An Advisory Committee Statement (ACS) 
National Advisory Committee on Immunization (NACI) 

Recommendations on the use of COVID-19 Vaccines
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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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 March 16, 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.

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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, 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 and available vaccines (Pfizer BioNTech COVID-19 vaccine, Moderna COVID-19 vaccine, AstraZeneca COVID-19 vaccine)

- mRNA vaccines are authorized for use in Canada for individuals 16 years of age and older (Pfizer-BioNTech COVID-19 vaccine) or 18 years of age and older (Moderna COVID-19 vaccine).
- A non-replicating viral vector vaccine is authorized for use in Canada for individuals 18 years of age and older (AstraZeneca 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 (approximately 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.
- 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 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 variant of concern first identified...
in the UK. 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.

- Following post-licensure use of AstraZeneca COVID-19 vaccine, rare cases of serious blood clots associated with thrombocytopenia have recently been reported in Europe (with three confirmed cases out of over 700,000 doses of AstraZeneca COVID-19 vaccine administered in Canada as of April 20, 2021) mostly between 4 and 14 days after receipt of the vaccine. The rate of Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) is most commonly estimated to be between 1 per 100,000 and 1 per 250,000 persons vaccinated with the AstraZeneca COVID-19 vaccine. Investigations are ongoing.

- 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. If an mRNA vaccine is contraindicated, another authorized COVID-19 vaccine should be offered.

A complete series with the AstraZeneca COVID-19 vaccine may be offered to individuals 30 years of age and older without contraindications only if the individual does not wish to wait for an mRNA vaccine and all of the following conditions apply:

a) The benefit-risk analysis* determines that the benefit of earlier vaccination with the AstraZeneca COVID-19 vaccine outweighs the risk of COVID-19 while waiting for an mRNA COVID-19 vaccine; AND

b) The benefits and relative risk* and consequences of VITT and COVID-19 for the individual are clearly outlined, factoring in the anticipated waiting time to receive an mRNA vaccine as well as the availability of other effective personal public health measures to mitigate risk of COVID-19, and the individual makes an informed decision based on an understanding about these risks and benefits; AND

c) There will be substantial delay to receive an mRNA vaccine.

Note: Provinces and territories should adapt the age limit, based on their local epidemiology.
*See Risk Assessment Framework and Management Options Table to assist with this determination

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. In the context of limited vaccine supply, initial doses may be prioritized for those who have not had previously PCR-confirmed SARS-CoV-2 infection. Testing for previous SARS-CoV-2 infection is not needed prior to COVID-19 vaccination.

For some specific populations who were either excluded from, or were represented by small numbers of participants in clinical trials, NACI recommends that a complete vaccine series with a currently authorized COVID-19 vaccine may be offered, if a risk assessment deems that the benefits of vaccination outweigh the potential risks for the individual (e.g., where the risk of severe outcomes of COVID-19 and/or risk of exposure to SARS-CoV-2 is high) or for the fetus/infant (in the case of pregnancy/breastfeeding) and if informed consent includes discussion about the insufficient evidence in these populations:

- Immunosuppressed due to disease or treatment
- Individuals with an autoimmune condition
- Pregnant or breastfeeding
- Adolescents 12 to 15 years of age (Only Pfizer-BioNTech COVID-19 vaccine may be offered)

These recommendations may change as more evidence on safety and/or efficacy/effectiveness in these populations becomes available.

NACI also recommends that:

- All individuals should continue to practice recommended public health measures for prevention and control of SARS-CoV-2 infection and transmission regardless of vaccination with COVID-19 vaccine, at this time, due to insufficient evidence on the duration of protection and effectiveness of COVID-19 vaccines in preventing asymptomatic infection and reducing transmission of SARS-CoV-2.
- 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, seniors living in congregate care settings, children and adolescents) 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 systematically 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 and available COVID-19 vaccines are administered intramuscularly in a two-dose schedule (Pfizer-BioNTech, Moderna, AstraZeneca).
- Attempts should be made to complete the vaccine series with the same vaccine product.
- 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 should not be given simultaneously with other live or inactivated vaccines at this time, unless other vaccines are required for post-exposure prophylaxis.
- 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, available COVID-19 vaccines that are recommended for use by NACI in this Statement have been shown to be safe (with the exception of very rare cases of VITT reported following vaccination with the AstraZeneca vaccine), 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 and available for use in Canada, and as evidence on these vaccines evolves.

There are four COVID-19 vaccines currently authorized for use in Canada, but only three (Pfizer-BioNTech, Moderna, AstraZeneca) are currently available:

1. The Pfizer-BioNTech COVID-19 vaccine was authorized for use in Canada on December 9, 2020.
2. The Moderna COVID-19 vaccine was authorized for use in Canada on December 23, 2020.
3. The AstraZeneca COVID-19 vaccine was authorized for use in Canada on February 26, 2021.
   - 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 on March 5, 2021.

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 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 to plan for the efficient, effective, and equitable allocation of an eventual 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) 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 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** 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 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** (AstraZeneca vaccine should not be used in adults under 55 years of age at this time) while the safety signal of Vaccine-Induced Prothrombotic Immune Thrombocytopenia (VIPIT) [now and hereafter referred to as Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)] following vaccination with AstraZeneca COVID-19 vaccine is investigated further.

7. **Recommendations on the use of COVID-19 vaccine 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 and available for use in Canada. This evergreen document will be updated as COVID-19 vaccines are authorized and become available 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 appendixes.

**II. METHODS**

Details of NACI’s recommendation development process can be found elsewhere (1, 2).

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 (2). The NACI Secretariat applied this framework with accompanying evidence-informed tools (Ethics Integrated Filters, Equity Matrix, Feasibility Matrix, 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 and April 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, including the Health Canada’s safety assessment report issued on April 14, 2021, was formally reviewed on April 13,15, 17 and 20, 2021. Related recommendations were approved on April 20, 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.

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 and the Equity Matrix (3) 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 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 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. 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). 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) (4).

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). 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 in Table 1). A moderate certainty of evidence of at least a 2-fold increase in hospitalization and mortality from COVID-19 in people living with two or more medical conditions was found. However, there is no direct evidence on the combination of medical conditions that increase this risk (4).

Caution should be taken when interpreting evidence of low certainty (e.g., for medical conditions listed as Level 2 in Table 1). As evidence accumulates, observed associations may change. For example, a previous rapid review by ARCHE (4) 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

<table>
<thead>
<tr>
<th>Increased risk of severe outcomes from COVID-19 (hospitalization/mortality)</th>
<th>Increased risk of exposure to COVID-19 (e.g., due to inability to physically distance/reduced access to IPC)&lt;sup&gt;5&lt;/sup&gt;</th>
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| **Increasing age (strong evidence)** (based on moderate certainty of evidence of ≥2-fold increase in mortality)  
- ≥60 years (particularly ≥ 70 years)  

| **Medical conditions – Level 1 (strong evidence)**<sup>5</sup> (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§  
- Type 1 and 2 diabetes  

| **Medical conditions – Level 2 (limited evidence)**<sup>5</sup>  
**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 drug use for the condition in the past 6 months  
- Obesity class III (BMI 40 kg/m2 or more)  
- Parkinson’s disease  
- Sickle cell disease or severe immunodeficiency, transplant (any type)  
- Kidney 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)  

- 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 |
Increased risk of severe outcomes (hospitalization/mortality)\(^c\) and Increased risk of exposure \(^5\)

- 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.
\(^5\) 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. Many jurisdictions include medical conditions involving the heart, lungs, liver and spleen. The ARCHE review found fairly strong evidence (moderate certainty) of little-to-no increase in severe outcomes for several cardiovascular and respiratory conditions. There was some evidence (low certainty) for little-to-no increase in hospitalization or mortality with cirrhosis. No studies met selection criteria for other liver conditions, asplenia, or splenic dysfunction.

