize this study's findings to assume that prior infection would provide adequate immunity in these groups, there is also no reason to expect a vaccine to provide additional protection in these same groups. Lastly, it is necessary to emphasize that these findings are based on the prevailing assortment of virus variants in the community during the study. It is not known how well these results will hold if or when some of the newer variants of concern become prominent. However, if prior infection does not afford protection against some of the newer variants of concern, there is little reason to suppose that the currently available vaccines would either. Vaccine breakthrough infections with variants have indeed been reported [17].

Our study's findings have important implications. Worldwide, COVID-19 vaccines are still in short supply. As of March 9, 2021, dozens of countries had not been able to administer a single dose of the vaccine [18]. As of May 17, 2021, only 17 countries had been able to reach ten percent or more of their populations with at least the first dose of vaccine [19]. Given such a scarcity of the vaccine, and the knowledge that vaccine does not provide additional protection to those previously infected, it would make most sense to limit vaccine administration to those who have not previously had the infection. In addition to profession, age, and comorbid conditions, previous infection should be an important consideration in deciding whom to prioritize to receive the vaccine. A practical and useful message would be to consider symptomatic COVID-19 to be as good as having received a vaccine, and that people who have had COVID-19 confirmed by a reliable laboratory test do not need the vaccine.

In conclusion, individuals who have laboratory-confirmed symptomatic SARS-CoV-2 infection are unlikely to benefit from COVID-19 vaccination, and vaccines can be safely prioritized to those who have not been infected before.

TRANSPARENCY DECLARATION

Conflict of Interest

Selection of "no competing interests" reflects that all authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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None received.

Author contributions

NKS: Conceptualization, Methodology, Validation, Investigation, Data curation, Software, Formal analysis, Visualization, Writing- Original draft preparation, Writing- Reviewing and Editing, Supervision, Project administration.

ASN: Methodology, Formal analysis, Visualization, Validation, Writing- Reviewing and Editing.

PCB: Resources, Investigation, Validation, Writing- Reviewing and Editing.

PT: Resources, Writing- Reviewing and Editing.

SMG: Project administration, Resources, Writing- Reviewing and Editing.

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TABLES

Table 1. Study Subject Characteristics

Characteristic	Previously Infected (N = 2579)	Not Previously Infected (N = 49659)	*P* Value
Age, y, mean ± SD	39±13	42±13	<0.001
Patient-facing job	1676 (65)	25504 (51)	<0.001
Job location			<0.001
Cleveland Clinic Main Campus	1011 (39)	19595 (40)	
Regional hospitals	1096 (43)	16433 (33)	
Ambulatory centers	313 (12)	7767 (16)	
Administrative centers	138 (5)	4424 (9)	
Remote location	21 (<1)	1440 (3)	
Job category			<0.001
Professional staff	89 (4)	3775 (8)	
Residents and fellows	72 (3)	1669 (3)	
Advanced practice practitioners	154 (6)	2806 (6)	
Nursing	1142 (44)	13623 (27)	
Pharmacy	44 (2)	1274 (3)	
Research	328 (13)	6776 (14)	
Clinical support	111 (4)	3500 (7)	
Administration	614 (24)	15050(30)	
Administration support	25 (1)	1186 (2)	

Data are presented as no. (%) unless otherwise indicated

FIGURES

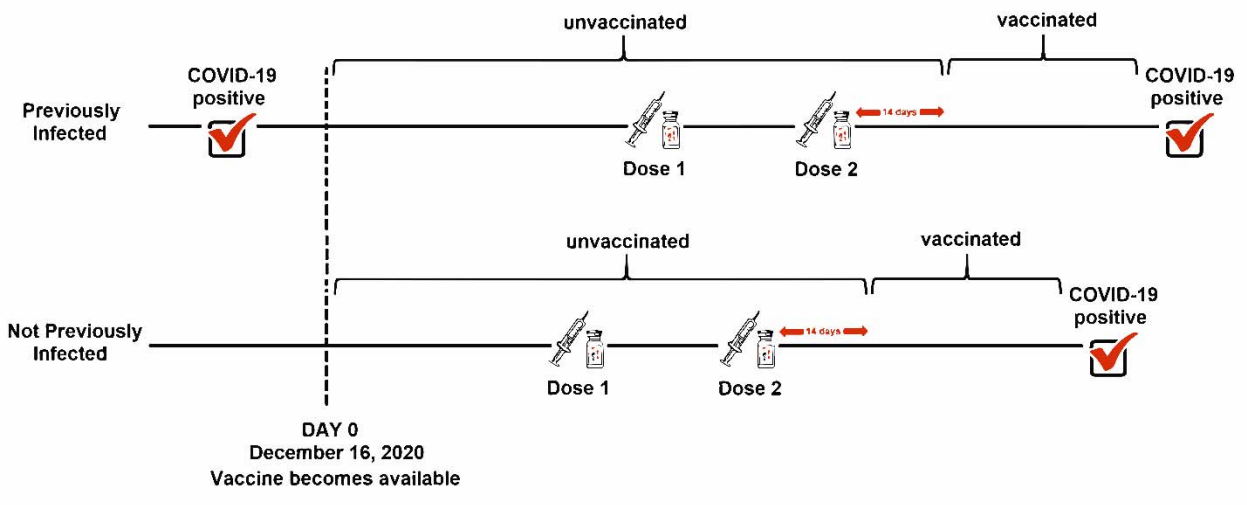

Figure 1. Explanation of "previously infected" analyzed as a time-independent covariate and "vaccinated" treated as a time-dependent covariate.

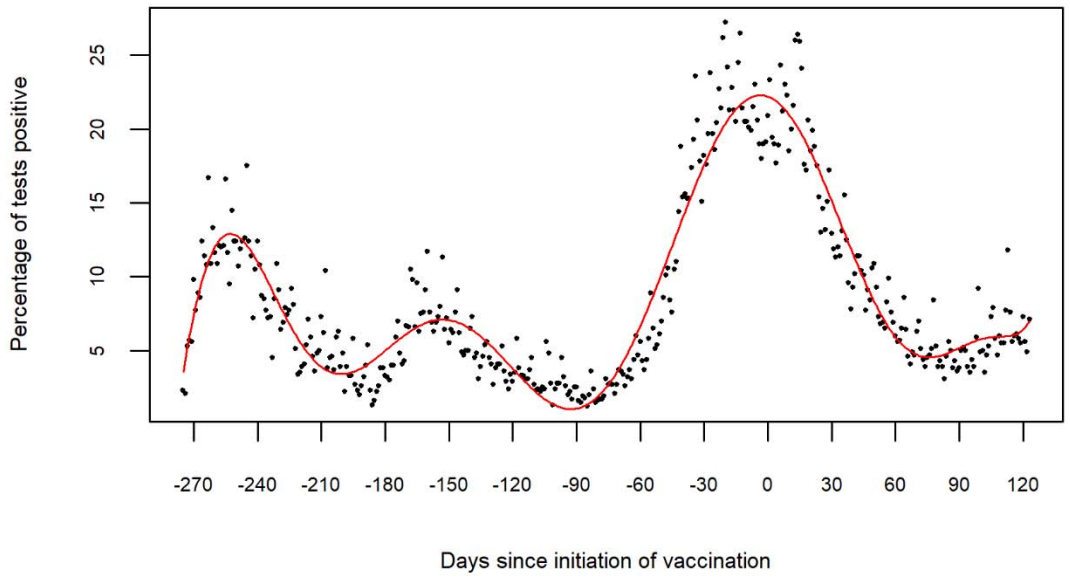

Figure 2. COVID-19 epidemic curve before and after vaccine rollout. Points on the scatter plot represent the proportion of all COVID-19 PCR tests done at Cleveland Clinic that were positive on any given day. The colored line represents a fitted polynomial curve.

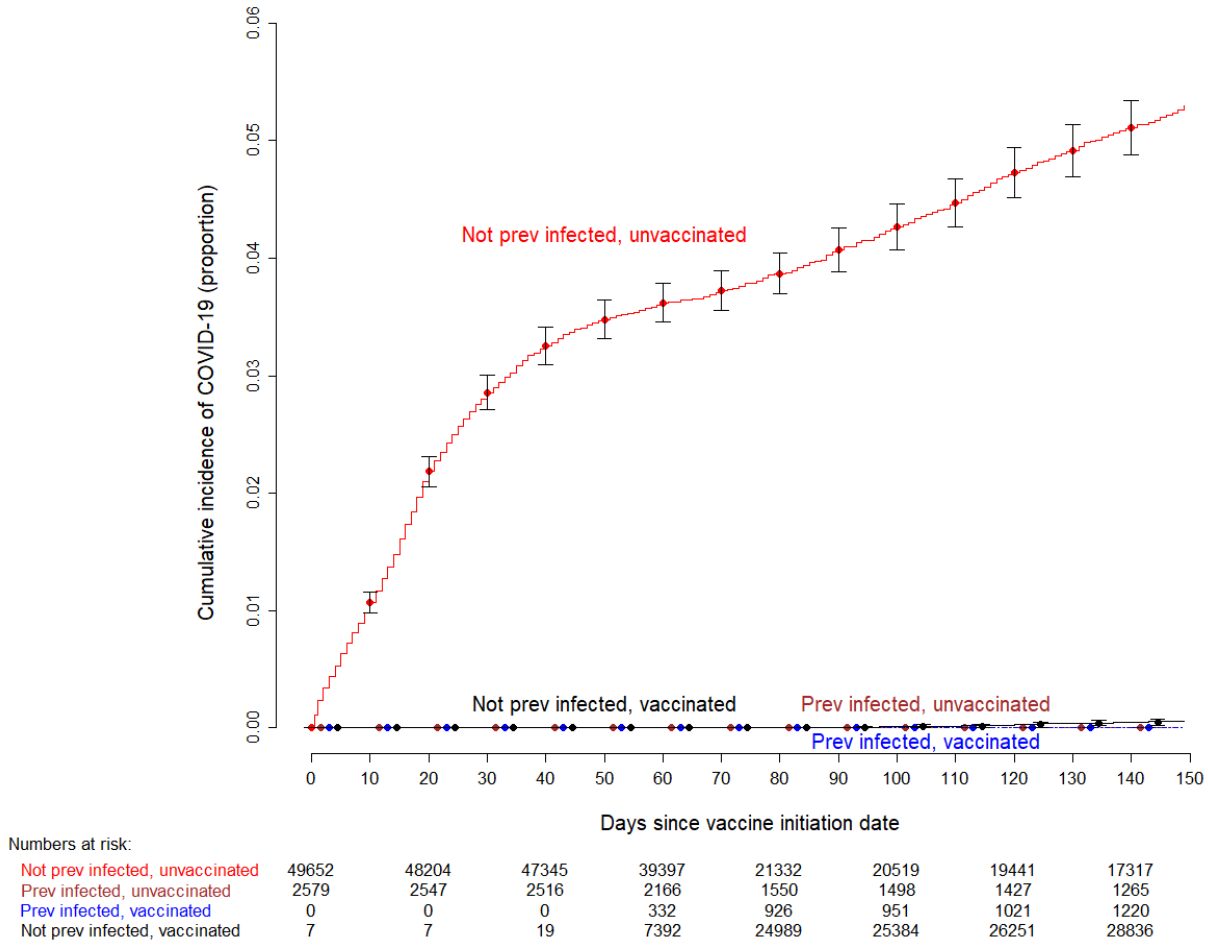

Figure 3. Simon-Makuch plot showing the cumulative incidence of COVID-19 among subjects previously infected and not previously infected with COVID-19, who did and did not receive the vaccine. Curves for the unvaccinated are based on data for those who did not receive the vaccine during the duration of the study, and for those waiting to receive the vaccine. Day zero was Dec 16, 2020, the day vaccination was started in our institution. Error bars represent 95% confidence intervals. Seven subjects who had been vaccinated earlier as participants in clinical trials were considered vaccinated throughout the duration of the study. Twelve subjects who received their first dose in the first week of the vaccination campaign managed to get their second dose three weeks later, and were thus considered vaccinated earlier than 42 days since the start of the vaccination campaign.

TAB 32

Effectiveness of BNT162b2 mRNA vaccine against infection and COVID-19 vaccine coverage in healthcare workers in England, multicentre prospective cohort study (the SIREN study)

Authors:

Hall V FFPH[1,2], Foulkes S MSc[1], Saei A PhD[1], Andrews N PhD[1,5], Oguti B[1,3], Charlett A PhD[1,4,5], Wellington E MSc[1], Stowe J PhD[1], Gillson N BA[1], Atti A MSc[1], Islam J PhD[1], Karagiannis I PhD[1], Munro K MSc[1], Khawam J BSc[1], The SIREN Study Group∞, Chand MA FRCPath[1,6], Brown CS FRCPath[1], Ramsay M FFPH[1,5], Lopez-Bernal J PhD[1], Hopkins S FRCPath[1,2*].

Corresponding author: PHE Colindale, 61 Colindale Avenue, London NW9 5EQ.*

susan.hopkins@phe.gov.uk

SIREN study group∞ contributors listed in attached file

Author affiliations:

1. Public Health England Colindale;
2. The National Institute for Health Research Health Protection Research (NIHR) Unit in Healthcare Associated Infections and Antimicrobial Resistance at the University of Oxford, Oxford, UK.
3. Oxford Vaccine Group, University of Oxford
4. NIHR Health Protection Research Unit in Behavioural Science and Evaluation at University of Bristol in partnership with Public Health England.
5. NIHR Health Protection Research Unit in Immunisation at the London School of Hygiene and Tropical Medicine in partnership with Public Health England.
6. St Guys and Thomas's Hospital NHS Trust

ABSTRACT

Background

BNT162b2 mRNA and ChAdOx1 nCOV-19 adenoviral vector vaccines have been rapidly rolled out in the UK. We determined the factors associated with vaccine coverage for both vaccines and documented the vaccine effectiveness of the BNT162b2 mRNA vaccine in our healthcare worker (HCW) cohort study of staff undergoing regular asymptomatic testing.

Methods

The SIREN study is a prospective cohort study among staff working in publicly funded hospitals. Baseline risk factors, vaccination status (from 8/12/2020-5/2/2021), and symptoms are recorded at 2 weekly intervals and all SARS-CoV-2 polymerase chain reaction (PCR) and antibody test results documented. A mixed effect proportional hazards frailty model using a Poisson distribution was used to calculate hazard ratios to compare time to infection in unvaccinated and vaccinated participants to estimate the impact of the BNT162b2 vaccine on all (asymptomatic and symptomatic) infection.

Findings

Vaccine coverage was 89% on 5/2/2021. Significantly lower coverage was associated with prior infection (aOR 0.59 95% confidence interval [CI] 0.54-0.64), female (aOR 0.72, 95% CI 0.63-0.82), aged under 35 years, being from minority ethnic groups (especially Black, aOR 0.26, 95% CI 0.21-0.32), porters/security guards (aOR 0.61, 95% CI 0.42-0.90),or midwife (aOR 0.74, 95% CI 0.57-0.97), and living in more deprived neighbourhoods (IMD 1 (most) vs. 5 (least) (aOR 0.75, 95% CI 0.65-0.87). A single dose of BNT162b2 vaccine demonstrated vaccine effectiveness of 72% (95% CI 58-86) 21 days after first dose and 86% (95% CI 76-97) seven days after two doses in the antibody negative cohort.

Conclusion

Our study demonstrates that the BNT162b2 vaccine effectively prevents both symptomatic and asymptomatic infection in working age adults; this cohort was vaccinated when the

dominant variant in circulation was B1.1.7 and demonstrates effectiveness against this variant.

Funding: Public Health England and the Department of Health and Social Care; NIHR

RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed and medRxiv for studies including “asymptomatic” and “symptomatic” SARS-CoV-2 results after vaccination. Only a single paper existed for ChAdOx1 which stated that it reduced all (symptomatic or asymptomatic) infection by 51.9% (95% CI 42.0-60.1%). Three studies from Israel demonstrated that those who attended symptomatic testing had reduced infections two weeks post vaccination; a single healthcare worker cohort study in Israel, demonstrated vaccine effectiveness of 75% (95% CI 72 – 84%) from 15 to 28 days following the first dose of the BNT162b2 vaccine to reduce symptomatic infection. No data on asymptomatic infection through routinely collected swabs asymptomatic testing was available for the BNT162b2 vaccine.

Added value of this study

This is a large established cohort study in HCWs that enables accurate measurement of asymptomatic and symptomatic infection rates in the vaccinated and unvaccinated population.

It measures the impact of a single dose of vaccine over the first 8-week period. We have estimated the vaccine effectiveness against all (symptomatic and asymptomatic) infection for the BNT162b2 vaccine to be at least 70% 21 days after the first dose, which increased to at least 85% seven days after the second dose.

It also highlights the vaccine coverage and uptake among hospital staff. Further engagement is required in groups that have not yet accepted the vaccine offer.

Implications of all the available evidence

We provide strong evidence that vaccinating working age adults will substantially reduce asymptomatic and symptomatic SARS-CoV-2 infection and therefore reduce transmission of infection in the population. However, it does not eliminate infection risk completely and

85 therefore personal protective equipment, non-pharmaceutical interventions and regular
86 asymptomatic testing will need to be continued until prevalence of SARS-CoV-2 is extremely
87 low to reduce the risk of transmission in healthcare settings.

INTRODUCTION

Since the World Health Organization (WHO) declared the emergence of Coronavirus Disease 2019 (COVID-19) a pandemic on 11 March 2020, over 2.4 million people have died around the world [1], including over 120,000 people in the United Kingdom (UK) [2]. There has been an unprecedented international effort by private and public institutions to develop a vaccine against its causative agent, the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2).[3] In less than a year, three COVID-19 vaccine candidates have been granted Emergency Use Authorization by the UK Medicines and Healthcare products Regulatory Agency (MHRA),[4] with several more in the development pipeline. The BNT162b2 mRNA (Pfizer-BioNTech) and ChAdOx1 nCoV-19 adenoviral (Oxford AstraZeneca COVID-19) vaccines, were approved on 2 December and 30 December 2020 respectively, based on interim analyses from phase 3 Randomized Controlled Trials (RCT)[6, 7],[5,6] and were deployed for use within seven days of authorisation.

Following advice from the Joint Committee on Vaccination and Immunisation (JCVI), the UK Government selected a vaccination strategy with the aim of rapidly reducing hospitalisations, severe outcomes and preventable deaths from COVID-19.[7] The initial phase targeted individuals at high-risk of severe COVID-19, such as care home residents and their carers, people aged 80 years and over, and frontline HCWs, recognising this group's particular high exposure and potential role in transmission. On 30 December, the JCVI published their recommendation to delay the 2nd dose of the deployed coronavirus vaccines by up to 12 weeks with the aim of optimising the public health impact of the vaccination campaign in the population by doubling the number of people who would receive the first dose.[8] By 19 February 2021, the UK had vaccinated more than 17.2 million people (25% of the population).[9] However, population-level vaccine effectiveness studies are needed to assess the impact of coronavirus vaccination in the real world and inform developments of the public health policy.

The SARS-CoV-2 Immunity and Reinfection Evaluation (SIREN) Study is a large, multi-centre prospective cohort study of HCWs and support staff in publicly funded (National Health Service (NHS) hospitals in the United Kingdom.[10] SIREN initially investigated the effect of prior infection on protection against re-infection and was amended to investigate COVID-19 vaccine effectiveness in January 2021.

In this study, we aimed to describe the factors associated with both BNT162b2 and ChAdOx1 nCoV-19 vaccine coverage and early vaccine effectiveness of BNT162b2 vaccine against all (asymptomatic and symptomatic) infection in this large-scale cohort of HCWs in England.

METHODS

Study design and setting

The SIREN study is a prospective cohort study among staff working in the publicly funded hospitals (NHS) across the UK. The SIREN protocol is described elsewhere.[11]

Participants

HCWs, support staff and administrative staff working at hospital sites participating in SIREN, who could provide informed consent and anticipated remaining engaged in follow-up for 12 months were eligible to join SIREN. Participants were excluded from this analysis if they enrolled after 7 December 2020, had no PCR tests after 7 December 2020, or had insufficient PCR and antibody data to complete cohort assignment.

Variables

The primary outcome variable for the vaccine coverage analysis was the binary 'ever vaccinated' variable. Participants were categorised as 'ever vaccinated' if they had at least one vaccine dose recorded from 8 December 2020 to 5 February 2021 from at least one of the two vaccination data sources available. Data on vaccination date, manufacturer and batch

number was available for each dose. Second doses were excluded if they preceded the first dose and marked as 'short interval' if they were less than 19 days after the first dose.

The primary outcome variable for the vaccine effectiveness analysis was a PCR confirmed SARS-CoV-2 infection. This was defined as a new PCR positive result during follow-up for the negative cohort and a reinfection during the follow-up in the positive cohort, irrespective of symptom status.[10] Participants were assigned into either the positive cohort (antibody positive or history of infection (prior antibody or PCR positive)) or the negative cohort (antibody negative with no prior positive test) at the beginning of the follow up period (7 December 2020).

Data sources and measurement

Vaccination data was obtained directly from participants completing the enrolment and follow-up questionnaires and from linkage on personal identifiable information (NHS number, surname, date of birth and postcode) to the National Immunisation Management System (NIMS), the registry of COVID-19 vaccination in England.

SIREN participants undergo fortnightly asymptomatic PCR testing (anterior nasal swabs or combined nose and oropharyngeal swabs) and monthly antibody testing at their site of enrolment. In addition, hospitals introduced twice weekly asymptomatic testing using a lateral flow device (LFD), Innova SARS-CoV-2 Antigen Rapid Qualitative Test (Innova), to all frontline HCWs for twice weekly asymptomatic testing in November 2020. All positive LFD tests were confirmed by PCR. Participants consent for the release of all SARS-CoV-2 PCR and antibody test results before or after enrolment to the study team through the Public Health England (PHE) national laboratory testing surveillance system. The SIREN SQL database runs automated data linkage with the laboratory surveillance system daily to extract new positive and negative test results.

Participants are requested to complete online questionnaires at enrolment and fortnightly intervals, capturing data on demographics, symptoms, testing and exposures (household, community and occupational). Index of Multiple Deprivation a measure of neighbourhood relative deprivation, calculated by the Office of National Statistics, was obtained through linkage on participant postcode.

Data was extracted from all sources on 08 February 2021.

Bias reduction

Data were collected on potential confounders, including site and participant demographics to enable adjusted analysis. Analysis was restricted to one manufacturer only, where sufficient follow-up time had accrued; data was truncated on participants with an unreliable date of second dose (<19 days). Sample date of a PCR positive result was used as the event date which may have introduced some misclassification of vaccination status relative to infection or onset in the period shortly after vaccination and informed our decision to calculate cumulative vaccine effectiveness after suitable intervals (21 days post first dose and 7 days post second dose), in order to focus on infections acquired since vaccination after a sufficient interval for biological protection.

Study size

Prior to vaccine introduction calculations of the precision of effectiveness estimates were performed on an estimated cohort size of 40,000, 65% seronegative at baseline, coverage averaging at 75% in the follow-up period, and incidence in the follow-up period ranging from 0.5% to 5%. Precision estimates around effectiveness of 60% and 90% gave 95% confidence intervals ranging from the widest for a VE of 60% (95%CI: 39-74) to the narrowest for a VE of 90% (95%CI: 88-92).

Person time at risk

Follow-up time for all participants started on 7 December 2020, the day before vaccine roll-out began, with all participants contributing at least one day of follow-up unvaccinated. Participants moved from unvaccinated to vaccinated within their assigned cohort on the date of the first vaccination dose. Participants contributed person-time to follow-up until either an event of interest (i.e. a new PCR positive in the negative cohort or a reinfection in the positive cohort); the date of the suspect second dose for those with an unreliable date of second dose; the date of their first dose for those vaccinated with the ChAdOx1 vaccine; or the censored date. We defined the end of follow-up in those who were not positive cases as the date of a negative test or 05 February 2021 if the test was after this date, in order to avoid immortal time bias. As symptomatic testing was done at any time of symptoms the most recent days could be biased towards symptomatic testing, therefore, the end of follow-up was defined at a date two days prior to the last date samples were available.

Statistical methods

Investigation of factors associated with vaccination was conducted using mixed effect multivariable logistic regression model (with hospital site as a random effect) to investigate confounding between demographic and occupational risk factors on the outcome variable 'ever vaccinated'. A backwards stepwise approach was used, removing variables from the model sequentially with those with the least effect at univariable analysis removed first, and goodness of fit was tested (likelihood ratio tests) after each change. Only the variables which demonstrated strong evidence of association on vaccine coverage were retained in the final model.

A mixed effect proportional hazards frailty model using a Poisson distribution was used to calculate Hazard Ratios to compare time to infection in unvaccinated and vaccinated participants to estimate the impact of the BNT162b2 vaccine on infection (including asymptomatic and symptomatic as the primary outcome). As the main covariate of interest (vaccination) changes as time elapses and the effect of vaccine changes over follow-up time,

we grouped time to infection into 12 vaccine intervals to analyse the short-term dynamics of post vaccination protection in detail. The models were fitted by Poisson regression with a log link, using COVID-19 infection as response, log of exposure times as an offset and dummies for the time intervals as explanatory variables to allow for different piecewise constant hazards.[12] The model fitting approach also provided estimates of the baseline hazard rates. The hospital site was added into models as a random effect to account for the extra variation and associated correlation that was not explained by risk/covariates variables. The frailty model was also extended by including individual within the site as an addition random effect. The results (not reported here) did not support heterogeneity among individuals after controlling for site effect and therefore our final model does not include individual. The fixed covariates included in the model were age, ethnicity, comorbidities, region, job role, frequency of COVID-19 patient contact, patient-facing role, workplace setting. Hazard ratios from 21 days after first dose and seven days after second dose were calculated using a weighted average method, the point at which an immunological response to the vaccine dose should have been provoked. Vaccine effectiveness was calculated as 1 – adjusted Hazard Ratio (vaccinated versus unvaccinated).

Three models were run on different cohorts within the study population. The main model included the full study population and adjusted for cohort assignment. Models were then run on the two cohorts separately, to provide estimates of vaccine effectiveness in the susceptible population (negative cohort) and the positive cohort with natural immunity following prior SARS-CoV-2 infection.

Ethics

The study was approved by the Berkshire Research Ethics Committee, Health Research Authority (IRAS ID 284460, REC reference 20/SC/0230) on 22 May 2020; the vaccine amendment was approved on 12/1/2021. The study is registered with ISRCTN (Trial ID: ISRCTN11041050).

Reporting

The study follows the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines and the checklists are included in the Supplementary Appendix.[13]

RESULTS

Characteristics of participants included in the analysis

By 7 December 2020, 29,378 participants were enrolled and maintained in SIREN for the England cohort; 23,324 met the inclusion criteria and were included in this analysis from 104 hospitals[1]. At the start date of follow-up (7 December 2020), 8,203 (35%) participants were assigned to the positive cohort (antibody positive or had a previous antibody or PCR positive test) and 15,121 (65%) were assigned to the negative cohort.

Most participants were female (84%; 19,692), of white ethnicity (89%; 20,424), in a patient-facing role (86%; 20,054) and in a clinical discipline (66%; 15,502). A quarter (26%; n=5,874) of participants had a reported medical condition; with asthma (n=2,893), obesity (n=1,988) and diabetes (n=677) the most frequent.

The total follow-up time in this analysis was two calendar months and 1,106,905 participant person-days, 710,587 person-days unvaccinated and 396,318 person-days vaccinated. Participants were followed-up for a maximum of 59 days post first dose (median 21, interquartile range: 13-31) and 39 days post second dose (median 23, interquartile range: 17-28). Total person-days of follow-up in the negative cohort was 711,135 and 395,770 in the positive cohort.

[1] Whilst recruitment of participants from Scotland and Northern Ireland began before 31/12/2020 their testing and vaccination data was not available for linkage by the study team at the time of this analysis, and therefore they were excluded. Recruitment of Welsh participants began in 2021.

Vaccine coverage with the SIREN cohort up to 5 February 2021

At least one dose of vaccine was administered to 20,641 (89%) participants by 5 February 2021; 94% (19,384) received the BNT162b2 vaccine and 6% (1,252) received the ChAdOx1 vaccine. Roll-out of the first dose of vaccine in this cohort peaked on 12 January 2021 (Figure 1). Two doses of vaccine were administered to a minority of participants (n=1,607, 8%) by 5 February 2021; 99.9% (n=1,605) received the BNT162b2 vaccine and 0.1% (n=2) received the ChAdOx1 vaccine. The median length of time between first dose and second dose was 23 days; IQR: 21-26 days; range 19-28.

Demographic, household and occupational factors associated with being vaccinated

A description of the demographic, household and occupational factors associated with being vaccinated, including the proportions vaccinated and odds ratios are presented in table 1. In multivariable analysis, after controlling for all other risk factors and given site, having a prior infection, gender, age, ethnicity, IMD score and staff group remained significantly associated with vaccine coverage. Participants were less likely to have been vaccinated if they had a prior infection (aOR 0.59, 95% CI 0.54-0.64), were female (aOR 0.72, 95% CI 0.63-0.82), were aged under 35 (aOR 0.78, 95% CI 0.64-0.96), were from Black, Asian or minority ethnic groups, especially if they were Black (aOR 0.26, 95% CI 0.21-0.32), lived in areas of higher deprivation (IMD 1 (most) vs. 5 (least) aOR 0.75 , 95% CI 0.65-0.87) or worked as a porter/security/estates (aOR 0.61, 95% CI 0.42-0.90) or midwife (aOR 0.74, 95% CI 0.57-0.97).

Vaccine effectiveness against infection

There were 977 new infections during 710,587 person days of follow-up in the unvaccinated group, an incidence density of 14 infections per 10,000 person days of follow-up (table 2). In the vaccinated group, 21 days after the first dose, there were 71 new infections (incidence density 8 per 10,000 person-days of follow-up) and nine new infections seven days after the second dose (incidence density of 4 per 10,000 person days of follow-up).

Classic COVID-19 symptoms (fever, cough, change/loss of taste or smell) were reported by 620 (63%) cases in the unvaccinated group 14-days before or after their positive test date; 139 (14%) had other symptoms[2]; 51 (5%) were asymptomatic; and 167 (17%) did not complete the symptom status questionnaire within 2 weeks of their PCR test date. In comparison, of the infections 21 days after first dose and seven days after second dose in the vaccinated group, 32 (40%) had classic COVID-19 symptoms, 13 (16%) had other symptoms, 10 (13%) were asymptomatic and 25 (31%) did not complete the symptom status questionnaire for the time period.

After controlling for the other risk factors, cohort and at a given site, vaccine effectiveness against infection 21 days after the first dose of BNT162b2 vaccine in the overall study population was 70% (95% CI 53-87%) and increased to 85% (95% 74-96%) seven days after the second dose (table 2). Protection was higher when the negative cohort was modelled separately, and after adjustment for the other risk factors and at a given site; vaccine effectiveness was72% (95% CI 58-86%) 21 days after first dose and 86% (95% 76-97%) 7 days after the second dose. There was insufficient information to separately model the positive cohort at this analysis timepoint. The overall model showed that the positive cohort already had 90% protection (95% CI 88-92%) compared to the negative cohort following their natural infection (supplementary material).

Figures 2a and 2b show the trends in vaccine effectiveness measured over short post-vaccination intervals in the full cohort and negative cohort; this demonstrated a reduced risk of infection in vaccinated individuals immediately (0-3 days) following the first dose; there

[2] Participants were recorded as having 'other symptoms' if they reported ANY of the following symptoms: shortness of breath, sore throat, runny nose, headache, muscle aches, extreme fatigue, diarrhoea, nausea or vomiting or small itchy red patches on fingers or toes, on the follow-up questionnaire with a symptom onset date within 14-days before or after the PCR positive sample date.

was no significant effect between days 4-9, with a significant protection from infection increasing from day 10 onwards, and plateauing after 21 days. Following the second dose a similar pattern is observed. The hazard ratios, adjusted and unadjusted for each time period post vaccination in the full cohort and the negative cohort are provided in Appendix A Tables 3a & 3b.

DISCUSSION

Our follow-up of this large cohort of over 23,000 HCWs, whose prior SARS-CoV-2 infection history is known for two months after vaccine roll-out provides unique real-world data on the short-term vaccine effectiveness of the BNT162b2 vaccine against both symptomatic and asymptomatic infection. The regular PCR-testing of participants, regardless of symptom status, allowed for the detection of asymptomatic infection, an important proxy for reduction in transmission. Two months after roll-out commenced, 89% of our cohort had received at least one dose of COVID-19 vaccine; 8% had received two doses. We detected modest variability in coverage, with lower coverage observed in participants with prior infection, from Black, Asian and minority ethnic backgrounds, and living in areas of higher deprivation. We estimated the vaccine effectiveness against infection for the BNT162b2 vaccine to be at least 70% 21 days after the first dose, increasing to at least 85% 7 days after the second dose in our study population. This demonstrates that the BNT162b2 is effective against the B1.1.7 variant given its predominance throughout the studyperiod.[14]

The high vaccine coverage in SIREN may not be generalisable to UK HCWs or the general population, as those who have self-selected to participate in a research study may not be representative of UK HCWs or the population more generally.

With fewer of the cohort vaccinated with the ChAdOx1 vaccine, and the later roll-out resulting in less follow-up time accrued, we are currently unable to investigate the effectiveness of the ChAdOx1 vaccine within this study.

The analysis is based on PCR positivity, which may miss infections depending on the timing of the infection relative to PCR testing or PCR sensitivity, which if differential by vaccination status may lead to overestimation of the vaccine effect against all infections. However, given our cohort, irrespective of vaccine status, attended fortnightly asymptomatic PCR testing within SIREN, and additionally many also underwent twice weekly LFD testing with PCR confirmation, we believe most infections during this period will have been detected. The cohort will also have regular serological testing and the effect of seroconversion to both the S assay (for vaccine) and N assay (for infection) will be estimated in the future.

Given the high vaccine coverage and small proportion of participants remaining unvaccinated, the characteristics and exposures of this group may become sufficiently different from the vaccinated cohort to undermine the validity of future analyses. However, given the short follow-up period for this analysis, with all participants contributing follow-up time to the unvaccinated group, we do not consider this would have introduced significant bias at this stage.

Speculation of high levels of HCW vaccine hesitancy are not supported in our cohort study, with almost 90% receiving at least one dose of vaccination within two months of roll-out.[15] High and rapid vaccine HCW coverage was also reported in two single-centre cohort studies in Israel, reporting 79% and 90% coverage six weeks after roll-out.[16,17] Slightly lower uptake of 65% was reported in a single UK trust which also reported similar disparities in vaccination coverage by ethnicity.[18] Our findings also indicated that age, gender and occupation were associated with coverage, confirming a systematic review of 11 studies including 9,000 participants, on the intention of healthcare workers HCW to accept the COVID-19 vaccine, which concluded that older age, male gender and being a doctor were factors associated with increased willingness to get vaccinated.[15] Conversely, the authors also found that people with prior SARS-CoV-2 infection or co-morbidities expressed more willingness to take the vaccine,

not seen in our data. We also observed a significant trend of lower COVID-19 vaccination coverage in those living in more deprived areas, corresponding to a population study of 23.4 million patients in the UK.[19]

Our analysis identified a reduced risk of infection in vaccinated individuals immediately (0-3 days) following the first dose, which cannot be plausibly explained by the immune response to the vaccine; this is likely a deferral effect bias where those that are symptomatic, currently PCR positive or have been recently exposed to a COVID-19 case may defer their vaccination and be under-represented in accordance with national guidance.[20]

We found a vaccine effectiveness, at a given site, of at least 70% overall (72% in the negative cohort) against both asymptomatic and symptomatic infection, from 21 days post-first dose of the BNT162b2 vaccine. This is comparable to a single-centre Israeli HCW cohort study vaccine effectiveness of 75% (95% CI 72 – 84), 15-28 days following first dose of BNT162b2 vaccine [16]. However, this study had no routine laboratory surveillance to pick up asymptomatic cases and only detected cases if symptomatic, whereas SIREN had regular asymptomatic testing; in addition, their adjustment for other potential risk factors was more limited.

Another population-level study in Israel reported a 51% reduction in PCR-confirmed SARS-CoV-2 infections 13-24 days after individuals received the first dose of BNT162b2 vaccine, compared to historical controls' 1-12 days [21]. This mirrors the 52.4% (95% CI: 29.5 - 68.4) vaccine efficacy estimated by Pfizer-BioNTech researchers, between the first and second dose.[6] Whilst follow up periods differed, the RCT included true controls and the Israeli study included PCR-positivity regardless of symptom status compared to symptomatic confirmed cases in the phase III BNT162b2 RCT. A preprint from researchers re-analysing the data from the Israeli study using daily incidence of infection, calculated a vaccine effectiveness of 91% at day 21 post-vaccination.[22] This estimate is closer to the 92.6% vaccine efficacy 14–21 days

after the first dose, calculated by researchers using data submitted by the manufacturers to the Food and Drug Administration from vaccine trials.[23]

The differences in the vaccine effectiveness estimates may be due to the differences in study design and populations included. Nonetheless, BNT162b2 is making a substantial impact in reducing SARS-CoV-2 infection rates in vaccinated populations. A study with a comparable methodology to SIREN, focussing on "Covid-19 Vaccine Effectiveness in Healthcare Personnel in Clalit Health Services in Israel", is currently underway [ClinicalTrials.gov number NCT04709003], but results are awaited. A notable difference is that people in Israel that have recovered from SARS-CoV-2 infection are not eligible for vaccination at present;[24] therefore, their population studies do not include the seropositive people that would be present in a general population. Weekly swabbing of a sub-set of asymptomatic and symptomatic participants was carried out in the Oxford-AstraZeneca RCT and investigators reported reduced viral load and PCR positivity in the COVID-19 vaccinated participants; a signal that transmission may be reduced by their vaccine.[25] This is the first study that describes the reduction in all cases of infection with BNT162b2.

Most data on vaccinated UK individuals are from people aged >75years old, where vaccine effectiveness may be lower due to immunosenesence.[27] The SIREN cohort is taken from working age people, making the conclusions more relevant for the overall adult population. However, the healthy worker effect bias may underestimate the disease impact compared to the general population.[28]

Further work on this cohort is underway including measuring the impact of vaccination on symptoms, serological responses, potential hospitalisations, and development of post-acute-COVID. We will attempt to sequence infections occurring at least 21 days post vaccination to determine proportion of novel variants.

This study clearly demonstrates that the vaccine does not prevent all cases of infection and therefore HCWs will need to continue to wear personal protective equipment while caring for all patients, observe physical distancing and other non-pharmaceutical measures in and outside work and continue to perform regular asymptomatic testing (especially as typical symptoms were reduced post vaccination) until COVID prevalence is considerably lower.

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Trial Registration

IRAS ID 284460, REC reference 20/SC/0230 Berkshire Research Ethics Committee, Health Research Authority and Health and Care Research Wales approval granted 22 May 2020. Trial registered with ISRCTN, Trial ID: ISRCTN11041050.

https://www.isrctn.com/ISRCTN11041050

Author Contributions

SH conceived this study, commented on the draft protocol, supervised the study, drafted and edited the final manuscript. JLB, NA and VH wrote the first draft of the protocol and analysis plan for the vaccine effectiveness sub-study. SF and VH cleaned and analysed data. VH and BO performed the literature search and drafted the manuscript. AS performed the statistical modelling of VE supervised by NA and AC. All authors contributed to the study design. All authors contributed to drafting the protocol and revised the manuscript for important intellectual content. All authors gave final approval of the version to be published.

Conflict of interest statement

The Immunisation and Countermeasures Division has provided vaccine manufacturers (including Pfizer) with post-marketing surveillance reports on pneumococcal and meningococcal infection which the companies are required to submit to the UK Licensing authority in compliance with their Risk Management Strategy. A cost recovery charge is made for these reports.

Data sharing statement

The metadata will be available through the HDR-UK Co-Connect platform and available for secondary analysis once the study has completed reporting.

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Table 1: Characteristics of vaccinated and non-vaccinated SIREN participants and factors associated with vaccine coverage in multivariable logistic regression analysis, (n=23,324)

Characteristics		Not Vaccinated	Vaccinated	OR (95% CI)	p-value	aOR** (95% CI)	p-value
		n (%)	n (%)				
Prior COVID-19 infection*							
	Negative	1405 (9.3)	13716 (90.7)	Reference			
	Positive	1278 (15.6)	6925 (84.4)	0.56 (0.51-0.60)	<0.001	0.59 (0.54-0.64)	<0.001
Gender							
	Male	333 (9.2)	3270 (90.8)	Reference			
	Female	2346 (11.9)	17346 (88.1)	0.75 (0.67-0.85)	<0.001	0.72 (0.63-0.82)	<0.001
	Other	4 (13.8)	25 (86.2)	0.64 (0.22-1.84)	0.404	0.94 (0.30-2.93)	0.913
Age group							
	Under 25	136 (16.1)	711 (83.9)	Reference			
	25-34	886 (19.7)	3614 (80.3)	0.78 (0.64-0.95)	0.014	0.78 (0.64-0.96)	0.018
	35-44	650 (11.5)	4998 (88.5)	1.47 (1.20-1.80)	<0.001	1.45 (1.18-1.79)	<0.001
	45-54	600 (8.4)	6566 (91.6)	2.09 (1.71-2.56)	<0.001	2.22 (1.80-2.73)	<0.001
	55-64	382 (8.0)	4412 (92.0)	2.21 (1.79-2.73)	<0.001	2.31 (1.85-2.87)	<0.001
	Over 65	29 (7.9)	340 (92.1)	2.24 (1.47-3.42)	<0.001	2.19 (1.42-3.37)	<0.001
Ethnicity							
	White	2119 (10.4)	18305 (89.6)	Reference			
	Mixed Race	69 (19.4)	287 (80.6)	0.48 (0.37-0.63)	<0.001	0.56 (0.43-0.75)	<0.001
	Asian	250 (15.8)	1337 (84.2)	0.62 (0.54-0.71)	<0.001	0.65 (0.56-0.76)	<0.001
	Black	162 (34.9)	302 (65.1)	0.22 (0.18-0.26)	<0.001	0.26 (0.21-0.32)	<0.001
	Chinese	17 (12.7)	117 (87.3)	0.80 (0.48-1.33)	0.383	0.73 (0.43-1.25)	0.252
	Other ethnic group	56 (17.8)	258 (82.2)	0.53 (0.40-0.71)	<0.001	0.54 (0.39-0.73)	<0.001
	Prefer not to say	10 (22.2)	35 (77.8)	0.41 (0.20-0.82)	0.012	0.30 (0.14-0.65)	0.002
Pre-existing medical condition^							
	No medical condition	2060 (11.8)	15390 (88.2)	Reference			
	Immunosuppression	56 (11.7)	421 (88.3)	1.01 (0.76-1.33)	0.965	-	-

Chronic Respiratory conditions	305 (10.4)	2619 (89.6)	1.15 (1.01-1.31)	0.032	-	-
Chronic Non-Respiratory conditions	262 (10.6)	2211 (89.4)	1.13 (0.99-1.29)	0.079	-	-
Household size						
Just you	283 (12.1)	2063 (87.9)	Reference			
Two to four	2080 (11.2)	16494 (88.8)	1.09 (0.95-1.24)	0.213	-	-
Over four	297 (12.7)	2037 (87.3)	0.94 (0.79-1.12)	0.492	-	-
Prefer not to say	23 (32.9)	47 (67.1)	0.28 (0.17-0.47)	<0.001	-	-
Index of Multiple Deprivation						
5 (least deprived)	507 (9.0)	5107 (91.0)	Reference			
4	534 (9.7)	4947 (90.3)	0.92 (0.81-1.04)	0.199	1.02 (0.89-1.16)	0.795
3	591 (11.1)	4731 (88.9)	0.79 (0.70-0.90)	<0.001	0.92 (0.81-1.05)	0.216
2	577 (14.1)	3512 (85.9)	0.60 (0.53-0.69)	<0.001	0.78 (0.69-0.90)	<0.001
1 (most deprived)	436 (16.6)	2198 (83.4)	0.50 (0.44-0.57)	<0.001	0.75 (0.65-0.87)	<0.001
Not known	38 (20.7)	146 (79.3)	0.38 (0.26-0.55)	<0.001	0.53 (0.36-0.78)	0.001
Region						
Yorkshire and the Humber	239 (11.5)	1832 (88.5)	Reference			
East Midlands	248 (10.1)	2200 (89.9)	1.16 (0.96-1.40)	0.128	1.14 (0.80-1.62)	0.461
East of England	299 (10.8)	2462 (89.2)	1.07 (0.90-1.29)	0.437	1.12 (0.80-1.56)	0.505
London	444 (15.5)	2416 (84.5)	0.71 (0.60-0.84)	<0.001	1.00 (0.73-1.37)	1.000
North East	53 (9.7)	496 (90.3)	1.22 (0.89-1.67)	0.212	1.31 (0.76-2.26)	0.340
North West	350 (12.7)	2403 (87.3)	0.90 (0.75-1.07)	0.218	0.96 (0.70-1.32)	0.803
South East	247 (9.1)	2462 (90.9)	1.30 (1.08-1.57)	0.006	1.24 (0.91-1.71)	0.176
South West	464 (9.7)	4335 (90.3)	1.22 (1.03-1.44)	0.019	1.11 (0.82-1.49)	0.506
West Midlands	339 (14.3)	2035 (85.7)	0.78 (0.66-0.93)	0.007	0.87 (0.63-1.19)	0.380
Staff group						
Admin	377 (10.5)	3223 (89.5)	Reference			
Nursing/Healthcare Assistant	1275 (13.0)	8551 (87.0)	0.78 (0.69-0.89)	<0.001	0.96 (0.84-1.09)	0.515
Doctor	189 (7.5)	2332 (92.5)	1.44 (1.20-1.73)	<0.001	1.82 (1.49-2.22)	0.000
Midwife	88 (15.5)	478 (84.5)	0.64 (0.49-0.82)	<0.001	0.74 (0.57-0.97)	0.027
Specialist staff	156 (11)	1262 (89.0)	0.95 (0.78-1.15)	0.584	1.28 (1.04-1.57)	0.020
Estates/Porters/Security	38 (17.1)	184 (82.9)	0.57 (0.39-0.82)	0.002	0.61 (0.42-0.90)	0.012
Pharmacist	35 (10.0)	316 (90.0)	1.06 (0.73-1.52)	0.770	1.59 (1.09-2.33)	0.016

Healthcare Scientist	91 (11.1)	729 (88.9)	0.94 (0.74-1.19)	0.599	1.16 (0.90-1.49)	0.261
Other	434 (10.8)	3566 (89.1)	0.96 (0.83-1.11)	0.594	1.13 (0.97-1.31)	0.126
Occupation setting⁺						
Offices and laboratory (lower risk)	932 (11.2)	7384 (88.8)	Reference			
Patient facing non-clinical	112 (12.9)	757 (87.1)	0.85 (0.69-1.05)	0.138	-	-
Outpatient	469 (11.6)	3590 (88.4)	0.97 (0.86-1.09)	0.567	-	-
Inpatient wards and ambulance	498 (14)	3069 (86.0)	0.78 (0.69-0.87)	<0.001	-	-
Intensive Care (higher risk)	157 (13.0)	1053 (87.0)	0.85 (0.71-1.01)	0.071	-	-
Other	515 (9.7)	4788 (90.3)	1.17 (1.05-1.31)	0.006	-	-
Contact with patients or working in patient-facing areas						
No	330 (10.1)	2940 (89.9)	Reference			
Yes	2353 (11.7)	17701 (88.3)	0.84 (0.75-0.95)	0.006	-	-
Frequency of contact with COVID-19 patients in the workplace						
Never	793 (9.6)	7484 (90.4)	Reference			
Daily	871 (15.4)	4777 (84.6)	0.58 (0.52-0.64)	<0.001	-	-
Weekly	448 (10.8)	3688 (89.2)	0.87 (0.77-0.99)	0.029	-	-
Monthly	239 (11.3)	1883 (88.7)	0.83 (0.72-0.97)	0.021	-	-
Less than monthly	332 (10.6)	2809 (89.4)	0.90 (0.78-1.03)	0.113	-	-
All Participants	**2683 (11.5)**	**20641 (88.5)**				

*Ever antibody or PCR positive as of 07 December 2020; ^pre-existing medical condition categories: immunosuppression (cancers affecting the immune system in the last 5 years, rheumatological/autoimmune conditions and on immunosuppressive therapy, organ or bone marrow transplantation, asplenia), Chronic respiratory conditions (asthma, chronic respiratory disease), chronic non-respiratory conditions (diabetes, obesity, chronic heart disease, chronic kidney disease, chronic liver disease, other cancers, dementia, other neurological disorder and HIV) and no reported medical conditions. Where participants reported multiple conditions, they were assigned to a category dependent on which condition was considered by the study team to be the most severe.
⁺Occupation setting: 1 = office, laboratory, estates; 2: community pharmacy, hospital pharmacy, communal areas open to the public, mobile across areas (porters); 3: outpatient, radiology, day ward, general practice, renal dialysis unit; 4: inpatient ward, theatres, emergency department, maternity unit/labour ward, ambulance; 5: intensive care; Other
**multivariable model included and adjusted for: site (as a random effect), and fixed effects: prior infection status, age, gender, ethnicity, IMD, region and staff group

Table 2: Effectiveness of the BNT162b2 COVID-19 vaccine against infection in SIREN participants, stratified by cohort, between 7 December 2020 and 5 February 2021, (n=23,324)

Vaccine group	Total person time (days)	Number of PCR positives	Incidence Density per 10,000 person days	Unadjusted Hazard Ratio (95% CI)^	Adjusted Hazard Ratio (95% CI)*
Full cohort					
Unvaccinated	710587	977	14	Reference	Reference
d1 ≥21	87278	71	8	0.43 (0.23-0.64)	0.30 (0.15-0.45)
d2 ≥7	20978	9	4	0.23 (0.06-0.40)	0.15 (0.04-0.26)
Negative cohort					
Unvaccinated	442605	902	20	Reference	Reference
d1 ≥21	59748	66	11	0.33 (0.17-0.49)	0.28 (0.14-0.42)
d2 ≥7	14746	8	5	0.18 (0.04-0.31)	0.14 (0.03-0.24)
Positive cohort**					
Unvaccinated	267982	75	3	-	-
d1 ≥21	27530	5	2	-	-
d2 ≥7	6232	1	2	-	-

^Unadjusted includes vaccine effect (period) only; *the full model was adjusted for site as a random effect, period, and fixed effects: age, gender, ethnicity, comorbidities, job role, frequency of contact with COVID-19 patients, employed in a patient facing role, occupational exposure. **there was insufficient information to model the positive cohort separately so stratified hazard ratios are not available for the positive cohort.

FIGURES

Figure 1: Number of vaccinated SIREN participants by dose, manufacturer and day, 8 December 2020 to 5 February 2021 (n=20,641)

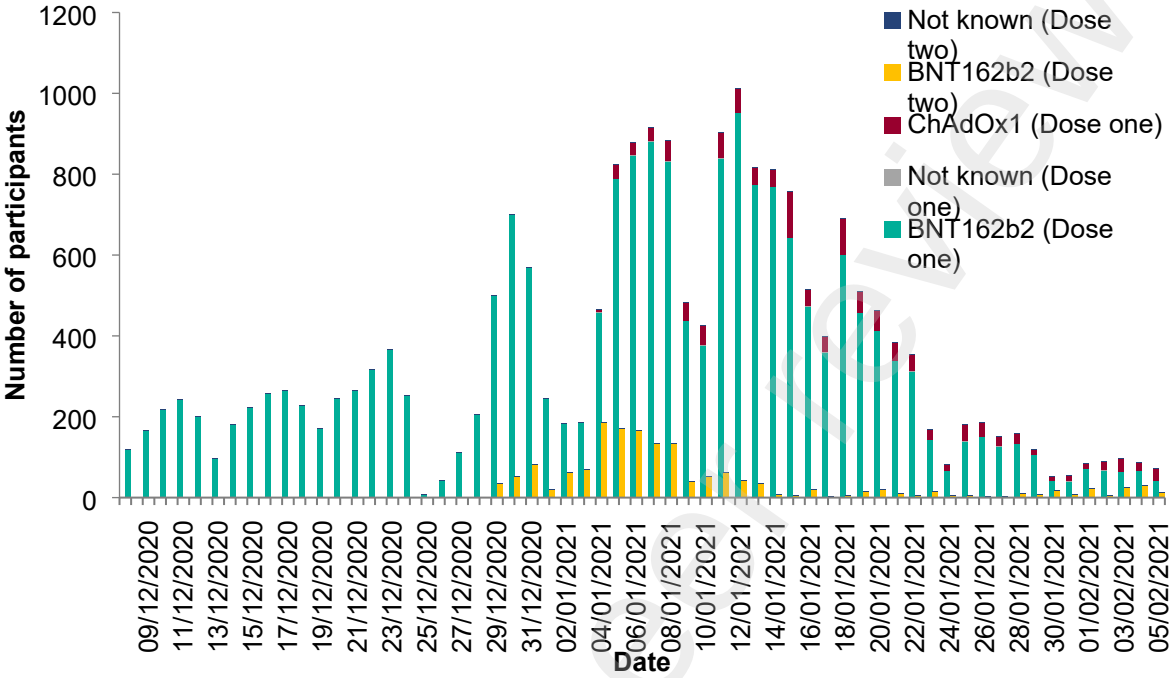


Figure 2a: Graph of adjusted Hazard Ratios at post-vaccination intervals, 7 December 2020 – 5 February 2021, full cohort (n=23,324)

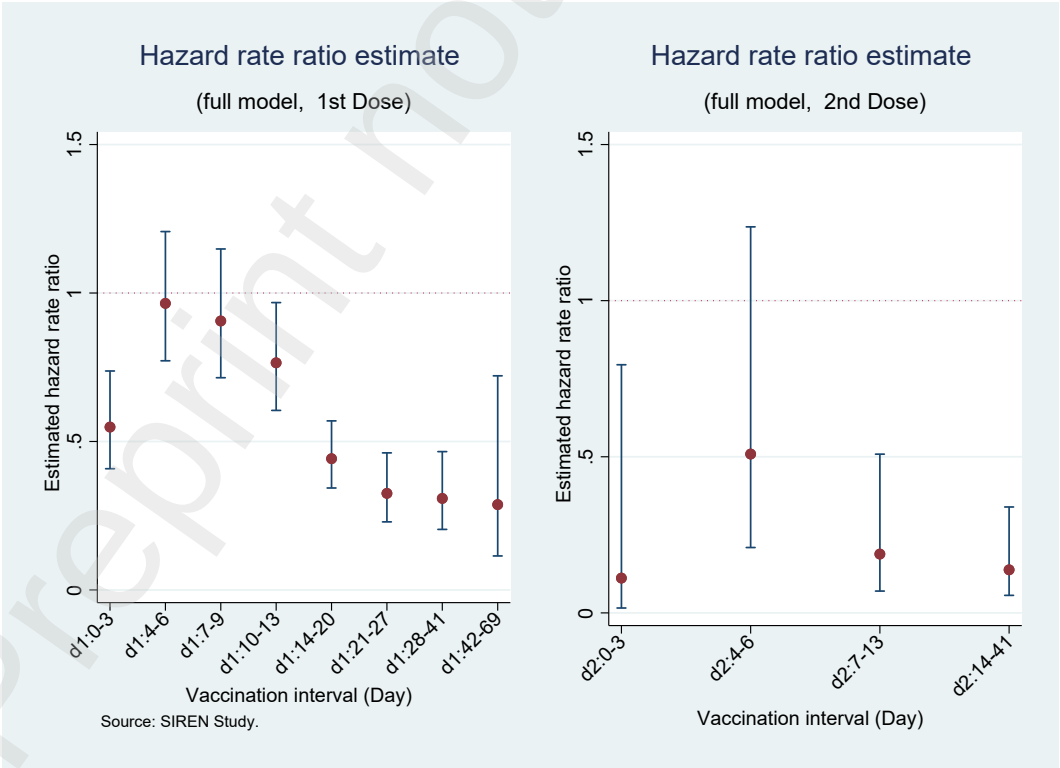
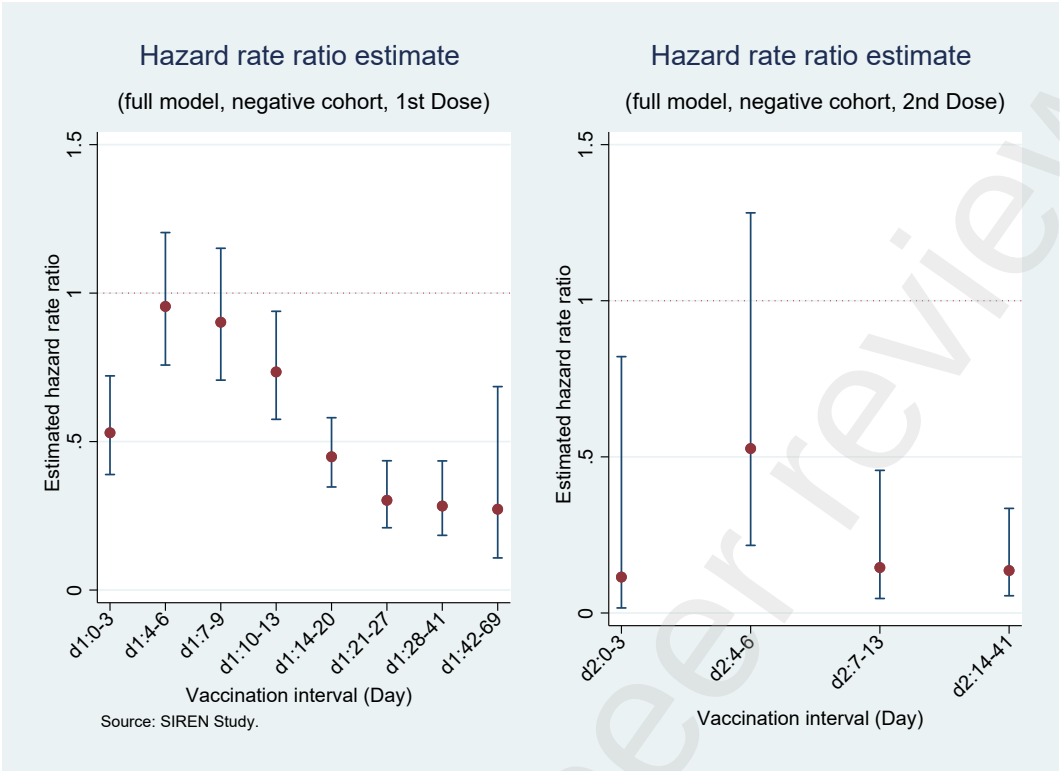


Figure 2b: Graph of adjusted Hazard Ratios at post-vaccination intervals, 7 December 2020 – 5 February 2021, negative cohort (n=15,121)



TAB 33

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TAB 39

An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

Interim guidance on booster COVID-19 vaccine doses in Canada

Published: October 29, 2021

PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH

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Canada

Preamble

The National Advisory Committee on Immunization (NACI) is an External Advisory Body that provides the Public Health Agency of Canada (PHAC) with independent, ongoing and timely medical, scientific, and public health advice in response to questions from PHAC relating to immunization.

In addition to burden of disease and vaccine characteristics, PHAC has expanded the mandate of NACI to include the systematic consideration of programmatic factors in developing evidence based recommendations to facilitate timely decision-making for publicly funded vaccine programs at provincial and territorial levels.

The additional factors to be systematically considered by NACI include: economics, ethics, equity, feasibility, and acceptability. Not all NACI Statements will require in-depth analyses of all programmatic factors. While systematic consideration of programmatic factors will be conducted using evidence-informed tools to identify distinct issues that could impact decision-making for recommendation development, only distinct issues identified as being specific to the vaccine or vaccine-preventable disease will be included.

This statement contains NACI's independent advice and recommendations, which are based upon the best current available scientific knowledge. This document is being disseminated for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph. Recommendations for use and other information set out herein may differ from that set out in the product monographs of the Canadian manufacturers of the vaccines. Manufacturer(s) have sought approval of the vaccines and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

Background

NACI's recommendations on booster doses will be based on the decision-making framework outlined in this document, triggered by evidence of the need for (e.g., evidence of decreased vaccine effectiveness against severe illness and/or infection depending on the population) and benefit of (e.g., safety and effectiveness) a booster dose in the Canadian context.

The public health goal of Canada's pandemic response is to minimize serious illness and death while minimizing societal disruption as a result of the COVID-19 pandemic. COVID-19 vaccines have played a vital role in the response and have been shown to be very effective against symptomatic laboratory confirmed SARS-CoV-2 infection, severe disease, hospitalization, and death from COVID-19. Unfortunately, the COVID-19 pandemic is ongoing and continues to cause significant morbidity and mortality, as well as social and economic disruption in Canada and worldwide (including impacts on health system capacity). COVID-19 vaccination with a complete primary series is critical. Fully vaccinated individuals have much lower rates of SARS-CoV-2 hospitalizations, ICU admission and mortality compared to those who are unvaccinated. In addition, those who have been vaccinated are less likely to get infected, and therefore less likely to transmit SARS-CoV-2 infection to others. NACI continues to strongly recommend that all individuals in the authorized age groups should be immunized with a primary series of an authorized COVID-19 vaccine, and preferably with mRNA COVID-19 vaccines (Moderna Spikevax and Pfizer-BioNTech Comirnaty) [(1)].

To date, COVID-19 vaccines have been shown to maintain high vaccine effectiveness (VE) against serious illness, hospitalization, and death from COVID-19 in most populations. However, evidence is emerging that VE against asymptomatic infection and mild COVID-19 disease may decrease with time, and that currently authorized COVID-19 vaccines may be less effective against the highly transmissible Delta variant (B.1.617.2), which could contribute to increased transmission of infection. Therefore, an additional or booster dose may be needed to obtain more durable protection in some populations.

Evidence from clinical trials suggests that booster doses of mRNA vaccines given six months after the primary series elicited a robust immune response against the wild type strain and variants of Concern (VoC), with titres often higher after the booster dose than after the primary series. Real-world data from Israel suggest that a booster dose provides good short-term effectiveness against SARS-CoV-2 infection and has a safety profile comparable to that observed after the second dose of the vaccine.

The intent of a booster dose is to restore protection that may have decreased over time to a level that is no longer deemed sufficient in individuals who initially responded adequately to a complete primary vaccine series. This is distinguished from the intent of an additional dose which might be added to the standard primary vaccine series with the aim of enhancing the immune response and establishing an adequate level of protection. For example, evidence suggests that compared to the general population, individuals who are moderately to severely immunocompromised have lower immune responses to COVID-19 vaccines. Therefore, NACI has recommended that

moderately to severely immunocompromised individuals[a] in the authorized age groups should be immunized with a primary series of three doses of an authorized mRNA vaccine.

Historically in other vaccine programs, it can take years of post-market use to determine the optimal intervals and dose number needed for a complete primary series to sustain long-term protection. At present, there is scientific debate about whether a third dose for COVID-19 vaccines truly constitutes a booster dose in the traditional sense. NACI continues to monitor the emerging scientific data on how best to use these vaccines, and will study the important differences between a primary series (to establish strong immune memory), versus a booster (to stimulate the memory response once protection has truly waned). Over time, it may be learned that a short 2-dose primary series, with a booster at least 6 months after the second dose, can in fact be adjusted to achieve durable protection with a more streamlined primary series. For example, NACI has already highlighted benefit in terms of longer-term protection when the second dose is provided at least 8 weeks after the first dose. In this guidance document, additional doses of COVID-19 vaccines after the authorized series are being described as booster doses but it should be acknowledged that over time, what defines an optimal primary series could also evolve and be refined.

NACI's recommendations on booster doses are occurring in the context of the World Health Organization's (WHO's) call for global vaccine equity, and take into consideration conclusions in its Interim statement on booster doses for COVID-19 vaccination including the call for evidence-based decisions: "Introducing booster doses should be firmly evidence-driven and targeted to the population groups in greatest need. The rationale for implementing booster doses should be guided by evidence on waning vaccine effectiveness, in particular a decline in protection against severe disease in the general population and in high-risk populations, or due to a circulating VoC. To date, the evidence remains limited and still inconclusive on any widespread need for booster doses following a primary vaccination series. The focus remains on urgently increasing global vaccination coverage with the primary series [(2)]." NACI's recommendations on booster doses in those who have completed a primary series will be triggered by evidence on the need for a booster dose (in key populations at increased risk or in the general population), as well as the benefit of a booster dose.

Internationally, several countries, including the United States [(3)], the United Kingdom [(4)], France [(5)], and Germany [(6)], have recently recommended booster doses of COVID-19 vaccines at least 6 months following a primary vaccine series for certain high-risk groups, such as older adults, long-term care residents, and healthcare workers. Israel initially recommended a booster dose in adults 60 years of age and older and subsequently recommended a booster dose for the general

[a] Moderately to severely immunosuppressed includes individuals with the following conditions:

- Active treatment for solid tumour or hematologic malignancies
- Receipt of solid-organ transplant and taking immunosuppressive therapy
- Receipt of chimeric antigen receptor (CAR)-T-cell therapy or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)
- Moderate to severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Stage 3 or advanced untreated HIV infection and those with acquired immunodeficiency syndrome
- Active treatment with the following categories of immunosuppressive therapies: anti-B cell therapies (monoclonal antibodies targeting CD19, CD20 and CD22), high-dose systemic corticosteroids (refer to the CIG for suggested definition of high dose steroids), alkylating agents, antimetabolites, or tumor-necrosis factor (TNF) inhibitors and other biologic agents that are significantly immunosuppressive.

population 12 years of age and over, at least 5 months following the primary series administered at the authorized dosage interval [7].

Countries that have rolled out primary series of COVID-19 vaccines using different vaccines and different intervals between doses of vaccines are experiencing different levels of protection over time, which is to be expected. NACI's recommendations for booster doses will differ from recommendations in other countries because of differences in a number of contextual factors including:

- the vaccine product(s) used to complete the primary series,
- the time that has elapsed since last dose in the primary series,
- the intervals between the first and second doses in the primary series,
- indirect protection from high vaccination coverage, and
- the use of other public health measures such as masking and physical distancing policies.

NACI reviewed available evidence on the factors presented in Table 1 in the context of the current Canadian epidemiology, vaccine programs, and vaccine schedules. Over 80% of Canadians aged 12 years and older have completed a primary COVID-19 vaccine series. Most are at a lower risk of declining protection due to receipt of mRNA vaccines (following NACI's preferential recommendation for mRNA vaccines [1]) or a combination of vaccine products in some instances (following NACI's recommendation on the interchangeability of authorized COVID-19 vaccines [8]), and at intervals longer than the manufacturer authorized intervals (following NACI's recommendation for extended intervals [9]). Furthermore, the Moderna Spikevax vaccine, authorized for use in Canada, appears to offer more durable protection against severe disease and asymptomatic infection [10]. There is no evidence of decreasing protection over time against severe disease in the general Canadian population who have been vaccinated against COVID-19 disease. To date, Health Canada has not authorized booster doses of COVID-19 vaccines. NACI will continue to closely monitor the evidence and encourages a coordinated evidence-informed national approach.

On September 28, 2021, NACI recommended that a booster dose of an authorized mRNA vaccine should be offered to all long-term care residents and seniors living in other congregate settings who have received a primary COVID-19 vaccine series (with the primary series being a homologous or heterologous schedule using mRNA and/or viral vector vaccines) at an interval of at least 6 months after the primary series has been completed [11]. This population was also initially prioritized as a key population to receive initial doses of a primary series of COVID-19 vaccines based on evidence of an increased risk of severe illness and death and increased risk of exposure to SARS-CoV-2. The recommendation for a booster dose was triggered by increases in COVID-19 cases and outbreaks in long-term care homes with signs emerging that protection from vaccination might not persist as long in this population compared to other populations in Canada. In addition, long-term care residents are at high risk of exposure to SARS-CoV-2 due to their congregate living environment and at high risk of severe outcomes due to age and underlying health status. Longer time since last dose and shorter intervals between doses in the primary series, as well as older age/immunosenescence, also contribute to waning vaccine protection against infection and severe outcomes in this population. Assessment of the need for and benefit of a booster dose in other populations based on the criteria in Table 1 in the Canadian context and NACI's decision-making framework inform and guide NACI's recommendations herein subsequent to the Rapid response: Booster doses in long-term care residents and seniors living in other congregate care settings.

Guidance objective

The objective of this advisory committee statement is to provide evidence-informed guidance on the equitable, ethical, and effective use of additional doses of authorized COVID-19 vaccines in the Canadian context based on the need for, and benefit of, booster doses to minimize serious illness and deaths while minimizing societal disruption as a result of COVID-19.

Methods

The evidence pertaining to COVID-19 and COVID-19 vaccines is rapidly evolving. NACI reviewed the decision-making framework and evidence on the need for and benefit of additional doses of COVID-19 vaccines in various populations on September 7, 14, 27, October 12 and 15, 2021. NACI consulted with the Public Health Ethics Consultative Group (PHECG) on the ethical implications of booster dose recommendations in various populations on September 2 and 21, 2021. Following a comprehensive review of available evidence and consultations with the provinces and territories through the Canadian Immunization Committee (CIC) and the Chief Medical Officers of Health (CMOH), NACI made and approved these recommendations on October 22, 2021.

NACI's decision-making framework on booster doses was modified from NACI's original prioritization framework of key populations for COVID-19 vaccination. The evidence supporting the development of the original framework is summarized in NACI's previously published guidance:

1. Preliminary guidance on key populations for early COVID-19 immunization (November 2020)
2. Guidance on the prioritization of initial doses of COVID-19 vaccines (December 2020)
3. Guidance on the prioritization of key populations for COVID-19 immunization (February 2021)

To guide ethical decisions that are based on evidence and on clear, transparent criteria, NACI developed a decision-making framework for booster doses modified from its original evidence-informed prioritization framework for COVID-19 vaccination [12]. NACI's recommendations on booster doses will be based on this decision-making framework, triggered by evidence of the need for, and benefit of, a booster dose in the Canadian context (Table 1).

Key populations prioritized for a primary series of COVID-19 vaccination in NACI's original framework were based on evidence of increased risk of severe illness and death from COVID-19 and increased risk of exposure to SARS-CoV-2, summarized in NACI's 2020 guidance [12-17]. NACI's decision-making framework on booster doses also considered populations with emerging evidence suggesting decreased protection from the primary series (e.g., vaccination with only viral vector vaccines, a longer time since completion of the primary series, shorter interval between doses of the primary series). NACI's recommendations are also guided by ethics and rooted in the foundational elements of equity, feasibility and acceptability.

Table 1. Underlying factors for consideration based on evolving evidence to determine the need for and benefit of a booster dose of COVID-19 vaccine in various populations

Underlying factors for consideration	Evidence reviewed to determine the need for and benefit of a booster dose of COVID-19 vaccine
Risk benefit analysis	• Risk of severe illness and death • Risk of exposure (including ability to physically distance and access to infection prevention and control • measures and healthcare) • Risk of transmission to vulnerable populations • Risk of societal disruption
Vaccine characteristics in different groups against wild-type and VoC	• Duration of protection • Immunogenicity • Efficacy/effectiveness • Safety and reactogenicity of boosters • Effect of vaccine in preventing transmission
Vaccine supply/types/intervals	• Number and type of available vaccines • Initial vaccination series (type, interval between doses, time since initial series)
COVID-19 epidemic conditions	• Circulation of SARS-CoV-2 wild-type and VoC • Breakthrough cases, outbreaks • Case rates and implications for health system capacity

NACI recommendations on the use of COVID-19 vaccines are available here.

Data on COVID-19 vaccination coverage and doses administered in various key populations in jurisdictions across Canada is available here.

Further information on NACI's process and procedures is available elsewhere [18, 19].

Summary of evidence

Vaccine principles for booster doses

The immune responses to a vaccine are determined by a number of factors including vaccine type, interval between doses in the primary series, time since completion of the primary series, and underlying health status and age.

Higher antibody titres occur with the Moderna vaccine compared to the Pfizer-BioNTech vaccine and both have a higher titre than the viral vector vaccines [20]. A longer interval between the first and second doses also results in higher titres [21, 22]. Although correlates of protection against SARS-CoV-2 have not yet been clearly defined, a higher antibody titre appears to be associated with longer duration of protection against symptomatic infection, including against VoC.

While there are various studies showing decreasing levels of circulating neutralizing antibodies as well as binding antibodies over time, studies also show that the mRNA vaccines elicit a memory

B and T cell response [23, 24]. Even if circulating antibodies decrease, future exposure to SARS-CoV-2 is expected to drive a 'recall' response and long-lived memory T and B cells will help produce new antibodies. Therefore, even if a vaccinated individual is infected with SARS-CoV-2, vaccine-induced immunity through immune memory is expected to help to prevent progression to severe disease in most individuals, although the duration of immune memory is not known at this time.

For more information on vaccine principles, please consult the chapter on basic immunology and vaccinology in the Canadian Immunization Guide.

Recent COVID-19 epidemiological trends

There is currently a resurgence of COVID-19 cases in regions of Canada fuelled by the highly transmissible Delta variant. Outbreaks continue to occur in multiple settings, including long-term care homes and retirement residences, industrial settings, school and daycare settings, as well as other settings that are enclosed and crowded, and can be a significant source of spread of SARS-CoV-2 infection. School and daycare settings have experienced an increasing number of outbreaks since mid-August [25] due in part to a large proportion of ineligible and unvaccinated population (children under 12). In early August, the rate of active cases started rising in First Nations communities for the first time since mid-January 2021, and was 4.2 times higher than the rate in the general population as of October 12 [26]. As such, this NACI guidance is provided in the midst of the fourth COVID-19 pandemic wave driven by the Delta variant.

Canadian surveillance data up to October 2, 2021 shows that rates of new SARS-CoV-2 infection are highest among persons who are unvaccinated and lowest in persons who are fully vaccinated. Unvaccinated persons have also had much higher rates of hospitalizations, ICU admission and deaths compared to those fully vaccinated. Compared to those who are fully vaccinated, the rate of SARS-CoV-2 infection in unvaccinated persons was 8 times higher and the rate of COVID-19 related hospitalization in unvaccinated persons was 25 times higher, on average, for each week during the period of September 5 to October 2, 2021. While the incidence rate of infection is much lower in fully vaccinated people, it increased slightly across all age groups since mid-July, but has declined as of the week of September 26 - October 2, 2021 for all age groups.

Compared to fully vaccinated younger age groups, fully vaccinated cases 80 years of age and over have the highest rates of hospitalizations and deaths, followed by those aged 70 to 79 years. Among the fully vaccinated, these older age groups have the highest proportion of cases who are hospitalized and who have died from COVID-19. The weekly proportions of fully vaccinated cases who are hospitalized or who died has remained relatively low and stable since mid-July and the case fatality has decreased more recently in the older age groups, indicating that fully vaccinated people who become infected do not appear to be getting more severely ill over time.

Duration of COVID-19 vaccine protection against infection

Emerging evidence suggests a decrease in COVID-19 vaccine protection against SARS-CoV-2 infection over time following completion of the primary series. However, it can be challenging to distinguish potential signals of waning from increasing case numbers driven by community spread during the fourth wave of the pandemic and the rise of the Delta variant. Evidence on increasing incidence of infection in vaccinated individuals coincides with periods when the Delta variant predominated, and estimates of lower VE may be a reflection of decreased effectiveness against

the Delta variant rather than waning in COVID-19 vaccine protection. Further, increasing incidence in vaccinated individuals may also be observed in areas with lower vaccine coverage as a result of overall higher community rates driven by SARS-CoV-2 infection in the unvaccinated population. Continued research evaluating VE is needed to accurately determine trends in protection over time, as well as to learn more about the effects on transmission and the magnitude, if any, of potential decrease in protection. Immunogenicity data alone is insufficient to assess waning of protection against disease, and may not be indicative of protection against severe outcomes. To date, protection against severe COVID-19 outcomes, such as hospitalization and death, consistently appear to be more durable than protection against infection. There are some data that suggest decreases in protection may be greater in older age groups and in individuals with clinical risk factors for more severe outcomes [27, 28].

A recent rapid review [29] on vaccine efficacy/effectiveness over time in COVID-19 vaccinated individuals identified seven studies that examined vaccine efficacy/effectiveness longitudinally over a period of 4 months or longer and provided both baseline and follow-up data. Studies that reported on confirmed infection [30-32] as an outcome generally indicated a decrease in VE against SARS-CoV-2 infection at 4 and 6 months after primary series completion compared to 7 to 14 days after primary series completion. Trends were similar for studies reporting on symptomatic infection [27, 30, 33, 34]. In contrast, the studies that reported on COVID-19 related hospitalization [27, 31, 32, 35] and deaths [27, 30, 32] indicated that VE against severe COVID-19 outcomes remained stable over time thus far. These patterns were generally similar across vaccine products and in individuals over 60 years old. However, evidence was limited by the small number of heterogeneous studies, which were observational in design.

Studies on duration of protection have typically examined protection after a manufacturer-recommended dosing interval of 3 or 4 weeks between first and second doses for mRNA vaccines. It is currently uncertain how a longer interval between first and second vaccine doses in a primary series might affect the duration of protection. Provincial data from British Columbia and Quebec found that shorter intervals between doses in a primary series result in lower VE against SARS-CoV-2 infection and COVID-19 related hospitalizations compared to extended intervals. Further, emerging evidence suggests that shorter intervals between doses may be associated with lower VE against infection over time [27, 28]. Evidence to date suggests that delaying the second dose by several weeks leads to higher antibody titres and greater VE of the series [22, 36, 37] which is likely to result in a more durable immune response and longer protection over time.

It is currently unclear to what extent the duration of protection may vary by vaccine product. In general, VE against symptomatic SARS-CoV-2 infection and severe COVID-19 outcomes has consistently been somewhat lower with viral vector vaccines compared to mRNA vaccines [38]. Emerging data on effectiveness suggests that vaccine protection against infection and symptomatic disease decreases more quickly with viral vector vaccines in comparison to mRNA vaccines, whereas the difference is less pronounced for severe disease [27, 28]. Limited real-world data from Canada and the United States suggests that protection from Moderna Spikevax may be more durable compared to Pfizer-BioNTech Comirnaty [28, 39], but more research is required.

There is limited evidence on duration of protection following a mixed COVID-19 vaccination schedule. Data from two studies indicate that VE for those who received a mixed schedule of AstraZeneca Vaxzevria/COVISHIELD followed by an mRNA vaccine is similar compared to those who received a complete series of mRNA vaccines [28, 40].

Despite some evidence of increasing risk of breakthrough infection over time, those vaccinated against COVID-19 with a two-dose series continue to demonstrate significantly lower odds of SARS-CoV-2 infection compared to unvaccinated individuals and, when infections occur, symptoms tend to be milder in vaccinated cases [41]. VE against severe COVID-19 outcomes with all vaccine types remains high, even in the context of the Delta variant. Breakthrough infections in vaccinated persons could contribute to ongoing transmission of SARS-CoV-2. Early evidence from when the Alpha variant predominated suggested that vaccinated individuals who became infected were less infectious [42]. The evidence on transmission with the Delta variant is less clear, with some studies suggesting the differences in viral load between vaccinated and unvaccinated persons who become infected may be less compared to when the Alpha variant was predominant [42-46].

Immunogenicity, Safety, and Effectiveness of COVID-19 vaccine booster doses

Ongoing manufacturer-sponsored trials on mRNA vaccines have reported higher titres following the third doses compared to those after the initial series [47, 48] of two doses (administered at manufacturer authorized intervals), suggesting that the higher titres produced by a booster dose may lead to longer lasting protection than the primary series administered at manufacturer authorized intervals. Early results also show a favourable reactogenicity profile for booster mRNA vaccine doses, similar to that of the second dose in the primary series [47, 48]. Evidence from these trial data is limited by small sample size (less than 350 participants in each published manufacturer-sponsored trial [49, 50]) and short duration of follow-up of study populations. Pfizer-BioNTech Comirnaty and Moderna Spikevax have filed submissions for booster doses ≥ 6 months after the primary series to Health Canada for regulatory approval as of October 1 and 5, 2021 respectively. The regulatory submission for a Moderna Spikevax booster dose is for half the current dosage of Moderna Spikevax primary series dose (i.e., a 50 mcg booster dose vs. 100 mcg full dose). The regulatory submission for a Pfizer-BioNTech Comirnaty booster dose is the same as the current dosage of the primary series dose for this vaccine (i.e., a 30 mcg booster dose).

Emerging real-world data from Israel's booster dose program with Pfizer-BioNTech Comirnaty indicates that a third dose (after a primary series using the manufacturer authorized interval of 21 days between doses) resulted in improved short-term vaccine effectiveness against infection and severe illness [51]. In one Israeli study of individuals ≥ 60 years of age, a booster dose of Pfizer-BioNTech Comirnaty at least 5 months after the primary series decreased the relative risk of confirmed SARS-CoV-2 infection by 11.3-fold and of severe illness by 19.5-fold at 12 or more days from the booster dose, compared to those with two doses [52]. An extension of this analysis [53] found that, compared to a two-dose series, a booster dose resulted in about a 10-fold reduction in confirmed infection rates in persons ≥ 16 years of age. In another Israeli study of persons ≥ 40 years of age, those who received a third dose had a 70 to 84% reduction in the odds of testing positive for SARS-CoV-2 infection 14 to 20 days after receiving the booster compared to people who received two doses of Pfizer-BioNTech Comirnaty [54]. There are no data currently on the long-term effectiveness of booster doses so it remains unknown at this time how long benefit might last. The effect of booster doses on transmission is unknown.

Studies evaluating boosters following different primary series vaccine schedules are ongoing [55, 56]. Unpublished data from the Cov-Boost trial presented to the United Kingdom's Joint Committee on Vaccination and Immunisation (JCVI) suggest that mRNA booster doses are generally well

tolerated and provide a strong booster effect regardless of the vaccine used in the primary series [4]. Similarly, recent data from the US National Institutes of Health "Mix and Match" trial indicates that heterologous booster doses given at least 12 weeks following completion of the primary series of mRNA vaccines or Janssen COVID-19 vaccine were well-tolerated and immunogenic. Additionally, those who received an mRNA booster following a dose of Janssen COVID-19 vaccine had higher antibody titres compared to those who received a second dose of Janssen as a booster [57].

The safety and effectiveness of a third dose in persons who had a previous SARS-CoV-2 infection is currently unknown.

Rare cases of myocarditis and pericarditis following vaccination with COVID-19 mRNA vaccines have been reported, more frequently after the second dose compared to the first dose, and more commonly in younger males and adolescents. Canadian data also suggest that myocarditis/pericarditis occur more frequently after Moderna Spikevax compared to Pfizer Comirnaty COVID-19 vaccines. The rate of myocarditis and pericarditis following a booster dose of a COVID-19 mRNA vaccine is currently unknown. Initial surveillance data from Israel up to October 10, 2021 has reported 17 cases of myocarditis or peri-myocarditis out of approximately 3.7 million booster doses of Pfizer-BioNTech Comirnaty administered [51]. In Israel, this rate is lower than observed after the second dose, but higher than observed after the first dose. Data collection is ongoing. NACI will continue to monitor the evidence and update recommendations as needed.

Optimal primary series to booster dose interval

There are currently limited data to determine the optimal interval between the completion of the primary series and administration of the booster dose. Most studies on mRNA COVID-19 vaccine booster doses have used an interval of 6 months or more following the completion of the primary series, although some have used an interval as short as 3 months [55, 56]. Submissions filed with regulatory authorities in the US, EU and Canada are for 6 months or more following the second dose, which was the interval used in booster doses trials for Pfizer-BioNTech Comirnaty and Moderna Spikevax [49, 50]. However, it is currently unknown at what interval a maximum boosting effect is achieved. For older adults who may have a decrease in protection over time, delaying the booster dose will increase the period during which individuals may have reduced protection against SARS-CoV-2 infection, although to date protection against severe outcomes has been shown to be more durable than protection against infection.

Summary of primary COVID-19 vaccine series that have been used in Canada to date

Vaccine types received in the primary series in Canada

As of October 9, 2021, 82% of eligible Canadians have been fully vaccinated with a COVID-19 vaccine, while 87% have received at least one dose. Of those fully vaccinated, the majority received a complete two-dose series of mRNA vaccines. A small percentage received a complete series with a viral vector vaccine. At least 469,371 Canadians have received a viral vector vaccine primary series and 1,395,324 Canadians have received a heterologous primary series containing both a viral vector vaccine and an mRNA vaccine. Almost all viral vector primary series were with AstraZeneca Vaxzevria/COVISHIELD vaccines. Data on vaccination coverage by vaccine product was missing for two provinces.

Refer to COVID-19 vaccination in Canada for the most current information on vaccination coverage.

Intervals between doses in the primary series of COVID-19 vaccines in Canada

Shorter intervals between doses results in lower antibody titres which may wane to below protective levels over time. While individuals who received their second dose in the primary COVID-19 vaccine series at a shorter interval from the first dose were well protected in the short-term, they may have produced lower antibody levels, which may decrease over time compared with those who had a longer interval between doses.

Intervals between the first and second doses of a two-dose primary series of COVID-19 vaccines varied across Canada as vaccine supply and evidence evolved. Groups prioritized for vaccination early in the vaccine roll-out [12] often received their vaccines using the manufacturers' recommended interval of 21 days for Pfizer-BioNTech Comirnaty and 28 days (or as short as 21 days) for Moderna Spikevax. Subsequently, intervals between doses were extended up to 16 weeks to optimize early vaccine rollout and population protection in Canada in the context of limited vaccine supply [9]. As vaccine supply was no longer limited, and in the context of the increasing prevalence of the Delta variant, jurisdictions accelerated second doses with shorter intervals. Aggregated vaccination coverage data obtained from provincial and territorial vaccination registries up to August 14, 2021, showed that an interval of 7-11 weeks between first and second doses was the most common dosing interval across all vaccine products. Dosing intervals varied widely by jurisdiction and age group. Most notably, 66% of vaccinated adults aged 80 years old and older had an interval of 12 weeks or more between first and second dose, while 9% had an interval of 28 days or less. Data on vaccination coverage by dosing interval was missing for one province.

There is evidence that the Moderna Spikevax vaccine remains efficacious against severe disease and asymptomatic infection at more than 5 months when given at the authorized interval of 28 days between doses [10]. There is evidence that while the Pfizer-BioNTech Comirnaty vaccine prevents COVID-19 for up to 6 months, there is a gradual decline in efficacy when given at the authorized interval of 21 days between doses [34]. Though limited data suggests that protection from Moderna Spikevax may be more durable compared to Pfizer-BioNTech Comirnaty [28, 39], more research is required.

Time since completion of primary COVID-19 vaccine series in Canada

As noted above, protection against infection may decrease with time since completion of the second dose of vaccine. Key populations at highest risk of severe illness due to COVID-19 and/or highest risk of exposure to SARS-CoV-2 (e.g., residents and staff of congregate living settings that provide care for seniors, older adults, frontline healthcare workers, adults in or from Indigenous communities) were prioritized to receive COVID-19 vaccines earlier than others when initial vaccine supply was limited [12]. Therefore, many in these populations would have completed their primary series longer than 6-8 months ago. A number of these key populations received their second doses between January and April 2021. The vast majority of Canadians who are fully vaccinated completed their primary series in June or July 2021 (84%). Only 4% received their second doses between January and April 2021. Data on vaccination coverage by time since last dose was missing for one province.

Ethics, Equity, Feasibility and Acceptability Considerations

Ethics

Advice provided to NACI by the PHAC Public Health Ethics Consultative Group (PHECG) on the ethical implications of booster dose recommendations included the following [58, 59]:

- Decisions about extending boosters ought to be evidence-informed and fair, and clearly communicate why and when groups will become eligible for boosters. It is necessary to be clear about the rationale for offering an additional dose, including how the criteria fit within, and are consistent with, a broader booster framework, if and when such a recommendation is made.
- Besides a general duty to protect the public's health, Canada also has a duty to protect the most vulnerable. The precautionary principle supports offering a booster dose of a COVID-19 vaccine to those who are at greatest risk of serious harms due to COVID-19, prior to a significant degree of waning VE against severe outcomes being observed.

Equity

Global equity:

- On September 8, 2021 the WHO called for a global moratorium on booster doses until at least the end of 2021, to enable every country to vaccinate at least 40 percent of its population [60]. NACI acknowledges the importance of global equity in this pandemic, although global vaccine supply considerations are outside the purview of NACI's mandate. As advised by the PHECG, global vaccine equity requires that need (e.g., risk of severe illness and death and risk of exposure) be taken into account when allocating vaccines. This includes prioritizing high-risk groups globally who have not yet received first or second doses over individuals who are at lower risk due to having completed a primary vaccine series [58].

Domestic equity:

- Inter-jurisdictional equity is also a relevant consideration both for reasons of promoting fairness and fostering trust. As advised by the PHECG, consistency and transparency in public health messaging and programs contribute to public trust in public health advice. Equity may not necessarily require a uniform response across all jurisdictions, since there are a variety of ethically-relevant factors that could justify triggering a recommendation for one jurisdiction but not in another. For example, in order to offer equitable protection against risk of COVID-19-related harms, disparate recommendations across jurisdictions may be justified when the populations in these jurisdictions face disparate levels of risk [58]. This includes the continued allocation of resources to encourage high acceptance and uptake of the primary series, which offers the most benefit against severe outcomes and deaths due to COVID-19, for those who have not yet received the vaccine. However, where possible, alignment across jurisdictions is expected to positively impact inter-jurisdictional equity and public trust in public health advice.

Feasibility

- COVID-19 vaccine supply in Canada has increased and mechanisms for distributing and administering vaccines have been established. However, if boosters are administered all at once for the general population, there may be operational challenges with implementation. Consideration should also be given to minimizing wastage of product reaching its expiry date and open vials that need to be used within a specified period of time.

Acceptability

- According to survey data from August 2021, there is generally high acceptability for COVID-19 booster doses amongst Canadians. Approximately 80% of individuals, regardless of vaccination status, are willing to get an annual booster or booster doses now or within the next year; and those aged 65 or older are the most likely to be willing to take a booster shot (92%) [61, 62].
- Of those who are already fully vaccinated, around 80-93% are willing to get a booster dose [61, 63]. Of those who received a mixed schedule with AstraZeneca and an mRNA COVID-19 vaccine, 58% agreed to get a third dose if studies show that a third dose is required [64].
- Most Canadians (74%) agree that the priority for vaccines should be first doses for those who want them before making booster shots available [63].

Refer to NACI's previous guidance for a comprehensive overview of the ethical, equity, feasibility and acceptability considerations for prioritizing key populations for COVID-19 vaccination [12, 13, 16, 17].

Recommendations

Please see Table 2 for an explanation of strong vs discretionary NACI recommendations.

NACI strongly reiterates its previous evidence-informed recommendations for the primary series of COVID-19 vaccines in all authorized age groups:

1. NACI preferentially recommends [1] that a complete series with an mRNA COVID-19 vaccine should be offered to individuals in the authorized age group without contraindications to the vaccine. *(Strong NACI Recommendation)*

   Additional details are available in the NACI statement on Recommendations on the use of COVID-19 vaccines.

2. NACI recommends [65] that moderately to severely immunocompromised individuals[b] in the authorized age groups should be immunized with a primary series of three doses of an authorized mRNA vaccine. For those who have previously received a 1- or 2-dose complete primary COVID-19 vaccine series (with a homologous or heterologous schedule using mRNA or viral vector vaccines), NACI recommends that an additional dose of an authorized mRNA COVID-19 vaccine should be offered. *(Strong NACI Recommendation)*

   Additional details are available in the NACI rapid response: Additional dose of COVID-19 vaccine in immunocompromised individuals following 1- or 2- dose primary series.

NACI's evidence-informed recommendations for booster doses of COVID-19 vaccines:

NACI recognizes that epidemiological and logistical/operational contexts, as well as impacts on health system capacity, vary between provinces and territories across Canada. NACI encourages jurisdictions to align with these recommendations as much as possible to ensure the equitable, ethical and effective use of booster doses of COVID-19 vaccines in Canada, maintaining vaccine acceptance and confidence, while considering their local contexts.

NACI also acknowledges that the epidemiology of COVID-19 (including the impact of SARS-CoV-2 variants of concern) and the evidence on booster doses of COVID-19 vaccines are rapidly evolving, and will continue to monitor the evidence in the Canadian context and provide additional recommendations and updates subsequent to this interim statement as data emerge.