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


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 and is expecting enough mRNA vaccines to fully vaccinate the currently eligible Canadian population before fall 2021.

**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).

**IV.1 Preparations of COVID-19 vaccines authorized and available for use in Canada**

<table>
<thead>
<tr>
<th>Product Brand Name</th>
<th>Pfizer-BioNTech COVID-19 Vaccine</th>
<th>Moderna COVID-19 Vaccine</th>
<th>AstraZeneca COVID-19 / Covishield Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of vaccine</td>
<td>mRNA</td>
<td>mRNA</td>
<td>Non-replicating viral vector (ChAd)</td>
</tr>
<tr>
<td>Date of authorization in Canada</td>
<td>December 9, 2020</td>
<td>December 23, 2020</td>
<td>February 26, 2021</td>
</tr>
</tbody>
</table>
### Product Brand Name

<table>
<thead>
<tr>
<th>Product Brand Name</th>
<th>Pfizer-BioNTech COVID-19 Vaccine</th>
<th>Moderna COVID-19 Vaccine</th>
<th>AstraZeneca COVID-19 / Covishield Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Authorized ages for use</td>
<td>16 years of age and older</td>
<td>18 years of age and older</td>
<td>18 years of age and older</td>
</tr>
<tr>
<td>Dose</td>
<td>0.3 mL (30 mcg of mRNA)(^a)</td>
<td>0.5 mL (100 mcg of mRNA)</td>
<td>0.5 mL (5 x 10(^{10}) viral particles)</td>
</tr>
<tr>
<td>Authorized Schedule (^b)</td>
<td>2 Doses, 3 weeks apart</td>
<td>2 Doses, 4 weeks apart</td>
<td>2 Doses, 4 to 12 weeks apart</td>
</tr>
<tr>
<td>Route of administration</td>
<td>IM</td>
<td>IM</td>
<td>IM</td>
</tr>
<tr>
<td>Nature of the antigen</td>
<td>Transmembrane prefusion spike protein</td>
<td>Transmembrane prefusion spike protein</td>
<td>Transmembrane spike protein</td>
</tr>
<tr>
<td>Adjuvant (if present)</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Primary storage requirements pre-puncture (^c)</td>
<td>-80°C to -60°C</td>
<td>-25°C to -15°C</td>
<td>+2°C to +8°C</td>
</tr>
<tr>
<td>Additional storage options pre-puncture (^c)</td>
<td>-25°C to -15°C for up to 2 weeks (^a) OR 120 hours (5 days) at +2°C to +8°C AND/OR 2 hours up to +25°C</td>
<td>30 days at +2°C to +8°C AND/OR 12 hours at +8°C to +25°C</td>
<td>+2°C to +8°C</td>
</tr>
<tr>
<td>Diluent</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Usage limit post-puncture</td>
<td>6 hours at +2°C to +25°C (^f)</td>
<td>6 hours at +2°C to +25°C</td>
<td>6 hours at room temperature (up to +30°C) or 48 hours at +2°C to +8°C.</td>
</tr>
<tr>
<td>Formats available</td>
<td>Multi-dose vial (6 doses)(^a), preservative-free</td>
<td>Multi-dose vial (10 doses), preservative-free</td>
<td>Multi-dose vial (8-and 10-dose presentations), preservative-free</td>
</tr>
</tbody>
</table>

**Abbreviations:** ChAd: Chimpanzee adenovirus; IM: Intramuscular; mRNA: Messenger ribonucleic acid

\(^a\) After dilution, one vial contains 6 doses of 0.3 mL each. However, vial labels and cartons may state that after dilution, a vial contains 5 doses of 0.3 mL. Information in the product monograph supersedes the number of doses stated on vial labels and cartons. 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 -40°C

\(^e\) Vials stored at -25°C to -15°C for up to 2 weeks may be returned one time to the recommended storage condition of -80°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

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**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, available viral vector-based COVID-19 vaccine (AstraZeneca 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) and Appendix C (for the AstraZeneca 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) from one to two weeks after receiving the full two-dose series. The authorized mRNA vaccines are similarly efficacious in adults with one or more comorbidities, as well as in younger adults and older adults. However, evidence in adults of a much more advanced age (e.g., 85 years and older) and in long-term care facilities is limited.

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 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 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 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 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 and was too small in the AstraZeneca clinic trial to assess efficacy. Efficacy against hospitalization was not assessed in the clinical trials of the mRNA vaccines, but evidence from the clinical trials involving the AstraZeneca vaccine 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) (6-8), Israel (9-11), the United States (US) (12), and Canada (13) suggests moderate to high vaccine effectiveness against severe COVID-19 outcomes after the first or second dose of mRNA COVID-19 vaccines (6-13), and after the first dose of AstraZeneca COVID-19 vaccine (6-8), including in older (6-8, 11) and frail (6) populations. COVID-19 related hospitalization was the most common severe COVID-19 outcome assessed (6-9, 12), while fewer studies provided estimates of effectiveness against severe disease (9, 10) and death (7, 9, 13). Emerging evidence from two Israeli studies suggest high vaccine effectiveness after the second dose of Pfizer-BioNTech COVID-19 vaccine against severe disease (9,10) and COVID-19 related hospitalization (9). 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 has not demonstrated efficacy against confirmed SARS-CoV-2 asymptomatic infection, however the number of asymptomatic infections was small. Studies are ongoing for these vaccines.

Evidence has begun to emerge from post-marketing studies conducted in Israel, (9) the UK, (14) and the US (15) on the effectiveness of COVID-19 vaccines 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 (9, 14) (depending on time since vaccination) and high after the second dose (9, 14). Similar results were reported for mRNA COVID-19 vaccines in general (i.e., Moderna and Pfizer-BioNTech) (15). 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 (14). 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 the currently available viral vector-based COVID-19 vaccine (AstraZeneca COVID-19 vaccine) against variants of SARS-CoV-2 is evolving. Please see Table 5 for a summary of this evidence.

There is evidence that both the Pfizer and AstraZeneca vaccines protect against the B.1.1.7 SARS-CoV-2 variant first identified in the UK. The AstraZeneca clinical trial was conducted when the B.1.351 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
- 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., in immunocompromised, 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 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 vaccine (AstraZeneca 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) and [Appendix C](#) (for the AstraZeneca 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. 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.

**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 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 COVID-19 Vaccine

Each dose is 0.5 mL, containing 100 mcg of SARS-CoV-2 spike protein mRNA.

No dilution is required.

AstraZeneca COVID-19 Vaccine

Each dose is 0.5 mL, containing $5 \times 10^{10}$ 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.