Following an evaluation of the need for, and benefit of, additional doses of COVID-19 vaccines based on evolving evidence on the criteria outlined in Table 1, as well as the systematic

[b] Moderately to severely immunosuppressed includes individuals with the following conditions:

- Active treatment for solid tumour or hematologic malignancies
- Receipt of solid-organ transplant and taking immunosuppressive therapy
- Receipt of chimeric antigen receptor (CAR)-T-cell therapy or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)
- Moderate to severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Stage 3 or advanced untreated HIV infection and those with acquired immunodeficiency syndrome
- Active treatment with the following categories of immunosuppressive therapies: anti-B cell therapies (monoclonal antibodies targeting CD19, CD20 and CD22), high-dose systemic corticosteroids (refer to the CIG for suggested definition of high dose steroids), alkylating agents, antimetabolites, or tumor-necrosis factor (TNF) inhibitors and other biologic agents that are significantly immunosuppressive.

assessment of ethics, equity, feasibility and acceptability considerations with the EEFA framework [19], NACI makes the following evidence-informed recommendations on booster doses of authorized COVID-19 vaccines in the context of ongoing risk of severe illness from COVID-19 and exposure to SARS-CoV-2 and VoCs in Canada:

For key populations at highest risk of severe illness from COVID-19 and highest risk of waning protection:

3. NACI recommends that a booster dose of an authorized mRNA COVID-19 vaccine* *should be offered* ≥6 months after completion of a primary COVID-19 vaccine series (where the primary series consisted of a homologous or heterologous schedule using mRNA or viral vector vaccines) to individuals in the following key populations:
    - Adults living in long-term care homes for seniors or other congregate living settings that provide care for seniors (as previously recommended by NACI)
    - Adults ≥80 years of age

    (Strong NACI Recommendation)

For key populations at increased risk of severe illness from COVID-19 and increased risk of waning and/or lower protection:

4. NACI recommends that a booster dose of an authorized mRNA COVID-19 vaccine* *may be offered* ≥6 months after completion of a primary COVID-19 vaccine series to individuals in the following key populations:
    - Adults 70-79 years of age (whose primary series consisted of a homologous or heterologous schedule using mRNA or viral vector vaccines)
    - Recipients of a viral vector vaccine series completed with only viral vector vaccines (AstraZeneca/COVISHIELD or Janssen COVID-19 vaccine), regardless of age

    based on local epidemiology and any evidence of diminished protection, and with consideration of individual risks and potential benefits.

    (Discretionary NACI Recommendation)

For key populations who may be at increased risk of severe illness from COVID-19 (due to intersecting social and health risk factors [13]) and waning protection (due to increased time since completion of the primary COVID-19 vaccine series after a shorter interval between doses) where infection can have disproportionate consequences [12]:

5. NACI recommends that a booster dose of an authorized mRNA COVID-19 vaccine* *may be offered* ≥6 months after completion of a primary COVID-19 vaccine series (where the primary series consisted of a homologous or heterologous schedule using mRNA or viral vector vaccines) to individuals in the following key population:
    - Adults in or from First Nations, Inuit and Métis communities based on local epidemiology, vaccine coverage, any evidence of waning protection and with consideration of individual risks and potential benefits. Whether or not booster dose vaccine programs are needed in distinct Indigenous communities should be determined by Indigenous leaders and communities, considering these same factors, and with the support of public health partners.

    (Discretionary NACI Recommendation)

For key populations who are essential for maintaining health system capacity and who may be at increased risk of waning protection (due to increased time since completion of the primary COVID-19 vaccine series after a shorter interval between doses) and who could pose increased risk of transmission to vulnerable populations:

6. NACI recommends that a booster dose of an authorized mRNA COVID-19 vaccine* may be offered ≥6 months after completion of a primary COVID-19 vaccine series (where the primary series consisted of a homologous or heterologous schedule using mRNA or viral vector vaccines) to individuals in the following key population:

- Adults who are frontline healthcare workers (having direct close physical contact with patients) and who were vaccinated with a very short minimum interval (less than 28 days) between the first and second doses of an mRNA COVID-19 primary vaccine series, based on local epidemiology, any evidence of waning protection, and impacts on health system capacity, and with consideration of individual risks and potential benefits.

(Discretionary NACI Recommendation)

For other populations not included in the above recommendations for a booster dose, NACI will continue to closely monitor the evidence and will make additional recommendations if there is evidence of the need for, and benefit of, a booster dose. This includes monitoring the specific evidence for:

- Individuals who have had previously PCR-confirmed SARS-CoV-2 infection and have completed a primary series of COVID-19 vaccines.
- Moderately to severely immunocompromised individuals who have completed a 3-dose primary series of COVID-19 vaccines. Populations with underlying medical conditions that may be at higher risk of severe disease after breakthrough infection

*****Either Moderna Spikevax or Pfizer-BioNTech Comirnaty vaccines may be used as a booster dose (regardless of which COVID-19 vaccine was used in the primary series). As previously recommended, adults living in long-term care homes for seniors or other congregate living settings that provide care for seniors are recommended to receive the full dose (100 mcg) if being offered Moderna Spikevax. For other adults recommended to receive a booster dose, the full dose (100 mcg) is recommended for adults 70 years of age or older, if offering Moderna Spikevax, while a half dose (50 mcg) is recommended for those less than 70 years of age. If offering Pfizer-BioNTech Comirnaty, the full dose (30 mcg) is recommended

Individuals who had a severe immediate allergic reaction (e.g., anaphylaxis) to a previous mRNA vaccine or who have a severe immediate allergic reaction (e.g., anaphylaxis) to a component of the mRNA vaccine should consult with an allergist or other appropriate physician as vaccination with an mRNA has been safely performed in these populations. Additional guidance for individuals with myocarditis/pericarditis after a previous dose of an mRNA vaccine is under consideration and will be forthcoming.

Summary of evidence and rationale

- To date, almost 2 in 10 eligible Canadians have not been fully vaccinated. Efforts should be made to encourage vaccination of those unvaccinated with a primary COVID-19 vaccine series.
- Unvaccinated individuals are at highest risk of SARS-CoV-2 infection and severe outcomes from COVID-19. There is no evidence to date of waning of protection against severe disease in the general Canadian population who have been vaccinated against COVID-19 disease.
- NACI continues to strongly recommend that all individuals in the authorized age groups should be immunized with a primary series of an authorized COVID-19 vaccine, and preferably with mRNA COVID-19 vaccines (Moderna Spikevax and Pfizer-BioNTech Comirnaty) [(1)].
- Fully vaccinated individuals are less likely to get infected, and therefore are less likely to transmit infection to others.
- Emerging evidence suggests a waning in COVID-19 vaccine immunogenicity and effectiveness against SARS-CoV-2 infection over time following completion of the primary series, although protection against severe COVID-19 outcomes appears to be more durable than protection against infection.
- Increased incidence of breakthrough infections amongst those fully vaccinated is expected in the context of high community rates of SARS-CoV-2 (especially where vaccination coverage rates for the primary COVID-19 vaccine series are low) and the predominance of the Delta variant in Canada, given the somewhat lower vaccine effectiveness against infection with this VoC.
- Decreased protection against infection could contribute to more transmission which can have significant impacts especially on some populations and on health system capacity. Vaccinated individuals infected with the Delta variant are less likely to develop severe disease. However, vaccinated individuals infected with this highly transmissible variant may be more infectious to others, potentially facilitating transmission if infected [(66)].
- Decreased protection against infection over time has been noted to potentially occur more quickly with the viral vector vaccines than the mRNA vaccines, while protection with Moderna Spikevax may be more durable than with Pfizer-BioNTech Comirnaty. Shorter intervals between the first and second dose for 2-dose COVID-19 vaccine series result in lower initial titres that may result in protection that decreases sooner.
- Studies suggest that booster doses of mRNA vaccines elicit a robust immune response, have a favourable safety profile (comparable to that of the second dose of the primary series) and provide good short-term effectiveness against SARS-CoV-2 infection and severe disease. Health Canada is reviewing the evidence submitted by Moderna and Pfizer BioNTech for regulatory approval of a booster dose, but neither vaccine is currently authorized for use as a booster dose in Canada. Post-market safety surveillance on mRNA COVID-19 vaccines found an increased frequency of myocarditis and pericarditis following a second dose of a COVID-19 mRNA vaccine in younger males and adolescents. Higher unadjusted rates of cases of myocarditis and/or pericarditis have been reported after the Moderna vaccine compared to Pfizer-BioNTech vaccine in some jurisdictions [(67, 68)]. Additional analyses are ongoing. The majority of cases reported while hospitalized were relatively mild and individuals tended to recover quickly. The rate of myocarditis and pericarditis following a booster dose of a COVID-19 mRNA vaccine is currently unknown,

although initial data from Israel to date has shown lower rates of myocarditis/pericarditis after the booster dose than after the second dose, but higher than after the first dose; data collection is ongoing. Informed consent for vaccination with a booster dose should include that a primary series of COVID-19 vaccines remains effective against severe COVID-19, and that a booster dose is intended to restore protection against infection that may have decreased over time. However, the effectiveness against transmission of infection, long-term effectiveness against infection and severe disease, and rate of myocarditis and pericarditis after a booster dose are currently unknown. In addition, recommendations for a booster dose of COVID-19 vaccines are currently off-label in Canada.

Key Populations included in this initial guidance on booster doses of COVID-19 vaccine:

- The key populations identified by NACI for early COVID-19 immunization were prioritized due to an increased risk of severe illness and exposure. The evidence and rationale for prioritizing these groups is summarized in Table 2 of NACI's previous guidance. Those prioritized in the earliest stages may now be at an increased risk of waning of protection because for some of them, more time has elapsed since their second dose and a number of them were vaccinated with a very short interval between doses to optimize protection as quickly as possible.
- The combined factors of high risk of severe outcomes, high risk of exposure, increased time since completion of primary series, shorter interval between doses in the primary series (in some cases), and immunosenescence in older age can contribute to decreased protection and increase the risk for infection and possibly severe outcomes in the key populations for whom NACI recommends a booster dose of COVID-19 vaccine.
- An individual's risk benefit analysis for a booster dose recommended in key populations should include an assessment of:
    - Risk of severe illness from COVID-19 (e.g., older age, underlying medical condition)
    - Risk of increased waning of protection (e.g., shorter interval between doses, longer time since completion of primary series, vaccination with only viral vector COVID-19 vaccines)
    - Local epidemiology (e.g., circulation of VoC, evidence of waning protection)
    - Vaccine coverage of primary series in the community (e.g., the risk of breakthrough infection in fully vaccinated individuals is higher in the context of high community rates of SARS-CoV-2 especially where vaccination coverage rates for the primary COVID-19 vaccine series are low)
    - Health system capacity

Long-term care residents and seniors living in other congregate settings

- Refer to NACI's Rapid response: Booster dose in long-term care residents and seniors living in other congregate settings for a summary of the evidence and rationale for booster doses in this population.

Older age

- There are some signs that decreasing protection may be greater in older age groups and in individuals with clinical risk factors for more severe outcomes [27, 28]. Among the fully vaccinated, older age groups (80 years of age and over, followed by those 70 to 79 years of age) have the highest hospitalization and mortality rates from COVID-19 compared to younger age groups who are fully vaccinated.
- There was a large independent association of severe COVID-19 with increasing age and moderate certainty of evidence for a very large association of hospitalization and mortality particularly in those over 70 years of age in OECD countries before vaccination [69].
- The proportion of individuals with at least one underlying medical condition associated with an increased risk of severe COVID-19 increases with increasing age [70].
- It is important to acknowledge that the regulatory submission for a Moderna booster dose is for half the current dosage of Moderna Spikevax (i.e., a 50 mcg booster dose vs. 100 mcg full dose). However, as older adults have dampened immune function, and may need to receive a higher dose formulation of a vaccine or an immunostimulatory adjuvant to increase the potency of their response to vaccines, this population may benefit from a full dose (100 mcg) of Moderna Spikevax as a booster dose [11].

Recipients of only viral vector vaccines

- Individuals who received a complete series with only a viral vector vaccine have somewhat lower initial VE and may experience waning protection. Emerging data suggests vaccine protection against infection and symptomatic infection decreases more quickly with viral vector vaccines in comparison to mRNA vaccines.
- NACI preferentially recommended COVID-19 vaccination with mRNA vaccines [1] due to their high efficacy and safety and the availability of mRNA vaccine supply in Canada. Only a small percentage of fully vaccinated Canadians to date (<1%) have been vaccinated with only viral vector vaccines.

Adults in or from First Nations, Inuit and Métis communities

- The rate of active COVID-19 cases started rising in First Nations communities in August 2021 and was 4.2 times higher than the rate in the general population as of October.
- Racialized and marginalized populations such as Indigenous Peoples have been disproportionately affected by COVID-19 due to a number of intersecting equity factors.
- The proportion of Canadians who identify as Indigenous and have at least one underlying medical condition associated with severe COVID-19 is higher compared to other Canadians for every age category above 20 years of age. This increases the risk of severe outcomes for COVID-19 in this population.
- Remote or isolated communities may not have ready access to sufficient healthcare infrastructure. Therefore, their risk for severe outcomes, including death, and societal disruption is proportionally greater than in other communities.
- The risk of transmission is higher in settings where physical distancing and other infection prevention and control measures are challenging and individuals may not be able to exercise sufficient precautions to adequately protect themselves from infection.

- Immunization of individuals in this population has the potential to reduce or prevent the exacerbation of intersecting health and social inequities.
- Adults in or from Indigenous communities were included in the earliest stages of initial COVID-19 immunization and may be at increased risk of waning of protection because for some of them, more time has elapsed since their second dose and a number of them were vaccinated with a very short interval between doses to optimize protection as quickly as possible.
- Autonomous decisions should be made by Indigenous Peoples with the support of healthcare and public health partners in accordance with the United Nations Declaration on the Rights of Indigenous Peoples [71].

Frontline healthcare workers

- Maintaining health system capacity is crucial to minimize serious illness and overall deaths while minimizing societal disruption as a result of the COVID-19 pandemic.
- Frontline healthcare workers can be at risk for occupational exposure and can potentially transmit infection to vulnerable populations. Healthcare workers are essential to the provision of healthcare, and their absence due to illness could compromise health system capacity. At present, the health system continues to be strained due to the hospitalization of people with COVID-19, especially where infection rates have been high during the fourth (Delta) wave in Canada. Optimizing the protection of healthcare workers can help to balance any disproportionate burden of those taking on additional risks to protect the public, thereby upholding the ethical principle of reciprocity.
- The risk of waning of protection is associated with shorter intervals between doses in the primary vaccine series. Therefore, while frontline healthcare workers who received their second dose at very short minimum intervals (less than 28 days) from the first dose were well protected in the short-term, the durability of that protection may wane more quickly than those who had a longer interval between doses.
- There is evidence that the Moderna Spikevax vaccine remains efficacious against severe disease and asymptomatic infection at more than 5 months when given at the authorized interval of 28 days between doses [10]. There is evidence that while the Pfizer-BioNTech Comirnaty vaccine prevents COVID-19 effectively for up to 6 months, there is a gradual decline in efficacy when given at the authorized interval of 21 days between doses [34]. Emerging data also suggest that protection from Moderna Spikevax may be more durable compared to Pfizer-BioNTech Comirnaty [28, 39]; more research is required.

NACI is continuing to monitor the evidence related to waning immunity in various populations and the evidence on immunogenicity, safety and effectiveness of booster doses (including those who have been previously infected with SARS-CoV-2 and have received a complete primary vaccine series with authorized COVID-19 vaccines). NACI will update guidance as required.

Refer to NACI's Recommendations on the use of COVID-19 vaccines for further information on COVID-19 vaccines.

Refer to NACI's Guidance on the prioritization of key populations for COVID-19 immunization for further information on NACI's initial framework and foundational elements guiding ethical decision-making.

Table 2. Strength of NACI Recommendations

Strength of NACI Recommendation *based on factors not isolated to strength of evidence* (e.g., public health need)	**STRONG**	**DISCRETIONARY**
Wording	"*should/should not be* offered"	"*may/may not be* offered"
Rationale	Known/anticipated advantages outweigh known/anticipated disadvantages ("should"), OR Known/Anticipated disadvantages outweigh known/anticipated advantages ("should not")	Known/anticipated advantages are closely balanced with known/anticipated disadvantages, OR uncertainty in the evidence of advantages and disadvantages exists
Implication	A strong recommendation applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present.	A discretionary recommendation may/may not be offered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

Research Priorities

1. What is the efficacy, effectiveness, immunogenicity and safety of booster dose COVID-19 vaccine individuals who have had a previous laboratory-confirmed SARS-CoV-2 infection?
2. What is the effect of booster doses of COVID-19 vaccines on transmission of infection at a population level? How long do any beneficial effects on transmission last?
3. Is a booster dose required after a 3-dose primary series of COVID-19 vaccines in those who are moderately to severely immunocompromised?
4. What is the optimal product (including the booster vaccine in relation to the product(s) received for the primary series), booster vaccine dose, interval between doses in the primary series, interval between the primary series and additional/booster dose, and potential need for (and frequency of) future booster doses in groups at high risk for severe COVID-19 outcomes and in the general population to ensure protection against SARS-CoV-2?
5. What is the optimal timing and trigger for booster doses? What are the risks associated with providing a booster dose earlier than necessary?
6. Will special adverse events that have been associated with the primary series (e.g., myocarditis/pericarditis) also be associated with additional/booster doses? Will any new or previously unrecognized adverse event occur with booster doses?

7. What is the efficacy, effectiveness, immunogenicity, and safety of booster doses of COVID-19 vaccine following a complete series across diverse population groups (e.g., adults of advanced age, those with high-risk medical conditions including autoimmune conditions and transplant recipients, individuals with social or occupational vulnerabilities, individuals who are pregnant or breastfeeding, adolescents, frailty)?

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NACI members: S Deeks (Chair), R Harrison (Vice-Chair), J Bettinger, N Brousseau, P De Wals, E Dubé, V Dubey, K Hildebrand, K Klein, J Papenburg, A Pham-Huy, C Rotstein, B Sander, S Smith, and S Wilson.

Liaison representatives: LM Bucci (Canadian Public Health Association), E Castillo (Society of Obstetricians and Gynaecologists of Canada), A Cohn (Centers for Disease Control and Prevention, United States), L Dupuis (Canadian Nurses Association), J Emili (College of Family Physicians of Canada), D Fell (Canadian Association for Immunization Research and Evaluation), M Lavoie (Council of Chief Medical Officers of Health), D Moore (Canadian Paediatric Society), M Naus (Canadian Immunization Committee), P Emberley (Canadian Pharmacists Association), L Bill (Canadian Indigenous Nurses Association), and S Funnel (Indigenous Physicians Association of Canada).

Ex-officio representatives: V Beswick-Escanlar (National Defence and the Canadian Armed Forces), E Henry (Centre for Immunization and Respiratory Infectious Diseases (CIRID), PHAC), M Lacroix (Public Health Ethics Consultative Group, PHAC), C Lourenco (Biologic and Radiopharmaceutical Drugs Directorate, Health Canada), S Ogunnaike-Cooke (CIRID, PHAC), K Robinson (Marketed Health Products Directorate, HC), G Poliquin (National Microbiology Laboratory, PHAC), and T Wong (First Nations and Inuit Health Branch, Indigenous Services Canada).

NACI High Consequence Infectious Disease Working Group

Members: R Harrison (Chair), Y-G Bui, S Deeks, K Dooling, K Hildebrand, M Miller, M Murti, J Papenburg, R Pless, S Ramanathan, N Stall, and S Vaughan.

PHAC participants: N Abraham, L Coward, N Forbes, C Jensen, A Killikelly, R Krishnan, J Montroy, A Nam, M Patel, M Salvadori, A Sinilaite, R Stirling, E Tice, B Warshawsky, R Ximenes MW Yeung, and J Zafack.

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TAB 40

See Tab 39 at Pg. 16

TAB 41

See Tab 39 at Pg. 18

TAB 42

See Tab 39 at Pg. 18

TAB 43

Standard on the Contraindications and Precautions Related to Immunization

Section : 5.0	**Contraindications and Precautions**		**Standard #: 05.100**
Created by:	Province-wide Immunization Program, Standards and Quality		
Approved by:	Dr. Gerry Predy, Senior Medical Officer of Health, Alberta Health Services		
Approval Date:	June 1, 2015	**Revised:**	September 12, 2016

Preamble

AHS Province-wide Immunization Program Standards and Quality, Population, Public and Aboriginal Health Division provides Public Health and other partners who administer provincially funded vaccines with ongoing and timely information relating to province-wide immunization program standards and quality. These standards are based on currently available evidence based information, Alberta Health (AH) policy, and provincial and national guidelines. Immunizers must be knowledgeable about the specific vaccines they administer.

Background

Vaccines are safe and an important strategy in communicable disease control, to prevent or reduce many communicable diseases; vaccines undergo stringent testing through clinical trials to ensure they are safe and efficacious and that there are measures in place to monitor side effects related to vaccines.

A contraindication is a condition in a recipient that **increases** the risk for a serious adverse reaction or a situation where the risks of vaccine outweigh any potential therapeutic benefit. Examples of contraindications are known anaphylaxis to a vaccine or a vaccine component or immune compromising conditions related to therapy or disease.

A precaution is a condition in a recipient that **may increase** the risk for a serious adverse reaction or that might compromise the ability of the vaccine to produce an optimal immune response. The majority of contraindications and precautions are temporary, and immunizations often can be administered later if one or more exist.

All vaccine providers should assess the current health and any chronic conditions of the client to identify contraindications and precautions to the vaccine before each dose is given.

Purpose

This standard is an important resource for immunizers to use for a consistent approach to client assessment prior to vaccine administration. It summarizes information available related to contraindications and precautions. This standard is not intended to replace information contained in the individual vaccine biological pages**.** It can be used in conjunction with the following standards (including but not limited to):

- *Standard for Recommended Immunization Schedules*
- AHS Immunization Policy Suite for Consent to Treatment(s) / Procedure(s) http://insite.albertahealthservices.ca/2270.asp

- *Standard for the Administration of Immunizations*
- *Vaccine Biological Pages*
- *Standard for the Immunization of Individuals with Chronic Health Conditions and/or Immunosuppression*
- *Standard for Reporting and Follow-Up of Adverse Events Following Immunization*
- *Standard for Immunization of Transplant Candidates and Recipients*

Applicability

This standard applies to all immunizers providing provincially funded vaccine to members of the public with the health conditions covered in this standard.

Definitions:

Contraindication:
Situation in which a vaccine should **not** be given because the risk of an adverse event outweighs any potential therapeutic benefit of the vaccine. The only true permanent contraindication to all vaccines is a history of anaphylactic reaction to a previous dose of vaccine or to a vaccine component. Many contraindications are temporary (e.g., pregnancy is a contraindication to live vaccine) and the vaccine can usually be given at a later time.

Precaution: A condition that may increase the risk of an adverse reaction following immunization or that may compromise the ability of the vaccine to produce immunity. In general, vaccines are deferred when a precaution is present. However, there may be circumstances when the benefits of giving the vaccine outweigh the potential harm, or when reduced vaccine immunogenicity may still result in significant benefit (e.g., providing inactivated vaccine to an immunocompromised individual). A risk benefit assessment is required.

Competency

In November 2008 the Public Health Agency of Canada published the Immunization Competencies for Health Professionals with a goal of promoting safe and competent practices for immunization providers. The following competencies outlined in that document are applicable for this standard:

- Explains how vaccines work using basic knowledge of immune system.
- Demonstrates an understanding of the rationale and benefit of immunization, as relevant to the practice setting.
- Applies the knowledge of the components and properties of immunizing agents as needed for safe and effective practice.
- Communicates effectively about immunization as relevant to the practice setting(s).
- Recognizes and responds to the unique immunization needs of certain population groups.

Section 1: Contraindications and Precautions/ Fit to Immunize

The following is a summary of the most common contraindications and precautions. It does not encompass every possible contraindication for each vaccine. It is important that an assessment of possible contraindications and precautions is done prior to each dose of vaccine. Consult with the Medical Officer of Health (MOH)/designate as required. Refer to *vaccine specific biological pages* for further detail.
The following is a general summary of areas that should be assessed for each client at every immunization appointment before vaccine is given. The Fit To Immunize Assessment Tool is also available for staff to use as a general guide for client assessment prior to immunization.

1. **Current or Recent Illness:**
   - A moderate or severe illness with or without fever is a reason to defer most vaccines until the person has recovered from the acute phase of the illness. This precaution avoids possible confusion between a symptom of the disease and an adverse effect from the vaccine.
   - A minor illness with or without fever; a recent viral infection from which the client is recovering; antibiotic therapy (with the exception of some live oral vaccines – e.g., oral typhoid); and recent exposure to a communicable disease are not generally contraindications or reasons to defer immunization.

2. **Chronic Health Conditions:**
   Certain health conditions may require alteration of immunization technique or schedule, depending on the condition and the vaccine to be given. Consultation with the physician or MOH/designate should be sought when required.
   - See *Standard for the Administration of Immunizations* for detail related to specific injection techniques.
   - See *Standard for the Immunization of Individuals with Chronic Health Conditions and/or Immunosuppression* for detail on specific health conditions such as Hematopoietic Stem Cell Transplant (HSCT), Solid Organ Transplant (SOT), immunocompromised individuals, etc.

2.1. Asthma

- Live Attenuated Influenza Vaccine (LAIV) should not be administered to individuals with severe asthma or those with medically attended wheezing in the seven days prior to immunization. See *influenza specific biological pages* for details.
- Severe asthma is defined as currently on oral or high dose inhaled glucocorticosteroids or active wheezing.
  - High dose inhaled steroid is defined as an individual taking greater than 500 mcg per day of inhaled steroid regardless of age and drug (AHS MOH recommendation).
- LAIV can be given to stable, non-severe asthmatics.

2.2. Immunocompromised Persons

- In general, individuals who are immunocompromised, whether from disease or from therapy, should not receive live vaccines because of the risk of disease caused by the vaccine strains. However, there may be situations where the benefit of vaccine outweighs the risk. When considering immunization of an immunocompromised person with a live vaccine, approval from the individual's attending physician and MOH/designate should be obtained before immunization.
- An immunocompromised person may not respond as well as a healthy individual to an inactivated vaccine, however, inactivated vaccine is unlikely to cause harm to the client. Refer to Standard on the Immunization of Individuals with Chronic Health Conditions and/or Immunosuppression for more detail.

2.3. Family History of Immunodeficiency Disorders

People who have a family history of immunodeficiency disorders (e.g., known or suspected congenital immunodeficiency disorder, HIV infection, or failure to thrive and recurrent infection), should not be immunized with a live vaccine until they have been fully investigated and immunodeficiency disorder has been ruled out. Immunodeficiency states may be undiagnosed in young children presenting for routine immunizations, which include live vaccines. This is particularly important to consider in infants receiving live vaccines (e.g., travel vaccines) before 12 months of age since underlying conditions are less likely to be diagnosed in younger children.

2.4. Tuberculosis, active, untreated

Measles, Mumps, Rubella (MMR), Measles, Mumps, Rubella-Varicella (MMR-V), varicella, and herpes zoster (shingles) vaccines are contraindicated in individuals with active, untreated tuberculosis as a precautionary measure. Although tuberculosis may be exacerbated by natural measles infection, there is no evidence that measles or varicella-containing vaccines have such an effect.

2.5. Transplant Recipients

Transplant candidates and recipients need special consideration when determining their immunization requirements. There are some vaccines which may be contraindicated for these individuals. See Standard for Immunization of Transplant Candidates and Recipients and individual biological pages for details.

2.6. Bleeding Disorders

Individuals with bleeding disorders (e.g., hemophilia or Von Willebrand disease) may differ from the general population with respect to the risk of hematoma formation from intramuscular (IM) injections, and the potential for increased risk of infection from their disease or frequent exposure to blood products. Control of bleeding disorders should be optimized prior to immunization. Individuals with bleeding disorders who may require immunization with large volumes of vaccine or biologicals (e.g., HBIG, RIG, IG) should be assessed by their attending physician on an individual basis for the need for clotting factor concentrates prior to immunization. See Standard for the Administration of Immunizations for additional details on administering vaccines to individuals with bleeding disorders.

Individuals receiving long-term anticoagulation with either warfarin or heparin are not considered to be at higher risk of bleeding complications, provided instructions found in Section 3 of the Vaccine Administration Standards are followed. They may be safely immunized through either the IM or subcutaneous (SC) route as recommended without discontinuation of their anticoagulation therapy. There is a lack of evidence on whether there is an increased risk of bleeding complications following immunization with the newer types of anticoagulants, such as antiplatelet agents but there is no reason to expect that there is a greater risk of bleeding complications than with other anticoagulants.

A history of an intramuscular hematoma following immunization or abnormal/unexplained bruising should prompt investigation of a possible bleeding disorder prior to immunization.

3. **Medications**
   There may be some medications that individuals are taking which can present a precaution or a contraindication for some vaccines. Some examples include:
   - **Immunosuppressive medication/therapy**
     Individuals who are immunosuppressed either from disease or therapy should generally not receive live vaccine. Some inactivated vaccines may be recommended although the individual will likely have a lower immunogenic response. Refer to *Standard on the Immunization of Individuals with Chronic Health Conditions and/or Immunosuppression* for details.

   - **Chronic Salicylate Therapy in Children**
     - Individuals receiving low doses of salicylate therapy (e.g., 3 to 5 mg/kg/day of acetylsalicylic acid [ASA]) are not considered to be at increased risk of bleeding complications following immunization.
     - If child is taking daily low doses (3 to 5 mg/kg/day) of ASA, varicella immunization can safely be given if the child is NOT immunocompromised.[6]
     - Live Attenuated Influenza Vaccine should NOT be given to children 2-17 yrs. who are receiving ASA or ASA-containing therapy due to the association of Reye syndrome with ASA and wild-type influenza infection.(NACI Statement on Seasonal Influenza Vaccine for 2014-15).

   - **Antivirals**
     Antiviral therapy does not interfere with response to inactivated vaccines or most live vaccines with the following exceptions:
     - Varicella vaccine and herpes zoster vaccine may have reduced effectiveness if given concurrently with antivirals active against varicella zoster virus (e.g., acyclovir, valacyclovir, famciclovir). Individuals taking long-term antiviral therapy should discontinue these drugs, if possible, from at least 24 hours before administration of varicella or herpes zoster vaccine and should not restart antiviral therapy until 14 days after immunization. If therapy cannot be discontinued for this timeframe, consult with the zone MOH. Refer to *varicella vaccine specific biological* page for details.
     - LAIV should not be administered until 48 hours after antiviral agents active against influenza (e.g., oseltamivir and zanamivir) are stopped, and antiviral agents should not be administered until at least 14 days after receipt of LAIV unless medically indicated. If antiviral agents are administered within this time frame (from 48 hours before to 14 days after LAIV), re-immunization should take place at least 48 hours after the antivirals are stopped. Refer to *LAIV vaccine specific biological page* for details.

4. **Congenital Malformation of Gastrointestinal Tract or History of Intussusception**
   - Rotavirus vaccine is contraindicated in infants with a history of intussusception or uncorrected congenital malformation of the gastrointestinal tract (e.g., Meckel's diverticulum) that would predispose for intussusception. See *Rotavirus vaccine specific biological page* for details.

5. **Neurological**
   Neurologic disorders appear at different ages and may affect immunization decisions. Disorders that usually begin during infancy, such as cerebral palsy, spina bifida, seizure disorder, neuromuscular diseases and inborn errors of metabolism may have symptom onset before the receipt of the vaccines routinely recommended in infancy. Other conditions, such as autism spectrum disorders, acute demyelinating encephalomyelitis, Guillain-Barré syndrome (GBS), transverse myelitis and multiple sclerosis are known to be diagnosed in childhood and adulthood

over the same time period as routine vaccines are administered and may occur before or after the administration of vaccines.

- Neurologic conditions whose onset clearly precedes immunization are generally not contraindications to subsequent immunization.
- Vaccines are safe to give when there is a history of a febrile seizure. Children with a history of febrile seizures have no increased risk of developing a seizure disorder, such as epilepsy. Oral analgesics/antipyretics (e.g., acetaminophen or ibuprofen) can be used for treatment of minor adverse reactions such as fever or injection site discomfort that might occur following immunization. There is no evidence that antipyretics prevent febrile seizures and therefore there is no need to recommend prophylactic antipyretic use.
- History of febrile seizures or any seizure in a first generation family member (parents or siblings) is not a contraindication to immunization.
- Significant head injury – immunization should be deferred for 24 hours to ensure any sequelae have resolved.

6. Recent Administration of Human Immune Globulin or Other Blood Products:

- Blood products and immune globulins may contain antibodies that interfere with the immune response to a live vaccine. See *Standard for Recommended Immunization Schedules* for detail on intervals that must be respected before giving a live vaccine after receipt of a blood product.

7. Live Vaccine in the Previous Month:

- Live vaccines must be administered concurrently or be separated by at least 4 weeks. Live attenuated influenza vaccine (LAIV) may be administered any time before or after the administration of other live attenuated or inactivated vaccines. Specialists recommending alternate spacing for specific high risk individuals may be accommodated on a case by case basis. Refer to the *MMR, MMR-Var and varicella vaccine specific biological pages* and the *Standard for Recommended Immunization Schedules* for specific recommendations for intervals between vaccines containing measles, mumps, rubella and varicella antigens.

8. Previous Adverse Reaction:

- An essential component of an immunization program is vaccine safety and the activities and processes to detect, assess, understand and communicate adverse events following immunization (AEFI) – vaccine pharmacovigilance. If reactions occur, they are usually mild, fairly predictable and self-limiting. More serious or unexpected reactions can occur but are rare. It is therefore important for health care providers to monitor vaccine side effects and to report immediately all serious or unexpected AEFI. Prior to immunization, an assessment of the client's reactions to previous vaccines should be conducted.
- Mild to moderate vaccine associated adverse events (e.g., swelling, redness, fever, pain) are expected, relatively common and self-limited. These are not a contraindication to immunization.
- If an adverse reaction has been previously reported, the provider should review the recommendations, consider current guidelines, consult the MOH/designate when required and proceed as appropriate.
- If an adverse reaction is being reported during the assessment, follow the guidelines to report in the Standard for Reporting and Follow-Up of Adverse Events Following Immunization.
- Follow the Guidelines for Immunization After an AEFI Has Been Reported or Submitted in the Standard for Reporting and Follow-Up of Adverse Events Following Immunization to determine whether or not to give vaccine while awaiting response to an AEFI report. Consultation with the zone MOH may also be necessary.

8.1. Guillain-Barré syndrome (GBS):

GBS is an illness that involves acute onset of bilateral flaccid weakness or paralysis of the limbs with decreased or absent deep tendon reflexes. It may be a contraindication to receiving vaccines as outlined below.

- Individuals who develop GBS within 6 weeks of receipt of a tetanus containing or influenza vaccine and where there is no other cause for the GBS identified, should not receive further doses of the same vaccine.
- Those who develop GBS outside the above timeframes may receive subsequent doses of the vaccine.
- There is no contraindication to immunization for individuals who have a history of GBS unrelated to immunization

8.2. Oculo-Respiratory Syndrome

Oculo-Respiratory Syndrome (ORS) is a set of signs and symptoms of both the eyes and respiratory system that can occur following influenza immunization. Refer to *vaccine specific influenza biological pages* as well as *Standard for Reporting and Follow-Up of Adverse Events Following Immunization* for further details.

9. Allergies:

An allergic reaction is an acquired hypersensitivity considered to be related either to the vaccine components or the antigen itself. Individuals may report an allergy to a number of vaccine components, such as gelatin, latex, neomycin or thimerosol. Anaphylactic reactions to these components are extremely rare. When mild hypersensitivity reactions occur, vaccines that are administered subcutaneously or intramuscularly are generally safe.

- Allergy to vaccine components must be ascertained prior to vaccine administration.
- Anaphylaxis to a vaccine component is a contraindication to further administration with the same vaccine or a vaccine with the same components. In situations where the need for the vaccine and/or a biologic outweighs the risks of anaphylaxis (e.g., post exposure prophylaxis) case by case consultation with the MOH/designate is required.
- The amount of egg/chicken protein in measles/mumps containing vaccines has been found to be insufficient to cause an allergic reaction in egg-allergic individuals.
  - Studies of egg allergic individuals have shown that there is no increased risk of severe allergic reaction to MMR/MMR-Var vaccines.
- Egg allergic individuals may be immunized with inactivated influenza vaccine (TIV or QIV) or live attenuated influenza vaccine (LAIV).
- Advise vaccine recipients to remain in the waiting area for at least 15 minutes after immunization administration.
- Advise vaccine recipients who have had an anaphylactic reaction to any agent, vaccine related or not, to wait for 30 minutes post immunization.
- Referral to an allergist may be indicated prior to immunization
- See *Standard for Reporting and Follow-Up of Adverse Events Following Immunization*

9.1. Latex Allergy

- Latex is sap from the commercial rubber tree. Latex is processed to form natural rubber latex and dry natural rubber. Both products contain the same plant impurities (plants peptides and proteins) found in natural latex and are believed to trigger allergic reactions.
- Dry natural rubber is used in some syringe plungers, vial stoppers and needle shields.
- Synthetic rubber and synthetic latex do not contain natural rubber or natural latex and therefore do not contain the impurities linked to allergic reactions.

- The most common type of reaction to latex is contact dermatitis, which is NOT a contraindication to immunization with a vaccine containing latex in the packaging.
- If an individual reports anaphylaxis to latex, consultation with the MOH/designate is required prior to immunization with a vaccine containing latex in the packaging. There may be an alternate vaccine product available that is latex free that could be provided.

10. Pregnancy:

Pregnancy is a temporary precaution or contraindication to immunization. There is very little data related to giving vaccines to a pregnant individual.

- For most inactivated vaccines, pregnancy is a precaution, rather than a contraindication, to immunization; however, human papillomavirus (HPV) vaccine is not recommended for pregnant women due to inadequate safety and immunogenicity data. Refer to *vaccine specific biological pages* for details on pregnancy.
- Live vaccines are generally contraindicated during pregnancy due to the theoretical risks to the fetus. Live vaccine would be considered for a pregnant woman only if the risk of disease is high and outweighs the theoretical risk to the fetus. This decision is always made in consultation with the physician and MOH/designate.
- Immunosuppressive therapy given to a mother during pregnancy can cause immunosuppression of infants. Consultation with zone MOH/designate is necessary to assess live vaccine eligibility.
- If a pregnant woman is inadvertently immunized with a live vaccine, check appropriate product monograph for instructions on reporting to manufacturer.

11. Lactation:

Routinely recommended vaccines may be safely administered to breastfeeding women. There are limited data available regarding the effects of maternal immunization on breastfed infants; however, there have been no reported adverse events thought to be vaccine-related. Generally, there is no evidence that immunization during breastfeeding will adversely influence the maternal or infant immune response. Refer to *vaccine specific biological pages* for detailed information on lactation.

- Immunosuppressive therapy given to a mother during lactation can cause immunosuppression of infants. Consultation with the zone MOH may be necessary to assess live immunization of the infant in these situations.

12. Limb Integrity:

Do not administer an immunizing agent in a limb that is likely to be affected by a lymphatic system problem, such as lymphedema or mastectomy with lymph node curettage. The vastus lateralis is an alternative site for all ages. Individuals who present with A-V fistula (vascular shunt for hemodialysis) and those who have had mastectomies, axilla lymphadenectomies, limb paralysis and upper limb amputations may have short term or long term circulatory (e.g., lymphatic systems) implications that may impair vaccine absorption and antibody production.

Section 2: Common Concerns which are Not Usually Contraindications

The following is a list of concerns which are commonly raised in a clinic setting, but are not usually contraindications to immunization. Each situation should be assessed on a case by case basis and consultation should be sought from the MOH/designate when required.

1. Recent surgery or upcoming surgery
- Minor surgery including dental procedures, is not a contraindication to immunization regardless of whether the procedure is done before or after immunization.
- Individuals awaiting splenectomy should ideally be immunized at least 14 days prior to or 14 days following the spleen being removed. See *Standard for the Immunization of Individuals with Chronic Diseases and/or Immunosuppression*

2. Family history of adverse event following immunization
- Adverse reactions to vaccines are not known to be inherited, except febrile seizures, and are therefore not usually a concern for the individual being immunized.

3. Prematurity
- Infants born prematurely regardless of birth weight should be immunized at the same chronological age and according to the same schedule and precautions as full term infants. An exception is preterm infants who weigh less than 2000 grams born to mothers with hepatitis B, who require an additional dose (see hepatitis B biological page).
- Antibody response to immunization is generally a function of post natal age and not maturity
- Very low birth weight infants (1500g) may experience a transient increase or recurrence of apnea and bradycardia following immunization. This subsides within 48 hours and does not alter the overall clinical progress of the child. If a child remains hospitalized at the time of their first immunizations, it is recommended that they have continuous cardiac and respiratory monitoring for 48 hours following immunization.

4. Topical Anesthetic Patches/Creams (e.g.,EMLA)
- The use of topical anesthetics is not an issue with regards to immunization.
- Placement of the product (cream or patch) should not interfere with appropriate siting for injection.
- See Standard for the Administration of Immunization for detail on the use of topical anesthetic products

5. Recent Exposure to an Infectious Disease
- Provided the client is fit to immunize at the time of the clinic visit, vaccines may be given according to recommendations outlined in the vaccine biological pages and notifiable disease follow-up guidelines. For non-immune contacts of vaccine preventable notifiable disease, the MOH/designate will have provided guidance on when immunization should be given to minimize the risk of exposure to an infectious contact.
- Counseling on incubation periods and expected reactions to immunization should be provided to the client/parent
- Previous disease does not always confer lifelong immunity; refer to vaccine specific biological pages.

6. Lactose
- Lactose is an ingredient in some vaccines. It does not have the potential to cause an immunogenic response.
- Dairy allergy is usually related to the milk protein and not the lactose.
- Lactose intolerance is not a contraindication to receiving vaccines which contain lactose.

Related Documents

- Fit to Immunize Assessment Tool (September 12, 2016)

References

1. Centers for Disease Control and Prevention. General Recommendations on Immunization: Recommendations of the Advisory Committee on Immunization Practices. MMWR 2011;60(2):
2. Alberta Health, Health System Accountability and Performance Division, Alberta Immunization Policy (2015 February 25). *Contraindications and Precautions to Immunization*.
3. Alberta Health, Acute Care and Population Health Division, *Adverse Events Following Immunization (AEFI) Policy for Alberta Health Services Public Health (2014, January)*.
4. BC CDC Immunization Manual (2009) http://www.bccdc.ca/dis-cond/comm-manual/CDManualChap2.htm (accessed 2015Feb06)
5. National Advisory Committee on Immunization. (2012). *Canadian immunization guide (Evergreen Edition).* Ottawa, ON: Public Health Agency of Canada. http://www.phac-aspc.gc.ca/publicat/cig-gci/

TAB 44

MMR

Measles-Mumps-Rubella Combined Vaccine

Implementation Date: January 1, 2021

Rationale for Update:

- Schedule change: Second dose of MMR moved from 4 years of age to 18 months of age.
- Recommendations for travelling updated.

Please consult the Product Monograph[1,2] for further information about the vaccine.		
	M-M-R® II	**PRIORIX®**
Manufacturer	Merck Canada Inc.	GlaxoSmithKline Inc.
Licensed use	Individuals 12 months of age and older.	
Off-license use	Infants 6 months up to and including 11 months of age who are: • Travelling to areas where measles is circulating (see indications). • Contact of a measles case (see indications for post-exposure). • Pre solid organ transplant (see Child Solid Organ Transplant for indications)	
Indications for use of provincially funded vaccine	**Pre-exposure:** **Infants:** 6 months up to and including 11 months of age **Note:** • Infants 6 months up to and including 11 months of age traveling to areas where measles is circulating in Canada and all countries outside of Canada should receive one dose of measles-containing vaccine.[3] • Two additional doses of measles-containing vaccine should be administered at 12 months of age and older and with the appropriate interval between doses are required for long term protection. **Children:** 12 months up to and including 17 years of age. **Note:** • When both MMR vaccine and varicella vaccine are indicated for children 12 months up to and including 12 years of age, MMR-Varicella combined vaccine should be considered. **Adults:** **Measles** ➢ Individuals born in 1970 or later without a documented history of two doses of measles-containing vaccine, history of laboratory confirmed measles disease or laboratory evidence of measles immunity.	

- Health care workers (HCW), regardless of their year of birth, without a documented history of two doses of measles-containing vaccine, history of laboratory-confirmed measles disease or laboratory evidence of measles immunity.[4]
- Students at post-secondary educational institutions born before 1970 without a documented history of measles-containing vaccine, history of laboratory-confirmed measles disease or laboratory evidence of measles immunity.[4]
- Adults born prior to 1970 without a documented history of measles-containing vaccine, history of laboratory-confirmed measles disease or laboratory evidence of measles immunity and who are travelling to areas where measles is circulating in Canada and all countries outside of Canada should receive one dose of measles-containing vaccine.[3]

Note: Individuals born before 1970 (regardless of country of birth) are generally presumed to have acquired natural immunity to measles; however, some of these individuals may be susceptible.[4]

Mumps

- Individuals born in 1970 or later without a documented history of two doses of mumps-containing vaccine or history of laboratory-confirmed mumps disease.
- HCW, regardless of their year of birth, without a documented history of two doses of mumps-containing vaccine or history of laboratory-confirmed mumps disease.[4]
- Students at post-secondary educational institutions born before 1970 without documented history of one dose of mumps-containing vaccine or history of laboratory-confirmed mumps disease.[4]

Note: Adults born before 1970 are generally presumed to have acquired natural immunity to mumps; however some of these individuals may still be susceptible.[4]

Rubella

- Individuals born in 1957 or later[5] without a documented history of one dose of rubella- containing vaccine, history of laboratory-confirmed rubella or laboratory evidence of rubella immunity.
- HCW (regardless of age) who have face-to-face contact with patients in health care facilities are required to have documented immunity to rubella under the Communicable Diseases Regulation, Alberta Regulation 238/1985.[6]
- Staff of daycare facilities (regardless of age). Communicable Diseases Regulation, Alberta Regulation 238/1985.[6]
- Rubella immunization should be prioritized for the following susceptible individuals:
  - Women of child-bearing age.
  - HCW
  - Staff of daycare facilities

Note: Adults born before 1957 are generally presumed to have immunity to rubella; however some of these individuals may still be susceptible.[5]

Notes:

- Immunization of HIV-infected children and adults should be completed under the direction of the infectious disease specialist attending the individual.

- Child and adult recipients of hematopoietic stem cell transplant (HSCT). See:
  - Immunization for Child Hematopoietic Stem Cell Recipients and
  - Immunization for Adult Hematopoietic Stem Cell Recipients.

- Child and adult candidates for solid organ transplant (SOT). See:
  - Immunization for Children Expecting Solid Organ Transplant before 18 Months of Age,
  - Immunization for Children Expecting Solid Organ Transplant after 18 Months of Age (Catch-up and Ongoing) and
  - Immunization for Adult Solid Organ Transplant Candidates and Recipients.

Post-exposure:

Measles

- Susceptible contacts of a measles case should receive either MMR or Immune Globulin (IG) depending upon the time-lapse from exposure, age and health status.
- Susceptible immunocompetent contacts 6 months of age and older should receive measles-containing vaccine. The vaccine should be administered within 72 hours of exposure and should not be delayed pending serology results.[7,8]
- Children younger than four years of age who have received one dose of measles-containing vaccine (considered up-to-date) should receive a second dose of measles-containing vaccine ensuring the recommended interval spacing between the vaccine doses.[8]
- If measles-containing vaccine is contraindicated or if more than 72 hours since exposure have elapsed, Immune Globulin (IG) may be indicated, See Biological Products- Immune Globulin (Human).
- If measles-containing vaccine is administered more than 72 hours after exposure, it may not provide protection against the current exposure but would offer protection against subsequent exposures.

Note: As an outbreak control strategy during a measles outbreak, the Medical Officer of Health may recommend MMR vaccine for children 6 – 11 months of age inclusive.[7]

For disease investigation, contact assessment and reporting requirements, refer to *Public Health Notifiable Disease Guidelines – Measles*.[8]

Mumps

- Susceptible contacts should be immunized.

Note: Post-exposure immunization with mumps-containing vaccine does not prevent or alter the clinical severity of mumps. However, if the exposure to mumps does not cause infection, the post-exposure immunization should induce protection against subsequent infection.[4]

For disease investigation, contact assessment and reporting requirements refer to *Public Health Notifiable Disease Guidelines – Mumps*.[9]

Rubella

- Susceptible contacts should be immunized

Note: Post-exposure immunization with rubella-containing vaccine does not prevent or alter the clinical severity of rubella after exposure. However, if the exposure to rubella does not cause infection, the post-exposure immunization should induce protection against subsequent infection.[4]

	For disease investigation, contact assessment and reporting requirements refer to *Public Health Notifiable Disease Guidelines – Rubella*.[10]
Use in infants younger than 12 months of age	Infants younger than 12 months of age may not respond sufficiently to the measles component of the vaccine in part due to the persistence of maternal measles antibody; therefore, any MMR-containing vaccine dose administered before 12 months of age should be repeated at 12 months of age or older.[4]
Dose	0.5 mL
Route	Subcutaneous
Schedule	**Children 12 months –17 years of age:** ❖ Dose 1: 12 months of age ❖ Dose 2: 18 months of age **Notes:** • Most children in Alberta routinely receive measles, mumps, rubella and varicella combined vaccine (MMR-Var) at 12 months and at either 18 months or 4 years of age. See Measles, mumps, rubella and varicella combined vaccine. • Children who have presented for their 18 month immunization prior to January 1, 2021 will be offered their second dose of measles-containing vaccine when they present for the preschool booster. • The second dose of MMR may be administered with a minimum interval of four weeks between the doses if child is off schedule or rapid protection is required.[4] • Children traveling to areas where measles is circulating in Canada and all countries outside of Canada should have two doses of measles-containing vaccine with the appropriate minimum interval between doses dependent upon the measles-containing vaccine used.[3] • Children who have received a dose of measles-containing vaccine before 12 months of age require two additional doses of MMR-containing vaccine. Both doses must be administered on or after the first birthday and separated by the appropriate interval. **Adults (18 years of age and older):** **Measles** **Adults born in 1970 or later**: ❖ Two life-time doses with at least four weeks between doses. **Health care workers**: ❖ Two life-time doses with at least four weeks between doses.[4] **Students at post-secondary educational institutions born before 1970**: ❖ One life-time dose.[4] **Note**: Individuals with two documented doses of a measles- containing vaccine do not require a third dose regardless of negative or indeterminate measles serology. Such persons should be considered to have presumptive evidence of immunity.[11]

	Mumps **Adults born in 1970 or later**: ❖ Two life-time doses with at least four weeks between doses. **Health care workers**: ❖ Two life-time doses with at least four weeks between doses.[4] **Students at post-secondary educational institutions**, ❖ Born before 1970 - one life-time dose should be considered.[4] **Rubella** **Adults born in 1957 or later**: ❖ One life-time dose. [5] **Health care workers and staff of daycare facilities (regardless of age)**: ❖ One life-time dose. [6] **Note**: Individuals with two documented doses of a rubella-containing vaccine do not require a third dose regardless of negative or indeterminate rubella serology.[12] Such persons should be considered to have presumptive evidence of immunity except for pregnant females.[5,11] **Pregnant females:** A third dose of rubella-containing vaccine is not indicated for pregnant females with two documented doses of rubella-containing vaccine. If pregnant females have negative or indeterminate rubella serology and are exposed to rubella disease - follow up as per *Public Health Notifiable Disease Guidelines – Rubella*.[10]
Specific Travel Indications and Recommendations	Individuals travelling to areas where measles is circulating in Canada and all countries outside of Canada. **Infants:** 6 months up to and including 11 months of age ❖ One dose of MMR vaccine.[3] **Note:** Two additional doses of measles-containing vaccine should be administered as per routine schedule at 12 months of age and older respecting recommended intervals. **Children:** 12 months up to and including 17 years of age. ❖ Dose 1: day 0 ❖ Dose 2: four weeks after dose 1 **Note:** When both MMR vaccine and varicella vaccine are indicated for children 12 months up to and including 12 years of age, MMR-Varicella combined vaccine should be considered. **Adults (18 years of age and older)** **Adults born in 1970 or later**: ❖ Two life-time doses with at least four weeks between doses. **Adults born prior to 1970:** ❖ Adults born prior to 1970 without a documented history of measles-containing vaccine, history of laboratory-confirmed measles disease or laboratory evidence of measles immunity should receive one dose of measles-containing vaccine.[3]

Spacing between MMR-Var and Yellow Fever vaccine	Recent limited data suggest it may be preferable for children aged 12-23 months of age to receive MMR-containing and YF vaccine at least 30 days apart if time permits, because of lower seroconversion rates for mumps, rubella, and yellow fever in those immunized simultaneously than in those immunized 30 days apart. The study did not include infants younger than 12 months of age, but it is reasonable to follow the same guidance for infants under 12 months of age.[7,8]

Contraindications	• Known severe hypersensitivity to any component of MMR vaccine.[1,2,4]
	• Anaphylactic reaction to a previous dose of vaccine containing measles, mumps or rubella antigens.[4]
	• Pregnancy.[1,2]
	• Impaired immune function, including those with primary or secondary immunodeficiency.[1,2]
	• Active untreated tuberculosis.[4]
	• Immunosuppressive therapy (including high dose corticosteroids).[1,4]
	• Family history of congenital or hereditary immunodeficiency, unless the immune competence of the potential vaccine recipient is demonstrated.[4]
	• Solid organ transplant recipients. See:
	  ○ Immunization for Children Expecting Solid Organ Transplant before 18 Months of Age,
	  ○ Immunization for Children Expecting Solid Organ Transplant after 18 Months of Age (Catch-up and Ongoing) and
	  ○ Immunization for Adult Solid Organ Transplant Candidates and Recipients.
	• Recent (within the previous 11 months) administration of immune globulins and blood products. The interval between the receipt of IG or a blood product and the subsequent MMR administration is dependent upon the IG of blood product received and the dosage administered.[4]
	Refer to Assessment Expected Prior to Vaccine Administration – Guidelines for Interval between Blood Products and Live Vaccines. See also Canadian Immunization Guide [4] – Blood products, human immune globulin and timing of immunization

Precautions	➢ Egg allergy is not a contraindication to immunization with MMR vaccine.[4] See Assessment Expected Prior to Vaccine Administration. ➢ The risk for vaccine-associated thrombocytopenia may be higher for persons who previously had thrombocytopenia, especially if it occurred in temporal association with an earlier MMR immunization.[15,16] Individuals, who develop vaccine-associated thrombocytopenia, should have serology to assess immunity to measles, mumps and rubella.[17] A second dose of vaccine should only be administered if non-immune and after careful consideration of the risks and benefits of the vaccine. ➢ Measles-containing vaccines are contraindicated in individuals with active, untreated tuberculosis as a precautionary measure. Tuberculosis may be exacerbated by natural measles infection, but there is no evidence that measles-containing vaccines have such an effect. It may be prudent to avoid vaccine in those with active TB disease until treatment is underway. Consultation with attending physician is recommended.[4] ➢ Immunization with a measles-containing vaccine can temporarily suppress tuberculin reactivity resulting in false-negative results.[4] If tuberculin skin testing is required, it should be done on the same day as immunization with a measles-containing vaccine or delayed for at least four weeks after immunization.[4] ➢ Live attenuated influenza vaccine (LAIV) may be administered any time before or after the administration of live parenteral vaccines (MMR, MMR-Var and VZ).[4]

Possible reactions	See Product Monograph
Pregnancy	MMR vaccine is contraindicated in pregnant women. Women of child- bearing potential should be advised to delay pregnancy for four weeks following immunization.[4]
Lactation	Breastfeeding mothers may be safely immunized with MMR vaccine. [4]
Program Notes	Program Notes: • 1982 October 1 – MMR®II introduced into routine program for 12 months of age. • 1983 September 04 to 1986 – MMR catch-up program for Grade 1 and 6. • 1996 June – MMR routine program second dose for 4-6 year olds. • 2007 November – MMR (second dose for HCWs and post-secondary students). Mass mumps campaign. • 2008 February 14 – Mumps-containing vaccine two doses for HCWs and post-secondary students born in 1970 or later. • 2010 September 1 – MMR-Var (Priorix-Tetra®) replaced MMR at 12 months for routine program. • 2017 June 1 – Adults born in or after 1970 eligible for 2 doses of mumps-containing vaccine. • 2018 April – Updated rubella vaccine indications to include: adults born before 1957 generally presumed to have immunity to rubella. Historical Notes: • 1966-1970 July – Killed Red Measles vaccine introduced. • 1969-1971 January 1 - E/Z Measles (Live) • 1970 July-1998 December 31 – Measles (red) dose catch up for Grades 1 to 9. • 1971 January 1 – Rubella became available. • 1972 January 1 to 1982 January 1 – Rubella (school program for Grade 6 girls) • 1982 February 1 to 2004 February 8 – Mumpsvax • 1997 January 1 to 1997 December 31 – Measles/Rubella second dose measles catch-up for Grades 1 to 9. • 1997 April 1 to 1998 June 30 – Measles (red) second dose measles catch-up for Grades 1 to 9 using monovalent measles vaccine. • 1997 January 1 – 1999 April 30 – Measles/Rubella – Second dose measles catch up for individuals in Grades 1 to 9. • 2013 September 26 – Two lifetime doses of mumps-containing vaccine recommended for all adults born in 1970 or later and HCWs regardless of year of birth. • 2021 January 1 – MMR second dose offered at 18 months instead of 4 years of age.

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TAB 46

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Alberta Health Services

Values-Based Decision-Making Toolkit

Find the complete ethical decision-making toolkit here

Ethics Decision-Making Process

MAKING GOOD DECISIONS

The following decision-making process can help you make sure appropriate questions are being asked and steps are being taken to address an ethical issue:

1 Clarify the key question	• Identify the central issue needing to be addressed
2 Identify facts & stakeholders	• Collect relevant facts and identify what you need but don't have • If it is a clinical issue, collect information about the medical diagnosis or prognosis, quality of life described in patient's terms, patient's preferences and contextual features • Are there any organizational policies or guidelines addressing the question? • What guidance do relevant laws give? • Which individuals are relevant to this issue and who should be part of the discussion and decision?
3 Identify values and prioritize	• What are the key values? • What is the central conflict in values? • How do you prioritize these values against each other? • What do you think is most important and why?
4 Identify options	• Identify all potential courses of action, even ones that don't immediately appear suitable
5 Make a decision & evaluate	• Assess each option against the values that you determined to be of priority in the step 3 above • Make a decision consistent with identified key values • Once the decision is made, follow up and evaluate so you can learn from this for next time

FURTHER INFORMATION

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For more resources, including the process toolkit, visit the **Clinical Ethics** page.

Questions

1. What question are we trying to answer?

The **Key Question**, that if answered will provide the team appropriate direction for how to move forward…

2. Identify the facts

Collect the relevant facts and identify anything missing that is critical to the decision.

What we know for sure: about the **patient/client/resident's identity, what is important to them, and their understanding of the context:**

What we know for sure: about the **person's medical condition,** treatment options, etc.

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What we know for sure: about the **person's sources of funding/ resources/supports**, where they live, what services/options are accessible

What we know for sure: about the **family, friends, and support people**

What we know for sure: about the other **care providers**, who is involved and what their perspectives are

What we know for sure: about **the system**, who else is affected, relevant policies, laws, etc.

What we don't know but can find out	**Who is responsible for getting this information?**

3. What are the key underlying values?

- Brainstorm what are important values that the decision should live up to (see Appendix for some examples)
- To be successful in this step requires a shared and clear agreement on the meanings of the values (and what living up to them would look like in real life)
- If there are values that can't be lived up to (because some are in tension/conflict/disagreement with others), prioritize them, then discuss your justifications for this

> **Tip:** avoid one-word values, these are open to different interpretations ("autonomy" vs. "support the patient to have final say over which treatment option they prefer")

VALUES LIST	How important are these relative to each other?
However we answer the question, it's important that…	Priority: 5 = *Crucial* 3 = Very *important* 1 = *Important*

4. Identify the options - what are some possible answers to the key question?

POSSIBLE OPTIONS

Option A	Option B	Option C

5. Make a decision and evaluate

ETHICS ANALYSIS: HOW WELL DOES EACH OPTION ALLOW US TO LIVE UP TO RELEVANT VALUES?

Possible ways of answering the question identified above include:	Option A *Enter answer from above table…*	Option B *Enter answer from above table…*	Option C *Enter answer from above table…*
Prioritized Value #1			

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How well does this allow us to				
	Prioritized Value #2			
	Prioritized Value #2			
	Prioritized Value #3			
	Prioritized Value #4			

Notes (if applicable)

Summary of decision recommendations

Our recommendation/decision
Our rationale for this decision/ recommendation is…

NEXT STEPS

Action that needs to be taken	Who will be accountable for doing this	Time line for action	How will outcomes be communicated back to decision team
Implementing the decision			
Communication - letting others know			
Reconvene to ensure decision having intended impacts			

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NECESSARY PARTNERSHIPS

People we should be working with	Contact Info	Who will be in touch with them?	Key questions or messages for the partner	How will outcomes be communicated to the decision team?
Professionals from other teams or services				
Loved ones or family members the patient would be comfortable including in the conversation				

Appendix

EXAMPLES OF COMMON VALUES IN HEALTHCARE DECISIONS

It's important that...

...we respect people's right to make decisions about their own lives, based on their own preferences, values, and beliefs.

...we promote the welfare of others, which may include preventing harm, removing harm, promoting well-being, or maximizing good.

...if decisions are made on behalf of a patient, they maximize benefits and minimize harms for the patient.

...we focus on relations between people and work to maintain those relationships.

...we accommodate, protect or support differences including cultural, religious, or others, among people and groups.

...we ensure we are faithful to the trust relationship with the patient; that we live up to our

commitments.

…we treat people and groups fairly by treating morally relevant cases alike.

…we promote fair relations among individuals and social groups.

…we ensure fair access to resources and opportunities, including fair distribution of benefits and burdens.

…we protect the vulnerable by assisting those who have to struggle to overcome social stigma, bias or historical injustice in order to achieve equal opportunity.

...we ensure people's quality of life. In other words, a person's ability to engage in activities they value, as judged from their perspective.

Adapted from the *Ethics Worksheet*, developed by the Core Curriculum Working Group of the Clinical Ethics Group at the Joint Centre for Bioethics, University of Toronto.


Alberta Health
Services

TAB 50

Public health ethics framework: A guide for use in response to the COVID-19 pandemic in Canada

On this page

Introduction

The public health threat posed by the COVID-19 pandemic has led all levels of government to take unprecedented measures to help slow the spread of COVID-19 and thereby minimise serious illness, death and social disruption resulting from the pandemic. Difficult choices are being made in a context of considerable uncertainty, as knowledge about COVID-19 and the impact of unprecedented public health measures evolves rapidly. Examples include decisions about allocation of scarce resources, prioritization guidelines for vaccines and medical countermeasures, curtailment of individual freedoms, and closing or re-opening public spaces, schools and businesses. Recognizing the fundamental ethical nature of these choices

can help decision makers identify competing values and interests, weigh relevant considerations, identify options and make well-considered and justifiable decisions.

Intended audience

This Framework is intended for use by policy makers and public health professionals making public health decisions in the context of COVID-19.

Intended application

This document is a guide to support ethics deliberation and decision-making in the public health response to the COVID-19 pandemic, including the transition to a new normal. It is based on several guidance documents and frameworks developed in Canada and internationally. Section 1 articulates ethical principles and values for public health authorities to consider, and Section 2 sets out a framework to help clarify issues, analyse and weigh relevant considerations, and assess options, in order to support decision making in real situations.

Ethical values and principles

Trust and Justice are the two key guiding values that underpin this framework. The ethical principles and procedural considerations that follow contribute to upholding and promoting trust and justice. Given that it may not be possible in some circumstances to uphold all values and principles equally, it will be important for decision makers to explain how they prioritised them, and to justify the trade-offs made in each situation.

Trust

Trust is the foundation upon which rest all relationships, whether between persons, persons and organisations, or citizens and government. Trust is essential to the success of the response to COVID-19. The effectiveness of many public health measures depends on the active cooperation of the public, and such cooperation is more likely if the public trusts the advice of public health authorities. Evidence that public health measures are achieving their intended outcomes, or alternatively, timely and transparent explanations of why they have not, also help to maintain and promote public trust. Without this trust, individual choices could contribute to the spread of COIVD-19 within the community. In the current context of uncertainty, being open, truthful and transparent in decision making and communication is essential to establishing and promoting trust.

Justice

Justice entails treating all persons and groups fairly and equitably, with equal concern and respect, in light of what is owed to them as members of society. This does not mean treating everyone the same, but it does mean considering who benefits and who is burdened by measures, avoiding discrimination, and minimising or eliminating inequities in the distribution of burdens, benefits, and opportunities to preserve health and well-being. In the context of COVID-19, it also means carefully considering the impact of decisions and their implementation on those who have the greatest needs, are especially vulnerable to injustice or are disproportionately affected by the pandemic and public health response measures, both in Canada and in the global context. A conscious and deliberate questioning of assumptions is essential in ensuring that responses and decisions do not reproduce the biases and stereotypes that are further entrenching inequalities in this pandemic.

Respect for persons, communities and human rights

Respect for persons and communities means recognizing the inherent human rights, dignity, and unconditional worth of all persons, regardless of their human condition (e.g., age, gender, race, ethnicity, disability, socioeconomic status, social worth, pre-existing health conditions, need for support). This entails recognizing the unique capacity of individuals and communities to make decisions about their own aims and actions, and respecting the rights and freedoms that form the foundation of our society. The right to autonomy is not absolute however. In the context of the response to COVID-19, respecting autonomy may entail: recognizing the importance of public consultation and of explaining the basis of decisions; providing information in a manner that is truthful, honest, timely and accessible; and providing individuals with the needed personal supports and the opportunity to exercise as much choice as possible when this is consistent with the common good. Respect for communities requires considering the potential impact of decisions on all communities and groups that may be affected, and respecting the specific rights of, and responsibilities towards, Indigenous Peoples.

Promoting well-being

Individuals, organizations and communities have a duty to contribute to the welfare of others. In the context of COVID-19, public health authorities' decisions and actions should promote and protect the physical, psychological and social health and well-being of all individuals and communities to the greatest extent possible. They should also consider the specific needs of, and duties towards, those who are marginalised, disadvantaged or disproportionately affected by response measures.

Minimising harm

Public health authorities have an obligation to avoid causing undue harm and, given that some harm is likely unavoidable, to minimise risk of harm and to reduce suffering associated with COVID-19 and public health response measures. This requires taking into consideration the variety of harms and suffering that may result from the current pandemic (such as ill health, increased anxiety and distress, isolation, social and economic disruption), as well as the differential impact of these harms on different groups and populations.

In order to promote well-being and minimise harm, the following must be considered when weighing options:

- **Effectiveness:** there should be a reasonable likelihood that the proposed decision or action will achieve its goals, and that its implementation is feasible. If scientific evidence is available, the proposed action or decision should be supported by the evidence;
- **Proportionality:** potential benefits should be balanced against risks of harm. Measures should be proportionate to the relevant threat and risks, and the benefits that can be gained. If a limitation of rights, liberties or freedoms is deemed essential to achieve an intended goal, the least restrictive measures possible should be selected, and imposed only to the extent necessary to prevent foreseeable harm;
- **Reciprocity:** those who are asked to take increased risks or face greater or disproportionate burdens in order to protect the public good should be supported by society in doing so, and the burdens they face should be minimised to the greatest extent possible;
- **Precaution:** scientific uncertainty should not prevent decision makers from taking action to reduce risks associated with COVID-19. The continued search for scientific evidence should nonetheless be a goal.

Working together

Because individuals are part of a greater whole, whether an organization, a local community, a nation or the global community, collective action in the face of common threats is justified. Helping each other and working together to plan for, respond to, and recover from, the pandemic is important because the pandemic affects all of society. It implies strong links between all jurisdictions within Canada, and at the international level.

Procedural considerations

Ethical decisions are based on the best information available and a solid, shared understanding of what values, principles and considerations are important. A good decision-making process helps to build trust, to increase legitimacy and acceptability of decisions, and to effectively implement them. Its hallmarks are:

- **Accountability:** decision makers are answerable to the public for the type and quality of decisions made or actions taken;
- **Openness and transparency:** decisions are made in such a way that stakeholders know, in a full, accurate and timely manner, what decisions are being made, for which reasons, and what criteria were applied, and have the opportunity to provide input;
- **Inclusiveness:** groups and individuals who are most likely to be affected by a decision are engaged in the decision-making and planning processes to the greatest extent possible;
- **Responsiveness:** decisions are revisited and revised as new information emerges;
- **Intersectionality:** an intersectional lens is applied to deliberation and decision making.

Ethical framework

This framework consists of five steps. It sets out questions to guide the systematic analysis of ethical issues – using the values and principles articulated in Section 1 – and the assessment of options, in order to support decision-making.

Step 1: Identify the issue and gather the relevant facts in order to clearly understand the problem

- What is the issue that needs to be addressed?
- What are the relevant facts, scientific evidence and other contextual factors? What misinformation surrounds the issue? What is not known?
- Who is affected by this decision? How can all stakeholders be engaged throughout the decision-making process?
- How do the different stakeholders view the issue, and what are their concerns?

Step 2: Identify and analyse ethical considerations, and prioritise the values and principles that will be upheld

- What ethical values, principles and considerations are involved in this issue?
- Are any of these values and principles in conflict?
- Which of these values or principles are most important?

Step 3: Identify and assess options in light of the values and principles

- What are the options (including doing nothing)?
- In light of the prioritised values and principles, what are the pros and cons of each option (e.g. potential benefits, harms, fair and equitable distribution, relative impact on disadvantaged individuals or groups,

intended and unintended consequences, level of certainty about effectiveness, respect for rights and interests)?
- What uncertainties exist for each option?

Step 4: Select best course of action and implement

- Which option best aligns with the prioritised values and principles?
- Are the decision makers and stakeholders comfortable with the decision?
- Who will implement the decision? How can it be implemented fairly?
- How, when and by whom will the decision be communicated?

Step 5: Evaluate

- What are the lessons learnt from implementation of the decision?
- Were the results of the decision consistent with the objectives? Were there any unintended consequences? Did its implementation create or exacerbate inequalities?
- Should the decision be revisited?

Selected resources

- World Health Organization, *Guidance for Managing Ethical Issues in Infectious Disease Outbreaks* (2016)
- UNESCO International Bioethics Committee and World Commission on the Ethics of Scientific Knowledge and Technology, Statement on COVID-19: Ethical Considerations from a Global Perspective (2020)
- Public Health Agency of Canada, *Framework for Ethical Deliberation and Decision Making in Public Health: A Tool for Practitioners, Policy Makers and Decision Makers* (2017)

- Alberta Health, *Alberta's Ethical Framework for Responding to Pandemic Influenza* (2016)
- British Columbia Ministry of Health, *COVID-19 Ethical Decision-Making Framework* (2020)
- Northwest Territories Health and Social Services Authority, *Territorial Ethical Decision-Making Framework* (2019)
- Québec, Comité d'éthique de la santé publique et Commission de l'éthique en science et en technologie, *Cadre de réflexion sur les enjeux éthiques liés à la pandémie de COVID-19* (2020) (in French only)
- University of Toronto Joint Centre for Bioethics Pandemic Influenza Working Group, *Stand on Guard for Thee: Ethical considerations in preparedness planning for pandemic influenza* (2005)
- Trillium Health Centre, *IDEA: Ethical Decision-Making Framework* (2013)
- Status of Women Canada, *Government of Canada's Approach: Gender-Based Analysis Plus* (2018)

Acknowledgements

The *Public Health Ethics Framework: A Guide for Use in Response to the COVID-19 Pandemic in Canada* was developed by PHAC's Public Health Ethics Consultative Group and its Secretariat with input from the Canadian Pandemic Influenza Task Group, the Federal/Provincial/Territorial Special Advisory Committee on COVID-19 and the COVID-19 Disability Advisory Group. PHAC greatly appreciates the time and effort that all contributed to this endeavour.

Related links

- Points to consider: Public disclosure of outbreaks and cases of infectious diseases

Date modified:

2021-02-16

TAB 51

Alberta Health

Alberta's Ethical Framework for Responding to Pandemic Influenza

January 2016

Alberta Government

Foreword

Alberta's Ethical Framework for Responding to Pandemic Influenza (AB Ethics Framework) is based on the extensive work completed by British Columbia, the UK, and Alberta. It has been reviewed by the three lead organizations, Alberta Health, Alberta Health Services (AHS) and Alberta Emergency Management Agency (AEMA). As Alberta's planning for pandemic influenza evolves, the AB Ethics Framework will be reviewed and updated regularly to reflect new learnings.

The AB Ethics Framework is based on a consistent set of well–recognized ethical principles and outlines a transparent and clear process to assess potential choices against. The purpose of this document is to assist in making public health decisions on pandemic influenza related ethical dilemmas. It may also assist Albertans in understanding the ethical implications of their own decisions during a pandemic influenza event. This framework is not intended for use in making clinical ethical decisions. For more information on clinical ethics see the following link http://www.albertahealthservices.ca/info/Page6671.aspx.

Table of Contents

Introduction

Public health ethics focus on the health and interests of a population and are distinct from clinical ethics which focus on the health and interests of the individual. For example, in public health ethics, decision-makers may have to decide which segment of the population should be prioritized for the pandemic influenza vaccine (e.g., seniors, pregnant women) when the initial batches are approved and available. In contrast, clinical ethics would be used to decide if vaccine is an appropriate intervention for an individual patient based on a number of factors including their condition and personal wishes. Alberta's Ethical Framework for Responding to Pandemic Influenza (AB Ethics Framework) does not replace clinical judgment nor is it a checklist for a single, clear conclusion. Ethics should be considered within a larger decision-making context[1] (e.g., scientific evidence, program considerations such as logistics or treatment strategies, legal considerations). For direction on clinical level ethics, health care providers should contact the AHS Clinical Ethics Service or refer to their professional body as appropriate.

The AB Ethics Framework is a resource to help planners and strategic policymakers from Alberta Health, Alberta Health Services (AHS) and Alberta Emergency Management Agency (AEMA) consider ethical implications of the choices they face. The framework provides a widely recognized, consistent set of principles to work through and outlines a transparent and understandable process to assess the potential choices. This framework can be used to assist in making decisions on common pandemic influenza-related ethical dilemmas such as vaccine priority decisions, compensation for health care workers, antiviral prioritization and many others.

History of Pandemic Influenza Ethics in Alberta

Pandemic influenza occurs when a novel influenza A virus, to which most humans have little or no immunity, acquires the ability to cause sustained human-to-human transmission that leads to a rapid worldwide spread. When exposed to the new virus, most people become ill as they have no immunity. This can lead to overwhelming demand on the health system and the need to make ethically challenging decisions surrounding the allocation of scarce resources (i.e., staff, equipment and supplies).

In 2003, the Alberta Clinical Subcommittee on Pandemic Influenza Planning recommended that Alberta Health form a committee to address ethical issues that could arise during a pandemic influenza in Alberta. In 2007, the committee completed "Pandemic Ethics: Navigating through Complexity: A Map for Decision Making" intended to provide core values and a systematic approach to guide policy makers. In response to 2009's pH1N1 event, AHS and Covenant Health published "Clinical Ethics and Pandemic Influenza: an ethics framework to guide clinicians' decision-making".

Post pH1N1 2009, the Minister of Health authorized the Health Quality Council of Alberta (HQCA) to conduct a formal review of the provincial response. Recommendation #17, "Alberta Health and AHS develop and maintain an ethical framework and strategies to guide operational and clinical decision-making that is understood by the public" was accepted by the Minister in principle, as some work had already been done in the province and it was felt that a public health ethical framework should be initiated at a national level.

In 2014, as part of the revision of Alberta's Pandemic Influenza Plan, this framework was developed to assist policymakers in the absence of a finalized national approach. A detailed literature review and environmental scan were conducted to identify the leading practices most applicable to Alberta. The review revealed that the principles found in British Columbia's ethical framework were based largely on the work done by the United

[1] Public Health Agency of Canada. *Canadian Pandemic Influenza Plan for the Health Sector.* (2011, September 13). Retrieved from http://www.phac-aspc.gc.ca/cpip-pclcpi/index-eng.php

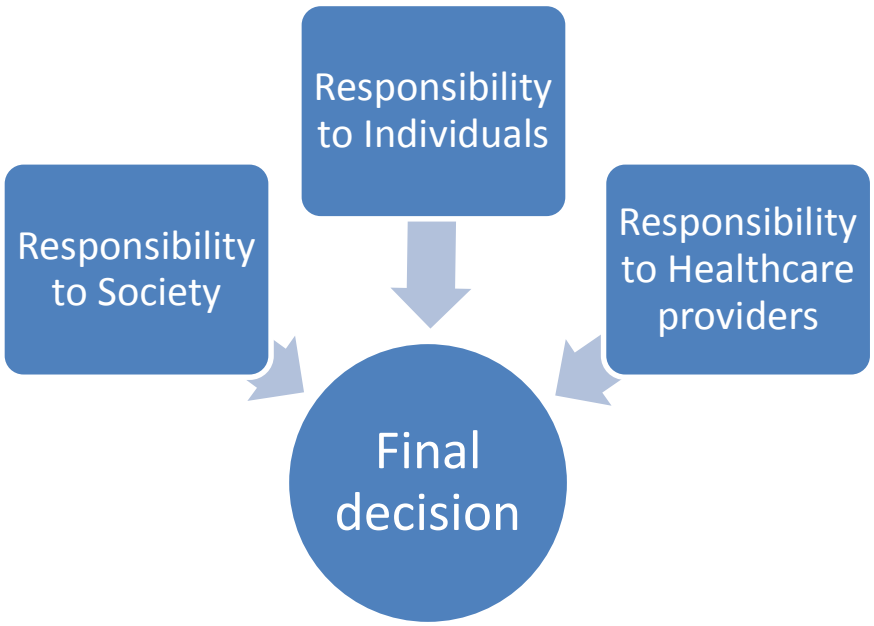
Kingdom (UK) Department of Health. In addition, this framework aligns with the University of Toronto's Joint Centre for Bioethics' "Stand on Guard for Thee: Ethical Considerations in Preparedness Planning for Pandemic Influenza", which contributed to the Canadian Pandemic Influenza Plan (CPIP) and was significantly influential in the World Health Organization's global pandemic influenza ethics consultation, "Global Consultation on Addressing Ethical Issues in Pandemic Influenza Planning".

The AB Ethics Framework is based on the extensive work completed by British Columbia, the UK, and Alberta. It has been reviewed by three lead organizations, Alberta Health, AHS and AEMA, as well as a number of provincial groups with policy, ethics and technical expertise including the Alberta Pandemic Influenza Planning Joint Advisory Committee and the Alberta Health Pandemic Influenza Planning Task Group (Appendix 2).

This framework aligns with the current principles and model for ethical decision-making found in the CPIP. As this and other leading practice documents are revised, and as Alberta's planning for pandemic influenza evolves, AB Ethics Framework will be reviewed and updated to reflect new learnings.

Understanding Ethical Tensions in a Pandemic

When a risk like a pandemic influenza affects a population, the health system is obliged to respond to the needs of the affected individuals, society, and healthcare providers that put themselves at risk for the good of others. Ethical tensions are inevitable; in an effective health system these tensions are held in a dynamic balance. For example, individual freedoms might be affected through restricting access to certain locations or confining people through quarantine; the decision to temporarily implement these public health measures must be weighed against the social and economic functioning of the community. In cases where responsibilities to individuals and groups are held in tension, decision-makers can use the ethical principles to find the best possible solution.



Ethical Framework for Responding to Pandemic Influenza

This section is taken directly from British Columbia's "An Ethical Framework for Decision Making: Supporting British Columbia's Pandemic Influenza Planning and Response". Small adjustments have been made to the content for applicability to Alberta.

Ethical Principles

Equal concern and respect underpin this ethical framework. This means that:

- Everyone matters.
- Everyone matters equally - but this does not mean that everyone is treated the same.
- The interests of each person are the concern of all of us, and of society.
- The harm that might be suffered by every person matters, and so minimizing the harm that a pandemic influenza might cause is the central concern.

Equal concern and respect draws together a number of different ethical principles, each of which is outlined below. The individual principles are numbered for convenience but are not ranked in order of significance.

When a particular decision has to be made, using the list of principles can help in considering a range of ethical issues. It is not, however, a checklist for *the one right answer*.

In thinking about the principles, decision-makers will need to use the best information that is available to them at that time. Whether or not a decision was ethically sound has to be judged in relation to the situation that existed at the time it was made, rather than by reference to facts that became apparent at a later stage.

Often, there will be tension both within and between these principles - for example, in weighing different sorts of harm, and in trying to both minimize harm and to be fair.

There are often no absolute right answers. A judgement may have to be made on the priority to be given to each element of a principle and to the principles themselves in the context of particular circumstances. Sometimes, use of the first seven principles may indicate that more than one possible decision would be ethically justifiable and would be in accordance with the fundamental principle of equal concern and respect. In such a case, the principle of "good decision-making" (#8, below) should be used to decide which one to take.

Individual Principles

1. Respect

This principle means that:

- People should be kept as informed as possible.
- Whenever possible, people should have the chance to express their views on health care decisions that affect them.
- People's personal choices about their treatment and care should be considered as much as possible.
- When people are unable to make their own health care decisions and have not provided any written expressed wishes to refuse or consent to future health care (such as identification of goals of care), then those who must decide for them should do so in consideration of what the person may have wanted and supported by the standards and duties of the health care providers involved in the decision at the time.

Respect applies to all individuals including patients, health care workers and the general public. There should be the widest possible involvement of people in planning for a pandemic influenza. The urgency of the situation may mean that it is not possible to consult widely (or indeed at all); However, treating people with respect means keeping them informed of the situation, what is happening and what is going to happen, as much as possible.

People's choices about their treatment and care are very important. Respect means balancing people's personal choices with the reality of the situation. For example, this may not mean that people are entitled to have the treatment of their choice if those caring for them would not consider it effective or is not suitable for them or if treatment resources were limited.

2. Minimizing the harm caused by pandemic influenza

During a pandemic influenza, some harm is likely to be unavoidable. This principle means that there is a need to:

- Try to minimize the spread of a pandemic influenza if it reaches Alberta.
- Minimize the risk of complications for the ill, for example, through the appropriate use of antivirals.
- Learn from experience, both at home and abroad, about the best way to fight the pandemic influenza and to treat people who are ill.
- Minimize the disruption to society caused by pandemic influenza.

This principle is intended to cover the physical, psychological, social and economic harm that pandemic influenza might cause. Examples of actions relevant to minimizing harm include those that save lives, support the health service in saving lives, and are designed to help society cope with and recover from pandemic influenza.

3. Fairness

The principle of fairness means that:

- Everyone matters equally but may not be treated the same.
- People with an equal chance of benefiting from health resources should have an equal chance of receiving them; however, it may be considered fair to tell people who could get the same benefit from an intervention at a later date to wait.

The implications of the principles of minimizing harm and fairness often arise together in many planning and policy decisions. So, in considering a particular decision, a first question might be: How could harm be minimized? Then it is necessary to ask: Would it be fair to do this? Could the same outcome be achieved in a fairer way? This involves thinking about the interests of everyone who may be affected by the decision. There needs to be good reasons to treat some people differently from others, which the decision-makers should be prepared to explain. The decision-making process also needs to be fair, which is considered part of the principle of good decision-making (#8 below).

4. Working together

This principle means:

- Working together to plan for, respond to, and recover from pandemic influenza.
- Helping one another.
- Being prepared to share information that will help others, without compromising the privacy and dignity of the individuals involved.

Because pandemic influenza will affect the whole of society, it is important that different agencies collaborate and coordinate at provincial, regional and local levels.

Working together also implies strong links at the international, national and inter-provincial levels. This includes both providing and seeking timely information from partners across Canada.

5. Reciprocity

The principle of reciprocity is based on the concept of mutual exchange. Therefore:

- If people are asked to take increased risks, or face increased burdens during a pandemic influenza, they should be supported in doing so, and the risks and burdens should be minimized as far as possible.

Some people, such as healthcare workers, may face very heavy burdens in trying to help us through pandemic influenza; it is important to think about how to minimize those burdens. An example of this could be providing those with the highest risk of contracting influenza at work with priority access to a vaccine.

6. Keeping things in proportion

This principle means that:

- Those responsible for providing information should neither exaggerate nor minimize the situation and should give people the most accurate information that they can.
- Decisions on actions that may affect people's daily lives, which are taken to protect the public from harm, should be proportionate to the relevant risk and benefits that can be gained from the proposed action. Proportionality requires that the least restrictive means possible is used when limiting liberty and freedom in the face of a pandemic influenza. For example, hospitals or long term care centres may restrict visitations to prevent patients from exposure to pandemic influenza.

At the start of a pandemic influenza, much will remain unknown about how it is going to affect people and the country as a whole. The media and other people responsible for communication will have an important role to play in helping people understand what the real situation is and what they need to do, without exaggerating or minimizing the situation.

7. Flexibility

This principle means that:

- Plans should be adapted to take into account new information and changing circumstances.
- People should have as much opportunity as possible to express concerns about or disagreement with decisions that affect them.

8. Good decision-making

Respect for this principle involves the following components:

i. Openness and transparency

This means that those making decisions should:

- Consult those concerned as much as possible in the time available.
- Be open about what decisions need to be made and who is responsible for making them.
- Be as open as possible about what decisions have been made and why they were made.

ii. Inclusiveness

This means that those making decisions should:

- Involve people to the greatest extent possible in aspects of planning that affect them.
- Decision makers should take into account all relevant views expressed.
- Work to make sure that particular groups are not excluded from becoming involved. Some people may find it harder to access communications or services than others, and decision-makers should consider how they can express their views and have a fair opportunity to get their needs for treatment or care met.
- Take into account any disproportionate impact of the decision on particular groups of people.

iii. Accountability

This means that those responsible for making decisions may have to justify the decisions that they do or do not make.

iv. Reasonableness

This means that decisions should be:

- Rational.
- Not arbitrary.
- Based on appropriate evidence, available at the time.
- The result of an appropriate process, taking into account how quickly a decision has to be made and the circumstances in which a decision is made.
- Practical- what is decided should have a reasonable chance of working.

Ethical Decision-Making Tools

Ethical decision-making tools are designed to encourage a systematic process for exploring in what way the ethical principles are reflected in a difficult decision. Depending on the context of the decision, these tools can be used by an individual or to facilitate a group discussion. The ethical principles contribute to but do not represent the entire decision-making process and should be used within a broader context when dealing with complex problems. When considering options, the goal should be to find a solution based on all information available and consider all relevant factors (scientific evidence, program considerations, policy considerations).

Generally, planners and policymakers will already be considering the ethical components of their recommended actions, even if not done so explicitly. Therefore, another key function of this kind of tool is to demonstrate in what manner the ethical principles were considered.

Many factors impact how decisions are made, such as familiarity with ethical issues, time constraints and the expertise of the group. Different tools are available to satisfy different needs. Two are outlined here; however, there are many tools which can be used in different contexts.

- **Ethical Considerations Assessment Worksheet** (Appendix 1)
  Designed to assess already identified potential courses of action against the eight ethical principles and provide rationale for the recommended decision.

- **Good Decisions: A map to the best decision, all things considered**
  Developed in BC and used in conjunction with their ethical framework. This is a longer, more complete guide that takes users from the first step of articulating the issue to identifying ethical concerns and finally a recommendation. This tool includes a step to determine who needs to be involved in a decision. It can also help users define the "key question" and identify which ethical issues are most important (http://www2.gov.bc.ca/assets/gov/health/about-bc-s-health-care-system/office-of-the-provincial-health-officer/reports-publications/bc-pandemic-influenza-ethics-framework-2012.pdf , p. 13-29).

Formal Decision-Making Mechanism(s)

Ethical decision making is a component of the established emergency management structures used during a response, as outlined in the Alberta Pandemic Influenza Plan (http://www.health.alberta.ca/health-info/pandemic-influenza.html).

Although we can and should identify potential situations ahead of time, planning scenarios cannot incorporate all potential factors that can affect the impact of a pandemic influenza. Some factors are population-wide and could affect all scenarios, such as seasonality, pre-existing immunity or antiviral resistance, whereas others may be setting-specific, such as the effects on a remote community. Because these impacts are hard to predict, some decisions will have to be made rapidly at the time of a pandemic influenza.

In order to assist the ethical decision-making process, mechanisms such as pre-established relationships and committees should be in place to bring the right expertise and decision-making capability to the table (e.g., Pandemic Influenza Planning Joint Advisory Committee, Alberta Health Pandemic Influenza Planning Task Group, Appendix 2). Membership should be determined by the group leading the pandemic influenza response so that the most relevant program area expertise is included.

Appendix 1 – Ethical Considerations Assessment Worksheet

Purpose:
To compare/weigh potential options against the eight ethical principles identified in Alberta's Ethical Framework for Responding to Pandemic Influenza (AB Ethics Framework).

To use this tool effectively, it will be necessary to review the Ethical Principles found on pages 5-9 of the AB Ethics Framework. This tool is intended to be used in conjunction with scientific, policy and program considerations and assumes some potential courses of action have been produced.

Instructions:

- Write each of the potential courses of action in the Option boxes along the top row.
- For each of the Ethical Principles, identify how each Option will or will not fulfill the responsibilities of that Ethical Principle.
    - If the Option does not fulfill the Ethical Principle, you may also wish to provide justification for why this Option may still be appropriate.
- Once all of the Options have been evaluated against the Ethical Principles, the table can be used to determine which Option(s) best addresses the ethical dilemma.
- The *Summary of Decision* then makes explicit the Option that is recommended based on the information in this table.

The following example is for illustrative purposes only and does not necessarily reflect corporate human resource policies.

Example: You witness a co-worker who has worked with the organization a long time taking stationary supplies out of the office.

Ethical Principles:	**Option 1:** Report this to your supervisor immediately.	**Option 2:** Confront the co-worker about what you saw.	**Option 3:** Do nothing.
Respect	This respects the workplace and your supervisor, as they will be informed of the incident. It doesn't necessarily respect the employee as he was not informed before the report.	This option incorporates respect, as it addresses the issue but gives the employee a chance to express their side of the story. Your supervisor may not be informed, but since inappropriate actions may be corrected, it may not be necessary.	This option does not reflect respect, as you have made no effort to understand what you saw or let your supervisor know if there is in fact an issue.
Keeping things in proportion	This option seems out of proportion. Without taking the time to understand the situation, one might actually report inaccurate information that could jeopardize the reputation of the employee.	This option is in proportion. It addresses the issue, but allows the employee to share their side of the story and possibly correct the inappropriate actions without losing face, especially since the supplies are not worth much money.	It could be argued that this option is proportional as the supplies are not worth much, and their loss won't greatly affect the business. Not reporting it will ensure that the employee's reputation is not duly or unduly affected.

Ethical Considerations Assessment

Ethical Principles:	Option 1:	Option 2:	Option 3:
Respect			
Minimizing the harm			
Fairness			
Working together			
Reciprocity			
Keeping things in proportion			
Flexibility			
Good Decision-Making			

Summary of Decision

For the question…	
We recommend that…	
This allows us to best…	
This solution does not…	
We argue that this is justified because…	

Appendix 2 – Pandemic Influenza Planning Joint Advisory Committee and Alberta Health Pandemic Influenza Group

Alberta Pandemic Influenza Planning Joint Advisory Committee

The Joint Advisory Committee (JAC) is made up of senior-level decision-makers from each of the three pandemic influenza lead organizations, Alberta Health, Alberta Health Services (AHS) and the Alberta Emergency Management Agency (AEMA). The JAC provides ongoing advice and coordination for pandemic influenza preparedness in Alberta.

Current members include:

Alberta Health

- Executive Director, Health Protection (Chair)
- Director, Emergency Planning and Preparedness
- Deputy Chief Medical Officer of Health

AHS

- Executive Director, Emergency/Disaster Management
- Special Project Lead, Emergency/ Disaster Management
- Senior Medical Officer of Health

AEMA

- Director, Central Operations

Alberta Health Pandemic Influenza Planning Task Group

The Task Group provides content expertise for the *Alberta's Pandemic Influenza Plan* (APIP) and related organizational / operational planning as required, and aligns the work across divisions and work units of Alberta Health.

The Task Group is made up of technical expertise from the following areas:

- Public Health Emergency Planning
- Clinical Advisory and Research
- Communicable Disease
- Communications
- Drug Program Operations and Policy
- Emergency Preparedness and Response
- Enterprise Risk Management
- Epidemiology and Surveillance
- Immunization
- Intergovernmental Relations
- Infection Prevention and Control
- Legal & Legislative Services
- Addiction and Mental Health
- Office of the Chief Medical Officer of Health
- Workforce Policy and Planning

References

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British Columbia Ministry of Health. (2012). *British Columbia's Pandemic Influenza Response Plan (2012): An Ethical Framework for Decision MakingL Supporting British Columbia's Pandemic Influenza Planning and Response.* Victoria: Government of British Columbia.

Pandemic Influenza Working Group, University of Toronto Joint Centre for Bioethics. (2005). *Stand On Guard for Thee: Ethical Considerations in Preparedness Planning for Pandemic Influenza.* Toronto: University of Toronto Joint Centre for Bioethics.

Public Health Agency of Canada. (2011, September 13). *Canadian Pandemic Influenza Plan for the Health Sector.* Retrieved August 15, 2014, from Public Health Agency of Canada: http://www.phac-aspc.gc.ca/cpip-pclcpi/index-eng.php.

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TAB 52

Alberta Health Services

POLICY

TITLE
IMMUNIZATION OF WORKERS FOR COVID-19

SCOPE
Provincial

DOCUMENT #
1189

APPROVAL AUTHORITY
Alberta Health Services President and Chief Executive Officer

INITIAL EFFECTIVE DATE
September 14, 2021

SPONSOR
Workplace Health and Safety

REVISION EFFECTIVE DATE
November 29, 2021

PARENT DOCUMENT TITLE, TYPE, AND NUMBER
Not applicable

SCHEDULED REVIEW DATE
March 31, 2022

NOTE: The first appearance of terms in bold in the body of this document (except titles) are defined terms – please refer to the Definitions section.