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, available COVID-19 vaccines.
Table 3. Recommended immunization schedule, by COVID-19 vaccine

<table>
<thead>
<tr>
<th>Vaccine product</th>
<th>Immunization schedule</th>
<th>Minimum interval</th>
<th>Authorized interval</th>
<th>Extended interval&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer-BioNTech COVID-19 vaccine</td>
<td>2-dose schedule</td>
<td>19 days&lt;sup&gt;b&lt;/sup&gt;</td>
<td>21 days</td>
<td>16 weeks</td>
</tr>
<tr>
<td>Moderna COVID-19 vaccine</td>
<td>2-dose schedule</td>
<td>21 days&lt;sup&gt;c&lt;/sup&gt;</td>
<td>28 days</td>
<td>16 weeks</td>
</tr>
<tr>
<td>AstraZeneca COVID-19 vaccine</td>
<td>2-dose schedule</td>
<td>28 days</td>
<td>4 to 12 weeks</td>
<td>16 weeks&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Based on emerging evidence of the protection provided by the first dose of a two-dose series for COVID-19 vaccines currently authorized and available in Canada, NACI recommends that in the context of limited COVID-19 vaccine supply and ongoing pandemic disease, jurisdictions should maximize the number of individuals benefiting from the first dose of vaccine by extending the second dose of COVID-19 vaccine up to four months after the first. NACI will continue to monitor the evidence and update this interval as needed.

<sup>b</sup> 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.

<sup>c</sup> 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.

<sup>d</sup> The AstraZeneca COVID-19 vaccine clinical trial demonstrated optimal efficacy when the interval between the first and second doses was ≥12 weeks.

Refer to Timing of Vaccine Administration in the CIG, Part 1 - Key Immunization Information for additional general information.

**Extended intervals for COVID-19 vaccines to optimize early vaccine roll-out and population protection**

Currently, no data on medium- or long-term efficacy of COVID-19 vaccines are available. In general, interruption of a vaccine series resulting in a greater than recommended interval between doses does not require restarting the series, as delays between doses do not result in a reduction in final antibody concentrations for most multi-dose (prime-boost) 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. However, the follow-up time in COVID-19 vaccine clinical trials is short, the duration of protection after one or both doses is unknown, and mRNA and viral vector-based vaccines represent relatively new vaccine technologies.

Morbidity and mortality from COVID-19 is ongoing. Extending the interval to the second dose of a COVID-19 vaccine maximizes vaccine supply to immunize the largest number of people as quickly as possible. Principles of immunology indicate that a longer interval between priming and boosting doses of a vaccine series results in a better, more durable response. Please 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 for a summary of the evidence.

Follow-up of vaccine effectiveness in individuals for whom the second dose is delayed or who have otherwise missed their second dose (e.g., missed a follow-up immunization appointment) will be important to inform future recommendations and ensure completion of the vaccine series as soon as possible. NACI will continue to monitor the evidence and update recommendations as needed.
IV.4.2 Booster doses and re-immunization

There is currently no evidence on the need for booster doses of COVID-19 vaccine after the vaccine series is complete. Given the emergence of VOC against which vaccine effectiveness may be decreased, additional vaccine doses may be necessary. NACI will continue to monitor the evidence and update recommendations as needed.

IV.4.3 Interchangeability

NACI recommends that the vaccine series be completed with the same COVID-19 vaccine product.

Currently, no data exist on the interchangeability of COVID-19 mRNA vaccines. However, the spike proteins encoded by either of the authorized mRNA vaccines are stabilized in the same manner to remain in the pre-fusion conformation, though other vaccine components like the lipid nanoparticle and the mRNA sequence may be different. Currently, no data exist on the interchangeability of the AstraZeneca COVID-19 vaccine with other COVID-19 vaccines.

If the vaccine product used for a previously received dose is not known, or not available, attempts should be made to complete the vaccine series with a similar type of COVID-19 vaccine (e.g., complete a series started with an mRNA vaccine with another mRNA vaccine). In the context of limited COVID-19 vaccine supply and the absence of evidence on interchangeability of COVID-19 vaccines, the previous dose may be counted, and the series need not be restarted.

At this time, it is not recommended that vaccines of different types (e.g., mRNA vaccine and viral vector vaccine) be used in the same series, however, studies involving mixed schedules with different vaccines are ongoing. Recommendations on which vaccine product to complete a vaccine series in individuals who have received one dose of the AstraZeneca COVID-19 vaccine will be made immediately after evidence on mixed COVID-19 vaccine schedules is available (expected within 6 weeks). Active surveillance of effectiveness and safety of a mixed schedule are important and these recommendations may change as further evidence becomes available. Accurate recording of vaccines received will be critical. NACI will continue to monitor the evidence and update recommendations as needed.

Refer to Principles of Vaccine Interchangeability in the CIG, Part 1 - Key Immunization Information for additional general information.

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 on the 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.

Anyone receiving the AstraZeneca COVID-19 vaccine should be informed of the recently recognized adverse event of VITT and advised to seek immediate medical attention if they develop symptoms of thromboembolism and/or thrombocytopenia between days 4 and 20 following receipt of the AstraZeneca vaccine (although most occur between days 4 and 14 post-vaccine) \((16)\). 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 Ontario Science Table guidelines).

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 COVID-19 vaccine**

**Frozen vials prior to use**

The Pfizer-BioNTech COVID-19 vaccine must be stored at ultra-low temperatures of -80°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 -80°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 120 hours (5 days) 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 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 12 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 6 hours from the time of first puncture.

**AstraZeneca COVID-19 vaccine**

**Unopened multidose vial**
The AstraZeneca vaccine can be stored between +2°C to +8°C 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 +30°C) or 48 hours in a refrigerator (+2°C to +8°C).

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.

For more information, consult the product leaflet or information contained within the product monograph available through [Health Canada's Drug Product Database](https://www.canada.ca). Refer to [Storage and Handling of Immunizing Agents](https://cig-cip.hc-sc.gc.ca) in the CIG, Part 1 – Key Immunization Information for additional general information.
IV.7 Simultaneous administration with other vaccines

NACI recommends that COVID-19 vaccines should not be given simultaneously with other vaccines (live or inactivated).

Currently, no data exist on the simultaneous administration of COVID-19 vaccine with other vaccines. In the absence of evidence, attempts should be made to avoid simultaneous administration to maximize benefits of COVID-19 vaccination while minimizing any risks of harm, including the potential for immune interference or the erroneous attribution of an adverse event following immunization (AEFI) to a particular vaccine. However, if a COVID-19 vaccine is inadvertently administered at the same time as another vaccine, neither dose should be repeated.

In the absence of evidence, it would be prudent to wait for a period of at least 28 days after each vaccine dose of an mRNA or viral vector COVID-19 vaccine before the administration of another vaccine (except in the case where another vaccine is required for post-exposure prophylaxis) due to the elicitation of an inflammatory cytokine response. It would be prudent to wait for a period of at least 14 days after the administration of another vaccine before administrating a COVID-19 vaccine to prevent erroneous attribution of an AEFI to a particular vaccine.

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 and available 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), and Appendix C (for the AstraZeneca COVID-19 vaccine). Refer to Appendix D 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 D 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, available 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 adults 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.