If you have any questions or comments regarding the information in this document, please contact Policy Services at policy@ahs.ca. The Policy Services website is the official source of current approved policies, procedures, directives, standards, protocols, and guidelines. Only the electronic version of this document, as hosted on the Policy Services website or www.ahs.ca, is valid.

OBJECTIVES

- To set out **worker** immunization requirements for COVID-19 to protect the health and safety of workers, patients, and the communities that Alberta Health Services (AHS) serves.

PRINCIPLES

AHS is committed to protecting the health and safety of its workers, patients, visitors, and others accessing AHS sites. Immunization against COVID-19 is the most effective means to prevent the spread of COVID-19, to prevent outbreaks in AHS facilities, to preserve workforce capacity to support the health care system, and to protect our workers, patients, visitors, and others accessing AHS sites. Immunization against COVID-19 also supports the AHS Values of Compassion, Accountability, Respect, Excellence, and Safety.

This Policy is in addition to other AHS policy documents supporting worker and patient safety during the COVID-19 pandemic including, but not limited to, the AHS *Use of Masks During COVID-19* Directive, *Attending Work with COVID-19 Symptoms, Positive Test, or Close Contact* Directive, and the *Fit for Work Screening (COVID-19)* Protocol.

This Policy shall be reviewed regularly, and at least prior to March 31, 2022, to ensure alignment with public health measures and regulations, and to confirm it adequately covers the health and safety risks that it addresses.

APPLICABILITY

Compliance with this document is required by Alberta Health Services, Alberta Precision Laboratories, Carewest, CapitalCare, and Covenant Health employees, members of the medical and midwifery staffs, students, volunteers, and other persons acting on their behalf. Compliance requirements for other contracted service providers, such as continuing care, will be

communicated directly to the contracted service providers. This document does not apply to physicians with community appointments.

ELEMENTS

1. Immunization Requirements

1.1 Effective December 13, 2021, all workers must be **fully immunized** against COVID-19.

1.2 A worker on an approved Leave of Absence must be fully immunized prior to returning to work.

1.3 A worker hired after November 30, 2021 must be fully immunized prior to commencing work.

2. Proof of Immunization Records

2.1 No later than November 28, 2021, workers shall disclose accurate proof of their immunization status to:

a) AHS or an AHS subsidiary, if the worker is an AHS employee, medical staff, midwifery staff, or volunteer;

b) Covenant Health, if the worker is a Covenant Health employee, medical staff, or volunteer;

c) their educational institution, if the worker is a student or instructor; or

d) their employer, if the worker is a contracted service provider.

2.2 Proof of immunization is being collected to protect the health and safety of workers, patients, and other persons accessing AHS sites and to preserve AHS' workforce capacity to support the health care system.

2.3 Proof of immunization records collected under this Policy shall be securely and confidentially retained, accessed, and used as necessary to determine fit for work status of workers, to manage and administer employment and other working relationships with workers, to address accommodation requests, and to comply with all applicable laws, such as the *Occupational Health and Safety Act* (Alberta) and *Regional Health Authorities Act* (Alberta).

2.4 Proof of immunization records are collected under the authority of Section 33(c) of the *Freedom of Information and Protection of Privacy Act* (Alberta) and shall be used, accessed, and disclosed in accordance with the legislation and the AHS *Collection, Access, Use, and Disclosure of Information* Policy.

3. Workplace Accommodation

3.1 Any AHS employee who is unable to be immunized due to a medical reason, or for another protected ground under the *Alberta Human Rights Act*, will be reasonably accommodated, up to the point of undue hardship, in accordance with the AHS *Workplace Accommodation* Policy. An AHS employee will not be permitted to undergo rapid testing as a reasonable accommodation unless Section 4 of this Policy applies.

3.2 Employees of AHS subsidiaries, Covenant Health, and applicable contracted service providers, who are unable to be immunized due to a medical reason, or for another protected ground under the *Alberta Human Rights Act,* will be reasonably accommodated, up to the point of undue hardship, in accordance with their applicable workplace accommodation policies. An employee of AHS subsidiaries, Covenant Health and applicable contracted service provider, will not be permitted to undergo rapid testing as a reasonable accommodation unless Section 4 of this Policy applies.

3.3 Any current AHS employee requesting workplace accommodation shall make a request for the accommodation as soon as reasonably possible, and no later than October 16, 2021, and provide required information in accordance with the AHS *Workplace Accommodation* Policy (or the appropriate accommodation policy of an AHS subsidiary or Covenant Health, if applicable).

3.4 Any current AHS member of the medical or midwifery staff who is not an employee of AHS, an AHS subsidiary, or Covenant Health, and who is unable to be immunized due to a medical reason, may request an exception as soon as reasonably possible and no later than October 16, 2021. A request for an exception shall be made on the *Medical or Midwifery Staff Request for Exception COVID-19 Mandatory Immunization for Workers* form and shall be submitted as directed on the form. The lack of immunization may affect the safe exercise of their Clinical Privileges as described in the *Medical Staff Bylaws* and *Rules* (Rule 3.4.4.2), or may directly impact their ability to practice and patient safety as described in the *Midwifery Staff Bylaws* and *Rules,* as applicable.

4. Rapid Testing at Facilities at Significant Risk of Service Disruption

4.1 Section 4.2 of this Policy only applies to current workers in facilities that are at a significant risk of service disruption.

a) Section 4.2 of this Policy does not apply to a worker hired after November 30, 2021 or to any worker in a facility that is not at significant risk of service disruption.

b) Facilities at significant risk of service disruption are determined by the Vice President and Chief Operating Officer, Clinical Operations and will be communicated to affected workers at these facilities.

4.2 Workers who are not fully immunized and are working in a facility that is at a significant risk of service disruption will be required to undergo regular rapid testing. The following conditions apply:

a) The worker must be tested using a Health Canada-approved COVID-19 test.

b) The test must be conducted at an existing private testing location (e.g., a pharmacy). Publicly-funded COVID-19 testing (e.g., through AHS) shall not be accepted.

c) The worker must have a negative test completed no more than 48 hours prior to the start of their shift.

d) The cost of the tests are at the worker's expense, unless an approved workplace accommodation or exception (for medical or midwifery staffs) applies.

e) The testing must be completed on the worker's own time.

f) The worker must retain proof (paper or electronic) of a negative test result and show that proof to their leader before the start of their next scheduled shift and if asked during their shift.

(i) If the worker tests positive for COVID-19, the worker must be tested for COVID-19 using a polymerase chain reaction (PCR) test. If the PCR test is positive, the worker must isolate in accordance with applicable Chief Medical Officer of Health Orders and the AHS *Attending Work with COVID-19 Symptoms, Positive Test, or Close Contact* Directive.

g) Workers who refuse to be tested or fail to comply with these conditions shall be considered non-compliant with this Policy and subject to Section 5 of this Policy until they are fully immunized.

5. Non-Compliance

5.1 A worker is considered to be in non-compliance with this Policy if they are:

a) not working in a facility that is at a significant risk of service disruption and have not met the requirements of Sections 1-3 of this Policy; or

b) working in a facility that is at a significant risk of service disruption and have not met the requirements of Sections 1-4 of this Policy.

5.2 With respect to students, instructors, and applicable contracted service providers, failure to comply with this Policy shall result in AHS reviewing the applicable contract or other relevant circumstances and initiating further discussions with the applicable educational institution or contracted service provider and, in this

respect, AHS reserves all rights it has at law, equity, or pursuant to any applicable agreement to address such non-compliance.

5.3 In all other cases not outlined in Section 5.2 above, except where a workplace accommodation or exception (for medical or midwifery staff) applies, failure to comply with this Policy shall result in:

a) a meeting being held with the worker to discuss their concerns with vaccination against COVID-19 and provide educational materials on the COVID-19 vaccines; and

b) if the worker remains non-compliant with this Policy, the worker being placed on an unpaid leave of absence for the period of time required to become fully immunized or, in the case of medical or midwifery staff, Immediate Action being taken as set out in Part 6 of the *Medical Staff* Bylaws or *Midwifery Staff* Bylaws.

DEFINITIONS

Fully immunized means a worker:

a) who has received two doses of a vaccine considered valid by Alberta Health in a two-dose COVID-19 vaccine series or one dose of a vaccine considered valid by Alberta Health in a one-dose COVID-19 vaccine series; and
b) for whom fourteen days have elapsed since the date on which the person received the second dose of the COVID-19 vaccine considered valid by Alberta Health of a two-dose series or one dose of the COVID-19 vaccine considered valid by Alberta Health in a one-dose vaccine series.

Worker means AHS, its subsidiaries and Covenant Health employees, members of the medical and midwifery staffs, students and instructors, volunteers, and applicable contracted service providers (including anyone providing services for AHS on behalf of an applicable contracted service provider).

REFERENCES

- Alberta Health Services Governance Documents:
  - *Attending Work with COVID-19 Symptoms, Positive Test, or Close Contact* Directive (#1188)
  - *Collection, Access, Use, and Disclosure of Information* Policy (#1112)
  - *Fit for Work Screening (COVID-19)* Protocol (#1184-01)
  - *Medical Staff Bylaws* and *Rules*
  - *Midwifery Staff* Bylaws and *Rules*
  - *Use of Masks During COVID-19* Directive (#HCS-267)
  - *Workplace Accommodation* Policy (#1156)
- Alberta Health Services Forms:
  - *Employee Request for Accommodation* Form (#19566)
  - *Got My COVID-19 Immunization* Form

  - *Medical or Midwifery Staff Request for Exception COVID-19 Mandatory Immunization for Workers* Form
- Alberta Health Services Resources:
  - AHS Immunization Information Insite Page
  - AHS Values
- Non-Alberta Health Services Documents:
  - *Alberta Human Rights Act*
  - *Freedom of Information and Protection of Privacy Act* (Alberta)
  - *Occupational Health and Safety Act* (Alberta)
  - *Regional Health Authorities Act* (Alberta)

TAB 53

See Tab 50

TAB 54

Federal/Provincial/Territorial Public Health Response Plan for Ongoing Management of COVID-19

Download in PDF format
(4.81 MB, 58 pages)

Organization: Public Health Agency of Canada

Date published: 2021-04-19

Table of contents

Executive summary

This document is the second edition of the Federal/Provincial/Territorial (FPT) plan which was developed in collaboration with federal, provincial and territorial public health officials (via the FPT Special Advisory Committee on COVID-19, see Appendix 1), First Nations, Inuit and Metis partners, and health system partners, for these and other stakeholders. It is an evergreen document that is intended to provide a common forward planning approach for ongoing management of COVID-19 in Canada. The plan acknowledges jurisdictional roles and responsibilities, identifies when pan-Canadian approaches are anticipated and when provincial/territorial flexibility and customization are expected. First Nations, Inuit and Metis communities may choose to adapt approaches to the specific needs and contexts of their communities.

Key elements of the plan include:

- a goal statement,
- public health response objectives,
- planning assumptions,
- a reasonable worst-case scenario, and

- summaries of current and planned response activities for each main component of the public health response (i.e., Surveillance, Laboratory Response Activities, Public Health Measures, Infection Prevention and Control and Clinical Care Guidance, Vaccination, International Border and Travel Health Measures, Health Care System Infrastructure, Risk Communications and Outreach, and Research).

There is also content specifically addressing planning with Indigenous Communities, planning for high-risk settings and populations, and the role of modelling in the response. Much like other technical guidance, this document may require updating as our scientific knowledge of the SARS-CoV-2 pathogen increases, the epidemiological picture evolves in Canada and globally, pandemic control measures change, and new medical countermeasures become available (e.g., additional vaccines, effective treatment).

The pandemic response goal, to minimize serious illness and overall deaths while minimizing societal disruption as a result of the COVID-19 pandemic, is unchanged in this edition. While the COVID-19 response has been unprecedented with the swift implementation and public adoption of public health measures (PHM), appropriate ongoing use of these measures in the context of variants of concern (VOCs), increasing vaccination coverage, and public fatigue with the pandemic and in particular with restrictive community-based PHM will be challenging. PHM have disproportionally impacted some groups within Canada, including seniors, essential workers, racialized populations, people living with disabilities, and women. “Pandemic fatigue” is now ubiquitous and while everyone in Canada has borne the burden of these measures to protect those most at risk of severe COVID-19 disease, now more than ever there is a need to tailor the response to minimize burden and negative impacts while maximizing the benefit of protective measures like COVID-19 vaccines.

PHM have been successful in reducing the number of cases of COVID-19 and associated serious illness and deaths in Canada, however, the restrictive nature of many of these measures have had some negative health, well-being and societal consequences. Many of these consequences have disproportionately affected specific segments of the Canadian population. The goal statement and objectives continue to reflect the need to respond in a way that achieves a better balance between minimizing the impact on morbidity and mortality with the impact on societal disruption in order to support a long-term, sustainable response.

To facilitate a common approach and appropriate level of preparedness across Canada, the plan includes a list of planning assumptions, a “reasonable worst-case scenario”, and a list of capabilities and requirements needed to mitigate this scenario. The scenario is not the most likely scenario, rather, it provides a realistic common scenario to guide consideration of key capabilities, capacity issues, and identification of resource needs that will help focus planning activities in light of new challenges like VOCs and pandemic fatigue. It is provided as a “stress-test”, not a prediction, and is intended to stimulate thinking concerning our current response efforts and resources, capacity thresholds and resiliency. The reasonable worst-case scenario includes an epidemic curve with a large, prolonged third peak in near term driven by a combination of factors including the spread and dominance of highly transmissible VOCs, pre-mature easing of restrictive community-based PHM, and lower levels of public adherence to recommended PHM. This is followed by ongoing surges or resurgences for the rest of 2021, with surges in incidence creating a demand for resources that exceeds system capacity. It also assumes that vaccine conferred immunity is not long lasting and therefore there will be some level of ongoing transmission for the foreseeable future.

What needs to be done to mitigate this scenario, and for the ongoing management of COVID-19 in general, include the ability to:

- detect signals indicating a significant surge in cases may occur;
- prevent a large prolonged peak and surges, especially those that exceed capacity to respond;
- reduce surges in cases, hospitalizations, and deaths;
- increase health care and public health capacity;
- monitor demand for health care resources; and,
- foster ongoing public vigilance and adherence to measures and recommendations.

When and how to mitigate this scenario is described in terms of the timing and adjusted use of restrictive community-based PHM. Adjustments to restrictive PHM must be considered in the context of threat associated with VOCs and the effect of increasing vaccine coverage, while taking into account the social, economic, and situational factors that may impede the ability to comply with public health measures, particularly for marginalized population groups.

This plan, in conjunction with other foundational federal/provincial/territorial response plans, provides public health leaders with a coordinated approach to: address common issues, and to support the provincial/territorial responses to COVID-19 in the Canadian population. It includes information regarding the current focus of the public health response and anticipated needs for the short, mid and long term ongoing management of COVID-19, which will facilitate awareness and coordination both within and beyond the public health sector.

Purpose

The purpose of the *Federal/Provincial/Territorial Public Health Response Plan for Ongoing Management of COVID-19*, is to provide federal, provincial and territorial public health officials, First Nations, Inuit and Metis partners, health system partners and other stakeholders with a common forward planning approach for ongoing management of COVID-19 in Canada. This plan promotes a long-term approach. The first edition covered immediate planning imperatives for the fall/winter 2020 period. Plans must continue to be re-visited and updated until implemented measures and population immunity, is sufficient to decrease COVID-19 activity in Canada to a low, manageable, and tolerable level. As an evergreen document this second edition has been updated as our scientific knowledge of the SARS-CoV-2 pathogen has increased, the epidemiological picture has further evolved in Canada and globally, understanding of the disproportionate impact the pandemic has had on marginalized population groups has grown, control strategies have shifted, and new medical countermeasures have become available (i.e., vaccines and therapeutics).

Building on the ongoing public health response, this document identifies federal/provincial/territorial (FPT) public health preparations that are needed and already underway for the short, mid and long-term management of COVID-19 in Canada. It provides overarching guidance that is informed by existing intergovernmental pandemic preparedness, public health emergency planning and data, information and resource sharing agreements, arrangements and protocols (see Appendix 1) and draws extensively on the Canadian Pandemic Influenza Preparedness guidance (CPIP). The CPIP stipulates that while it is a guidance document for pandemic influenza, much of its guidance is also applicable to other public health emergencies, which has been the case for the COVID-19

response. It is assumed that an ongoing (but appropriately scaled) FPT coordinated response structure and activities as outlined in the FPT Public Health Response Plan for Biological Events (FPT PHRPBE), will be needed for the foreseeable future.

To facilitate a common approach and appropriate level of preparedness across Canada, this edition of the plan includes an updated “reasonable worst-case scenario.” While this scenario is not necessarily the most likely scenario, it provides a baseline to guide consideration of key capabilities, capacity issues, and identification of resource needs that will help focus planning, response and recovery activities. As with other FPT plans, this document outlines overarching goals and objectives, acknowledges jurisdictional roles and responsibilities, identifies when national approaches are anticipated and when provincial/territorial (PT) flexibility and customization are expected. This document has been developed to facilitate planning for an ongoing COVID-19 response that is not only flexible and adaptive but also sustainable.

Context

COVID-19 continues to represent an unprecedented threat to the health, social and economic well-being of Canadians, Canadian society and the global community. On January 30, 2020, the Director General of the World Health Organization (WHO) determined that COVID-19 constituted a Public Health Emergency of International Concern (PHEIC) and declared it a pandemic on March 11, 2020, due to extensive international spread. More than a year into responding to this unprecedented event, the Canadian response has been strengthened by the availability of vaccines but further challenged by the emergence of VOCs and pandemic fatigue. There is a need for ongoing adjustments and tailoring of the response as knowledge regarding both the impact of vaccines and VOCs increases. Furthermore, there is an ongoing need to take into consideration the changing attitudes and behaviours of a fatigued, and often frustrated or confused population, and the impact this has on the success of the response. Mitigating the impact of COVID-19 in Canada requires a comprehensive, integrated and cross-sectoral “whole-of-society”, “whole-of-government” strategy that focuses on what is within the span of control of our country while trying to reduce the risk and impact of what is not. The context of our planning, therefore, is primarily Canadian-centric but recognizes that the global situation has a significant effect on our response activities.

Mobilizing Canada's health sector response to COVID-19 remains a critical part of that overall effort. This plan and its more detailed components that are described herein, draws heavily on the experience acquired and the work completed during the response to the introduction and subsequent waves of COVID-19 in Canada, in addition to past experience and lessons learned from the implementation of previous mass immunization campaigns. While Canada's FPT public health officials have conducted pandemic planning for years, plans must be customized and supplemented as the pandemic unfolds, as each pandemic is different. On the vaccine front alone, the simultaneous use of multiple vaccines using different and novel vaccine technologies while significant ongoing community transmission is occurring and threats of new VOCs with immune escape characteristics start to manifest, is unprecedented. Further unique challenges include: vaccine supply issues, prioritization of vaccine recipients by product, potential for product specific hesitancy, and the need to ensure vaccination occurs in a manner that is consistent with recommended public health measures. Through the Variants of Concern Strategy, integrated teams from a variety of backgrounds including public health laboratories, academia, and research hospitals are leveraging their shared knowledge in areas such as diagnostic testing, epidemiological analysis, and clinical expertise to proactively search for and rapidly characterize VOCs. This will ensure that public health management and control measures can be efficiently and effectively put in place to reduce transmission for VOCs. Despite the incredible effort and pace of COVID-19 response in Canada to date, we are still operating from a place of significant uncertainty and need to continue learning and adapting as we move ahead with planning activities.

While the pandemic has affected Canadians in diverse ways, Canadians have not experienced these impacts equally. Evidence indicates that social determinants of health, including low-income status, adverse physical environments, precarious housing, and race/ethnicity, among others, correlate with increased risk of COVID-19 infection [1] and unequal access to health care and other services. These social determinants put people at risk for a range of chronic conditions [2], such as obesity, heart disease, diabetes, and lung disease, which may contribute to increased morbidity and mortality from COVID-19. Similar to other countries [3], in Canada the rate of deaths due to COVID-19 is higher in males than in females but overall numbers of deaths are highest in females likely due to the higher proportion of females in the oldest, high-risk age groups [4].

These same determinants of health also contribute to other disproportionate impacts of COVID-19 restrictions on health and well-being, including impacts on mental health, family violence and problematic substance use and related overdoses. Job losses have been higher for women, with recent recoveries in the workforce disproportionally benefitting men. [5] Partly as a result of the economic downturn triggered by the pandemic, visible minorities have been particularly affected, with a larger share reporting having difficulties meeting their financial obligations or essential needs compared to White workers. [6] Visible minorities and new comers to Canada are also more likely to work in multiple jobs, in positions (e.g., personal support workers, grocery store clerks) in the food and accommodation sector and public-facing positions where there may be a higher likelihood of exposure to COVID. They also may live in multi-generation homes, which can lead to circular disease transmission patterns from work settings to the home and back to work, thus perpetuating the disproportionate impact on people in these groups. Similarly, Indigenous Peoples, persons living with disabilities, and LGBTQ2IA+ communities, among others, have been disproportionally affected by the pandemic. [7]

Furthermore, some populations have been particularly impacted by the measures implemented to control the pandemic; for example, the unprecedented extent and duration of school closures which may have long-term effects on child development, health and education [8] [9]. As efforts shift towards the next phase of the response, it is imperative that the needs of diverse groups within Canada continue to be considered in order to mitigate adverse consequences and reduce both known and reasonably anticipated inequities.

COVID-19 response goal, objectives and response to date

Goal

Canada's goal for responding to COVID-19 is based on that established for pandemic influenza in the *Canadian Pandemic Influenza Preparedness: Planning Guidance for the Health Sector* document (last updated August 2018). The goal is:

- To minimize serious illness and overall deaths while minimizing societal disruption as a result of the COVID-19 pandemic.

This goal has guided FPT public health response actions. Measures and strategies implemented with this goal in mind have helped reduce the incidence of COVID-19 in Canada and associated serious illness and deaths. Reducing the health impact of COVID-19 while minimizing societal disruption has been extremely challenging especially as "pandemic fatigue" has increased and led to related challenges with respect to public adherence to recommended measures, which have placed an unequal burden across populations in Canada. Recognizing that some groups of Canadians face disproportionate barriers in adhering to these measures is an important first step towards establishing strategies to address them.

With the availability of vaccines and rollout of population-based vaccine programs that prioritize reducing the health impact in the most vulnerable groups first, significant progress is being made on the first part of the goal statement with respect to COVID-19 associated serious illness and overall deaths. However, a high level of adherence to the recommended public health measures (PHMs) remains essential, especially given the emergence of VOCs, which by definition [10] may be associated with increased transmission, increased virulence or change in clinical disease presentation and/or decreased effectiveness of some public health and social measures or available diagnostics, vaccines or therapeutics, depending on the variant.

The pandemic circumstances, not only in Canada but globally, led to the extraordinary implementation of broad, restrictive community-based PHM (e.g., school closure, restrictions on gatherings, workplace/ business restrictions), and the need to offer an unparalleled level of societal support measures (e.g., income support, housing support, and expansion of social services such as mental health and food assistance). Restrictive community-based PHM do reduce the risk of transmission, even transmission of VOCs, however they come at a cost with respect to societal disruption and subsequently the level of benefit is influenced by public adherence and risk tolerance. Going forward these measures will be continually adapted to fit the local context and COVID-19 activity in alignment with the response goal and objectives, taking into consideration the diverse needs of population groups based on situations of vulnerability, ethnicity/culture, ability status, and other socioeconomic and demographic factors. This requires adapting these measures to reduce barriers faced by populations in situations of vulnerability, while also taking into account local conditions.

When the original CPIP pandemic goal was developed, it was thought that the main cause of societal disruption would be the absence of essential workers (including health care providers) from the workplace due to illness, need to care for ill family members, workplace outbreak control measures and/or refusals to work. The closure of international borders, businesses, schools and restrictions on social gatherings was always understood as a source of societal disruption in a severe pandemic. The COVID-19 response has been unprecedented with the swift implementation and public adoption of PHM. The restrictive measures that have averted widespread essential service disruption due to illness have, however, had significant broader direct and indirect impacts on health and wellbeing, particularly for seniors, essential workers, racialized populations, people living with disabilities, and women. At a population level physical, mental health and well-being have, in many situations, been negatively impacted by recommendations that affect non-essential services and organizations, for example, those involving sports, recreation and performance arts. These impacts together with the need for ongoing or repetitive use of restrictive measures have subsequently affected adherence levels, which are critical to the collective effectiveness of PHM.

Objectives

As the focus of planning has shifted to a long-term sustainable response, striking an optimal balance between minimizing both health impacts and societal disruption remains a significant challenge. The following public health objectives aim to achieve this balance.

Objectives are to mitigate both health and societal impacts of the pandemic by:

- Taking public health action to reduce the incidence, morbidity and mortality of COVID-19 to a locally manageable level (including operationalizing the vaccine strategy);
- Ensuring access to health care services (both COVID-19 and non-COVID-19 related services), supplies and treatment options;
- Protecting high-risk populations and communities, including Indigenous communities on and off reserve;
- Reducing negative physical and mental health consequences of COVID-19 response actions;
- Taking a risk and evidence based approach to the use of restrictive public health measures;
- Facilitating and supporting high levels of adherence to all recommended measures;
- Countering misinformation and disinformation;

- Leveraging Canada's research, surveillance, national collaborating centres, public health agencies, health care and laboratory systems;
- Working with other sectors to strengthen the social and economic services and policies that protect health and prevent disease (e.g., adequate housing, employment and income supports); and
- Working collaboratively with the international community.

Response to date

FPT response actions to date have been comprehensive and have contributed significantly toward achieving these national public health objectives. These actions include but are not limited to:

- supporting evidence-informed decision-making by rapidly and continually collecting, analyzing and sharing surveillance and other scientific information to inform and target interventions;
- case identification, confirmation, and isolation for the period of communicability;
- contact tracing, identification, communication and quarantine of contacts for the duration of the incubation period;
- development of a comprehensive strategy for the prioritized use and monitoring of vaccines, vaccine effectiveness, and vaccine safety;
- allocating, distributing, and administering available vaccines as safely, efficiently, and equitably as possible;
- rapid outbreak identification and containment activities;
- mobilizing multi-sectorial emergency response teams;
- preventing the importation of COVID-19 through border and travel restrictions and requirements;
- providing guidance to multiple stakeholders and sectors including: public health partners, health care delivery stakeholders, and non-health sectors/settings, that facilitates an evidence-informed, risk-based approach;
- reducing the spread of infection through frequent communication to the public to promote the importance of individual, family, community and organizational mitigation strategies and PHM;
- promoting modifications to day-to-day activities to reduce transmission of COVID-19 in community settings as much as possible;

- use of COVID-19 response frameworks based on level of COVID-19 activity locally and associated levels of PHM and restrictions;
- supporting adherence to recommended measures through effective communication of: rationales, expected duration of measures, and feedback on impact/progress/success;
- protecting those most at risk of serious illness through the provision of resources, guidance and public messaging;
- promoting access to health services through alternative mediums, e.g., telehealth, virtual care visits;
- protecting those most at risk of serious illness in congregate settings and health-care facilities through targeted communications, guidance and response actions;
- establishing a protective stance through community-level screening, guidance and quarantine measures for Northern/remote/isolated communities, and Indigenous populations;
- supporting community-level health and social interventions aimed at supporting and protecting populations at high risk and mitigating negative impacts of public health interventions;
- promoting community resiliency;
- facilitating rapid access to health care supplies, personal protective equipment, healthcare equipment and resources, including medical evacuation from remote, isolated and under-serviced communities;
- supporting the continuity of health care and other essential services;
- providing additional mental health resources and social services; and
- adjusting PHM to facilitate a gradual, cautious return to community functioning in the context of ongoing COVID-19 activity.

Maintaining the trust and confidence of Canadians through timely and transparent communication of evidence-informed public health decisions; communicating appropriate and timely advice (including changes to this advice) to decision-makers, health professionals and the public; taking into consideration the diverse needs of population groups based on vulnerability, ethnicity/culture, ability status, and other socioeconomic and demographic factors; and supporting a coordinated response by working collaboratively with all orders of government, Indigenous partners and stakeholders, continue to be essential in this ongoing response. We need to prepare the public for the reality of living with COVID for the foreseeable future and the changes that will come in terms of the role of vaccination and PHM in sustaining an appropriate level of population protection against COVID-19.

In order to achieve the response goal and objectives it is essential that the effectiveness of COVID-19 control measures be assessed against any negative effects of implementation of these measures (including the re-allocation of other public health program resources); with the objective of reducing COVID-19 incidence and associated serious illness to a locally manageable level. Any reliance on State of Emergency status to achieve the necessary support for ongoing response should be considered and accounted for prior to discontinuing this declared State in order to ensure response goals and objectives will be met. This is key to a sustainable long-term response.

Public health officials are prepared to respond to the variety of challenges that the management of COVID-19 will involve as the pandemic continues to unfold. Advice, recommended measures and interventions have been made based on these shared pandemic goals and objectives. As our collective knowledge increases, these objectives will be revisited and updated as needed.

Forward planning: Assumptions and epidemiological drivers

Planning assumptions and areas of uncertainty

This plan aims to support consistent but flexible public health planning at all levels of government in order to prepare for short, mid and long-term COVID-19 response activities. Plans should reflect a combination of nationally agreed upon approaches with regionally and locally adaptable actions and be aligned with the pandemic response goals and objectives, taking into account the needs of diverse groups within Canada on the basis of health status, age, gender, ethnicity/culture, ability status, and other socio-economic and demographic factors.

Table 1 identifies general planning assumptions that aim to provide a common basis for planning in the Canadian context for the next several months to years. The areas of uncertainty, listed in the table, help identify current unknowns. Given these areas of evolving evidence and knowledge, plans need to include flexible elements or placeholders that can be updated as the pandemic progresses, and knowledge and experience increase. Both planning assumptions and areas of uncertainty require validation and/or updating and may be triggers for re-visiting and modifying plans.

Table 1. Summary of planning assumptions and areas of uncertainty

General planning assumptions

- SARS-CoV-2 spreads from an infected person to others through respiratory droplets and aerosols when an infected person coughs, sneezes, sings, shouts, or talks.
- The droplets vary in size, from large droplets that fall to the ground rapidly (within seconds or minutes) near the infected person, to smaller droplets, sometimes called aerosols, which linger in the air under some circumstances.
- Infectious droplets or aerosols may come into direct contact with the mucous membranes of another person's nose, mouth or eyes, or they may be inhaled into their nose, mouth, airways and lungs. Direct contact with mucous membranes, or inhalation of, infectious droplets and aerosols is accounting for the majority of transmissions.
- The virus may also spread when a person touches another person (i.e., a handshake) or a surface or an object (fomite) that has the virus on it, and then touches their mouth, nose or eyes with unwashed hands.
- Compared to influenza, COVID-19 has higher transmissibility (i.e., it has a higher basic reproductive number or R0) is more transmissible prior to symptom onset, and has a higher infection fatality rate.
- Transmission by asymptomatic and pre-symptomatic cases is occurring.
- Public health measures and personal protective measures reduce the risk of exposure to SARS-CoV-2, however, optimal effectiveness is dependent on comprehensive application of, and public adherence to these measures.
- Variants of concern have the potential to impact transmissibility, severity, laboratory tests, and/or effectiveness of vaccines and therapeutics, depending on the mutations present in the genome of the variant.
- A significant level of population immunity, together with PHM and other measures will be required to reduce COVID-19 to a low, manageable and tolerable level.
- Vaccine conferred immunity duration may not be long-lasting or not be able to prevent all transmission. It may reduce transmission to relatively low levels but not result in elimination of COVID-19.
- The immune response to natural infection may not be long-lasting or sufficient to prevent re-infection with all variants.
- Safe and efficacious vaccines will continue to be rolled out in a targeted manner until the whole population has access to vaccine.
- The vaccination strategy will evolve based on new evidence, availability of new vaccines and related supply, and the epidemiological situation in Canada.
- There will be a national approach to prioritization/targeting of any limited resource, which will be based on an ethics framework. Policy development around prioritizing

General planning assumptions

limited resources will also be informed by other logistical, epidemiological and societal considerations, for example the Declaration of the Rights of Indigenous Peoples (PDF).

- The national epidemic curve will be a compilation of the epidemic activity in each province and territory, which will be influenced by the locally implemented public health response measures and public adherence with these measures.
- The risk of imported cases sparking localized outbreaks is ongoing.
- International borders will be open over time with corresponding increases in non-essential travel (during the period covered by this plan).
- Response measures implemented in one jurisdiction could have an impact on neighbouring jurisdictions, even if they themselves do not implement that measure.
- The level of response across Canada will vary based on local epidemiology (e.g., could be surging in multiple jurisdictions at same time, different times or lulls could coincide) and available health system resources.
- Our health care system and public health system capacity has limits that could be breached during peaks of COVID-19 activity. Public health workforce fatigue and burnout may also affect response capacity and timeliness.
- The impact of concurrent circulation of influenza and other respiratory viruses on health care (including long-term and other community care) and public health system capacity will be lower than usual seasonal increases while there is a high level of adherence to COVID-19 public health and infection prevention and control measures and recommendations.
- The occurrence of multisystem inflammatory syndrome in children (MIS-C) correlates with COVID-19 rates in children and youth (under 18 years of age), and could increase hospitalization rates in these age groups.
- Public health programs (e.g., seasonal influenza vaccination programs) that mitigate surges in the demand for hospital resources are part of the overall long-term strategy for the ongoing management for COVID-19.
- Public health capacity to respond to other priorities (e.g., the overdose crisis and higher rates of problematic substance use) needs to be maintained. Capacity to catch-up on interrupted program delivery may also be required.

Areas of uncertainty

General planning assumptions

- The degree to which new variants will require adjustments to the pandemic response in order to achieve current goals and objectives.
- How best to prevent takeover of VOCs and/or reduce their impact until coverage with an effective vaccine is higher.
- To what degree different vaccines and different vaccine series will prevent transmission.
- How potential global vaccine supply disruption may affect progress with vaccine roll-out.
- How easily the virus spreads through contact with surfaces or objects.
- Duration of immunity, what constitutes immunity, and whether infection with other coronaviruses provides cross-protection.
- Duration of vaccine conferred immunity and whether there will be a need for booster doses and/or seasonal vaccine programs akin to influenza.
- The number of people who need to be immune to COVID-19 to achieve sufficient population immunity (i.e., sufficient to reduce and maintain low, manageable and tolerable levels of COVID-19 in Canada).
- How effective different vaccines will be in response to new VOCs.
- How adverse events following immunizations (AEFI) will affect vaccine confidence.
- How much impact vaccine hesitancy/confidence and vaccine preference will have on vaccine coverage and timelines to achieving sufficient population immunity.
- Whether COVID-19 will eventually have a seasonal pattern similar to other respiratory infections.
- Whether lack of adherence to restrictive community based PHM will impact effectiveness of these measures to the point where their utility is compromised.
- How potential variations in risk tolerance over time and in different geographic areas will impact response actions.
- How variations in public adherence to PHMs will evolve over time.
- Sequelae and long-term health impacts of COVID-19 infection.
- Whether in the long-term significant rates of co-infection with SARS-CoV-2 and a seasonal influenza virus or other respiratory pathogen will occur and whether co-infection will significantly impact morbidity or mortality cases and subsequently demand on the health care system and resources.
- Robustness of international COVID-19 data and testing.

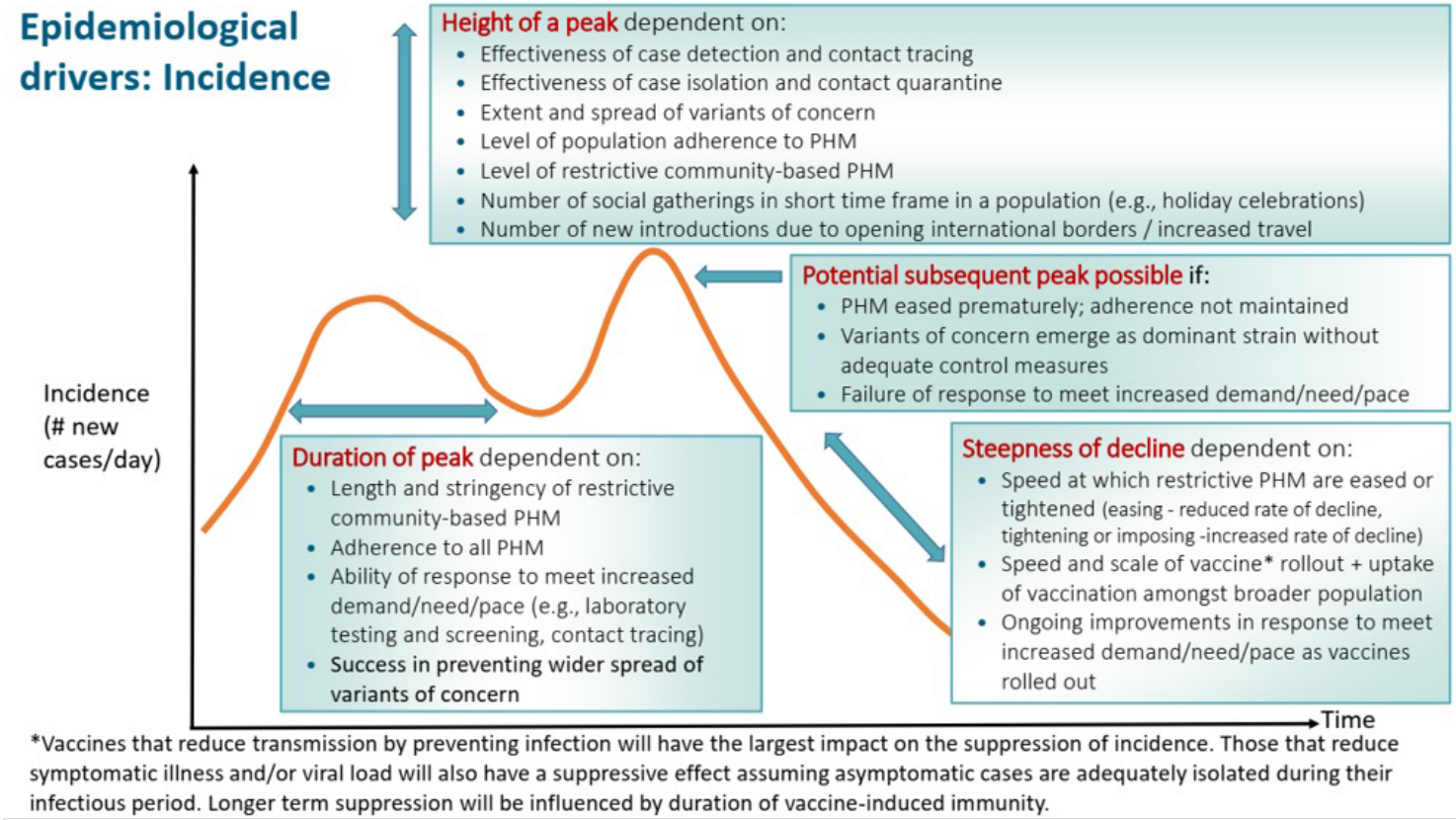
Modelling and epidemiological drivers

Modelling and capacity assessments may facilitate planning by exploring how possible ranges of parameters relevant to these issues affect the extent and impact of the pandemic in Canada. All modelling outputs are influenced by the underlying assumptions. Forecasting models are best suited to inform what may occur in the coming 2-3 months; therefore, the role of modelling in long-term planning is focused on providing additional information to decision makers regarding the potential impact of control measures as opposed to providing possible incidence rates.

Mathematical modelling supports planning our response to epidemics and outbreaks, and the COVID-19 pandemic has demonstrated the important role and need for the full range of modelling tools required to support decision-making during a complex public heath crisis. This role and the types of models currently in use are described in Appendix 2: Modelling support for forward planning.

It is important to recognize that the national epidemic curve will be a combination of the epidemic curve patterns from each province and territory, which in turn will be dependent on the effect of the escalation and suppression drivers in each jurisdiction. Where daily incidence is very low it is important to look at incidence over time (e.g., 2-4 weeks at a time) in order to assess the overall response and recent trends. Figure 1 identifies epidemiological drivers that will influence the number and timing of new cases and therefore illustrates how these drivers of incidence impact the shape of the epidemic curve we experience in Canada.

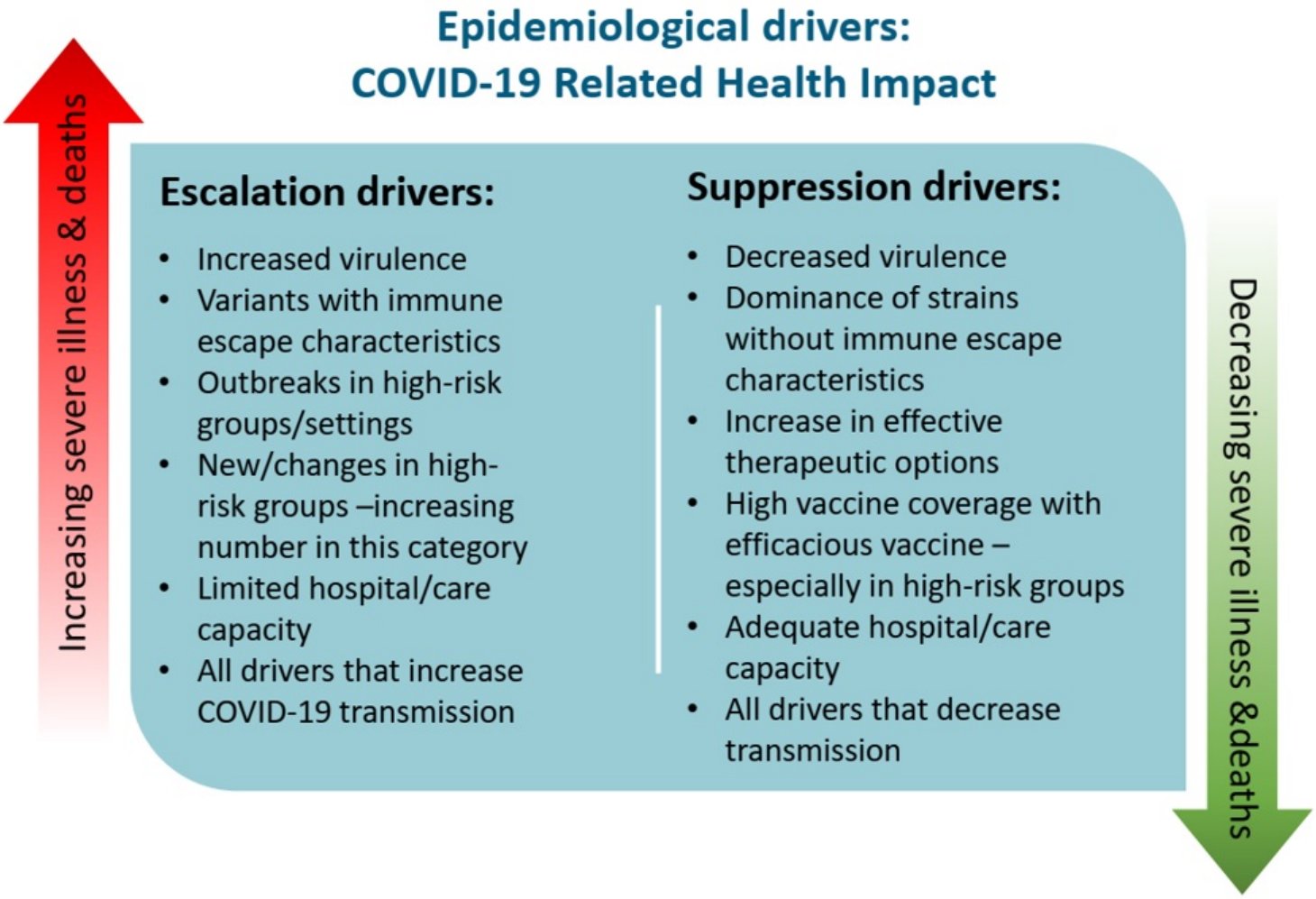
Figure 1. Epidemiological drivers: Incidence



▶ Figure 1 - Text description

An epidemic curve pattern is one part of a planning scenario as it reflects the potential changes in the number of new cases occurring over a period of time. To ensure optimal planning it is important to consider not only the number of cases but variables that may shift the health and societal impacts of those new cases and subsequently possible surges that exceed current health care and public health capacity thresholds. Figure 2 describes epidemiological drivers of health impact in terms of variables that may increase or decrease the occurrence of severe illness and deaths due to COVID-19. These variables include but are not limited to: changes in severity of illness experienced by the majority of cases due to increased virulence, changes in high-risk groups (i.e., both the demographic characteristics of who is getting severely ill and identification of new risk factors for severe illness), the impact of variants of concern, availability of effective therapeutics and hospital care, and vaccine coverage. The manifestation of these variables will also influence public risk perception and therefore, in a somewhat circular manner, epidemiological drivers like adherence to recommended PHM.

Figure 2. Epidemiologic drivers: COVID-19 related health impact



▶ Figure 2 - Text description

Planning and the reasonable worst-case scenario

Response activities currently assume a significant level of immunity in the population, conferred by vaccination and recovery from natural infection, being achieved by the fall of 2021. This is dependent on achieving a high level of vaccination in the population with vaccines that are effective against the dominant strains and that confer immunity for a prolonged period of time. This level of population immunity will be considered significant when it is sufficient to decrease and sustain COVID-19 activity in Canada at a low, manageable, and tolerable level.

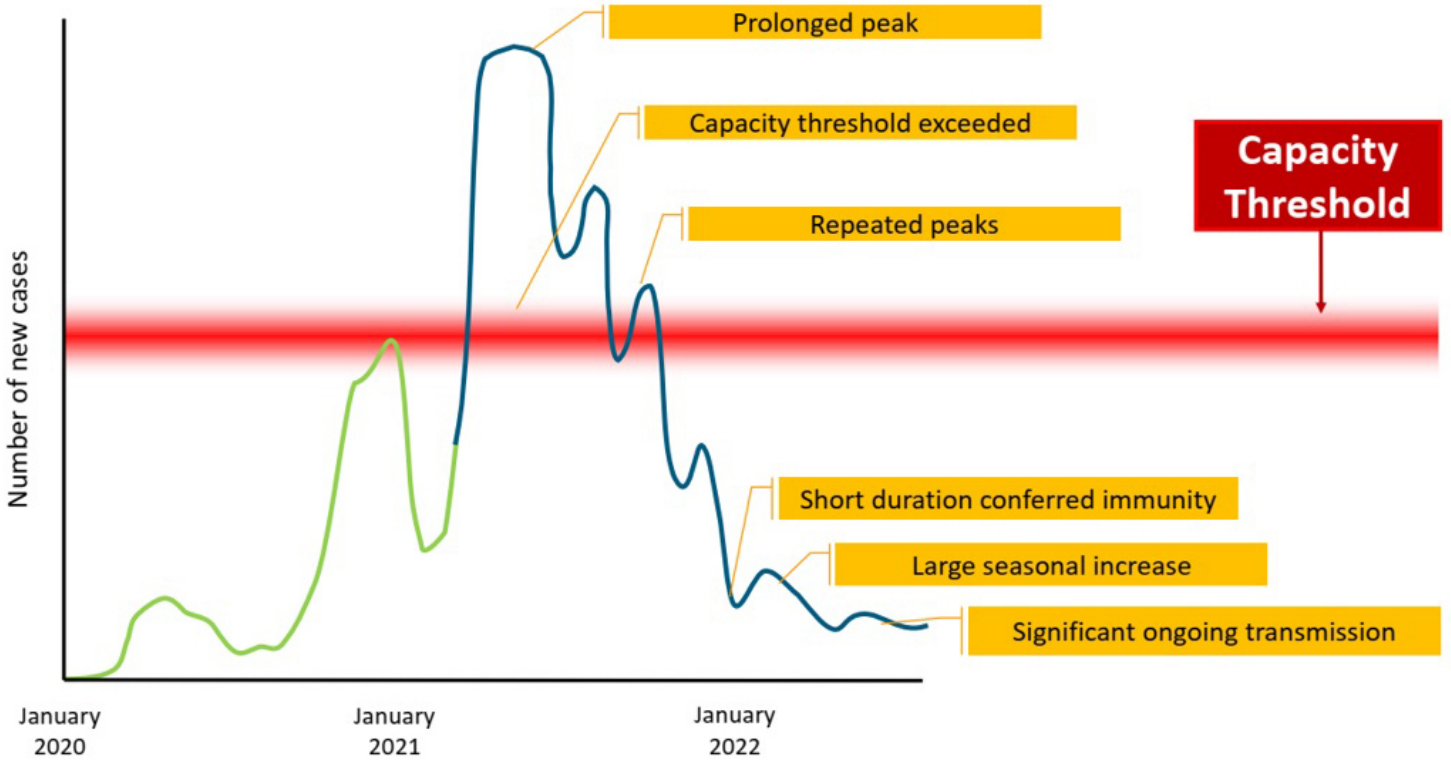
Given current uncertainties, it is also prudent to plan for delayed achievement of significant population immunity (into 2022) and the potential need for booster doses or seasonal vaccination in sustaining vaccine conferred immunity and/or protecting the those at high-risk of severe disease. In light of uncertainty regarding the duration of immunity (both from vaccination and natural infection), the propensity for respiratory viruses to spread during

winter seasons, the impact of variants and travel related importations, it is possible that going forward COVID-19 will settle into a seasonal pattern similar to influenza. Regardless, living with COVID-19 will likely involve some level of PHM not only during the period of pandemic activity but on an ongoing basis.

Relaxation or lifting of restrictive community-based public health measures in the absence of a comprehensive and timely case detection, contact tracing and isolation/quarantine capability can lead to a resurgence in cases; especially if highly transmissible variants become the dominant strain in the period prior to achieving sufficient population immunity. This is what we are now seeing in some parts of the country. The size and duration of resurgence (depicted as peaks in the epidemic curve) and steepness of decline following a peak in incidence are impacted by multiple epidemiological drivers (previously described). Resurgences may be considered more tolerable as vaccine coverage increases amongst those most at risk for severe illness and death given the positive impact of lifting restrictions on minimizing societal disruption. This presumes, however, that the vaccine is effective against the circulating strain, there is no shift in virulence or high-risk groups and no significant long-term sequelae of infection. Ongoing planning needs to achieve a balance so that the pandemic response goal of minimizing all serious illness and deaths while also minimizing societal disruption is reached as soon as possible.

To facilitate ongoing planning in the context of a high degree of uncertainty, particularly around VOCs and vaccination impact, the “reasonable worst-case scenario” has been updated from the first edition of this plan. This scenario is not a prediction, but rather a common set of characteristics that will support robust forward planning (see Text box 1).

Figure 3. Epidemic curve for reasonable worst-case scenario



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Text box 1. Reasonable worst-case scenario characteristics

- A large third wave starting with a early spring peak of prolonged duration followed by ongoing peaks of decreasing amplitude but several exceeding health care delivery, laboratory and public health capacity thresholds and a relatively high level of ongoing transmission into 2022.
- Early spring peak is 2-3 times higher than the incidence experienced at the peak of the second wave.
- Relatively high seasonal peak in winter 2021-22 occurs concurrently with severe influenza/other respiratory pathogens season.
- Similar timing of peaks across the country (each jurisdiction experiences peaks at same time).
- VOCs with high transmissibility, increased severity and immune escape properties become the dominant strain(s).
- VOCs with immune escape properties reduce vaccine effectiveness.
- There is reluctance to take the licensed vaccines (or specific vaccines) or vaccine supply is insufficient or delayed, reducing vaccine coverage and delaying achievement of sufficient population immunity.

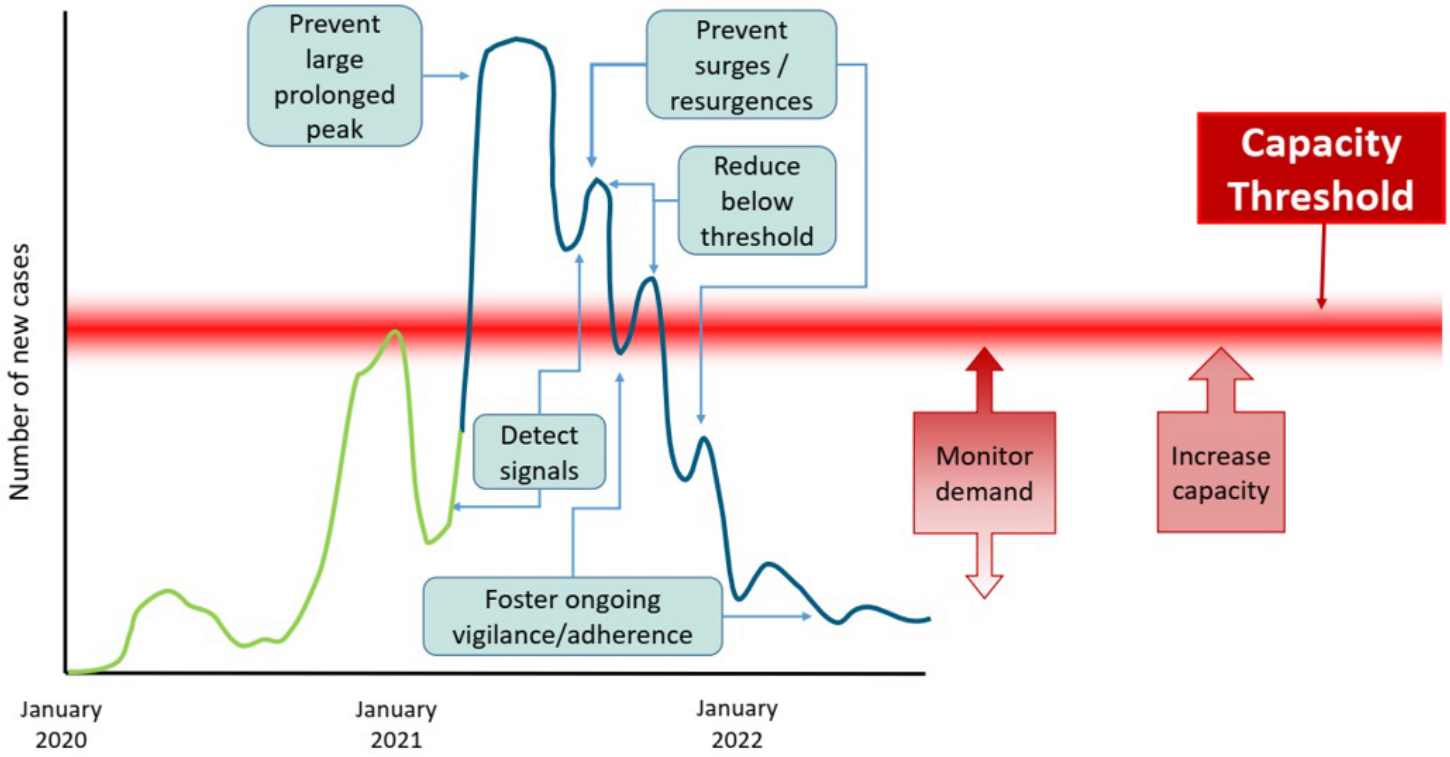
- Available vaccines do not significantly reduce transmission and do not confer long-term immunity.
- Available treatment/therapeutics are less effective against dominant variant.
- Weak/non-sustained post-infection immunity (recovered cases become susceptible again).
- Demand for health care resources (hospitalizations, ICU beds, ventilators, personal protective equipment (PPE), Long-term care spaces, etc.) exceeds system capacity (during early third wave peaks).
- Shortage of health care providers (e.g., due to illness, burnout, work refusal, international competition).
- Demands on both laboratory and public health resources exceed capacity (during all early third wave peaks).
- Low level of compliance with public health measures.
- Permeation of mis/disinformation in Canadian society and/or loss of public trust/confidence.

Nationally the incidence was approximately 31/100,000 population or 11,849 new cases reported during the peak week in the initial wave and 149/100,000 population or 56 638 new cases reported in the peak week of the second wave. A third wave driven by the dominance of highly transmissible variants could be substantially larger than the last given that control would require enhanced, timely public health test, trace and isolate capacity at a time when much of those same resources are needed for vaccination programs. There continues to be a high degree of variation in epidemiology and response between PTs with the most populous PTs having the greatest impact on the national epidemic curve. The previous reasonable worst-case scenario included planning for a fall or winter peak, which has now occurred, however it did not specifically factor in the role of vaccine and VOCs.

The updated reasonable worst-case scenario can be used to identify any new or outstanding preparedness and response needs or issues that would require, or benefit from, a coordinated FPT effort should Canada be faced with this scenario. It is provided as a “stress-test” not a prediction and is intended to stimulate thinking concerning our current response efforts, capacity thresholds and resiliency.

More specifically, the scenario presents a set of potential risks, each requiring mitigation strategies based on an assessment of capacity requirements and our collective capability to manage the risks. Figure 4 identifies high-level capabilities that need to be in place for this scenario and Table 2 identifies associated requirements that should be considered at all levels of government.

Figure 4. Capabilities for management of the reasonable worst-case scenario



▶ Figure 4 - Text description

Table 2. Reasonable worst-case scenario risk management requirements

Capability	Risk management requirements

Capability	Risk management requirements
Detect: signals indicating a significant surge in cases may occur	• timely surveillance data (local, PT, national and international) • analysis of international data for the same or similar strain • laboratory resources to rapidly distinguish between COVID-19 strains (including VOCs) and other respiratory viruses and to identify mutations associated with immune escape and/or increased transmissibility • rapid analysis/investigation to assess risk of large peak based on international, national, PT and precise/granular local level data (to assess risk of change in dominant strain, risk of importation into and within Canada, and risk of exceeding local health care and public health response capacity) • screening activities including targeted use of point of care screening tests • health system-wide early warning for increased demand on resources and response activities • communication/education/sensitization regarding what constitutes a signal and how to ensure appropriate timely notification of potential signal • ongoing vigilance/commitment to COVID-19 response
Prevent: large prolonged peak and surges, especially those that exceed capacity to respond	• continued use of restrictive community-based measures until key locally-adapted indicators for relaxation of measures have been achieved • public health resources to ensure ongoing response measures are adequate to control spread by highly transmissible variants and prevent new cases (e.g., use of highly conservative assumptions for defining exposure, household quarantine approach) • capacity for rapid detection (through screening and testing) and isolation of cases, and rapid identification and quarantine of high exposure risk contacts • public cooperation with surveillance and case and contact management activities and tools (i.e., to facilitate timely identification and isolation/quarantine, optimize use of alerting apps) • use of suitable isolation and quarantine sites and high adherence to recommended measures in place in these locations

Capability	Risk management requirements
	• gradual, controlled "re-opening" of settings and gradual resumption of activities (with modifications) that are known to be associated with increased transmission risk • high adherence to ongoing modifications/controls put in place especially as restrictive PHM are lifted • modified restrictions for essential workers • screening strategies that aim to prevent and/or rapidly detect introduction of the virus into a susceptible high-risk population or setting • consistent, clear localized indicators for implementation or re-implementation of restrictive PHM • rapid deployment of targeted outbreak control/containment resources (including implementation of local “lockdowns”, deployment of outbreak response teams) • high compliance with personal protective measures • proactive international border control measures (i.e., including quarantine, testing requirements, travel restrictions) • increased messaging and public education regarding personal protective measures, effectiveness of vaccines and requirement for PHM following vaccination • evidence-based results from vaccine hesitancy efforts and work with diverse populations to support vaccine trust, interest in getting informed, and in being vaccinated • increased health care system capacity (especially in high-risk settings such as long-term care) and consideration of how to deliver needed health care (e.g., at alternate sites, using retired workers or students or alternate care providers)

Capability	Risk management requirements
Reduce: surges in incidence and hospitalizations	• rapid implementation and maximizing efficiency of vaccine administration programs • use of vaccine strategies that prioritize immunization of high-risk individuals, groups and settings • adequate public health resources to ensure ongoing response measures to control current spread and prevent new cases, hospitalizations and deaths • focus on rapid detection and isolation of cases, and rapid identification and quarantine of contacts • rapid detection of outbreaks in high-risk settings and deployment of outbreak control/containment resources • consideration of how to re-implement restrictive community PHM and which PHM to re-implement based on clear local-level triggers • increased use of/compliance with, personal protective measures • ongoing international border control measures with possible re-introduction of restrictions

Capability	Risk management requirements
Increase: health care and public health capacity	• laboratory surge capacity to: ensure rapid diagnosis and case notification, identify new VOCs, and lab-epi linkage to characterize and learn from current variants • sufficient resources to facilitate optimal delivery of the vaccine program (including clinic staff; immunizers; security; schedulers; local, accessible and appropriate facilities; clear communication on who, when and how; tracking programs/registries etc.) • availability of public health resources for surges in case and contact management requirements in the community (including isolation of cases and quarantine of contacts at home/alternative designated sites), development of new guidance products and provision of expert advice based on evolving scientific literature • resources (i.e., human and equipment/supplies), planning and training for outbreak control activities in high-risk settings, including clear emergency back-up contact points • surge capacity to ensure availability/access to health care resources including equipment (e.g., ventilators, PPE) during peaks • availability of sufficient health care providers to meet surge in demand • ability to access and distribute effective therapeutics • ongoing monitoring of scientific literature, networks and expert advice to inform best practices for treatment and identification of effective therapeutics that reduce hospitalization requirements and/or duration of hospitalization • recovery policies and measures (e.g., discharge for recovery at home or alternate site) to avert potential backlogs in the hospital system

Capability	Risk management requirements
Monitor: demand for health care resources	• surveillance for early indicators that other illnesses that may cause a surge in demand for health care resources (e.g., seasonal influenza, other respiratory pathogens) • strategic clearing of “backlog” – i.e., re-scheduling of delayed treatments, procedures and surgeries, in a way that demand is met without exceeding capacity thresholds • linkages between health care delivery and public health to ensure timely establishment of alternative/over-flow care sites • enhanced monitoring of global supply chains that could trigger drug shortages and identified alternatives and strategies to prioritize and conserve supply (e.g., critical supply reserve etc.)

Capability	Risk management requirements
Foster: ongoing public vigilance and adherence to measures and recommendations	• ongoing public trust in public health authorities • clear, effective, culturally-safe and appropriately tailored communication and education products to support continued public adherence to personal protective measures, community-based public health measures and to support vaccine confidence and uptake • transparency and clarity regarding rationales for recommendations • ability to provide feedback on impact, progress and success of measures • public knowledge, attitudes and behavior research to inform sustainable effective behavioral changes and to combat pandemic fatigue and vaccine hesitancy • monitoring of risk tolerance and public opinion in order to maximize adherence while adjusting measures to locally tolerable/sustainable levels • support for enabling policy changes (e.g., paid sick leave) that facilitate adherence to public health measures and compensate affected sectors • addressing of equity issues – especially those that affect access to needed resources (e.g., availability of suitable isolation and quarantine settings), ensuring public messaging is providing in multiple languages and formats etc., and ensuring these resources are shared with various partners such as Indigenous partners. • consideration of incentives for adherence or adoption of new practices • empowerment focused initiatives • involvement of community to ensure community needs and potential barriers to adherence are considered in public health measures • transparent, clear, and equitable application of reasonable enforcement activities (if necessary)

Table 2 outlines the capabilities needed to mitigate the risk of the reasonable worst-case scenario – the “what” is needed. Typically guidance and other products address the “when and how” to optimally use these capabilities. At this time, while vaccine coverage is

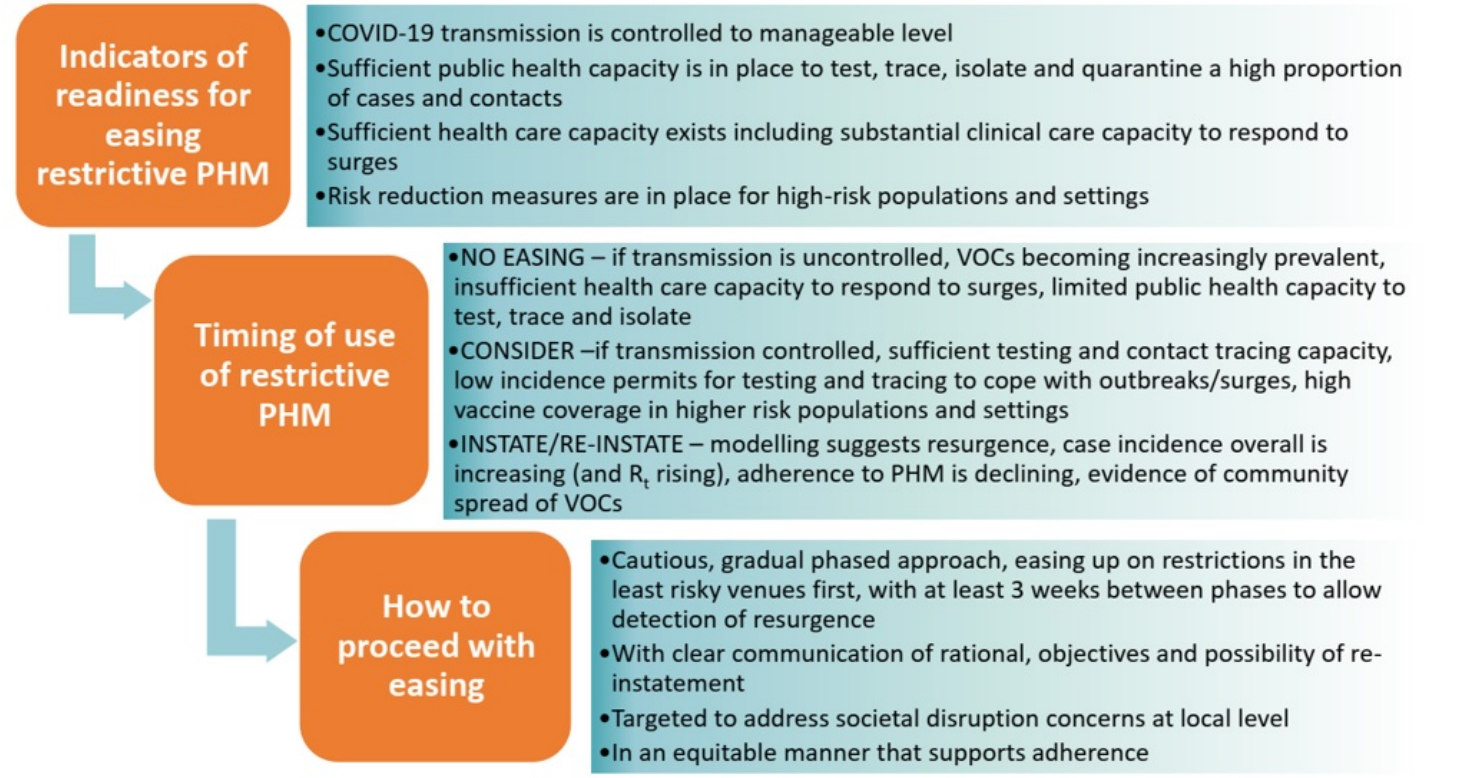
increasing, one of the keys to preventing a large prolonged wave and ongoing surges/resurgences is the timing and adjusted use of restrictive PHM.

Adjustments to restrictive PHM must be considered in the context of risk associated with VOCs, the effect of increasing vaccine coverage, and other factors. Specifically:

- The spread of VOCs is facilitated by less restrictive public health measures and/or insufficient application and adherence to PHM.
- More transmissible strains are more difficult to control – VOCs can be controlled by public health measures but they must be optimized. In the U.K. where VOC B1.1.7 is now the dominant strain, an increase in the stringency of public health measures resulted in declining incidence [11] [12].
- As restrictive PHM are eased, VOCs will spread much faster in the community than earlier strains, necessitating stronger test, trace and isolate/quarantine capacity.
- If isolation, quarantine and other PHMs cannot control spread, closures may need to be maintained until vaccine rollout is more complete.
- High priority groups for vaccine delivery were selected to minimize serious illness and death from COVID-19.
- Current high priority groups for vaccine receipt are not the populations that are driving community transmission (i.e., younger age groups).
- When enough people in the population are immune to infection so that the virus cannot continue to spread and the disease begins to die out on its own.
- It is not yet known if the vaccines against COVID-19 can prevent disease transmission and contribute to developing sufficient population immunity, or if they simply protect against illness.
- Efforts are underway by vaccine manufacturers, governments and others to better understand the effectiveness of COVID-19 vaccines on variants.

Due to the critical role PHM play during this time period prior to achieving sufficient population immunity, Figure 5 provides a summary of considerations for the “when and how” to ease restrictive PHM.

Figure 5. Easing of restrictive PHM



▶ Figure 5 - Text description

COVID-19 FPT response components

Forward planning will also be informed by ongoing reflection regarding what has worked well, what we have learned and what can be adjusted based on evidence and experience. Using the response components identified in the CPIP, with a focus on those requiring FPT public health leadership and consultation, this section provides details on FPT activities planned or already underway that will assist and expedite complementary planning in each federal government department, province and territory.

The components covered in this section are:

- Surveillance
- Laboratory response activities
- Public health measures
- Infection prevention and control, and clinical care guidance
- Vaccination
- International border and travel health measures
- Health care system infrastructure
- Risk communications and outreach
- Research

Surveillance

The purpose of surveillance and risk assessment activities is to provide decision makers with the timely epidemiological and risk information they need to inform action. Similar to national influenza surveillance (FluWatch), COVID-19 surveillance is a pan-Canadian initiative that integrates numerous data streams including existing surveillance systems with novel, non-traditional data sources.

Current status/focus

Currently, the following data sources are facilitating monitoring across the spectrum of disease (i.e., from mild cases in the community based on sentinel surveillance to severe illness based on hospitalization data).

- Case-level data reported by PTs: Revised national dataset including more information on cases, risk factor data, improved occupational data, and the addition of race/ethnicity data is a key priority.
- Aggregate laboratory result data: Provincial public health laboratories and PHAC's National Microbiology Lab report numbers of people tested for SARS-CoV-2, as well as confirmed VOC cases.
- Aggregate sampling: Wastewater surveillance is underway and showing some promise as a surveillance and alert component.
- Data on travellers and border testing: Is used to identify positive cases at the border and prevent travel associated transmission in Canada
- Apps: User data from Canada COVID-19 and other symptom tracking applications.
- Mobility data: Partnership with BlueDot Inc., and other sources that may become available, to monitor indicators of population movement as a proxy measure for compliance with PHM, and the levels of inter-PT movement.
- Special surveys: Impact of COVID- 19 on specific populations (e.g., health care worker).
- Sentinel Surveillance Networks:
    - Hospital networks - Several hospital-based data streams measure the impact of COVID-19 in Canadian hospitals and collect detailed case information on most severe cases.
    - Canadian Pediatric Surveillance Program - occurrence of Multi Inflammatory System in Children (MIS-C).
    - Community-based systems/ networks - Assess the level of transmission in the community and the epidemiologic characteristics of outpatient cases.

- Syndromic surveillance data: PHAC monitors individuals in Canada reporting influenza-like illness via its participating sentinel practitioners in FluWatch.
- Publicly available data: supplementary data source to add situational awareness on COVID-19 transmission in jurisdictions.
- The federal, provincial and territorial public health partners are leveraging existing mechanisms and operating procedures to collaborate on multijurisdictional and complex COVID-19 outbreak investigations. This allows sharing of capacity and resources toward the common goal of better understanding COVID-19 in our communities.
- The process to conduct joint epidemiological and laboratory investigations for variants of interest (VOIs) in Canada is currently being developed, and will be based on the current process for investigating foodborne disease.

Preparations/forward planning

Forward planning will support continued improvement of national surveillance and monitoring to support decision making as the pandemic evolves. The focus will be on: monitoring vaccine performance and changes in the epidemiology of COVID-19, including the impact on priority populations and reductions in severe outcome; flexible surveillance and monitoring that can adapt to new evidence, including the evolution of the virus over time and the emergence of VOCs; interpretation of surveillance data in the context of local epidemiologic trends and, the information required to inform the appropriate easing of PHM driven by epidemiological trends. Multiple data streams are being configured in order to pick up signals and changes in epidemiology. These preparations and ongoing activities based on the anticipated short, mid or long-term timeframe are identified below.

Short term:

- Updating data dictionary, case report form and surveillance guidance as necessary.
- Monitor vaccine performance, including coverage, safety and effectiveness, waning immunity and vaccine escape.
- Implement the national Variants of Concern Strategy and Network.
- Support ramp-up of genomic capacity and screening for positive cases and linkage to associated epidemiologic data to monitor on-going viral evolution including VOCs.
- Identify signals that may require public health response.
- Further examination and use of wastewater testing as an early detection mechanism.

- Support rapid epidemiologic investigations to characterise the transmission and impacts of new variants and impact of vaccination in the context of outbreaks.
- Provide federal surge capacity support.
- Conduct surveillance to identify broader consequences of COVID-19 and associated control measures on health of Canadians.
- Enhance data and analytics by improved modelling and data access capacity.
- Share timely information effectively with partners and publicly with Canadians.

Medium to long term:

- Support rapid epidemiologic investigations to identify areas of on-going transmission.
- Monitor vaccine performance, including coverage, safety and effectiveness, including issues such as waning immunity and vaccine escape.
- Conduct targeted surveillance on broader consequences to inform public health action.
- Enhance data integration to evaluate evolving epidemiology in the context of increased vaccination and immunity to support recovery.
- Continue to build and maintain data and analytics capacity and knowledge transfer networks to support on-going development and sharing of intelligence.

Planning variables or signals

It is possible that a new syndrome or rare event would require the development of a new, or adjustments to, the surveillance strategy as has occurred for Multisystem Inflammatory Syndrome in Children (MIS-C).

New settings or populations affected by outbreaks could emerge in outbreak surveillance (or via outbreak intelligence gathering) which could precipitate new data needs, additional surveillance activities or new variables to be collected to inform actions. For example, outbreaks among temporary foreign workers have highlighted the need to be prepared to rapidly implement specific surveillance and coordination mechanisms, as well as drawn attention to how social determinants of health (e.g., crowded housing, precarious work, access to medical services) can impact transmission and control of COVID-19.

Laboratory response activities

Laboratory-based surveillance is an integral part of monitoring respiratory virus activity. Since the start of the COVID-19 outbreak, Canada’s National Microbiology Laboratory (NML) has been providing leadership in regard to testing for COVID-19 and surge capacity for

provincial and territorial public health laboratories. The NML has also contributed to domestic and international efforts to better understand COVID-19 virus characteristics that can inform the development of medical countermeasures.

Canada's public health laboratories, working through the long-standing Canadian Public Health Laboratory Network (CPHLN), have been successful in optimizing molecular testing to reduce reagent consumption by reducing the number of PCR target genes (when appropriate), pooling of samples, multiplexing, evaluating the optimal types of samples, swabs and transport media. Through this effort, testing capacity has been increased to 227,000 tests/day as of February 2021. CPHLN has worked closely and successfully with northern, remote, and Indigenous communities to enable those communities to have greater access to laboratory diagnostic tools (e.g., diagnostic platforms, reagents, training, and supply chain management). Through close work with the NML, the territories have been able to set up COVID-19 testing within each territory.

Current status/focus

The evolution of several different virus variants with altered characteristics, such as increased transmissibility and potential immune escape, poses a new challenge to Canadians. Canada's public health laboratories, working through the CPHLN, are meeting this new challenge while continuing to address other key COVID-19 and non-COVID-19 pressures through the following activities:

- development and validation of diagnostic VOC screening assays;
- continued support for implementation of whole genome sequencing of priority samples;
- undertaking work to standardize naming and confirming VOCs, defining what may constitute a SARS-CoV-2 variant of concern as well as acquiring variants quickly to support Canadian diagnostic initiatives and research, including vaccine efficacy in the face of evolving variants;
- continued work to evaluate serological testing kits as well as developing in-house serological tools such as ELISA, neutralization assays and point of care tests (serological work is in support of the broader Canadian Immunology Task Force), incorporating the ability to distinguish natural infection from vaccine-derived antibodies;
- continued work geared toward the augmentation of Transport of Dangerous Goods (TDG) sample shipping requirements) to meet pandemic and non-pandemic sample transport challenges in those and all Canadian communities;

- collaboration with other partners, such as CIHR and academic, to undertake studies that help us understand pathogen characteristics, including the differences brought on by virus variants; and,
- continued readiness to tackle multiple respiratory virus outbreaks as needed, recognizing that the PHM in place have largely suppressed influenza and RSV activity but a resurgence might be observed with the relaxation of PHM.

Preparations/forward planning

At this time, federal and provincial public health laboratories and facilities in the territories perform on average 97,000 tests per day and have the capacity to perform as many as 227,000 test per day if required.

The NML together with the CPHLN, is undertaking the following activities in order to continue to prepare for potential surges/resurgences based on the reasonable worst-case scenario but also as part of the laboratory preparedness long-term vision.

Short term:

- Continuing strong communication among Canada's public health partners through CPHLN to ensure laboratory response strategies are aligned and appropriate.
- Continuing a strong collaborative approach toward developing and validating diagnostic testing.
- Provide support for point of care testing.
- Work together to develop a robust collaborative research agenda into SARS-CoV-2 variants of concern, their detection and public health impacts as vaccines are administered.

Mid term:

- Continue optimizing various testing platforms and their uses to determine whether individuals have been previously infected, especially for healthcare and other service providers such as police, fire fighters, employees in long-term care facilities, etc.
- Continue streamlining molecular and serological testing as well as variant screens and whole genome sequencing, including stewardship of reagents so they are conserved as testing demands increase.
- Continue developing, validating, and enabling greater access to faster diagnostic tools such as Point of Care tests (prioritizing northern, remote, isolated and Indigenous communities).

- Continue working with manufacturers to enhance the sourcing of critical laboratory supplies that meet appropriate standards to ensure continuity of operations.
- Continue working with PTs and other stakeholders to inform the use of testing in specialized settings (such as borders).

Planning variables or signals

Epidemiological data from February 2021 demonstrated reassuring declines in case counts in most Canadian jurisdictions, but with the combination of relaxation of public health measures and expansion of VOCs, data from April 2021 clearly shows initiation of a third wave largely driven by surges of VOC cases in the most populated provinces ahead of widespread vaccination. The timelines, strategy, and prioritization of the above activities, therefore, must now be expedited.

Public health measures

PHM are the range of non-pharmaceutical interventions implemented by public health authorities at the FPT and local level to reduce the risk of infectious disease transmission. PHM range from those applied at individual-level to community-based measures including for settings (e.g., schools, workplaces, healthcare settings). Individual-level measures include personal preventive practices such as wearing masks, physical distancing, practising hand hygiene, self-monitoring for symptoms to those measures aimed at detecting and isolating cases as well as tracing and quarantine of contacts. Community-based measures range from public education campaigns and advice on enhanced cleaning and disinfection for public spaces to restrictive measures to reduce interactions and prevent transmission in population groups, settings and the community at large. “Restrictive” community-based measures aim to reduce contacts by limiting movement, activities, or access to resources and public spaces (e.g., school closure, restrictions on gatherings, workplaces/businesses restrictions).

PHM have been shown to be effective in controlling transmission even where VOCs with increased transmission are dominant [9] [10]; however, many of these measures have important consequences beyond the scope of COVID-19 management. These consequences require careful consideration and prioritization in relation to other determinants of health, such as impacts on childhood development, access to health services, mental health, domestic and intra-family violence, social isolation and exclusion, and at-risk communities. PHM

effectiveness depends on the level of adherence by the public, which is influenced by pandemic fatigue and factors such as living, working, community conditions, and financial and social circumstances.

Since the start of the COVID-19 pandemic the FPT public health response has involved working closely with multilateral partners, other government departments, First Nations, Inuit and Métis partners to develop, update and disseminate appropriate public health guidance for a range of target audiences on how to detect, report, prevent and manage COVID-19 infection. One example of this is the formation of the Public Health Working Group on Remote, Isolated and Northern Indigenous Communities that adapts public health measures guidance to the unique needs, context and considerations of these communities in the response.

Current status/focus

The focus of current FPT PHM activities includes:

- developing and updating national guidance as new information becomes available and/or response needs change;
- increasing testing and contact tracing capacity to ensure chains of transmission are disrupted;
- rapidly detecting and isolating all cases, and tracing and quarantine of all high-risk contacts in a culturally sensitive way;
- promoting adherence to personal preventive practices by empowering individuals to play an active role in reducing transmission;
- monitoring the evolving domestic and international situation, and evaluation of PHMs to inform updated advice and adjustments to PHM accordingly (e.g., non-medical mask use, ventilation, risk associated with different settings and activities, emergence of VOCs, vaccine roll-out);
- careful easing restrictive PHM by PTs based on assessed readiness, while monitoring for signals of concern (e.g., increases in unlinked cases, transmission of VOCs); maintaining readiness to rapidly reinstate restrictive measures if surges/resurgence occurs; and protecting populations at higher risk of severe disease and outcomes;
- promoting risk based approaches to using PHM based on the setting (e.g., workplaces, gatherings, outdoor recreational spaces, child and youth settings) and consideration of the broad impacts of PHM on pandemic fatigue, health and wellbeing of diverse population groups; and,

- supporting and informing workplaces/businesses by working with the Canadian Centre for Occupational Health and Safety, to provide for safe and healthy workplaces.

Preparations/forward planning

In terms of FPT preparations, the focus is on building, adjusting and updating existing PHM guidance and resource products as needed, based on new knowledge, expert scientific opinion, experiences to date, and risk assessments.

It is important that these ongoing activities continue to be as timely and responsive as possible and take into consideration the specific needs of high-risk populations including social, economic and demographic factors. Community-based PHM are most effective when implemented as early as possible and as a set of measures using a "layered approach" in response to epidemiological signals of concern. Therefore, preparations include ongoing readiness to reinstate restrictive community-based PHM when required, while easing them when possible to avoid negative impacts on health, wellbeing and society. Communication activities that continue to build public trust and confidence will be critical to facilitating public understanding and adherence to recommended PHM. As vaccine coverage increases in key settings and once indicators of readiness to ease measures are met (Figure 5), public health authorities will adjust public health advice, measures and restrictions accordingly. These adjustments may include changes in advice for key settings where mitigation measures and layers of protection are in place (e.g., long-term care homes) and where there is high vaccination coverage. Living with COVID-19 will likely involve some level of PHM and personal preventive practices not only during the period of epidemic activity but for a longer period of time, for example, mask wearing in crowded places, hand, respiratory and environmental hygiene, and avoiding enclosed poorly ventilated spaces.

These preparations and ongoing activities based on the anticipated short, mid and long-term timeframe are identified below.

Short term:

- Ongoing updates to existing or development of new evidence-based national guidance as evidence evolves.
- Monitoring the emerging evidence and modelling the effectiveness of PHM and adjusting as appropriate.
- Monitoring the situation related to new VOCs and advising on changes to recommended PHM if warranted.

- Monitoring public adherence to PHM and adjusting messaging and enforcement as required.
- Updating public and health professional communication, guidance and education products and assessing their effectiveness (e.g., through public opinion and behavioural research).
- Developing and maintaining sufficient public health capacity to isolate cases, trace and quarantine contacts in place, including through the use of digital tools.
- Ongoing provision of comprehensive public health advice to workplaces/businesses.
- Monitoring the impact of vaccine roll-out (e.g., effectiveness to prevent asymptomatic infection, vaccine coverage rates) and updating advice on public health measures for individuals, settings and communities accordingly.

Mid term:

- Ongoing situational monitoring and international collaboration on COVID-19, including VOCs, and broader impacts of PHM and recommendations, updating advice and adjusting PHM accordingly.
- Ongoing monitoring of public adherence with PHM, and adjusting messaging and enforcement as required.
- Provide recommendations/advice on the need to reinstate restrictive PHM when a resurgence in COVID-19 is identified at PT and national levels.
- Monitoring the impact of vaccine roll-out and adjusting advice on public health measures accordingly.
- Supporting, as necessary, Logistics Advisory Committee (LAC) re-evaluation of FPT plans for acquiring, stockpiling and distributing supplies (e.g., hand sanitizer, gloves, masks, disinfectant supplies) in consideration of PHM.

Long term:

- Collaborating on pandemic recovery, and adjusting PHMs as required.
- Evaluating the PHM component of the COVID-19 pandemic response and incorporating lessons learned into planning for future pandemics.
- Establishing strategy to update existing or write new FPT pandemic plans to address robust PHM and minimizing societal disruption, as outlined in Canada’s pandemic goal.
- Providing public education to entrench PHMs as a core practices that will become the new baseline practices based on effectiveness of measures from evidence reviews.

- Working with other sectors to strengthen the social services to protect health and mitigate risk.

Planning variables or signals

Preparations and forward planning will consider adaptations to current activities, recommendations and guidance, e.g., if there are significant changes in disease activity, high-risk groups or public adherence to recommended PHM, and the impact these may have in various population groups.

Infection prevention and control and clinical care guidance

While impacting the FPT public health response, the provision of infection prevention and control (IPC) and clinical care guidance and expert advice has predominantly been aimed at informing practising health care professionals, including infection prevention and control professionals. Therefore engagement with stakeholders outside of the public health sector, in particular front line health care and infection prevention and control professionals, is a key part of supporting preparedness.

Current status/focus

The current focus of response activities pertaining to IPC and clinical care include:

- ensuring that previously published COVID-19 infection prevention and control documents continue to provide up-to-date relevant and evidence-informed guidance;
- updating (based on new information) the interim guidance for the clinical management of patients with moderate to severe COVID-19 and care of residents in long-term care during the COVID pandemic;
- providing clinical guidance on the changing presentation, complications, risk factors and outcomes of COVID-19;
- completing any outstanding guidance products;
- planning for joint PHAC/Association of Medical Microbiology and Infectious Disease Canada (AMMI) webinars addressing ongoing key clinical issues that will occur once a month starting July 2020, potentially through to June, 2021; and
- providing key clinical journal articles review and summation to FPT public health tables.

Preparations/forward planning

All clinical care guidance and infection prevention and control documents are being reviewed on an ongoing basis to ensure they reflect the most up to date information on clinical care and IPC. This includes key clinical findings in the literature, responding to new and/or changing science.

Planning variables or signals

If additional clinical or infection prevention and control information emerges, (e.g., a change in mode of transmission, dominance of VOCs with immune escape characteristics, or additional risk groups), there may be a need to revise or develop additional IPC or clinical care guidance documents. Similarly, the identification and availability of new effective treatments would require updating of clinical care guidance.

Vaccination

In line with the overarching objective of Canada's COVID-19 response of minimizing serious illness and overall deaths while minimizing societal disruption, the goal of Canada's COVID-19 immunization response is:

- To enable as many Canadians as possible to be immunized as quickly as possible against COVID-19, while ensuring that high risk populations are prioritized.

This goal guides collaborative work across jurisdictions to allocate, distribute and administer vaccines as efficiently, equitably and effectively as possible; provide safe and effective vaccines as quickly as possible for all who want them; and monitor the safety, coverage and effectiveness of COVID-19 vaccines.

In December 2020, Canada received its first shipments of vaccines and proceeded to administer more than one million doses in the first two months of the national vaccination campaign. The Government of Canada anticipates having sufficient supply of authorized COVID-19 vaccines to offer a full series of vaccine to all eligible persons in Canada, by September 2021. To facilitate this, the Government of Canada signed advance purchase agreements to secure access to seven vaccine candidates, including Moderna Spikevax, Pfizer-BioNTech Comirnaty, AstraZeneca Vaxzevria, and Janssen COVID-19 vaccines, when these products were in development. PT governments, together with federal stakeholders, have developed plans for the efficient, effective and equitable allocation of COVID-19 vaccines across Canada as well as priority setting for key populations for early vaccination based on risk of severe outcomes and risk of COVID-19 exposure. This work is informed by

guidance from Canada's National Advisory Committee on Immunization (NACI), an external advisory body that provides independent advice on the use of authorized vaccines in Canada. NACI has developed guidance on the optimal use of COVID-19 vaccines, including guidance on the prioritization of key populations for COVID-19 vaccination, that is being used to optimize public health benefits from COVID-19 vaccination during the pandemic, as well as guidance on COVID-19 vaccine research priorities.

Current status/focus

With the Health Canada authorization granted to a total of four COVID-19 vaccines as of March 5 2021, implementation of plans as documented in the Comprehensive Distribution Plan, guided by the Vaccine Annex of the CPIP is proceeding. For example, enhanced tracking systems for adverse events following immunization (AEFI), the Vaccine Injury Support Program (VISP), vaccine effectiveness (VE) assessment and uptake/coverage; allocation, storage and handling; vaccine delivery strategies, are all being utilized as part of the vaccine strategy for COVID-19 vaccination in Canada. Federal/provincial/territorial governments, First Nations, Inuit and Metis leadership and public health authorities are collaborating [13] to ensure that vaccination programs and clinics are designed and implemented in a manner to respond to out-sized demand for vaccination in a global environment of constrained supply.

An Immunization National Operations Centre (NOC) for COVID-19 has been established as the federal logistical coordination entity and focal point for managing vaccine delivery and collaboration with provinces and territories for distribution. Supported by a multi-disciplinary team of experts, including the Canadian Armed Forces, the NOC has been designed to support partners involved in Canada's immunization roll out and lead the tracking of vaccine delivery and distribution, and reports to the President of PHAC through the Vaccine Roll-out Task Force.

As vaccines have thus far been sourced from manufacturers that do not have an existing Canadian presence, require importation from overseas locations, and/or require onward distribution from a central point in Canada, PHAC has contracted Logistics Service Providers (LSPs) who are supporting importation, storage and distribution for several candidates. The LSPs are working to complement provincial and territorial supply chains, and align with the activities that PTs have undertaken to strengthen supply chains within their jurisdiction.

In addition, the Government of Canada has strengthened vaccine cold chain supply systems through the provision of equipment and training to manage ultra low and frozen vaccine products safely and securely, and proactively procured essential supplies (e.g., needles, syringes, epinephrine, etc.) on behalf of the PTs via the National Emergency Strategic Stockpile to mitigate against potential supply shortages. Federal procurement activities also complement those being undertaken at the PT level, ensuring that all jurisdictions have contingencies in both supply chain capacity and ancillary supplies.

The federal government is also continuing to work with provinces, territories, and other partners to provide the necessary training and educational tools on COVID-19 vaccines so that vaccinators have the information they require.

Recognizing that all partners must work collaboratively to address vaccine hesitancy, cross-jurisdictional cooperation is underway to better understand public opinion and behavioural science. This enhanced understanding informs the development of educational tools and communication strategies to further educate and build trust in COVID-19 vaccines. In particular, the Federal Government is leveraging the Immunization Partnership Fund to support the efforts of key stakeholders to increase vaccine acceptance and uptake among Canadians and reduce vaccine preventable disease including COVID-19.

In addition, to support planning and response activities, the Vaccine Annex of the CPIP has been adapted to guide the implementation of the Equitable Allocation Strategy, as well as the operational work of the National Operations Centre, leveraging existing mechanisms where possible to support ordering, shipment and delivery of vaccines, logging and follow up on complaints, and reporting on inventory and wastage. Finally, VaccineConnect, a digital vaccine management platform has been designed to facilitate end-to-end vaccine tracking, monitoring of adverse events, data sharing and management of vaccination programs.

Preparations/forward planning

Guidance and tracking systems will continue to be updated as vaccine supply changes. The NESS continues to procure additional supplies as needed to support FPT vaccine administration.

The Government of Canada COVID-19 Vaccine Task Force is focusing on strategic investments in vaccine research, development, and domestic bio-manufacturing to facilitate domestic vaccine supply. In addition, a COVID-19 Vaccine Clinical Trial Discussion Forum is

convening academic, government, and industry partners to discuss vaccine clinical trial challenges and optimal designs.

Timelines for activities that support *Canada's COVID-19 Immunization Plan* are:

Short term:

- Updating FPT public health recommendations and PT vaccine strategies, informed by NACI guidance, as additional vaccines are authorized and as evidence on these vaccines and COVID-19 evolves.
- Work on vaccine confidence including a mass public education campaign and coordinated outreach efforts targeted to all Canadians as vaccine becomes more widely available.
- Continuing to provide ancillary supplies to PTs for vaccine administration.
- Continued collaboration with manufacturers to obtain sufficient supportive guidance and training to build provinces, territories, First Nations, Inuit and Metis partners and federal department capacity and capability to manage anticipated supply and distribution of vaccines.
- Comprehensive engagement with provinces, territories, First Nations, Inuit and Metis partners and federal departments to ensure readiness to receive, store, handle, and administer COVID-19 vaccines, including those already authorized and those anticipated in the near future.
- Ongoing FPT dialogues for sharing challenges and lessons learned, including strategies to better leverage the private sector (e.g., pharmacies) to bolster vaccine roll-out capacity.
- Creation and maintenance of a "control tower" for the management of logistics and distribution, Vaccine Roll Out National Operations Centre, enabling clear and coordinated engagement with provinces, territories, Indigenous partners, and federal departments.
- Build additional functionality of VaccineConnect, the digital vaccine management system to support jurisdiction vaccine program management and national reporting.
- Continued logistical planning for supply chain, including for transport /storage /use of vaccines in northern, remote, isolated settings and Indigenous communities, in collaboration with provinces, territories, Indigenous stakeholders and federal departments.

Mid term:

- Ongoing work on vaccine confidence including a mass public education campaign and outreach efforts targeted to everyone in Canada as vaccine becomes more widely available.
- Data analysis to inform the need for: vaccine modifications (e.g., substitutions) to ensure protection against emerging VOCs, booster doses, and/or seasonal vaccination programs.