Systemic

Fatigue, headache, muscle pain, chills, and joint pain are all either common or very common after the administration of the currently authorized, available 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 AstraZeneca COVID-19 vaccine. 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 adults. For AstraZeneca COVID-19 vaccine, systemic reactions are milder and reported less frequently after the second vaccine dose than the first in all age groups.

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, available 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 not a solicited adverse event in the Pfizer-BioNTech or AstraZeneca clinical trials (see Appendix D) but was uncommonly reported after administration of the Pfizer-BioNTech, and AstraZeneca 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 and Thrombocytopenia following Vaccination with the AstraZeneca COVID-19 vaccine

Very rare cases of serious blood clots, including cerebral venous sinus thrombosis, associated with thrombocytopenia have been recently reported globally (with three cases reported out of over 700,000 doses of AstraZeneca COVID-19 vaccine administered in Canada as of April 20, 2021)
following post-licensure use of AstraZeneca COVID-19 vaccine, usually between 4 and 14 days after receipt of vaccine. This adverse event is being referred to as Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT). The exact mechanism by which the AstraZeneca COVID-19 vaccine may trigger VITT is still under investigation but the mechanism appears to be 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. The rate of this adverse event is most commonly estimated to be between 1 per 100,000 and 1 per 250,000 persons vaccinated with the AstraZeneca COVID-19 vaccine. The case fatality rate of VITT depends on prompt detection, diagnoses and treatment and typically ranges between 25 and 40%. For more information, see Appendix C and NACI rapid response: Recommended use of AstraZeneca COVID-19 vaccine in younger adults.

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.

IV.9 Contraindications and Precautions

Rare anaphylactic reactions have been reported following immunization with mRNA COVID-19 vaccines; investigations are ongoing to identify the allergen(s) responsible and the recommendations will be updated as evidence becomes available.

Table 4 lists potential non-medicinal ingredients in authorized, available 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, available COVID-19 vaccines that have been associated with allergic reactions in other products

<table>
<thead>
<tr>
<th>Vaccine product</th>
<th>Potential allergen included in the vaccine or its container</th>
<th>Other products where the potential allergen may be found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer-BioNTech COVID-19 vaccine</td>
<td>polyethylene glycol (PEG) (^a,b,c)</td>
<td>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).</td>
</tr>
<tr>
<td>Moderna COVID-19 vaccine</td>
<td>PEG (^a,b,c)</td>
<td>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).</td>
</tr>
<tr>
<td></td>
<td>tromethamine(^e) (trometamol or Tris)</td>
<td>Component in contrast media, oral and parenteral medications.</td>
</tr>
<tr>
<td>AstraZeneca COVID-19 vaccine</td>
<td>polysorbate 80(^c)</td>
<td>medical preparations (e.g., vitamin oils, tablets, and anticancer agents), cosmetics(^d,f).</td>
</tr>
</tbody>
</table>

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 the AstraZeneca viral vector vaccine. Investigations are ongoing and the recommendations will be updated as evidence becomes available. For more information, refer to Appendix C and NACI rapid response: Recommended use of AstraZeneca COVID-19 vaccine in younger adults.

Contraindications
An authorized COVID-19 vaccine should not be offered routinely to individuals with a history of severe allergic reaction (e.g., anaphylaxis) after previous administration of a COVID-19 vaccine using a similar platform (mRNA or viral vector). If a risk assessment deems that the benefits outweigh the potential risks for the individual; and if informed consent is provided, an authorized COVID-19 vaccine using a different platform may be considered for re-immunization (i.e. individuals with anaphylaxis post mRNA vaccine may be offered a viral vector vaccine and
individuals with anaphylaxis post viral vector vaccine may be offered a mRNA vaccine). If immunization with a different platform is offered, individuals should be observed for at least 30 minutes after immunization.

An authorized COVID-19 vaccine should not be routinely offered to individuals who are allergic to any component of the specific COVID-19 vaccine or its container. For a comprehensive list of components in each authorized COVID-19 vaccine and its container, please consult the corresponding product leaflet or information contained within the product monograph available through Health Canada’s Drug Product Database.

Patients who have experienced major venous or arterial thrombosis with thrombocytopenia following vaccination with AstraZeneca COVID-19 vaccine should not receive a second dose of AstraZeneca COVID-19 vaccine.

Precautions

If a risk assessment deems that the benefits outweigh the potential risks for the individual; and if informed consent is provided; vaccination may be considered 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 COVID-19 vaccines or any of its components. 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 vaccination is chosen, an extended period of observation post-vaccination of at least 30 minutes should be provided for the aforementioned individuals.

Individuals with proven severe allergic reaction (e.g., anaphylaxis) to injectable therapy not related to a component of authorized COVID-19 vaccines (e.g., 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 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.

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.

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.

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, it would be prudent to wait until all symptoms of an acute illness are resolved before vaccinating with an authorized COVID-19 vaccine.

The safety and efficacy of authorized COVID-19 vaccines in pregnancy have not yet been established. Pregnant individuals were excluded from the mRNA and viral vector COVID-19 vaccine clinical trials. Currently, there are limited data on the safety of COVID-19 vaccine from animal developmental and reproductive toxicity studies. In rats that received the Moderna COVID-19 vaccine prior to or during gestation, no safety concerns regarding female reproduction, fetal/embryonal development, or postnatal development were demonstrated. According to a report presented to the European Medicines Agency (EMA), studies in rats using four full doses of the Pfizer-BioNTech COVID-19 vaccine did not indicate adverse effects with respect to fertility, pregnancy, embryo/fetal development, or postnatal development, up to day 21. Developmental and Reproductive Toxicity (DART) animal studies for the AstraZeneca COVID-19 vaccine are ongoing.

Anyone receiving the AstraZeneca COVID-19 vaccine should be informed of the risk of VITT and advised to seek immediate medical attention if they develop symptoms of VITT.

Refer to Contraindications and Precautions in the CIG, Part 2 - Vaccine Safety for additional general information.

IV.10 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.11 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 (2) 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 and available 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, AVAILABLE COVID-19 VACCINES

These recommendations apply only to COVID-19 vaccines currently authorized and currently available for use in Canada (Pfizer-BioNTech COVID-19 vaccine; Moderna COVID-19 vaccine;
AstraZeneca 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. If an mRNA vaccine is contraindicated, another authorized COVID-19 vaccine should be offered.** *(Strong NACI Recommendation)*

2. **NACI recommends that a complete series with the AstraZeneca COVID-19 vaccine may be offered to individuals 30 years of age and older without contraindications, only if the individual does not wish to wait for an mRNA vaccine AND all of the following conditions apply:**
   a) The benefit-risk analysis* determines that the benefit of earlier vaccination with the AstraZeneca COVID-19 vaccine outweighs the risk of COVID-19 while waiting for an mRNA COVID-19 vaccine; AND
   b) The benefits, relative risk* and consequences of VITT and COVID-19 for the individual are clearly outlined, factoring in the anticipated waiting time to receive an mRNA vaccine as well as other effective personal public health measures to mitigate risk of COVID-19, and the individual makes an informed decision based on an understanding about these risks and benefits; AND
   c) There will be substantial delay to receive an mRNA vaccine.