Longer term:

- Strategic planning for ongoing COVID-19 vaccine supply, including domestic bio-manufacturing capacity, allocation and distribution models as needed.
- Ongoing consideration of vaccine strategies and vaccine-related research priorities to address changing epidemiological context and emerging evidence (e.g. evidence on the duration of vaccine protection and use of COVID-19 vaccines as post-exposure prophylaxis).
- Enhancements/preparations for AEFI analysis.
- Ongoing surveillance and research on duration of protection offered by COVID-19 vaccine.
- Integration of VaccineConnect to support pan-Canadian vaccination initiatives beyond COVID-19.
- Adaption of the contents of the CPIP Vaccine Annex for the COVID-19 context as necessary.
- Continued assessment and monitoring of vaccine quality, safety and effectiveness as per established processes [14].

Reducing hospitalizations due to seasonal influenza and invasive pneumococcal disease through increased vaccine coverage can preserve both public health (e.g., diagnostic/testing, outbreak response) resources and health care (i.e., outpatient visits and inpatient stays) capacity. For these reasons, it has been identified as an ongoing forward planning element.

Influenza vaccines and routine programs

FPT public health responders and professional groups are concerned about interruptions to routine immunization programs due to COVID-19 PHM and physical distancing, and are monitoring trends. To this end, PHAC issued guidance on the importance of immunization program continuity in particular to mitigate the risk of measles and other vaccine-preventable disease outbreaks once international travel resumes.

In anticipation of ongoing COVID-19 activity during the roll-out of seasonal influenza vaccination programs, PHAC also prepared guidance on the delivery of influenza vaccine in the presence of COVID-19. The guidance focuses on alternative delivery models, clinic set up, changes to immunization practices and processes, infection prevention and control, and PPE at influenza vaccine clinics. The impact of ongoing COVID-19 activity on seasonal influenza activity is unknown and will be monitored closely.

Planning variables or signals

It is important that, as new COVID-19 vaccines are rolled out, their characteristics (e.g., efficacy, safety, dosing schedule), effectiveness in different populations (e.g., elderly), and the supply situation continue to be monitored and communicated to FPT and First Nations, Inuit and Metis partners. COVID-19 vaccines are already displaying varying levels of effectiveness and their ability to prevent asymptomatic transmission or respond to variants remains unknown. The evolving evidence on vaccine effectiveness will be important to the ongoing management of COVID-19. Continued planning should include consideration of variations in vaccine effectiveness and response to AEFI reports or signals. This requires continued AEFI surveillance, health promotion and education, and risk communication expertise.

International border and travel health measures

Since the onset of the pandemic, the Public Health Agency of Canada (PHAC) has significantly shifted and expanded its border and travel health programs to focus primarily on mitigating the risk of COVID-19 importation and together with other response measures, protecting the capacity of provinces and territories to offer health services to Canadians. Prior to this pandemic, it was not envisioned that extensive international border closures would be implemented as a pandemic response measure. Successful implementation of border and travel health measures has required extensive ongoing multilateral engagement and cooperation with government and non-government stakeholders (e.g., the air travel industry).

Current status/focus

Several new and enhanced border and travel health measures critical to the COVID-19 response have been developed and implemented including:

- an increased capacity for PHAC to undertake health-related risk assessments and provide travel advice and other measures to minimize the risk of Canadians' exposure to the disease, including on conveyances (air, marine, land);
- linkages between federal and PT guidance and oversight for the management of international and domestic travellers;
- leveraging the provisions of the *Quarantine Act* and introducing more than 45 Emergency Orders;
- limiting entry of foreign nationals and imposition of new testing, enhanced quarantine and isolation requirements for incoming travellers to Canada;
- strengthening the compliance and enforcement regime through the establishment of a on-site compliance verification program to boost the capacity to follow up with travellers at their place of quarantine/isolation to verify their compliance, as well as new fines under the Contraventions Act;
- electronic case management tools to operationalize delivery of border measures, including exemptions, compliance and enforcement, etc.;
- increasing the public health presence at the border (i.e., public health officers being assigned to 36 high volume points of entry) as well as enhanced PHAC capacity to conduct virtual health assessments for COVID-19 via access to a 24/7 Central Notification System;
- the establishment of and increase in temporary federal quarantine facilities across the country and their continued management to support enforcement of public health Orders;
- ongoing cooperation and work with provincial and/or local law enforcement-related partners to support compliance verification and enforcement activities, including ticketing travellers not complying with the federal quarantine and/or testing requirements;
- enhanced partnerships with provincial and territorial health authorities and other key players to support data-sharing, compliance, enforcement of quarantine and awareness on COVID-19 (e.g., through the ArriveCAN app), and border testing pilots; and
- new and updated messaging and communication tools for the travelling public.

Preparations/forward planning

Moving forward as part of planning for a potential resurgence of the disease and introduction of VOCs, PHAC will continue to maintain a high level of readiness to respond to COVID-19 through a combination of border and travel measures that are calibrated to:

- evolution of the global COVID-19 situation, most notably with the aim of preventing and tracking importation of VOCs
- evolution of the domestic COVID-19 situation and provincial and territorial considerations;
- progression of COVID-19 vaccine coverage both domestically and internationally and ongoing scientific evidence on vaccine effectiveness;
- updated modelling and risk analysis of other countries and international experiences to ensure lessons learnt;
- operational capacity pre-, at- and post-border to handle anticipated incoming and outbound travel volumes along with additional measures as applied;
- evaluations of border restrictions or easing in coordination and alignment with FPT requirements (while factoring in whole of health system capacity);
- considerations of the public health/health system capacity to manage potential increase in imported cases (testing, contact tracing and reporting, provincial and territorial health care capacities); and,
- volumes that different classes/sectors or arrival modes bring to Canada.

Based on these considerations, PHAC will continue to adjust its border and travel health tools including:

- implementing enhanced border requirements, such as testing and quarantine;
- adjust the needs of online tools (such as ArriveCAN) to accommodate increased requirements, including testing, and evolving usage requirements by FPT partners;
- examination and adjustment of border exemptions during periods of reduced or increased infection and importation;
- updated case management reporting related to variant screening among F/T/P to meet evolving needs; and
- examination and application of amendment considerations to the OICs under the *Quarantine Act*.

Planning variables or signals

As international and domestic contexts shift, border and travel measures may be adapted accordingly. There is a variety of possible approaches that could be explored:

- **Global restrictions:** Increase/decrease global restrictions for all destinations, control through health-related measures. Possible exclusion of high-risk countries based on country risk assessments.

- **Country-specific restrictions:** Remove global advisory/prohibition of entry, but maintain/impose restrictions for individual states or regions by exception, based on risk of importation.
- **Sectoral/class restrictions:** Decrease exemptions to travel measures based on a sectoral analysis.
- **Reciprocal:** Leave global advisory/prohibition of entry, remove or ease restrictions based on reciprocal arrangements with individual states (or regions e.g., Caribbean) and assessment of respective COVID situations.
- **Modal:** Increase/ease measures for travellers entering by air, sea or land, based on risk and operational factors.
- **Testing and/or vaccination certification:** ease or impose measures according to travellers' proof of test results and/or vaccination, in a wary that is justified by available scientific evidence and is sensitive to legal and ethical issues, including around equity and accessibility.

Health care system infrastructure

A peak in pandemic activity greater than the first COVID-19 wave in any jurisdiction can have a substantial impact on health care service capacity and the ability of health care organizations to keep those providing or receiving health care services safe.

Canadian businesses have stepped up to offer their solutions and expertise, or pivoted their manufacturing facilities, and Canada is now successfully producing Made-in-Canada PPE, medical equipment and supplies to address the urgent needs of frontline workers, and the safety of Canadians at large. In addition, Innovation, Science and Economic Development Canada, Health Canada, PHAC and PSPC Canada are working closely together to quickly to increase Canadian PPE manufacturing capacity to address domestic needs.

With respect to therapeutics, the Interim Order Respecting the Prevention and Alleviation of Shortages of Drugs in Relation to COVID-19, made by the Minister of Health on October 16, 2020 introduces new tools for the Minister to address drug shortages, or the risk of drug shortages, that may be caused or exacerbated, directly or indirectly, by COVID-19.

Current status/focus

The FPT public health response in terms of health care system infrastructure has involved linking with those partners responsible for monitoring, anticipating and planning for surges in health care system capacity in order to increase mutual knowledge and situational

awareness, and support response activities regarding the delivery of health care to COVID-19 cases in Canada. To support this work:

- PTs have taken steps to support hospital surge capacity and ensure timely access to critical equipment and supplies;
- the Government of Canada is working with provinces and territories: to help ensure health care systems are ready for future waves of the virus, to support vulnerable Canadians – including those in long-term care, home care, acute care and palliative care – who are at risk of more severe cases of COVID-19, and to support people experiencing challenges related to mental health, substance use, or homelessness;
- PTs are working to develop, expand and launch virtual care and mental health tools, including through the use of new federal funding to support PT services;
- through the federal Safe Long-Term Care Fund, governments will work together to protect people living and working in long-term care, including carrying out infection prevention and control readiness assessments, making improvements to ventilation and hiring and training additional staff or topping up wages to support workforce stability;
- the federal government is supporting infection prevention and control measures in long-term care, including funding for the Canadian Foundation for Healthcare Improvement to expand its LTC+ initiative and funding to engage with third parties to help identify resources to conduct readiness assessments in long-term care facilities and support training on infection prevention and control;
- the Canadian Red Cross and other non-governmental organizations are being supported by the federal government to build and maintain a humanitarian workforce to provide surge capacity in response to COVID-19 outbreaks and other large-scale emergencies;
- modelling has been used to project anticipated demands;
- sharing of hospital-based data (on rates of admission, current capacity and equipment/supplies/resources usage) has been included in surveillance products; and
- the LAC was convened in February 2020 to provide an FPT forum for collaboration including identification of FPT PPE, equipment and supply needs, informing procurement and facilitating allocation.

Preparations/forward planning

In terms of forward planning, the Government of Canada will continue to:

- consult with PTs and use modelling to assess the overall pan-Canadian supply and demand landscape for PPE, essential supplies, and life-saving medical equipment to support PT health care systems and take action as necessary;
- collaborate and work with PTs to better understand the PPE needs across the Pan Canadian landscape;
- explore opportunities to consider sustainable domestic production capacity for critical PPE and other essential supplies;
- monitor for potential COVID-related drug shortages and work with PTs and stakeholders to proactively develop and implement strategies to manage these risks;
- through the Indigenous Services Canada (ISC) PPE Stockpile and PHAC's National Emergency Strategic Stockpile (NESS), provide PPE to First Nations, Inuit and Métis communities to support the health of workers and reduce likelihood of spread to FN, Inuit and Metis during the delivery of health care services;
- consult regularly with PTs to identify need for federal COVID-19 surge capacity supports to jurisdictions, including health human resources and mobile hospital units;
- facilitate sharing of best practices on alternate care facilities, triage and management of delivery of non-COVID-19 health care services review the latest available scientific evidence to inform guidance for health settings and develop tailored approaches for communities with specific health care needs, such as remote, northern and isolated communities as well as Indigenous peoples in urban settings;
- work with PTs to support safe resumption of in-person primary care and mental health services (where this were suspended/delayed or shifted to virtual care platforms);
- work with provinces and territories to set new national standards for long-term care so that seniors get the best support possible, and will also take more action to help people stay in their homes longer; and
- work with provinces and territories to make sure all Canadians get high-quality care, including ensuring all Canadians have access to a family doctor or primary care team, expanding capacity to deliver virtual care, and increasing access to mental health services.

Provincial and territorial governments, along with health care facilities, many of which are already working close to full capacity, continue to do further planning for how they have in some regions (and could in the future) accommodate potentially large influxes of patients,

including establishing triage protocols for the allocation of scarce resources such as ICU beds and ventilators. In remote, northern and isolated communities, it is also critical to plan for further potential supply-chain and medical evacuation interruptions due to weather.

Forward planning must consider the broad health care system impacts and changes that occurred during the initial wave of COVID-19 in Canada; for example, the unanticipated reduction in emergency room visits for serious conditions, the shift of primary care to virtual care, the unintended but severe health and safety consequences of removing family caregivers from long-term care facilities, increased incidence of opioid overdose, delayed/decreases in routine immunization, and the backlog of elective procedures. The implications of these impacts and changes include the need to plan for: more supportive care for seniors, “catch-up” of delayed medical tests, treatments and procedures and the need to plan for future waves in a way that doesn’t impede the health care system more than is necessary. In addition, understanding gaps that appeared, and lessons to be learned from how they were addressed, in the intersection between PHM, health care services and other social determinants of health will be important to consider in a holistic way for future planning. For example, how to make sure individuals experiencing homelessness receive adequate supports to be able to follow PHM (e.g., isolation and quarantine protocols).

Planning variables or signals

In the event health care institutions start to see an increase in the number or change in the characteristics (e.g., demographics, underlying medical conditions) of patients being treated for COVID-19, the Government of Canada will continue to work with PTs to monitor capacity and facilitate timely access to PPE, ventilators, intensive care unit (ICU) beds, and other critical supplies. The federal government continues to be ready to respond to PT requests for assistance and surge support, (e.g., health human resource support, facilitation of mobile health services capacity, safe voluntary isolation sites).

Risk communications and outreach

Communication of information and advice in a public health emergency is a critical public health intervention that helps to protect public health, save lives, and minimize the overall social and economic impacts. To ensure this, information must be accessible for those with low literacy and also presented in an accessible format to guarantee that Canadians living with disabilities are able to have equal access. Using a risk communications approach, the Public Health Agency of Canada, together with other government departments and PTs

counterparts and Indigenous partners, have worked hard to provide health care providers, Canadians and key stakeholders with the timely, trusted, accessible, evidence-informed and complete information they require to protect themselves, their families, their communities and businesses.

Current status/focus

The focus remains on communicating clear, concise and concrete messages that will cut through the current fatigue, confusion and fragile compliance, in order to: ensure Canadians have the information they need to protect themselves and others from the virus and the variants of concern; ensure Canadians can make informed decisions about the activities that they will participate in outside the home and how they can participate in a way that protects them, their families and communities; and ensure Canadians can make informed decisions about COVID-19 vaccination.

Key activities to date include:

- briefings by Chief Medical Officers of Health and local Medical Officers of Health in the PTs and nationally by the Chief Public Health Officer and Deputy Chief Public Health Officer –including modelling and epi updates;
- regular engagement and information sharing on COVID-19 to support response efforts by public health at federal, provincial and territorial levels with a diverse range of sectors, including health, civic society, business and labour, populations most affected by COVID-19, as well as critical infrastructure;
- targeted communications on enhanced border measures;
- specific communications and outreach efforts to encourage COVID-19 vaccine confidence and uptake, including outreach to populations disproportionately affected by COVID-19 (e.g., racialized communities, Indigenous Peoples, newcomer communities, seniors groups, families and persons living with disabilities);
- use of all communications and partnership levers (advertising, web, social media, regular media briefings, community radio, national mail outs, partnerships, community outreach, program funding etc.) to reach stakeholders, health system, Indigenous and community leaders (including the Canadian public) across a diversity of sectors (e.g., healthcare providers, faith-based leaders, agri-food-agriculture sector, retail/businesses, critical infrastructure sectors);
- engagement with diverse sectors to inform development of timely public health guidance for various settings such as workplaces, schools/childcare, post-secondary

education, and other community settings;
- the implementation of a four-phased COVID-19 Risk Communications Strategy with different foci (e.g., containment and delay, tools and empowerment, mitigation and working together to prevent the spread of COVID-19, perseverance and ongoing vigilance in context of disease reduction and re-opening of society); and
- FPT and Indigenous partner collaboration to share best practices and lessons learned and coordination to ensure messaging is aligned and consistent (via Public Health Network Communications Working Group and the Special Advisory Committee (SAC)).

Challenges and considerations:

Messages in the earliest phase of the pandemic were clear – stay home; wash your hands. Now the environment is much more complex.

- There are different epidemics across the country so different public health measures are in place across jurisdictions. Messages and their delivery must be clear to avoid any confusion.
- Communication and information on COVID-19 is overwhelming and it is hard to distinguish misinformation or disinformation, from credible health information and sources.
- Canadians have gone through two distinct waves of peak transmission across the country and there is a real balance that needs to continue to be communicated with the use of a layered-approach of public health measures, even as vaccination coverage increases. This must take into consideration the impact of pandemic fatigue.
- The risk perception (and compliance) of Canadians will vary based on their individual experiences and their unique reality.
- Canadians will need to be encouraged to not abandon personal protective measures during vaccine roll-out or as the spring approaches.
- There is still much uncertainty that impacts how precise and definitive we can be in our messaging, especially with the new VOCs. As science evolves and we learn more, advice to Canadians may change.
- Canadians are being encouraged to participate in the economy as it re-opens in this period of recovery. We need to help people make an informed and conscious decision each time they leave their home to help them protect themselves and others.
- Canadians need to assess their activity, their risk tolerance, their risk to others and the importance of their own behaviour in reducing risk. Our communications efforts must

arm them with the information to do so easily and accurately.
- Canadians must have access to credible information related to COVID-19 vaccines, vaccine safety and the vaccine rollout in Canada. Our communications efforts must address misinformation and provide everyone in Canada with evidence-based information to help them make the decision to vaccinate.
- Canadians expect timely and responsive communication using newer social media platforms (e.g., WhatsApp, TikTok, Instagram) and from leaders and influencers that are meaningful and trustworthy within their communities and social media circles.

Preparations/forward planning

It is now important to shift messaging as we transition Canadians into participating in the national vaccine administration campaign. The deployment of vaccines needs to be balanced with the message that certain PHM must remain in place in order to keep the level of transmission at a locally manageable rate. All levels of government need to communicate that Canadians should be prepared for a walk back or tightening of PHM if necessary to avoid surges/resurgences.

Forward planning for communications includes taking several approaches concurrently.

Provide clear, consistent, concise and concrete messages and advice with relatable examples and tools that are easily accessible for Canadians.

- Apply behavioural science to test a variety of public health messages and tools.
- Guidance to help the public minimize risk while venturing out into public spaces.
    - checklists for when you leave the house
    - decision making tools
- Information on vaccine safety and development to support vaccine confidence.
    - toolkit and training for healthcare providers to help them answer patient questions
    - evidence-based vaccine resources for the public

Use personal stories to motivate behaviour.

- Showcase community members/organizations/spokespersons who are “doing it right.”
- Leverage more storytelling to motivate behavior (continue youth testimonials, etc.).
- Sharing of images and personal stories of vaccination.
- Consider role of incentives to motivate behaviours (including adherence to PHM).

Communicate with empathy and honesty.

- The efforts of Canadians through the first phase have very likely saved thousands of lives; need to acknowledge that, and encourage everyone to keep doing that.

These approaches will be supported by FPT strategies, content and implementation plans that include:

- sufficient public opinion research (POR) and behavioural insights (re. behaviours, vaccine, public health measures, back to school) to identify all Canadians' priorities, values and concerns, and capture regional variations;
- public education campaigns (COVID-19 vaccines, PHMs and mental health);
- "Not the time to travel" campaigns; and,
- testing and contact tracing related communication activities.

This will be achieved through strategic outreach and engagement by the Chief Public Health Officer (CPHO), Deputy Chief Public Health Officer (DCPHO), Chief Medical Officers of Health and other PT and local spokespersons, public education campaigns, media relations, and issues management, social media, and website updates. Significant outreach and engagement with a range of health and non-health stakeholders has been an essential part of the national response to COVID-19. This outreach and engagement has evolved throughout the pandemic from a focus on proactively sharing the latest public health developments and resources to identifying stakeholder information needs and perspectives, to collaborating on guidance development and joint communication initiatives. A range of stakeholders have been engaged through regular COVID-19 briefings, teleconferences and webinars including the following: CPHO Health Professionals Forum (national health professional organizations), national allied health organizations, local public health medical officers of health, critical infrastructure stakeholders, agriculture and agri-food stakeholders, business groups, travel associations, airlines, and childcare and education stakeholders. A range of community-level leaders have also been engaged including faith-based organizations, organizations representing racialized communities, and engagement with national and community level First Nations, Inuit and Metis organizations.

It has been and continues to be especially important to engage community leaders from: Indigenous communities, racialized communities/communities of color, groups representing newcomers to Canada, and faith-based organizations to help deliver critical information [15].

Planning variables or signals

Surges in cases requiring change in or implementation of restrictive community-based PHM along with any changes in science (e.g., new information about COVID-19 or COVID-19 vaccines that requires a shift in Canada's public health response or guidance to specific populations), changes to border measures, indicators of vaccine hesitancy and vaccine availability, will all necessitate updating of the current FPT communication strategy and products.

Research

The Government of Canada quickly mobilized Canada's research and scientific communities in response to the spread of the novel coronavirus (COVID-19). Early in the pandemic, research areas focused on medical countermeasures (vaccines, therapeutics, and diagnostics), clinical management research, predictive modelling, as well as social and policy research. Since then, the research focus has expanded to areas such as mental health and substance use during the pandemic, safety in long-term care homes, Indigenous communities' experiences with COVID-19, and variants of concern. Community engagement is important to ensure culturally appropriate research approaches.

Current status/focus

- The Government of Canada established mechanisms for mobilizing rapid research responses for this type of emergency, which have been activated to accelerate development of medical countermeasures, to support priority research on the transmission and severity of COVID-19, and to understand the potential benefits and potential limitations of medical, social and policy countermeasures.
- Health Canada established and continues to apply a number of temporary innovative and flexible measures to help prioritize and expedite the regulatory review of COVID-19 health products without compromising Canada's high standards for safety, efficacy and quality (these measures have been put in place to facilitate safe and timely access to products Canadians and health care workers need).
- A wide array of Clinical Trials activities for therapeutics and vaccines are underway under the Canadian Treatments for COVID-19 (CATCO) trial.
- Several federal programs available aimed at mobilizing industry, innovation and research continue to respond to COVID-19.
- Networks such as CanCOVID, COVID-END and National Collaborating Centres, have been launched to facilitate research effort and leverage transdisciplinary knowledge

synthesis, translation and expertise among Canada's scientific, policy, and health communities.
- Capacity at federal research facilities is being leveraged, and federal granting agencies are strategically aligned to support Canadian research capacity.
- Knowledge on indoor air quality is being mobilized with federal, provincial, territorial and private sector partners.
- The Canadian private sector (R&D, manufacturing) is engaged in contributing to research and development solutions.
- The Government of Canada is also supporting various strategies to bring significant findings arising from these research efforts to decision-makers in a useful and timely way.

Preparations/forward planning

In an earlier version of this Plan, a number of needs had been identified in order to prepare against surges/resurgences based on the reasonable worst-case scenario. In addition to the activities described above, work has begun in earnest in several crucial areas.

Strengthening our capacity to deliver on relevant COVID-19 modelling work.

- The COVID-19 pandemic has demonstrated the important role and need for greater and ongoing capacity to implement the full range of modelling tools required to support decision-making during a complex public heath crisis. Models help to predict where and when COVID-19 infections may emerge or re-emerge, emergence of new variants of concern, and they can be used to explore the best combinations of approaches to control disease progression and protect the health of Canadians, including vaccination. . Expert groups continue their ongoing work on modelling the reproductive number (Rt) over the course of the pandemic, and are working on modelling several scenarios for de-escalation strategies, including border reopening and lifting travel restrictions.

Examining and addressing the need to pursue research and surveillance studies aiming at better understanding mechanisms of infections, transmission and immunity against the SARS-CoV-2 virus.

- FPT governments are currently focusing on the investigation and tracking of the genetic diversity of SARS-CoV-2, across Canada to better respond to its spread, particularly new variants of concern. However, research is needed to examine the full potential of these variants in their transmissibility, virulence and vaccine efficacy, and to monitor their

emergence and presence over time. The Government of Canada launched the COVID-19 Immunity Task Force, which engages universities, hospitals and public health officials to use blood test (serologic) methods to track and study the immune status of various Canadian populations, and will be used to support vaccine surveillance, safety and efficacy. The need for research and research coordination with partners to understand transmission dynamics and impact of non-medical measures (e.g., ventilation, portable air cleaners, etc.) is beginning to take shape through early aerosol transmission studies in high-risk settings, such as hospitals, prisons, and long-term care homes. Discussions and work continues with domestic and international partners to develop COVID-19 animal models and medical countermeasures.

Strengthen our capacity to perform rigorous and rapid evidence review.

- More experts within and outside of government are being leveraged to generate evidence reviews and answer specific questions to provide the most up-to-date scientific evidence for optimal decision-making.

Exploring the epidemiological value of new, innovative methods to track community spread, such as testing SARS-CoV-2 from sewage water.

- Testing wastewater is providing early warning ability at the community level (municipality, special settings such as Long-Term Care Facilities, prisons, hospitals and remote communities). With its FPT partners, the federal wastewater-testing group has begun creating a system throughout Canada for surveillance of public health outcomes such as COVID-19.

Strengthen laboratory capacity in the area of genomic innovation and bio-informatics.

- The Government of Canada has begun to secure investments in this area.

Mobilizing knowledge from the social sciences.

- There continues to be a need to invest in and mobilize knowledge relating to social sciences such as sociology, anthropology and psychology. Specifically behavioural science and ethnic research can guide future policy and regulatory actions.

Short to mid term:

In the short to mid term, the approach to these preparations continues to be to:

- work collaboratively with National partners, FPT, stakeholders groups, Indigenous partners (including National Indigenous Organizations; Indigenous researchers and

scholars; the National Collaborating Centres for Public Health), and the Federal Science Community to support the work of key task groups mandated to support Canada's COVID-19 response (Immunity Task Force, the Vaccine Task Force, the Therapeutic Task Group) and Indigenous-led culturally grounded research (with appropriate community engagement and cultural safety in approaches);
- work collaboratively with federal science based departments and agencies with specific targeted engagement with the CIHR and the Chief Science Advisor of Canada; and
- continue engagement with the COVID-19 Governance Structure (via the Technical Advisory Committee (TAC), LAC and SAC). Activities include sharing research, data and local experience that will inform further planning in alignment with our stated public health pandemic goal and objectives (e.g., quantifying the negative and positive consequences of the PHM that were uses in the initial response to be better able to address the inequities that have arisen).

Planning variables or signals

Similar to the other COVID-19 response components above, there are several factors that could potentially impact preparations for the ongoing COVID-19 response, including: a significant shift in genomic pattern of SARS-CoV2 (leading to examination of possible shift in virulence or infectivity), significant increases in the mortality ratio, data from vaccine and therapeutic clinical trials, data on immunological protection of Canadians, new/rigorous knowledge on the impact of COVID-19 specific high-risk groups, and new/rigorous knowledge of the importance of a non-respiratory mode of transmission.

Planning with Indigenous communities

First Nations, Inuit and Metis communities have been supported as they worked to update and activate their community pandemic plans. Over 30 Indigenous organizations have been engaged and are collaborating together to support public health response through the Public Health Working Group on Remote, Isolated and Indigenous Communities as part of the SAC governance structure. Indigenous Services Canada (ISC) together with National Indigenous Organizations (NIOs), have been leading work with PHAC, Statistics Canada and the First Nations Information Governance Centre to address data gaps regarding the impacts of COVID-19 on Indigenous Peoples.

As a result of community supported response efforts, infection rates on-reserve and in the North remained lower than the rate in the overall Canadian population during the first wave of COVID-19. However, transmission has been greater in Indigenous communities during the second wave. It is important to note that gaps for First Nations, Métis and, Inuit living in urban and related locations are the product of historical, political, societal, and economic factors that have influenced Indigenous health. These inequalities persist in part due to systemic racism experienced in the healthcare system and increased connections to culturally safe services are required to support these populations. ISC and PHAC are working with Indigenous partners, provinces and territories, the Vaccine National Operations Centre, LAC of the COVID-19 Governance Structure, and other federal departments to ensure all Indigenous peoples, regardless of where they live, have access to support throughout the pandemic response, including prioritization for vaccines. ISC has established the COVID-19 Vaccine Planning Working Group and the COVID-19 Vaccination Task Group for First Nations, Inuit, and Métis living in Urban and Related Homelands to support linkages between provinces and territories, other federal departments and Indigenous partners for vaccine co-planning discussions. A summary of the response activities that have been supported to date in addition to the strategy/approach, actions and deliverables for these preparations for the short, mid and long term (i.e., being before September, September to December, and 2021 and beyond, respectively) are included in Appendix 3: COVID-19 response planning with Indigenous communities.

Planning for high-risk settings and populations

A specific setting may be considered as “high-risk” due to:

- the potential for higher rates of severe disease or death amongst those in the setting compared to that of the general population (because of clustering of people with underlying medical conditions, clustering of those in high-risk age group or both); and/or
- potential for high rates of transmission (because of unavoidable crowding indoors with limited ability to use or inconsistent use of protective measures, introduction of a VOC, or high-risk activities or conditions).

It can be challenging to significantly mitigate these risks; therefore planning activities need to look at the specific circumstances of each setting and what enhanced measures can be put in place to prevent and manage COVID-19 outbreaks in these highly variable contexts.

This should include measures to prevent introduction of the virus into these settings, (e.g., through screening of employees and visitors, restriction of visitation, efforts to prevent work at more than one high-risk location, implementation of a quarantine period for people entering the setting). Epidemiologic investigations of outbreaks in these settings are key to improving our understanding of transmission dynamics and setting-specific risks. It is particularly important to investigate outbreaks that are caused by different VOCs and to examine the potential role of vaccines in shortening outbreaks.

To date, high-risk settings that would benefit from special planning considerations have included:

- long-term care facilities;
- worksites necessitating close proximity to others (e.g., meat processing) or with communal housing (e.g., temporary foreign workers living on work farms, remote/fly-in work camps like northern mines);
- remote populations without ready access to advanced health services (e.g., fly-in only access communities), and with potentially elevated rates of underlying medical conditions or other pre-existing disparities (e.g., overcrowded housing);
- homeless shelters and other congregate living settings such as group homes; and,
- correctional facilities.

While guidance has been developed and measures have been put in place aimed at preventing further outbreaks in these settings, planning for the reasonable worst-case scenario necessitates that we undertake activities in the short term to shore up capacity to undertake prevention and outbreak response measures, as well as, continuously monitoring these measures and adjusting as necessary. For example:

- If there were to be a high level of activity caused by a VOC in the surrounding geographic areas would the response plans for these settings be applicable and sufficient?
- Given the vaccine strategy initially largely prioritizes those at greatest risk for severe disease and death but not specifically those in settings with potentially higher rates of transmission, under what circumstances would vaccine be considered for people in these other high-risk settings?
- What are the existing gaps in guidance, measures or resources, and how can these be addressed?

- Are prevention measures that were previously implemented sustainable and realistic for ongoing surges and/or the reasonable worst-case scenario?
- What impact could these measures have on high-risk populations?
- Have risk communication strategies been effective in these settings and populations?

This collaborative work to plan and support high-risk settings and populations will continue at all levels of government and across multiple sectors and stakeholders from public health, health care, education, agriculture/agri-food, immigration, economic development, corrections, social services/housing, science/research and labour.

As work continues, it is important to take into consideration the impact that these measures may have on the various sociodemographic groups most likely to be affected. Considerations for low-income workers, seniors, migrant workers, persons living in overcrowded housing, persons experiencing homelessness, and prisoners, among others, will need to remain a cornerstone of all response plans.

Assessment and evaluation

Assessing and evaluating pandemic response efforts during periods of relatively lower response tempo will help identify areas of improvement and prioritize future planning efforts. It is also vital, on an ongoing basis, to determine whether response activities have been effective and implemented efficiently to achieve the intended results and whether areas of uncertainty (see the section on Planning assumptions and areas of uncertainty) can or have been addressed. The FPT COVID-19 response governance structure (see Appendix 1), which includes the SAC, TAC and LAC, provides multiple fora for these discussions and opportunities for sharing of experience, lessons learned and identified best practices. More structured processes for assessment and evaluation, including in-action and after-action reviews should be considered at all levels of government and diverse sectors to inform forward planning and future pandemic preparations. Findings from formal audits undertaken by FPT governments will also be taken into consideration in future planning processes.

The broad direct and indirect consequences of the COVID-19 response in terms of other physical and mental health outcomes as well as societal and economic impacts must continue to be acknowledged and assessed so that reduction of negative impacts can be accounted for in comprehensive forward planning efforts.

This should involve consideration of the impact response measures may have on individuals' physical, social, mental and emotional health and wellbeing, including how this may affect the adoption of control measures. The broader impact of restrictive community-based PHM in terms of health, wellbeing, child development and welfare needs to be monitored and plans implemented to prevent other immediate health harms and to prevent increasing health inequities for higher risk populations. These include but are not limited to other direct impacts to health including; risks of delaying health procedures or reduced access to screening and preventive services, domestic violence, child welfare/neglect, reducing access to harm reduction services or safe drug supply and mental health services. It should also involve addressing indirect COVID-19 associated health and wellbeing risks such as congregate housing, low employment standards, lack of access to educational supports for high need students, and risk of visitor restriction policies (e.g., family caregivers in long-term care homes).

Resources and guidance to support mental health has been developed, however the need for other resources as population "pandemic fatigue" sets in needs to be considered. Furthermore, addressing social determinants of health (such as housing and employment conditions) that increase the risks associated with COVID-19, could also help reduce the health and societal impacts of future pandemics.

Appendix 1: Canada's Public Health Emergency Response System and inventory of resources, guidelines and agreements to inform COVID-19 preparedness and response

Canada's public health emergency response "system" comprises a series of complementary, mutually reinforcing plans, arrangements, protocols and networks that incorporate lessons-learned from previous outbreaks like SARS, 2009 H1N1 pandemic and Ebola which are regularly updated to reflect the latest evidence and scientific advance. Taken together, they span the local, provincial, territorial, pan-Canadian, North American and international levels and provide a strong and proven framework for Canada's response to COVID-19.

As public health in Canada is an area of shared jurisdiction, federal, provincial and territorial health officials and experts are working together through the *SAC on COVID-19* and its various expert committees and working groups to facilitate a coordinated and effective

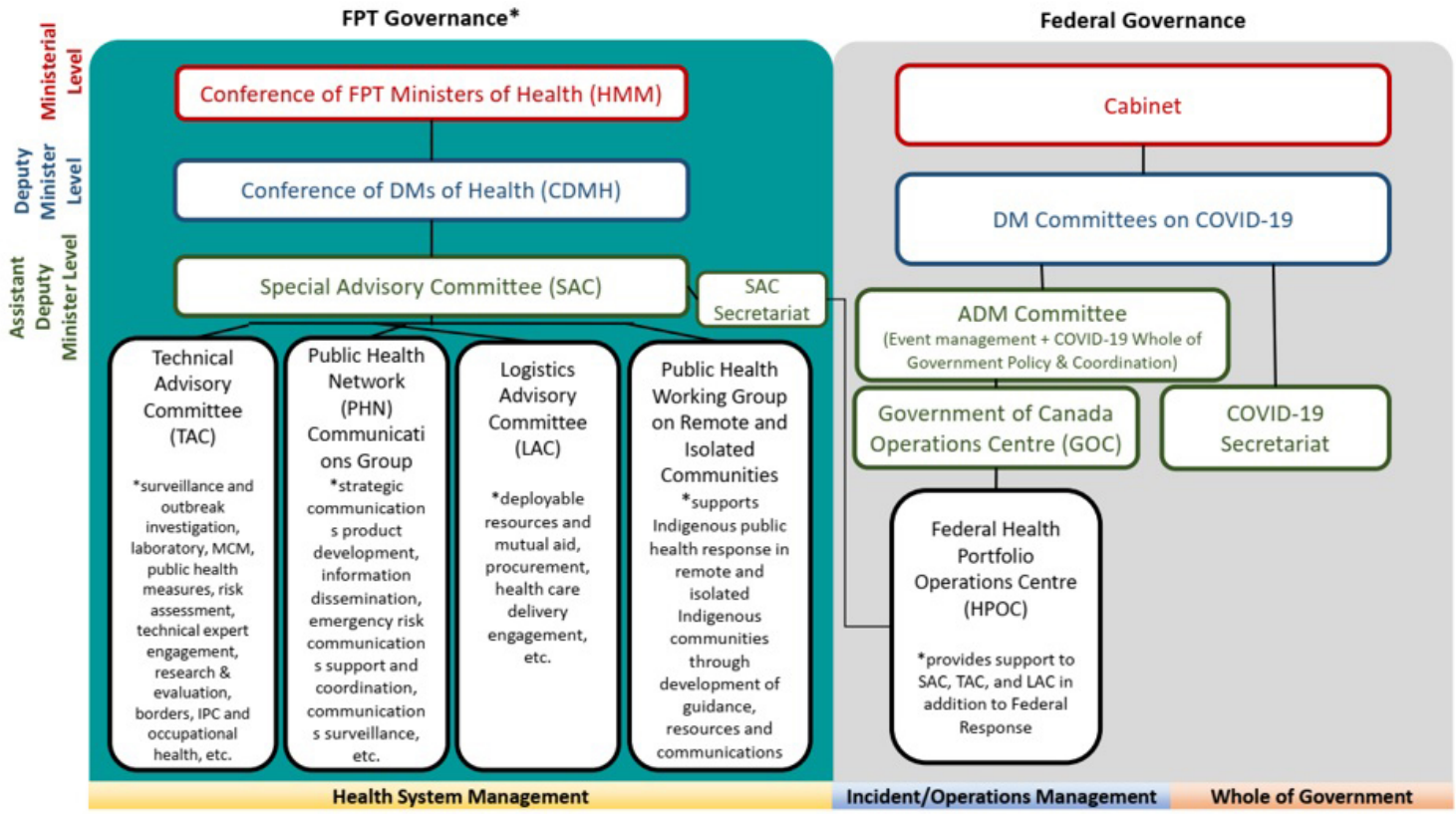
response to the COVID-19 pandemic in accordance with the *FPT Public Health Response Plan for Biological Events*. The Plan includes a summary of FPT roles and responsibilities in a public health emergency.

The SAC draws on the long-standing pan-Canadian Public Health Network (PHN) FPT governance structure. Established in 2005, the PHN reflects lessons-learned from the Severe Acute Respiratory Syndrome (SARS) outbreak, which highlighted the imperative for a proactive and collaborative approach to public health emergency planning and response in Canada. PHN has since proven its value and effectiveness as a vehicle for collaborative public health leadership during the 2009 H1N1 pandemic, Middle Eastern Respiratory Syndrome (MERS-CoV) and Zika outbreaks, as well as in non-communicable disease crises such as the ongoing contaminated street-drug overdose and overdose death epidemic.

SAC comprises members of the PHN Council and the Council of Chief Medical Officers of Health (CCMOH). Four expert groups comprising senior FPT officials and public health experts from across the country report to and support SAC:

- Technical Advisory Committee (TAC): monitors COVID-19 epidemiology, shares information and advises on technical issues through the development of recommendations, guidelines and protocols and leads on surveillance and outbreak investigation, laboratory, medical countermeasures (MCM), public health measures, risk assessment, technical expert engagement, research & evaluation, borders, infection prevention and control, and occupational health, etc.
- Logistics Advisory Committee (LAC): supports logistics (e.g., supplies, joint procurement, scarce resources), shares information and advises on logistical issues through the development of recommendations, guidelines and protocols, and leads on deployable resources and mutual aid, procurement, health care delivery engagement etc.
- Public Health Network Communications Group: supports consistent and coordinated public communications and messages on COVID-19 across jurisdictions and leads on strategic communications product development, information dissemination, emergency risk communications support and coordination, communications surveillance, etc.
- Public Health Working Group on Remote and Isolated Communities supports Indigenous public health response in remote and isolated Indigenous communities through development of guidance, resources and communications.

Figure 6. COVID-19 governance structure



▶ Figure 6 - Text description

The Government of Canada has also established a Cabinet Committee on the federal response to COVID-19 that meets regularly to ensure whole-of-government leadership, coordination, and preparedness for a response to the health and economic impacts of the virus. Additionally, existing and new expert groups (e.g., Surveillance Expert Working Group, Canadian Pandemic Influenza Preparedness-Task Group, Canadian Immunization Committee and its working groups, CPIP-TG) and networks (e.g., CanCoGen) have been contributing to the response through engagement with the governance structure.

The Canadian COVID Genomics Network (CanCOGeN) is a Genome Canada-led consortium of Canadian federal, provincial and regional public health authorities and their healthcare partners, academia, industry, hospitals, research institutes and large-scale sequencing centres. The mission of CanCOGeN is to establish a coordinated pan-Canadian, cross-agency network for large-scale SARS-CoV-2 and human host sequencing to track viral origin, spread and evolution, characterize the role of human genetics in COVID-19 disease and to inform time-sensitive critical decision making relevant to health authorities across Canada during the pandemic.

FPT collaborative agreements: Mutual aid, information sharing and emergency supplies

Federal/Provincial/Territorial Public Health Response Plan for Biological Events: is a federal, provincial, and territorial (FPT) guidance document that provides an overarching governance framework to ensure a coordinated intergovernmental health sector response to public health events that are biological in nature and of a severity, scope or significance to require a high level, coordinated FPT response.

***Canadian Pandemic Influenza Preparedness: Planning Guidance for the Health Sector* (CPIP)**: is an FPT guidance document that outlines how jurisdictions will work together to ensure a coordinated and consistent health-sector approach to pandemic preparedness and response. While CPIP is specific to pandemic influenza, much of its guidance is also applicable to other public health emergencies. CPIP consists of a main body, which outlines overarching principles, concepts, and shared objectives, as well as a series of technical annexes that provide operational advice and technical guidance, along with tools and checklists on specific elements of pandemic planning. CPIP is regularly updated to reflect new evidence and best practices.

Operational Framework for Mutual Aid Surge Requests for Health Care Professionals: is a guidance document that provides for a consistent and timely pan-Canadian approach to inter-jurisdictional health care professional mutual aid during health emergencies. The framework identifies roles and responsibilities and provides standard processes to guide jurisdictions making requests for, and offers of, mutual aid and the mobilization/demobilization of health care professionals. It also informs a complementary *Memorandum of Understanding (MOU) on the Provision of Mutual Aid in Relation to Health Resources During an Emergency Affecting the Health of the Public*.

***Multilateral Information Sharing Agreement* (MLISA)**: is a legal agreement that establishes standards on sharing, usage, disclosure and protection of public health information for infectious diseases and public health emergencies of international concern. The MLISA sets out what public health information is to be shared and how it will be used. It allows for trends and/or urgent public health events to be identified more rapidly and to reduce duplication of information requests. MLISA also informs an *FPT MOU on the Sharing of Information during a Public Health Emergency*. The Memorandum of Understanding (MOU) provides a framework for the sharing of information between and among its signatories during public health emergencies.

National Emergency Strategic Stockpile (NESS): located within PHAC, contains supplies that provinces and territories can request from PHAC in emergencies, such as infectious disease outbreaks, natural disasters and other public health events, when their own resources are not enough. These include a variety of items such as medical equipment and supplies, pharmaceuticals and social service supplies, such as beds and blankets.

Public Health Ethics Framework: A Guide for Use in Response to the COVID-19 Pandemic in Canada: is a framework is intended for use by policy makers and public health professionals making public health decisions in the context of COVID-19. Section 1 articulates ethical principles and values for public health authorities to consider, and Section 2 sets out a framework to help clarify issues, analyse and weigh relevant considerations, and assess options, in order to support decision making in real situations.

Federal emergency response plans

***Federal Emergency Response Plan* (FERP)**: is the Government of Canada's all-hazards response plan. The FERP outlines the processes and mechanisms required to facilitate a whole-of-government response to an emergency. The FERP is designed to harmonize federal emergency response efforts with the efforts of PT governments, non-governmental organizations (NGO) and the private sector.

***Federal Policy on Emergency Management* (FPEM)**: promotes an integrated and resilient whole-of-government approach to emergency management planning, which includes better prevention/mitigation of, preparedness for, response to, and recovery from emergencies. It provides direction to federal institutions on mandate-specific all-hazards risk identification and management within a federal institutions area of responsibility.

International response plans and protocols

***North American Plan for Animal and Pandemic Influenza* (NAPAPI)**: outlines how Canada, the United States and Mexico intend to strengthen their emergency response capacities, as well as trilateral and cross-sectoral collaborations and capabilities, in order to assist each other and ensure a faster and more coordinated response to outbreaks of animal influenza or an influenza pandemic. The NAPAPI complements national emergency management plans in each of the three countries.

***Global Health Security Initiative* (GHSI)**: is an informal, international partnership among like-minded countries and organizations to exchange information and coordinate practices within the health sector to strengthen public health preparedness and response globally, including pandemic influenza.

***International Health Regulations* (IHR)**: represent an international agreement between all World Health Organization (WHO) Member States to build capacity to detect, prevent, assess, notify and response to public health events. Canada has a legal obligation to meet the core public health capacities set out by the IHR.

World Health Organization (WHO) Strategic Response Plan: outlines the public health measures that the international community stands ready to provide to support all countries to prepare for and respond to COVID-19. Documentation (including the Strategic Response Plan) from the WHO takes what has been learned about the SARS-CoV-2 virus and translates that knowledge into strategic action that can guide the efforts of all national and international partners when developing context-specific national and regional operational plans. This plan, like other WHO documentation, is being updated throughout the response.

Appendix 2: Modelling support for forward planning

Modelling recreates the essential components of pathogen transmission cycles from our understanding of the biology of the pathogens and their interactions with their hosts. Models help to predict where and when infectious diseases may emerge or re-emerge, and they can be used to explore the best methods or combinations of methods to control disease outbreaks or epidemics and protect the health of Canadians. Models can take into account new events during the course of the pandemic such as vaccination or emergence of new variants of concern.

For response to COVID-19, there are three broad types of model being used:

1. **Deterministic compartment models.** These are Susceptible-Exposed-Infectious-Recovered (SEIR) type dynamic models in which the population is divided into “susceptible”, “exposed”, “infectious” and “recovered” classes. After encountering infection, individuals in a population move from one state to the next. This basic structure includes elements to model SARS-CoV-2 and impacts of public health measures, with more realism. These elements include compartments for isolated cases and quarantined “exposed” contacts from which onward transmission to susceptible

people is limited or absent, compartments for asymptomatic cases that may or may not be detected by surveillance, as well as flows to “isolation” and “quarantine” compartments that allow variation according to different levels of public health effort. These models are used to inform broad policies at a national level, including i) estimating numbers of cases, hospitalisations and deaths; ii) estimating the effects of non-pharmaceutical interventions (NPIs), (physical distancing, case detection and isolation, and contact tracing and quarantine), iii) design of vaccination programs; iv) the design of programs to enhance “herd immunity” via use of antivirals/therapies in combination of vaccination; and estimating the effect of the emergence of new variants of concern on the disease transmission.