Note: Provinces and territories should adapt the age limit based on their local epidemiology.

*(Discretionary NACI Recommendation)*

*See Risk Assessment Framework below and Management Options Table (Section V.I) to assist with this determination

*Risk Assessment Framework for the use of AstraZeneca COVID-19 vaccine*

The benefit-risk analysis for who to consider offering the AstraZeneca COVID-19 vaccine to while an authorized mRNA COVID-19 vaccine is temporarily unavailable or inaccessible may vary between jurisdictions and individuals and will depend on:

- **Local COVID-19 epidemic conditions** (e.g., consider offering available AstraZeneca COVID-19 vaccine to individuals in regions of moderate, high or very high epidemic transmission or in regions with increasing incidence rates, where immediate protection is needed to prevent symptomatic disease and preserve health system capacity, carefully considering the local transmission potential for viral variants of concern and anticipated protection against them.)
- **Local vaccine supply** (e.g., consider how long an individual will need to wait to be offered an mRNA vaccine, based on available and expected vaccine supply.)
- **Risk of severe illness and death** (e.g., consider offering available AstraZeneca COVID-19 vaccine to individuals at risk of severe illness and death who do not wish to wait to receive mRNA vaccine. The risk of severe outcomes of COVID-19 decreases as age decreases.)
• **Risk of exposure** (e.g., consider offering the available AstraZeneca COVID-19 vaccine to individuals at increased risk of exposure to SARS-CoV-2 due to inability to physically distance or reduced access to infection prevention and control measures who do not wish to wait to receive an mRNA vaccine.)

• **Logistical considerations** (e.g., although the AstraZeneca COVID-19 vaccine is refrigerator-stable, which makes this vaccine easier to store and handle, infrastructure now exists to support the use of ultra-frozen and frozen mRNA vaccines.)

• **Risk of Vaccination-Induced Immune Thrombotic Thrombocytopenia** (e.g., the rate of this adverse event is most commonly estimated to be between 1/100,000 and 1/250,000 persons vaccinated with the AstraZeneca COVID-19 vaccine. The case fatality rate depends on prompt detection, diagnoses and treatment and typically ranges between 25 and 40%. Other predisposing factors for VITT are unclear. NACI continues to monitor evolving evidence.)

• **Vaccine characteristics** (e.g., limited data suggests that all authorized, available vaccines offer protection against hospitalization and likely also death from COVID-19. Results from clinical trials of mRNA vaccines suggest superior efficacy against symptomatic COVID-19 disease compared to the AstraZeneca vaccine. There is evidence that both the Pfizer-BioNTech and AstraZeneca vaccines protect against the B.1.1.7 SARS-CoV-2 variant. In studies in South Africa, the AstraZeneca vaccine did not offer protection against the B.1.351 SARS-CoV-2 variant. Early evidence suggests that the Pfizer-BioNTech vaccine has moderate to high effectiveness against asymptomatic infection, with some evidence available for Moderna as well.)

• **Access to diagnosis and treatment for COVID-19 or VITT** (e.g., consider healthcare system capacity, access to tertiary and ICU care, as well as IVIG for treatment of VITT.)

• **Risk of exacerbating inequities** (e.g., the use of the AstraZeneca COVID-19 vaccine may increase inequities for individuals with limited ability to reduce their personal risk of infection or who work in occupations with direct close physical contact with the public, and due to the complexities of making an informed choice with regard to the risk and benefits of earlier vaccination with the AstraZeneca COVID-19 vaccine. Consider the impact of exacerbating inequities in these populations, many of whom belong to marginalized and disadvantaged groups disproportionately affected by the pandemic.)

Refer to the Management Options Table for COVID-19 vaccines authorized and available for use in Canada (**Section V.I**) 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 16 years of age and older (Pfizer-BioNTech COVID-19 vaccine) and in individuals 18 years of age and older (Moderna COVID-19 vaccine). A non-replicating viral vector vaccine is authorized and available for use in Canada for individuals 18 years of age and older (AstraZeneca COVID-19 vaccine).
- A complete series for all currently authorized and available COVID-19 vaccines is two doses.
- 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 to 95%) 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 VOC first identified in
the UK. 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).
- 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).

AstraZeneca 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 vaccine has a vaccine efficacy of 74.6% against the B.1.1.7
VOC first identified in the UK (compared to 84.1% against the non-B.1.1.7 strain).
Published data suggests a vaccine efficacy of 10.4% against mild to moderate illness from
the B.1.351 VOC first detected in South Africa.
- 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.
Rare but serious cases of blood clots, including cerebral venous sinus thrombosis,
associated with thrombocytopenia have been recently reported globally (with three cases
reported out of over 700,000 doses of AstraZeneca COVID-19 vaccine administered in
Canada as of April 20, 2021) following post-licensure use of AstraZeneca COVID-19
vaccine, usually between 4 and 14 days after receipt of vaccine. This adverse event is
being referred to as Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT). The
exact mechanism by which the AstraZeneca COVID-19 vaccine may trigger VITT is still
under investigation. The case fatality rate typically ranges between 25 and 40%.
• 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 $\geq 30$ kg/m$^2$).

**mRNA COVID-19 vaccines versus AstraZeneca COVID-19 vaccine**

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 $^2$ of its recommendations for the use of COVID-19 vaccines in Canada. NACI assessed the risk of being admitted to the ICU and dying from VITT compared to COVID-19 ICU admissions and deaths that could be prevented by an early dose of AstraZeneca vaccine (instead of waiting for an mRNA vaccine given Canada’s expected vaccine supply) by age across various COVID-19 epidemiologic scenarios (very low, low, moderate, high, very high activity). Please see Appendix E for details and limitations. Given the low numbers of events reported for VITT, there is a high level of uncertainty in the incidence of this adverse event by age group. Initial data suggested there may be a trend for increasing incidence of VITT with decreasing age, but this could be due to differences in reporting and vaccination with AstraZeneca in different age groups. While the epidemiology of COVID-19 may evolve with the circulation of VOCs, evidence to date reveals the risk of severe disease associated with COVID-19 increases with age, with younger adults at lower risk of hospitalization and death. NACI will continue to monitor the epidemiology of COVID-19 and reassess these recommendations as mRNA COVID-19 vaccine supply increases.

Upon analysis of the information available, NACI concluded that given an expected increase in mRNA vaccine supplies and their associated timelines, the differences in the epidemiology and risk of COVID-19 across Canada and between populations, and because of the evolving evidence for VITT, there is uncertainty in the evidence of advantages and disadvantages of the use of AstraZeneca COVID-19 vaccine in vaccine programs for all Canadians. Therefore, NACI made a discretionary recommendation on the use of AstraZeneca COVID-19 vaccine for individuals 30 years of age and older who do not wish to wait for an mRNA vaccine, only if certain conditions are met (including a benefit-risk analysis, informed consent, and substantial delay for receipt of an mRNA vaccine). NACI summarized various factors (in addition to age) to consider to facilitate a benefit-risk analysis by jurisdictions in its Risk Assessment Framework for the use of AstraZeneca COVID-19 vaccine. As demonstrated in Appendix E, the rate of ICU admission from COVID-19 potentially prevented by the AstraZeneca COVID-19 vaccine may be higher than the rate of ICU admission from VITT in areas of moderate, high, or very high COVID-19 activity and in areas where the COVID-19 incidence rate is increasing, in some circumstances (considering other individual risk factors such as risk of exposure, summarized in the Risk Assessment Framework). NACI cautions that in age groups younger than 30 years of age, the benefit of offering AstraZeneca COVID-19 vaccine instead of waiting for an mRNA vaccine is not a certainty, especially in areas of very low COVID-19 activity. On the other hand, the advantages of highly efficacious mRNA COVID-19 vaccines, with no safety signals of concern to date, clearly outweigh any possible disadvantages for most populations, and NACI made a strong recommendation for the preferential use of mRNA COVID-19 vaccines in all authorized age groups.

A summary of the evidence and rationale for NACI’s strong preferential recommendation for the use of mRNA COVID-19 vaccines in population-level programs and discretionary recommendation for the use of the AstraZeneca COVID-19 vaccine for individuals 30 years of age and older who do not wish to wait for an mRNA vaccine is below:
**Epidemiology**: The epidemiology and risk of COVID-19 vary across Canada and between populations. The incidence of cases due to VOC in Canada is increasing, particularly among younger individuals, but differences in risk for severe outcomes due to VOC by age group have yet to be determined. NACI will continue to monitor the evolving epidemiology. The benefit of the AstraZeneca COVID-19 vaccine increases in regions of moderate, high, or very high epidemic transmission of SARS-CoV-2 strains for which this vaccine offers protection and in areas of increasing COVID-19 incidence rates.

**Efficacy and Effectiveness**: Emerging data suggests that all authorized, available 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 AstraZeneca COVID-19 vaccine. There is evidence that both the Pfizer and AstraZeneca COVID-19 vaccines offer protection against the B.1.1.7 SARS-CoV-2 variant. Pfizer seems to offer protection against the B.1.351 SARS-CoV-2 VOC, but not the AstraZeneca COVID-19 vaccine. There is limited evidence on the protection of mRNA or AstraZeneca COVID-19 vaccines against the P.1 variant.

**Safety and VITT**: Evidence on the association between VITT following vaccination with the AstraZeneca COVID-19 vaccine is evolving but the association has been confirmed. Several countries have paused the AstraZeneca COVID-19 vaccination program while others have restricted its use to certain age groups (from 30 years and over to 70 years and over). No clear pattern or predisposing risk factors have been identified to date among cases of VITT.

**Public health benefit-risk assessment**: An age-based benefit-risk analysis was conducted to determine if the benefit of earlier vaccination with the AstraZeneca COVID-19 vaccine (instead of waiting for an mRNA vaccine) outweighs the risk of harms from VITT across various levels of COVID-19 activity (very low, low, moderate, high, very high). At the time the analysis was conducted, the risk of severe COVID-19 outcomes (such as ICU admissions and death) exceeded the risk of VITT in adults 30 to 69, in areas of moderate, high or very high epidemiology. The benefits of earlier vaccination with AstraZeneca COVID-19 vaccine were less clear in younger age groups in these areas. A benefit-risk assessment was not completed for adults 70 years or older as mRNA vaccine is already available to this age group in Canada. Refer to Appendix E for details on, and limitations of, this analysis.

**Ethics**: NACI consulted with the Public Health Ethics Consultative Group (PHECG) on the ethical considerations for restricting the use of the AstraZeneca 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 (e.g., enabling respect for persons and autonomy by incorporating informed consent into the discretionary recommendation for use of AstraZeneca vaccine; promoting justice and equity by specifically identifying risks to exacerbating inequities in the Risk Assessment Framework).

**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. Populations that receive the AstraZeneca COVID-19 vaccine may have 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). The risk of COVID-19 to individuals and their families who have limited ability to reduce their personal risk of infection or who work in occupations with direct close physical contact with the public, the anticipated waiting time for an mRNA vaccine, and the individual’s risk tolerance to wait for an mRNA vaccine should be considered. This may vary across Canada and between populations, so the Risk Assessment Framework may be used to assist with decision-making.

- **Feasibility**: NACI considered the impact of its recommendations on the successful implementation of COVID-19 immunization programs in the local setting with available resources. Canada has procured and is expecting enough supply of mRNA vaccines to enable vaccination of currently eligible Canadian population before fall 2021, with enough supply to enable all eligible Canadians to receive their first dose by June 2021. Expected supplies of AstraZeneca COVID-19 vaccines for Canada are minimal in comparison to expected supplies of mRNA vaccines in the coming weeks. Therefore, the anticipated waiting time to receive an mRNA vaccine will soon be reduced but may vary between populations and across jurisdictions. While the mRNA COVID-19 vaccines have more challenging storage and transportation requirements than the AstraZeneca COVID-19 vaccine, infrastructure now exists to support the use of ultra-frozen and frozen mRNA vaccines.

- **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 suggested 44-60% of Canadians had no preference on which vaccine they received, surveys conducted in April found that Canadians who are planning to get vaccinated are far more comfortable with the mRNA vaccines (90-92%) than the AstraZeneca vaccine (41%) (17). 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.

3. **Based on emerging evidence of the protection provided by the first dose of a two-dose series for COVID-19 vaccines currently authorized and available in Canada, NACI recommends that in the context of limited COVID-19 vaccine supply and ongoing pandemic disease, jurisdictions should maximize the number of individuals benefiting from the first dose of vaccine by extending the second dose of COVID-19 vaccine up to four months after the first. Second doses should be offered as soon as possible after all eligible populations have been offered first doses, with priority given to those at highest risk of severe illness and death from COVID-19 disease. Vaccinated people (with one or two doses) should continue to follow recommended public health measures. NACI will continue to monitor the evidence on effectiveness of an extended dose interval and will adjust recommendations as needed.** *(Strong NACI Recommendation)*
Jurisdictions may choose to shorten the time between the first and second dose of a two-dose series for COVID-19 vaccines in specific population groups based on their local epidemiology, vaccine supply and vaccine delivery mechanisms.

Summary of evidence and rationale:

- Morbidity and mortality from COVID-19 is ongoing and vaccine supply is limited. Extending the interval to the second dose allows vaccination of the largest number of people as quickly as possible, providing more people with direct protection and the possibility of indirect and community protection.
- An extended interval of up to four months allows as many eligible populations as possible to be offered vaccination with one dose before proceeding to offer second doses. However, as soon as all eligible groups have been offered their first dose of vaccine, second doses should be offered. The interval between first and second dose should not be extended any longer than needed to offer first doses of vaccine to all eligible individuals.
- This recommendation applies to all two-dose COVID-19 vaccines currently authorized for use and available in Canada.
- Current evidence suggests very good vaccine efficacy against symptomatic COVID-19 from one dose of COVID-19 vaccines, with good effectiveness shown in observational studies (generally between 60 and 80%, with some lower and higher estimates) against symptomatic disease and/or asymptomatic infection, as well as very good effectiveness against hospitalization (approximately 80%) and death (approximately 85% based on one study from the UK). While two doses of mRNA vaccines have shown excellent efficacy and effectiveness, one dose of mRNA vaccines appear to perform similarly to one or two doses of the AstraZeneca vaccine.
- Effectiveness has been documented for up to two months after the first dose of the mRNA vaccines, and the AstraZeneca clinical trial publication modelled one-dose efficacy up to 90 days after vaccination.
- Informed expert opinion based on principles of immunology indicate that a longer interval between priming and boosting doses of a vaccine series results in a better, more durable response. The AstraZeneca COVID-19 vaccine clinical trial demonstrated optimal efficacy when the interval between the first and second doses was ≥12 weeks.
- In situations where informed consent included assumptions about second dose timing, jurisdictions may consider offering second doses at shorter intervals for those who provided consent for the vaccine series prior to implementation of this recommendation.
- Because of ongoing disease transmission and less than complete individual protection from vaccination in either one-dose or two-dose vaccinated people, ongoing compliance with public health measures (masking, physical distancing and limiting social interactions as per public health guidance) should continue at this time.
- The vaccine effectiveness of the first dose will be monitored closely and the decisions regarding the second dose will be continuously assessed based on surveillance and effectiveness data and post-implementation study designs. In addition, effectiveness against variants of concern will also be monitored closely. If indicated based on these data, recommendations will be revised to offer earlier second doses to some cohorts or population groups.

Please see NACI’s Statement on Extended dose intervals for COVID-19 vaccines to optimize early vaccine rollout and population protection in Canada for a summary of the evidence and further rationale for this recommendation.
4. NACI recommends that all individuals should continue to practice recommended public health measures for prevention and control of SARS-CoV-2 infection and transmission regardless of vaccination with COVID-19 vaccine, at this time. (Strong NACI Recommendation)

**Summary of evidence and rationale**
- Currently, there is insufficient evidence on the duration of protection of COVID-19 vaccines and the effectiveness of COVID-19 vaccines in reducing transmission of SARS-CoV-2. Evidence of protection against asymptomatic SARS-CoV-2 infection is emerging for the mRNA vaccines, but the evidence is insufficient at this time to recommend discontinuation of public health measures. NACI will continue to monitor the evidence and update recommendations as needed.
- Although effectiveness against symptomatic disease and/or asymptomatic infection appears to be very high for two doses of mRNA vaccines (~90-95%), some individuals will still remain susceptible even after two doses of vaccine. One dose of an mRNA vaccine and one or two doses of the AstraZeneca vaccine have good, but somewhat lower, effectiveness, and does not appear to protect against asymptomatic infection based on clinical trial results. Therefore adherence to public health measures in vaccinated individuals (one or two doses) remains very important at this time when SARS-CoV-2 continues to circulate widely.
- Evidence of protection offered by COVID-19 vaccines against VOC is evolving (see Table 5).
- There is evidence to support the effectiveness of other recommended public health measures in pre-exposure and post-exposure scenarios, including physical distancing, masking, hand hygiene, as well as isolation and quarantine.
- Currently, there is no evidence on the use of COVID-19 vaccine for post-exposure prophylaxis.
- **Federal**, provincial/territorial, and local public health measures for the prevention and control of SARS-CoV-2 should continue to be followed.

5. 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. In the context of limited vaccine supply, initial doses may be prioritized for those who have not had a 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.
- Currently, there is a lack of evidence on potential differences in vaccine efficacy or safety between those with and without prior evidence of SARS-CoV-2 infection. 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 in this population is uncertain.
- The immune response to SARS-CoV-2, including duration of immunity, is not yet well understood. Reinfections with SARS-CoV-2 have been reported and research to establish the severity, frequency, and risk factors of reinfection with SARS-CoV-2 is ongoing.
- In the context of limited supply, to allow for the protection of a larger number of at-risk individuals, vaccination with a COVID-19 vaccine may be delayed for 3 months following a PCR-confirmed infection, as reinfections reported to date have been rare within the first
three months following infection. However, if challenging from a feasibility perspective, jurisdictions may elect to disregard prior PCR-confirmed SARS-CoV-2 infection status and vaccinate everyone in a given target group.

- 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 it is prudent to wait until all symptoms of an acute illness are completely resolved before vaccinating with COVID-19 vaccine, as well as ensuring that the individual is no longer considered infectious based on current criteria.

- NACI will continue to monitor the evidence regarding vaccination in those previously infected with SARS-CoV-2 and will update recommendations as needed.

**NACI also makes the following recommendations for COVID-19 immunization in some specific populations who were either excluded from or were represented by small numbers of participants in clinical trials.** Vaccine may be offered to some individuals in these populations in some circumstances on a case-by-case basis with a risk-benefit analysis (where the risk of exposure and/or severe COVID-19 disease outweighs the risk of vaccination), and with transparency about the insufficiency of evidence. Preference for mRNA COVID-19 vaccine (as outlined in Recommendation #1, above), if available, also applies to the populations described below. These recommendations may change as more evidence becomes available.

### Immunosuppressed persons

6. **NACI recommends that a complete COVID-19 vaccine series may be offered to individuals who are immunosuppressed due to disease or treatment in the authorized age group if a risk assessment deems that the benefits outweigh the potential risks for the individual, and if informed consent includes discussion about the limited evidence on the use of COVID-19 vaccines in this population and the possibility that individuals who are immunosuppressed may have a diminished immune response to any of the authorized COVID-19 vaccines. (Discretionary NACI Recommendation)**

### Summary of evidence and rationale

- Currently, there is limited evidence that immunosuppression is an independent risk factor for severe COVID-19, though evidence is evolving. A rapid review of evidence from OECD member countries found a low certainty of evidence for no association with mortality or hospitalization due to COVID-19 in those with unspecified immunosuppression. The review found a low certainty of evidence for at least a two-fold increase in mortality due to COVID-19 for those with sickle cell disease or severe immunodeficiency; metastatic cancer; chemotherapy in the past 12 months or radiotherapy in the past 6 months; solid organ, bone marrow, or stem cell transplant. 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.

- Currently, there are no data on COVID-19 vaccination in individuals who are immunosuppressed. 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.
• No safety signals of concern have been noted to date in non-immunosuppressed participants with an immunocompromising condition (e.g., stable HIV infection) included in the clinical trials.

• 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. Therefore, the balance of benefits and risks must be made on a case-by-case basis.

• Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the vaccine.

• In general, non-replicating vaccines may be administered to immunocompromised people because the antigens in the vaccine cannot replicate. However, the magnitude and duration of vaccine-induced immunity are often reduced. It is currently unknown whether immunocompromised individuals will be able to mount an immune response to the authorized COVID-19 vaccines.

• People living with HIV who are considered immunocompetent may be vaccinated.