2. **Agent-based models.** These are also SEIR models, and they can also be used to inform development of national strategies. However, because they can simulate disease transmission with some detail in and amongst homes, work places leisure spaces etc., they are particularly useful for decision-making at an individual community level regarding needs for NPIs, and strategies for relaxing restrictive closures.
3. **Branching models.** These are a more recent addition to the types of models used for COVID-19. They simply assess what factors cause single chains of transmission to expand or become extinct. They are being used to assess the needs for controlling transmission in work places and institutions.

The PHAC has developed models that can be shared, and are constantly undertaking modelling to support decisions. The PHAC External COVID-19 Modelling Expert Group was formed in February 2020, and currently comprises 33 members from 21 universities across Canada, as well as 43 members from other Federal departments/organisations provincial/territorial public health organisations. The group comprises the majority of infectious disease modelling group leads in Canadian universities, and is capable of supporting modelling needs for decision-making.

Appendix 3: COVID-19 response planning with Indigenous communities

Indigenous Services Canada (ISC), the Public Health Agency of Canada (PHAC) and the FPT response partners have been involved in various activities to support the COVID-19 response in First Nations, Inuit and Métis communities and organizations, including the work of SAC’s

FPTI Public Health Working Group on Remote and Isolated Communities. These supportive activities are summarized below.

- **Preparedness:** Resources to support pandemic planning updates/activation; access to medical supplies and PPE; training; and, guidelines.
- **Health Human Resources:** Resources to support surge capacity for health human resources, including nursing, medical and paramedical supports; as well as, charter services to get health human resources into communities with reduction to commercial airline service.
- **Infrastructure:** Resources to procure temporary shelter solutions and to support communities in efforts to re-tool existing spaces to offer safe assessment and overflow space; and, additional surge supports for food, water and other supply chain components; coordination of chartered flights to ensure availability of critical infrastructure supplies and professionals.
- **Infection prevention and control (IPC):** Ongoing sharing of information (i.e., guidance on public health measures and promoting personal health measures for individuals and health providers), training and increasing capacity to support community response, including public service announcements in Indigenous languages. Provision of training of community workers and health providers on IPC. Ongoing funding for communities and service providers to increase their capacity for infection prevention and control, including First Nations-run schools, boarding homes, family violence shelters and friendship centres.
- **Testing:** Resources to develop capacity to conduct COVID-19 testing including the provision of testing swabs and point-of-care testing devices and cartridges.
- **Governance:** Continue to work with First Nations, Inuit, and Métis partners, the Public Health Agency of Canada (PHAC), Health Canada, Public Safety's Government Operations Centre, and other departments, as well as their provincial and territorial counterparts for a coordinated and consistent Canadian approach to COVID-19 to protect the health and safety of all First Nations, Inuit and Métis peoples, regardless of where they live.
- **Communications:** Continue to develop and broadly disseminate communication messaging through Department's COVID-19 Single Window to networks with Public Service Announcements in multiple Indigenous languages. Using digital media to further reach stakeholders with communications such as public health measures and maintaining an online, publicly available repository of COVID-19 resources relevant for

Indigenous peoples in multiple languages and formats. Multilateral calls with partners at the national and regional levels continue.

- **Surveillance:** Adaptation of the Department's flu surveillance tool to track COVID-19 across First Nations communities; and development of a tracking tool to inform dashboards on key indicators of COVID-19. COVID-19 case data is updated regularly on the ISC COVID-19 webpage. ISC continues to fund and facilitate partnerships with Indigenous-led, distinctions-based data initiatives. PHAC is working with provinces and territories to support collection of COVID-19 case and vaccination information, including race/ethnicity and Indigeneity to support understanding of the impacts of COVID-19 and inform response planning and actions.
- **Vaccine response planning:** Collaborating with federal departments, provinces and territories, and First Nations, Inuit and Metis partners to ensure that health facilities in Indigenous communities have the necessary immunization supplies, PPE, and health human resources to deliver the vaccine when available. Facilitating two COVID-19 Vaccine Planning working groups with representation from federal, provincial and territorial, and First Nations, Inuit and Metis partners to co-develop approaches to support the access to COVID-19 vaccines for Indigenous communities and populations, including Indigenous Peoples living in urban settings.

Based on knowledge and feedback learned to date, ongoing collaboration and funding is needed to support First Nations, Inuit, and Métis communities and organizations to respond any future surges/resurgences. Continued access to timely testing supplies, PT labs for processing, and results, including point of care testing for northern, remote and isolated communities and capacity to detect VOCs.

Access to care to treat more severe symptoms of COVID-19 in remote and isolated communities also requires that ongoing arrangements, or new ones, are in place to ensure an adequate number of beds in hospitals south of 60, to support the treatment of Indigenous peoples living in northern, remote and/or isolated communities without this type of service. In communities where there are long-term care facilities, or Elders residences, it is important to have access to adequate resources to support their planning in keeping Elders safe and healthy, including funding for basic infection prevention control measures (i.e., PPE, high dose flu vaccine, cleaning supplies, etc.), as well as, engineered public health measures.

Learning from H1N1, we know that long standing public health gaps and health disparities between First Nations Inuit and Metis, and non-Indigenous Canadians increase the likelihood and potential severity of a COVID-19 outbreak in Indigenous communities, and we have seen this throughout the second wave of the disease. These disparities are often exacerbated in remote or fly-in communities, where access to necessary supplies and health care services is limited as compared to non-Indigenous communities. We also know that during H1N1, data for First Nations/Inuit/Métis populations was not captured in a consistent way, or a way that supported communities in their preparedness and response efforts. A distinctions-based approach has been adopted by the Federal Government to ensure that the unique rights, interests and circumstances of the First Nations, Inuit, and Métis peoples are acknowledged, affirmed, and implemented. In this context, it takes into account the cultural and socio-economic particularities of each of the Indigenous Nations involved. Distinctions-based, Indigenous-led analysis of COVID-19 data is necessary to advancing culturally appropriate and science-based approaches, for First Nations, Inuit and Métis Nation communities.

Surveillance activities are critical to informing public health responses to a pandemic. They support the early detection and description of potential health threats present in Canada, including on-reserve First Nations communities. In order to be able to make informed decisions, decision makers and leaders throughout the system need reliable public health data. Existing data quality and gaps for First Nations, Inuit and Métis populations living both on and off reserve are critical to effectively responding to future waves of COVID-19 amongst this population, protecting their health and safety by getting them the access to care required.

The strategy/approach, actions and deliverables for these preparations for the short, mid and long-term are presented below.

Short term:

In the short term, ongoing work to continue to ensure First Nations, Inuit, and Métis communities and organizations have access to necessary supplies (e.g., PPE, vaccines and related administration supplies), human resources, and funding to support the COVID-19 response and planning for future waves. Vaccine planning is a priority in the short term and is being conducted through collaborative efforts in working groups to facilitate culturally safe and equitable access to the COVID-19 vaccine for all Indigenous Peoples, regardless of where they live. Communications regarding the vaccine are being developed and distributed

in multiple Indigenous languages, in partnership with Indigenous leaders and organizations, to build vaccine confidence. ISC and PHAC continue to work with partners to advocate for the prioritization of Indigenous Peoples for access to the COVID-19 vaccine. There is a need for continued work on COVID-19 surveillance and tracking of the COVID-19 vaccine administration, which is underway in collaboration with federal departments, provinces and territories, and Indigenous partners. Resources to support Indigenous-led data collection/governance/infrastructure to support data optimization for the longer term in Canada are essential. Resources to bolster community-led public health supports, culturally appropriate communication and information, and work are required, as well as training and capacity building to support these functions.

Medium term:

As COVID-19 vaccine rollout continues and the supply of the vaccine increases, the tracking and reporting of vaccine uptake and effectiveness will be critical. ISC will also continue to work to increase vaccine confidence, building on lessons learned from the early vaccine rollout. Continued work is required to support access to patient care, as well as the work of community based workers and nurses in northern, remote and/or isolated communities, and increased funding for telemedicine and virtual health care providers is necessary. This will avoid a backlog of medical or specialist appointments after COVID-19, and support access to timely care supporting better health outcomes. Ongoing monitoring of forest fires and flood for possible evacuations and planning in light of COVID-19 will be maintained over the summer and fall months.

Longer term:

In the fall, planning for the influenza vaccine clinics will need to be informed by current, local epidemiology of COVID-19, with respect to existing public health measures. As community spread of COVID-19 decreases and vaccine coverage increases, ISC and FPT public health leaders will support First Nations, Inuit, and Métis communities in re-opening economies and guidance for adjusting and eventual lifting of individual and community-based public health measures following assessment of readiness indicators. Continued work to monitor vaccine uptake and effectiveness. ISC will work with partners to facilitate after action reviews that will inform emergency management funding and planning for future pandemics.

High-level signals that would necessitate a change in timelines or strategy/approach and sub-sequent actions and deliverables, include:

- community spread of VOCs;
- ongoing and prolonged active cases – either slow, or in a community outbreak scenario;
- signals and risks of community spread, where communities may be at a higher risk due to geographic location;
- access to health care to treat more severe symptoms;
- strain on system for medivacs should there be a greater need in PTs;
- shifts in hospitalization rate, ICU admission rate, case fatality rate;
- reproductive rate;
- outbreaks in long-term care facilities or Elder lodges; and,
- shift in age/sex distribution of cases.

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Date modified:
2021-09-16

TAB 55

See Tab 54 at Covid-19 response, goal, objectives and response to date

TAB 56

See Tab 54

TAB 57

Notifications

COVID-19 Updates: State of public health emergency declared.

- Public health restrictions to reduce transmission are now in effect.
- Book your vaccine: All Albertans 5+ can get vaccinated.
- Get the facts: Vaccines are safe and save lives.

Alberta.ca

Government → Priorities and initiatives → Key initiatives → Alberta's COVID-19 response

COVID-19 info for Albertans

Taking action to protect the health care system, increase vaccination rates, and reduce the transmission of COVID-19.

Current situation

Alberta declared a state of public health emergency. Public health restrictions are in effect.

Businesses participating in the Restrictions Exemption Program will require patrons 12 and older to show proof of vaccination or negative test result.

- Complete information for Albertans
- Chief Medical Officer updates

Translated resources

COVID-19 resources are available in عربي, 中文, हिंदी, 한국어, فارسی, ਪੰਜਾਬੀ, Af-Soomaali, Español, Français, Tagalog, Tiếng Việt and اردو on alberta.ca/CovidTranslated.

Cases in Alberta

- **337,420** Total cases
- **240** Cases on December 6
- **330,047** Recovered cases
- **3,268** Deaths

- **4,105** Active cases*

- **373** In hospital
- **76** In intensive care**

- **6,181,640** Total tests completed
- **5,478** Tests on December 6
- **2,597,485** People tested
- **7,028,981** Vaccine doses as of December 6

View all case and outbreak data

Updated December 7. Numbers are current as of end-of-day December 6. Case numbers are updated daily Monday to Friday.
**Active cases include both community cases and hospitalizations. **ICU cases are a subset of those in hospital.*

Information for Albertans

Vaccines and records

All Albertans 5+ can get the COVID-19 vaccine. Once vaccinated, find out how to get your vaccine record with QR code.

Public health actions

Public health restrictions are in effect. Businesses participating in the Restrictions Exemption Program require patrons 12 and older to show proof of vaccination or negative test for entry.

Get tested

COVID-19 testing is available to all Albertans with symptoms and anyone linked to an outbreak.

Isolate or quarantine

You must isolate for 10 days if you test positive or have any core symptoms not related to a pre-existing illness or health condition.

Search by keyword Search by keyword

Clear
Search result:

(searched 20 total entries)

Showing 20 total matches

Prevent the spread

Get vaccinated to prevent COVID-19

- COVID-19 vaccines are safe and help prevent you from getting infected and protect you from getting severely sick if you do get it.
- All Albertans 5 and older can book an appointment now.
- Some people most at risk of severe illness can get a third dose.
- Working Albertans can access 3 hours of paid, job-protected leave to get each dose of the vaccine.

Learn more: Vaccines and records with QR codes

Get vaccinated to prevent Influenza

Why get an influenza vaccine

An influenza vaccine (flu shot) won't prevent COVID-19 but it will reduce your chances of getting sick with influenza (flu) or spreading it to others.

All Albertans 6 months and older are encouraged to get an influenza vaccine. It's especially important for seniors, pregnant women, Indigenous people and people with chronic health conditions as they have a higher risk of severe complications.

By keeping influenza counts low, we can:

- help prevent people from being infected with COVID-19 and influenza at the same time
- make sure our health-care system has capacity to respond to the COVID-19 pandemic
- let health-care workers focus on treating people with other illnesses and injuries
- reduce outbreaks in care facilities

The vaccine is available free of charge starting October 18.

Where to get an influenza vaccine

- Alberta Health Services (AHS) public health clinics/sites for individuals 6 months to 4 years (and their families).
- Some doctors' offices for individuals 6 months old and older.
- Participating pharmacies if 5 years old or older.

How to book an appointment

- Book an influenza vaccine appointment online.
- Phone Health Link at 811 for help booking multiple appointments for children and family members.
- Check if your community pharmacy is offering drop-in appointments.
- Phone your physician's office to see if they're offering influenza vaccine appointments.

How to get vaccinated safely

- Stay home if you have symptoms of COVID-19, isolate and complete the AHS online assessment.
- Follow safety protocols: wear a mask, wash your hands, stay 2 metres apart when possible.
- Make an appointment at your pharmacy, physician clinic or public health site and arrive as close to the appointment time as you can.
- Fill out forms online when possible.

Staff and volunteers at clinics and venues offering influenza vaccination must follow their employer's policies for COVID-19 screening.

- Influenza and COVID-19 Immunization: Guidance for the 2021-22 season

Practice good hygiene

In addition to getting vaccinated, practicing good hygiene habits can protect you and those around you from spreading COVID-19 and other respiratory illnesses.

- Stay home if you are feeling sick.
- Wash or sanitize your hands often.
- Cover your coughs and sneezes.
- Avoid touching your face.

Gather safely

Mandatory restriction - Effective Sept 16.

Indoor social gatherings

- **Vaccinated:** Indoor private social gatherings are limited to a single household plus one other household to a maximum of 10 vaccine-eligible, vaccinated people and no restrictions on children under 12.
- **Unvaccinated:** Indoor social gatherings are not permitted for vaccine-eligible but unvaccinated people.

Outdoor social gatherings

- Outdoor private social gatherings limited to a maximum of 200 people, with 2 metre physical distancing at all times.

Learn more about gathering limits and other public health actions.

Monitor your symptoms

COVID-19 symptoms are similar to influenza and other respiratory illnesses and can range from mild to severe. Even people with mild symptoms can spread COVID-19 to others.

If you have any symptom, stay home and take the online assessment to arrange testing.

Isolate if required

Isolation and quarantine requirements are in place for individuals with COVID-19 symptoms.

How it spreads

COVID-19 is transmitted though tiny droplets of liquid produced by people who have the virus. The virus spreads by:

- breathing in air that contains infected droplets from people coughing, sneezing, talking, laughing, and singing
- touching objects or surfaces the virus has landed on and then touching your eyes, nose or mouth (bath towels, kitchen utensils, door knobs, etc.)

People who have COVID-19 can spread it to others before they start to feel sick.

COVID-19 does not appear to regularly transmit like measles through long-range transmission, but there are circumstances that raise the risk of aerosol transmission, such as crowded or poorly ventilated indoor spaces where people are engaging in activities like singing or high intensity exercise. Individuals and businesses should apply mitigation strategies where these risks exist.

We think the virus generally only survives for a few hours on a surface or object, but it may be possible for it to survive several days under some conditions.

Variants of concern

Variants of concern spread more easily than the original COVID-19 strain, which could result in more severe illness, hospitalizations and deaths.

Alberta is monitoring for variants of concern. The B.1.617.2 (Delta) variant is the dominant strain in our province.

Symptoms in variant cases are the same as the original virus, including cough, fever, shortness of breath, runny nose, and sore throat.

Learn more about COVID-19 variants

Financial supports

Restrictions Exemption Program Implementation Grant

A one-time payment of $2,000 to eligible Alberta small and medium-sized businesses, cooperatives and non-profit organizations is now available for those participating in the Restrictions Exemption Program.

Learn more about the Restrictions Exemption Program Implementation Grant.

Restrictions Exemption Program safety training

Online training is available at no cost to employers and their employees to help them assess and manage challenging situations that may arise during their daily operations.

The training includes information that workers need to keep themselves and customers safe while implementing COVID-19 safety requirements, such requesting proof of vaccination or a recent negative COVID-19 test, physical distancing or masking.

Employers must enroll for the training on behalf of their employees. After enrolling, employers will receive an access code via email to share with their employees.

Learn more and enroll in REP safety training.

Alberta Jobs Now program

The Alberta Jobs Now Program second application intake period will open on November 10 with changes to help employers meet their labour needs and provide more Albertans with the skills to find successful careers.

Private and non-profit businesses can apply for funding to offset the cost of hiring and training Albertans into new or vacant jobs.

Employers can get up to:

- $25,000 for each new hire, or
- $37,500 for each new employee with a disability

Workers cannot apply for the program directly, but can let potential employers know they can apply for the Alberta Jobs Now program if they hire you.

Learn more about Alberta Jobs Now

Paid vaccination leave

All working Albertans can access 3 hours of paid, job-protected leave to get each dose of the vaccine.

Individuals and families

Financial support programs are available to help people experiencing unemployment and those who cannot work because they are sick, need to isolate, or are caring for someone in isolation.

See all federal benefit programs

Businesses

Businesses and self-employed people may be able to access federal supports to help with COVID-19-related challenges. For the latest information on federal programs, see the Government of Canada's resources below.

- Find federal support based on your business needs.
- See list of all federal business support programs.

Get help

Mental health and addiction

The COVID-19 pandemic can have a significant impact on mental health.

Online resources are available if you need advice on handling stressful situations or ways to talk to children.

- Help in Tough Times (AHS)
- Mental health and coping with COVID-19 (CDC)
- Talking with children about COVID-19 (CDC)
- COVID-19 information for young kids and students (PDF, 122 KB)

If you need to talk, call the 24-hour help lines:

- Mental Health Help Line at 1-877-303-2642
- Addiction Help Line at 1-866-332-2322

Family and sexual violence

If you or someone you know is at risk of family or sexual violence, help is available.

Family violence

- Call our 24-hour Family Violence Info Line at 310-1818 to get anonymous help in over 170 languages.
- Chat live online with the Family Violence Info Line for support in English (8 am to 8 pm)

Sexual violence

- Alberta's One Line for Sexual Violence can provide assistance in finding sexual assault support services (9 am to 9 pm daily):
  - Call 1-866-403-8000 | 215+ languages
  - Text 1-866-403-8000 | English
  - Chat online | English

Other resources

- Family violence during COVID-19 information sheet (multiple languages)
- Find information on shelter and financial supports
- Learn how to recognize and prevent family violence

Child neglect and abuse

Children are at a higher risk for neglect and abuse during times of uncertainty and crisis.

Call the 24-hour child abuse hotline at 1-800-387-KIDS (5437) if you think a child is being abused, neglected or sexually exploited.

Learn the signs of abuse

Info for organizations and vulnerable Albertans

Caregivers support

Nearly one million Albertans act as caregivers for loved ones experiencing challenges related to illness, disability or aging. These caregivers need support too.

Caregivers can get psychosocial and other peer and community supports by calling the toll-free caregiver advisor line at 1-877-453-5088 or going online to caregiversalberta.ca.

Expectant parents

Pregnant people have a higher risk of severe illness from COVID-19 than for those who are not pregnant.

Infected pregnant people may also have a higher risk of adverse pregnancy outcomes, such as preterm birth, compared to those who are pregnant without COVID-19.

Because of this, pregnant people are encouraged to get the COVID-19 vaccine. There is no evidence vaccines are harmful when pregnant or breastfeeding.

Resources

- Talk to your health care provider if you have questions or concerns.
- If you aren't feeling well, take the online assessment to arrange testing
- For more information, read the AHS Vaccination while pregnant guide.

COVID Care Teams

We are working with the cities of Calgary and Edmonton to access local agencies and organizations to provide on-the-ground support to communities experiencing a high number of cases of COVID-19, compared to other areas across the province.

Residents in these communities may face barriers that could contribute to increased rates of COVID-19 transmission:

- employment in public-facing, higher risk jobs – for example, front-line health care, maintenance, transportation
- live in higher density, multi-family or multi-generational homes
- are a newcomer to Alberta and may not have supports in place
- have English language barriers
- earn a lower than average income

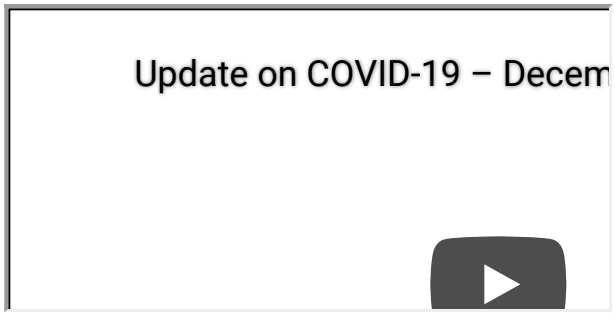
To help address these barriers, COVID Care Teams will:

- distribute care packages with masks, sanitizers and translated resources
- refer people to 811 for additional information in multiple languages
- inform residents of the nearest COVID-19 assessment and testing centres
- connect people to transportation to COVID-19 testing facilities, if needed

Chief medical officer updates

Watch updates from Alberta's chief medical officer of health, Dr. Deena Hinshaw. View all COVID-19 updates

- Listen to the Vaccines for Children town hall recording
- Read Dr. Hinshaw's letter to parents about vaccines for ages 5 to 11



Transcripts

- December 7, 2021
- December 1, 2021
- November 30, 2021
- November 29, 2021
- November 23, 2021
- November 16, 2021

- November 9, 2021
- November 3, 2021
- October 28, 2021

News

Situation updates

- Update 234: COVID-19 pandemic in Alberta (June 29)
- Update 233: COVID-19 pandemic in Alberta (June 22)
- Update 232: COVID-19 pandemic in Alberta (June 15)
- Update 231: COVID-19 pandemic in Alberta (June 10)
- Update 230: COVID-19 pandemic in Alberta (June 8)
- Update 229: COVID-19 pandemic in Alberta (June 3)

News releases

- Expanding COVID-19 booster to all Albertans 18-plus (December 1)
- Health-care workers vaccine policy updated (November 29)
- Restrictions Exemption Program updated (November 25)
- QR code vaccine record updated for travel (November 23)
- Pfizer pediatric vaccine rollout to begin (November 23)
- Children aged 5-11 now eligible for COVID-19 vaccine (November 19)

Alberta.ca

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Notifications

COVID-19 Updates: State of public health emergency declared.

- Public health restrictions to reduce transmission are now in effect.
- Book your vaccine: All Albertans 5+ can get vaccinated.
- Get the facts: Vaccines are safe and save lives.

Alberta.ca

COVID-19 public health actions

Public health restrictions are in place to reduce the impacts of COVID-19 on the health care system. Some businesses can participate in the Restrictions Exemption Program.

Overview

Alberta has declared a state of public health emergency. Measures to protect the health care system, stop the spread, and increase vaccination rates are in effect.

Businesses participating in the Restrictions Exemption Program can operate as usual if they require patrons 12 and over to show proof of vaccination or a recent negative test result.

Translated resources

COVID-19 resources are available in عربي, 中文, हिंदी, 한국어, فارسی, ਪੰਜਾਬੀ, Af-Soomaali, Español, Français, Tagalog, Tiếng Việt and اردو on alberta.ca/CovidTranslated.

Restrictions exemption program

As of September 20, 2021, in-scope organizations must follow one of these 2 options:

1. Implement the Restrictions Exemption Program requiring proof of vaccination, negative test results or medical exemption for patrons 12 and over, plus mandatory masking, to continue operating as usual, or
2. Comply with all restrictions as outlined in public health orders.

Financial support is available to help offset costs of implementing the program.

Program requirements

The Restrictions Exemption Program permits in-scope businesses, entities and organizers to operate without most public health restrictions as outlined in Order 52-2021. Masks are still mandatory indoors.

Operators that are out-of-scope or choose not to fully implement the program must comply with all public health restrictions outlined in Order 44-2021, modified by Order 53-2021.

How to participate

Operators do not need to apply, but must follow or exceed the program requirements at all times, including requiring all patrons aged 12 and over to provide valid:

- proof of vaccination, or
- proof of a privately-paid negative rapid test result taken within 72 hours of service, or
- documentation of a medical exemption

Resources

- Requirements for the Restrictions Exemption Program
- Alberta Vaccine QR Records and Verifier App helpdesk
- Guidance, posters and fact sheets

The program does not apply to

- Businesses or entities that need to be accessed by the public for daily living purposes, including all retail locations.
- Employees, contractors, repair or delivery workers, volunteers or inspectors entering the space for work purposes.
- Children under 12.

Enforcement

- Operators will be audited for compliance.
- Requirements can be enforced by AHS, AGLC and police units.
- Public can submit complaints if they believe operators are not in compliance.

Proof of vaccination and QR code scanner

To enter spaces participating in the Restrictions Exemption Program, people ages 12 and older must be fully vaccinated (at least 14 days from second dose of a 2-dose vaccine or a single dose of Janssen).

Valid proof of vaccination

- Alberta vaccine record with QR Code (paper or digital) is now the only valid Alberta-issued proof of vaccination accepted by operators participating in REP.

- Other accepted forms of proof of vaccination include:
  - Other provincial vaccine records with QR codes
  - First Nation vaccine records
  - Canadian Armed Forces vaccine records with QR codes
  - U.S. Military proof of vaccination and ID card
  - Out-of-country vaccine records
- Personal identification that matches the vaccine record is also required for all adults 18 and over.

Scanning QR codes

- Businesses can use the AB Covid Records Verifier app to scan vaccine QR codes, including those from other provinces, territories and Canadian Armed Forces.
  - If the record is valid, the app will display a green checkmark and the person's legal name and date of birth. It does not access or store any other personal information.
  - Internet connection is not required to scan codes.
  - Download the app for free from Google Play or the App Store.
- Tipsheet: How to use the AB Covid Records Verifier app

Repeat customers

- Learn more about options for checking proof of vaccination for repeat customers and protecting privacy.

Not vaccinated? Book your vaccination appointment.

Proof of negative test

To enter spaces participating in the Restrictions Exemption Program, people aged 12 and older can show proof of a negative test result.

- The test result should be a written or printed copy that indicates the individual has tested negative for COVID-19 on a Health Canada approved rapid antigen, rapid PCR, or lab based PCR test approved by Health Canada or the lab accreditation body of jurisdiction.
  - Valid test results should be a written or printed copy that clearly outlines the type of test, time of sample collection, clear indication of a negative result, and laboratory that completed the test, if applicable.
  - Photos of a rapid test or result taken offsite is not sufficient.
  - A self-test completed offsite or self-produced documentation of a negative test result is not valid.
  - Do not bring completed self-tests or rapid tests to businesses due to communicable disease risk.
- Tests must not be from the Alberta Health Services public COVID-19 testing system.
- Operators offering on-site rapid testing should seek expert medical oversight prior to implementing a rapid testing program.
- For more details, see requirements for the Restrictions Exemption Program.

Proof of medical exemption

To enter spaces participating in the Restrictions Exemption Program, people 12 and older can provide documentation of a medical exemption.

- A valid medical exemption is the original signed letter from a physician or nurse practitioner that includes:
  - date which the letter was provided
  - person's name that matches their identification
  - physician’s or nurse practitioner’s complete information, including:
    - name, phone number, contact information, professional registration number and signature
    - statement that there is a medical reason for not being fully vaccinated against COVID-19
    - duration that the exemption is valid

In-scope operators

The following in-scope businesses, entities and organizers are eligible to participate:

- Restaurants and food courts with closed access to the public
- Nightclubs
- Casinos, bingo halls, VLT lounges
- Entertainment and recreation centres, such as:
  - Bowling, racing entertainment, arcades, billiards halls, other similar entertainment
  - Museums, art galleries
  - Movie theatres, concert halls and other similar venues
- Fitness and recreation facilities for physical activity, performance activity or recreational activity
- Conferences, meeting spaces, halls, and rented space (excluding dwelling units)
- Weddings and funerals held in public facilities where the facility maintains responsibility for adherence to these requirements
- Indoor adult sport and performance activities (participants and spectators)
- Professional sporting or performance events (spectators)
- Private social events held in public facilities where the facility maintains responsibility for adherence to these requirements
- Adult recreational activities (for example, classes, groups)
- Amenities in hotels and condos, including fitness rooms, pools and game rooms

November 29 updates:

- Ski hills and facilities can operate under a hybrid model (see business restrictions for details)
- Paid-entry markets and trade shows, such as artisan and craft fairs, automotive shows, gun shows and holiday markets or similar events of a short-term nature
- Private passenger vehicles, such as buses or vans rented out or chartered for attending a private event, gathering, or activity, as well as privately-operated transportation services

Out-of-scope operators

The following out-of-scope operators are not eligible to participate:

- Child care settings
- Events in private dwellings
- Retail, including membership-only stores
- Shopping malls
- Libraries
- Workers and employees in/on a worksite for the purposes of their employment
- Schools (Kindergarten to Grade 12)
- School curriculum-based activities
- Accommodations (hotels, motels)
- Places of Worship – for faith services
- Mutual support groups
- Health services
- Personal services
- Wellness services
- Youth physical activity, performance activity and recreational activity, where all participants are under the age of 18
    - Note: coaches, instructors, trainers, referees, etc. are subject to the requirements of the facility if under the REP
- Public transit, taxis and paid ride shares
- Jury selection
- Election purposes and other related activities
- First responders attending for the purposes of responding to an emergency situation
- Publicly-funded post secondary institutions, including cafeterias and residence common areas (PSIs will fall under a separate and sector-specific exemption)
- First Nations College entities:
    - Maskwacis Cultural College
    - Old Sun Community College
    - Red Crow Community College
    - University nuhelot'ine thaiyots'i nistameyimakanak Blue Quills
    - Yellowhead Tribal College

Business restrictions

Entertainment, event and recreation facilities

Mandatory restriction - Effective Sept. 16 and 20

Indoor entertainment, event and recreation facilities (Sept 20)

- Indoor facilities that do not implement the Restrictions Exemption Program must follow these restrictions:
    - Capacity limited to 1/3 fire code occupancy.
    - Attendees must be with household members only, or 2 close contacts if they live alone.

Outdoor entertainment, event and recreation facilities (Sept 16)

- Events and facilities that are fully outdoors (excluding washrooms), have no capacity restrictions but must maintain 2 metres distancing between households or 2 close contact for those living alone.

Restaurants, cafes, bars, pubs and nightclubs

Mandatory restriction - Effective Sept. 20

The following restrictions apply to businesses that do not implement the Restrictions Exemption Program.

- Indoor dining is not permitted.
- Outdoor dining only with a maximum of 6 people per table (one household or 2 close contacts for those living alone)
- Liquor sales and consumption restrictions apply (sales end at 10pm, consumption by 11pm).

Retail and shopping malls

Mandatory restriction - Effective Sept. 20

Retail and shopping malls are not eligible for the Restrictions Exemption Program as public access is necessary for daily living. Therefore these restrictions apply:

- Capacity restricted to 1/3 fire code occupancy.
- Attendees must be with household members only, or 2 close contacts if they live alone.

Sport, fitness and performance activities

Mandatory restriction - Effective Sept. 16 and 20

Adult (18-plus) sport, fitness and performance activities (Sept 20)

- The following restrictions apply unless the facility or program implements the Restrictions Exemption Program:
  - Indoor group classes and activities are not permitted.
  - Indoor competitions are paused except where vaccine exemptions have been granted.
  - Indoor one-on-one training and solo activities are allowed with 3 metre physical distancing.
  - Outdoor activities can continue with no restrictions.

Youth (under 18) sport, fitness and performance activities (Sept 16)

- Indoor group classes, training, and competitions are permitted, but participants are required to:
  - screen for symptoms
  - maintain 2 metres distancing, except youth while engaged in physical activity
  - wear a mask, except youth while engaged in physical activity
- Spectator attendance is restricted to 1/3 fire code capacity, attendees are limited to a single household or 2 close contact if living alone and must be masked and maintain 2 metres physical distancing.

- Outdoor activities can continue with no restrictions.

Day and overnight camps (Sept 16)

- Day camps required to maintain physical distancing between participants and masking indoors.
- Overnight camps must follow cohort models.

Ski hills

Mandatory restriction - Effective Nov. 29

Ski hills can operate under a hybrid model where their indoor operations follow the Restrictions Exemption Program (REP) guidelines, and their outdoor operations are not required to do so.

- If participating in REP:
  - indoor dining and other indoor activities are permitted without physical distancing or capacity restrictions
  - physical distancing is not required on enclosed chairlifts and gondolas
  - masks are still required for enclosed indoor areas
- If **not** participating in REP:
  - indoor dining is not permitted
  - other indoor activities are subject to physical distancing and capacity restrictions
  - physical distancing is required on enclosed chairlifts and gondolas
  - masks are required for enclosed indoor areas
- Outdoor operations (applicable to all ski hills):
  - Open-air chair lifts do not require physical distancing and can be used by people who are not part of the same household or cohort

Working from home

Mandatory measure - Effective Sept. 16

- Mandatory work-from-home measures are in place unless the employer has determined a physical presence is required for operational effectiveness.
- If employees are working on location, they must mask in all indoor settings, except while alone in work stations.

Gathering restrictions

Social gatherings (indoor and outdoor)

Mandatory restriction - Updated October 5

Indoor social gatherings

- Vaccinated: Indoor private social gatherings are limited to 2 households (yours plus one other) up to a maximum of 10 vaccine-eligible, vaccinated people and no restrictions on children under 12.
- Unvaccinated: Indoor social gatherings are not permitted for vaccine-eligible people who are unvaccinated.
- This restriction does not apply to mutual support groups, or to workers who need to access your home to provide caregiving support or home repairs and maintenance.

Outdoor social gatherings

- Outdoor private social gatherings limited to a maximum of 20 people, with 2 metre physical distancing between households at all times.

Places of worship

Mandatory restriction - Effective Sept. 16

- Capacity limited to 1/3 fire code occupancy.
- Masks are mandatory.
- 2 metres physical distancing between households, or 2 close contacts for those living alone.

Weddings and funerals

Mandatory restriction - Effective Sept. 20

- Indoor wedding ceremonies and funeral services are permitted with up to 50 people or 50% of fire code occupancy, whichever is less, unless the hosting facility implements the Restrictions Exemption Program.
- Indoor wedding and funeral receptions are prohibited, unless the hosting facility implements the Restrictions Exemption Program.
- Outdoor ceremonies, services and receptions are permitted with up to 200 people and must follow liquor sales and consumption restrictions (sales end at 10pm, consumption by 11pm), unless the hosting facility implements the Restrictions Exemption Program.

Masks and schools

Masks and physical distancing

Mandatory restriction – Effective Sept. 16

- Masking and 2 metres physical distancing are mandatory in all indoor public spaces, workplaces, and places of worship.
- Employees must mask in all indoor work settings, except while alone in work stations.
- The Restrictions Exemption Program does not apply to masking. Masks are still required in places that implement the program.

Learn more about mask requirements

Schools (K to 12)

Mandatory measure - Effective Sept. 16

- Mandatory masking for students in Grades 4 and up, plus staff and teachers in all grades. Schools that implement an alternate COVID safety plan can be exempted from mandatory masking.
- Elementary schools to implement class cohorting.
- Indoor sports, fitness, recreation, and performance activities are permitted in schools, with requirements to maintain 2 metre physical distancing where possible.
    - Masks and distancing are not required by youth under 18 while engaged in physical activity.
    - Spectator attendance restricted to 1/3 fire code capacity and limited to households or 2 close contacts for those living alone. Attendees must be masked and distanced.

For more information, see K-12 learning during COVID-19

Post-secondary institutions

Mandatory measure – Effective Sept. 20

- Post-secondary institutions are not eligible for the Restrictions Exemption Program.
- However, post-secondaries can implement a proof of vaccination program for students to be eligible for an exemption that permits the following:
    - Students and staff do not have to maintain physical distancing in learning environments (where there is no access to persons not part of the program). Physical distancing is required in common spaces.
    - Cafeterias and dining halls can be open for staff and students to dine indoors, with no requirement to physically distance or sit only with members of your household or your 2 close contacts, and no limit on the number of people per table.
    - Note: other public health measures, such as mandatory masking in all public spaces and restrictions around adult physical and performance activities, continue to apply.
- All post-secondary proof of vaccine programs must ensure:
    - All student have been vaccinated with at least a first dose of a World Health Organization (WHO) approved COVID-19 vaccine no later than September 20, 2021, and be fully immunized with a WHO-approved COVID-19 vaccine no later than November 1, 2021.
        - Full immunization occurs 14 days after the second dose is received.
    - Students who remain unvaccinated or are vaccinated after these dates must be able to show:
        - proof of medical exemption from vaccination or
        - produce negative results from COVID-19 tests that are conducted regularly (for example, twice weekly) by the institution or a private test provider.
    - Note: Proof of vaccination is not required from staff and contractors.
- If a post-secondary institution decides not to implement a proof of vaccination program, it must follow all public health measures in Order 44-2021.
- Varsity sports teams at post-secondary institutions are considered to be semi-professional and may conduct group physical activity indoors and do not need to maintain distancing or wear face masks during play.

- Physical distancing and masking are required before and after play (for example, in change rooms, washrooms, etc.)

Testing, tracing and isolating

Testing

Measures in effect

- COVID-19 testing for Albertans with symptoms remains available at assessment centres.
- Asymptomatic testing is no longer recommended.
- A wastewater baseline testing program will be launched to provide area trend information and monitor variants of concern. More details will be released in the coming weeks.

Isolation and quarantine requirements

Measures in effect

- Isolation is still legally required for people who have COVID-19 symptoms or tested positive.
- Quarantine is no longer legally required for close contacts positive cases, unless directed to do so by local public health officials.
- However, anyone who is a household contact and is not fully immunized, should stay home for 14 days (i.e. not attend work, school or other activities).
- International travellers must still follow federal travel requirements.
- Isolation hotels and quarantine supports are no longer available.

Contact tracing and case investigation

Measures in effect

- Individuals with positive tests will continue to be notified.
- Contact tracers will not notify close contacts of positive cases, but will ask that individuals do so when informed of their positive result.
- Contact tracers will continue to investigate cases in high-risk settings, such as acute and continuing care.

Outbreaks

Measures in effect

- Outbreak management and identification will focus on high-risk locations, including continuing and acute care and high-risk workplaces.
- Community outbreaks with a surge in cases leading to severe outcomes will be addressed as needed.

Health care and congregate care settings

- Existing public health orders for acute care remain in place.
- Public health orders for continuing care remain in place.

For more information on current restrictions in these settings, see protecting residents at congregate care facilities.

Public health orders and exemptions

Public health orders and exemptions

Public health orders

- Order 53-2021
- Order 52-2021
- Order 47-2021
- Order 44-2021
- Order 34-2021

Mask exceptions

In the specific settings where a mask is required, anyone unable to wear a mask due to a medical condition will require a medical exception letter from an authorized health professional.

The medical exception letter may be presented when in a public setting if requested by enforcement officials, or retrospectively in court if a ticket is issued.

See mask requirements for more information.

Promoting safe public spaces

Public Health Order 30-2021 clarifies that large gatherings can be held on public land for political purposes (rallies, public demonstrations, protests, etc.).

To help protect health, masking and physical distancing requirements are in place.

As with other activities in general, participants at these gatherings are subject to enforcement actions if public health measures are not followed.

Guidance and posters

General guidance and resources are available to help Albertans and businesses follow best practices to prevent the spread of COVID-19.

Additional guidance for businesses and event organizers

- Requirements for the Restrictions Exemption Program
- General guidance for COVID-19 and other respiratory illnesses - optional mitigations to protect the health of your staff and customers.
- Guidance for activities with children - best practices to protect children ages 11 and under.
- Guidance documents - updated guidance for workplaces and settings that involve children, and archived sector-specific guidance from the previous stage for reference.
- COVID-19 proof of vaccination samples (PDF, 3.2 MB)

Posters and fact sheets

Some resources are available in multiple languages.

Posters

- Masks now mandatory
- Vaccinated? Come on in.
- Proof of vaccination required
- What is accepted as proof of vaccination
- How to verify an Alberta vaccine record
- Practice physical distancing (Not required for businesses participating in REP)

Fact sheets

- How to use the AB Covid Records Verifier app
- About the QR Verifier app
- Stay safe, Alberta (PDF, 138 KB)

Assessing personal risk

Albertans are encouraged to assess and manage their personal risk. It is reasonable for people to continue using precautions that will serve their needs.

Risk factors

When assessing your personal risk, it is important to consider your setting, individual health and wellness factors, and comfort level. Consult your health care provider if you want help assessing your personal risk of severe outcomes or determining your personal risk level.

Factors that increase COVID-19 risk:

- You are not fully vaccinated yet.
- You regularly interact with children 11 and under who cannot be vaccinated yet.
- You attend crowded indoor spaces.
- You have risk factors for severe health outcomes from COVID-19.

Factors that lower COVID-19 risk:

- You are fully vaccinated.
- You mostly socialize outdoors, instead of indoors.
- You have a small social circle.
- You can normally maintain distancing from other people.

Additional precautions

The best thing you can do to support your health and reduce the risk to the broader community is to get vaccinated. Vaccines are our best protection against COVID-19 and the safest and most effective way to protect against infection and severe illness.

Additionally, all Albertans should:

- practice good hand and respiratory hygiene
- stay home when they are sick

If you have risk factors as described above, it is reasonable to consider additional precautions such as:

- avoiding or limiting time spent in crowded indoor places
- minimizing close contact with anyone showing cold-like symptoms
- continuing to use a face mask

Mental health supports

We encourage Albertans to access supports that are available, if and when they are needed, and to respect how others are adjusting in this time of transition. For additional guidance, see mental health support (PDF, 270 KB).

Get vaccinated

COVID-19 vaccines are safe, effective and save lives. All Albertans 5 and older can book an appointment now. Some people most at risk of severe illness can now get a third dose.

Book your shot Get your vaccine QR record Get the facts

Enforcement

If you violate a public health order, you may be subject to a $4,000 fine. Additionally, you can be prosecuted for up to $100,000 for a first time offense.

If you are concerned someone is not following public health orders, you can:

- remind them that not following orders is against the law and puts people at risk
- request service from AHS public health inspectors online or call 1-833-415-9179

Submit a request online

Alberta.ca

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COVID-19 Info: For Albertans | For Health Professionals | Vaccine | Testing | Results | Family Support & Visitation

A CMOH order remains in effect that requires continuous masking at all AHS and Covenant facilities provincewide.

AHS' Four Foundational Strategies

How do we envision our future? Everything AHS employees, physicians and volunteers do should advance patient- and family-centred care. And we know that excellent patient and family-centred care is attainable when staff, physicians and volunteers feel safe, healthy and valued in the work environment.

Using the AHS Health Plan and Business Plan as our roadmap, AHS has worked with staff, physicians, volunteers and partners to build four foundational strategies. The four strategies will guide efforts to sustain safe, high-quality health-care delivery for the benefit of all Albertans. They are built on the base of our Values and Mission, and provide a solid framework for us to manage the demands within our system and to coordinate efforts across the province.

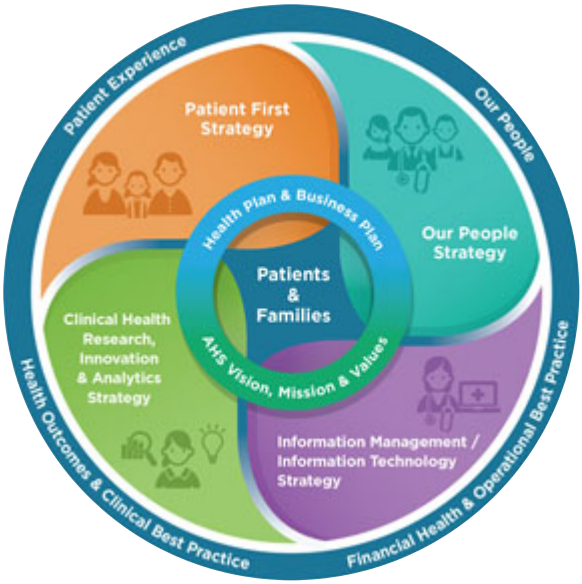
Foundational Strategies

Following extensive consultations with key stakeholders — including patients, clients and their families — Alberta Health Services developed four foundational strategies. Our foundational strategies will guide efforts to sustain safe, high-quality health-care delivery for the benefit of all Albertans.

The foundational strategies are:

- Patient First Strategy
  - **Main objective:** Strengthen AHS' culture and practices to ensure patients and families are at the centre of all health care activities, decisions and teams.

    - **How will AHS do it:** Promote respectful patient/provider interactions; improve communication between providers and patients/clients/families; adopt a team-based approach to care; and improve transitions in care.
- Our People Strategy
    - **Main objective**: Our People Strategy is about how we support each other. It is about creating a culture in which we all feel safe, healthy, and valued, and can reach our full potential. Through Our People Strategy, workforce engagement will be higher, and patient and family experiences will improve as a result.
    - **How will AHS do it**: Create a clear vision for the organization, with a shared purpose and common goals; build a safe, healthy and inclusive place to work; develop excellent leadership that will respect, value and support the workforce; create a culture of empowerment by giving people access to the resources and development opportunities they need to do their jobs effectively.
- Strategy for Clinical Health Research, Innovation and Analytics
    - **Main objective:** Generate, share and use evidence in the delivery of care to improve patient outcomes and to solve the complex challenges affecting the health system.
    - **How AHS will do it:** Use Strategic Clinical Networks to engage partners in research and innovation; identify gaps where research and innovation will have a significant benefit to patients and the health system; provide easy, timely and secure access to health information; apply and spread knowledge; and innovate to achieve service excellence.
- Information Management & Information Technology Strategy
    - **Main objective:** To make the right information available to the right people at the right time across the health system, so that providers and patients across the province have access to complete information at the point of care and to learn from in the future.
    - **How AHS will do it:** AHS will use information and technology to transform care in the following ways:
        - **Strengthen the Foundation** - improve understanding and use of technology, provide reliable infrastructure and info-structure, and enhance security of information.
        - **Optimize Operations** - make investments which provide best value, support critical services, and improve access and flow of information.
        - **Transform Care** - empower Albertans to participate in their health with better access to records and communication with providers; better clinical decision support tools at the point of care and learning and innovation which drives long-term improvement in the health system.



Quick Reference Links

- AHS Vision, Mission & Values
- 2016-17 Health Plan & Business Plan
- Patient First Strategy
- People Strategy
- Strategy for Clinical Health Research, Innovation and Analytics