• 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 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 recommends that a complete vaccine series with a COVID-19 vaccine may be offered to individuals with an autoimmune condition in the authorized age group if a risk assessment deems that the benefits outweigh the potential risks for the individual, and if informed consent includes discussion about the limited evidence on the use of COVID-19 vaccines in these populations. (*Discretionary NACI Recommendation*)

**Summary of evidence and rationale**

- The evidence that having an autoimmune condition is an independent risk factor for severe COVID-19, is evolving. A rapid review of evidence from OECD member countries found strong evidence (of moderate or high 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 found a low certainty of evidence of little or no association with mortality and a moderate certainty of evidence for little or no association with hospitalization from COVID-19 in those with rheumatoid arthritis, rheumatic disease, or systemic lupus erythematosus. Caution should be taken when interpreting low certainty evidence (5). 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.
- Currently, there are very limited data on COVID-19 vaccination in individuals who have an autoimmune condition. 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.
- 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. Therefore, the balance of benefits and risks must be made on a case-by-case basis.
- 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.
- 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**

8. NACI recommends that a complete vaccine series with a COVID-19 vaccine may be offered to pregnant individuals in the authorized age group if a risk assessment deems that the benefits outweigh the potential risks for the individual and the fetus, and if informed consent includes discussion about the limited evidence on the use of COVID-19 vaccines in this population. (*Discretionary NACI Recommendation*)
9. NACI recommends that a complete vaccine series with a COVID-19 vaccine may be offered to individuals in the authorized age group who are breastfeeding if a risk assessment deems that the benefits outweigh the potential risks for the individual and the infant, and if informed consent includes discussion about the limited evidence on the use of COVID-19 vaccines in this population. *(Discretionary NACI Recommendation)*

**Summary of evidence and rationale**

- The evidence of pregnancy as an independent risk factor for severe COVID-19 is evolving. A rapid review of evidence from 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). 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.

- Currently, there are no data on the safety and efficacy of COVID-19 vaccines in pregnancy or during breastfeeding. Pregnant or breastfeeding individuals were excluded from the mRNA and viral vector COVID-19 vaccine clinical trials.

- Currently, there are no data to inform outcomes of inadvertent administration of COVID-19 vaccine to pregnant individuals or their developing fetus in clinical trials. Outcomes in participants who became pregnant during the clinical trials and fetal outcomes will be reported through registries and NACI will reconsider recommendations when these data become available.

- It is unknown whether the vaccines are excreted in human milk, but there are no data on outcomes in breastfeeding individuals or their breastfed infants. There have been no theoretical concerns about these vaccines in breastfeeding individuals or their breastfed infants.

- Currently, there are limited data on the safety of COVID-19 vaccine from animal developmental and reproductive toxicity studies. In rats that received the Moderna COVID-19 vaccine prior to or during gestation, no safety concerns regarding female reproduction, fetal/embryonal development, or postnatal development were demonstrated. According to a report presented to the European Medicines Agency (EMA), studies in rats using four full doses of the Pfizer-BioNTech COVID-19 vaccine did not indicate adverse effects with respect to fertility, pregnancy, embryo/fetal development, or postnatal development, up to day 21. Developmental and Reproductive Toxicity (DART) animal studies for the AstraZeneca COVID-19 vaccine are ongoing.

- Individuals who are pregnant, breastfeeding, or of reproductive age may be at increased risk of exposure to SARS-CoV-2 (e.g., healthcare or essential workers) and/or at increased risk of severe COVID-19 disease (e.g., due to pre-existing medical condition, body mass index of 40 or more) and may wish to be vaccinated despite the lack of evidence of COVID-19 vaccination in pregnancy or during breastfeeding in order to protect themselves. Therefore, the balance of benefits and risks must be made on a case-by-case basis.

- There is currently no evidence to guide the time interval between the completion of the COVID-19 vaccine series and conception. In the face of scientific uncertainty, it may be prudent to delay pregnancy by 28 days or more after the administration of the complete two-dose vaccine series of a COVID-19 vaccine. A COVID-19 vaccine may be administered any time after pregnancy.
- Individuals who become pregnant during their vaccine series or shortly thereafter should not be counselled to terminate pregnancy based on having received a COVID-19 vaccine.
- If pregnancy is determined after initiation of the vaccination series, completion of the series may be delayed until after pregnancy, unless risk factors for increased exposure or severe COVID-19 are present and informed consent for vaccination is obtained as above. NACI also encourages additional research and surveillance of COVID-19 vaccination in pregnancy.
- Eligible individuals should be offered a complete vaccine series with an authorized COVID-19 vaccine post-partum and prior to attempting pregnancy so that the recommended interval between completion of the vaccine series and conception is maintained.
- Vaccine recipients and health care providers are encouraged to report COVID-19 vaccine during pregnancy or breastfeeding to the local public health authority as well as to the vaccine manufacturer for follow-up. 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 Pregnancy and Breastfeeding, Part 3 – Vaccination of Specific Populations of the CIG for additional general information.

Children and Adolescents

10. NACI recommends that COVID-19 vaccines should not be offered routinely to individuals who are not in the authorized age group. (Strong NACI Recommendation).

  a. However, a complete vaccine series with a Pfizer-BioNTech may be offered to individuals 12-15 years of age who are at very high risk of severe outcomes of COVID-19 (e.g., due to a pre-existing medical condition known to be associated with increased risk of hospitalization or mortality) or are at increased risk of exposure (e.g., due to living in a congregate care facility), if a risk assessment deems that the benefits outweigh the potential risks for the individual, and if informed consent with the individual and the parent or guardian includes discussion about the insufficiency of evidence on the use of COVID-19 vaccines in this population. (Discretionary NACI Recommendation)

Summary of evidence and rationale

- Evidence to date suggests that in general, children infected with SARS-CoV-2 are not at increased risk of severe disease. A rapid review of evidence from OECD member countries found a low certainty of evidence of at least a two-fold increase in hospitalizations due to COVID-19 among children (≤18 years of age) with obesity, hypertension, or immunodeficiency, compared to children without these conditions. Caution should be taken when interpreting low certainty evidence.
- Evidence on COVID-19 vaccination in those less than 12 years of age is absent, and only limited clinical data on the use of the Pfizer-BioNTech COVID-19 vaccine in those aged 12 to 15 years is available. The Moderna COVID-19 vaccine and AstraZeneca COVID-19 vaccine clinical trial results have to date only included adults 18 years of age and older. Clinical trials in children less than 18 years of age have been initiated and are ongoing; NACI is monitoring the evidence and will update recommendations when results become available.
- For adolescents with certain pre-existing medical conditions compounded by an increased risk of exposure to SARS-CoV-2 (e.g., due to living in a congregate setting such as a
group home), the balance of risks and benefits of vaccination with a COVID-19 vaccine must be made on a case-by-case basis.

- Active surveillance in these vaccine recipients is strongly encouraged. NACI will monitor the evidence as it evolves, and update recommendations as needed.

**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.

Refer to Vaccine Safety and Pharmacovigilance in the CIG, Part 2 – Vaccine Safety for additional information.

**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 MANAGEMENT OPTIONS FOR COVID-19 VACCINES AUTHORIZED AND AVAILABLE FOR USE IN CANADA

There are currently three authorized COVID-19 vaccines that are available in Canada for the prevention of symptomatic COVID-19 that use two different vaccine platforms. To assist with the decision on which vaccine to offer to different populations or groups, a comparison of the relative merits of both have been summarized in Table 5 below. Caution should be taken when comparing vaccines due to differences in studies conducted for each vaccine (e.g., different endpoints, different analyses, different time periods/countries and circulating strains).

Table 5. Management options for types of COVID-19 vaccines authorized and available for use in Canada

<table>
<thead>
<tr>
<th>Factor for consideration</th>
<th>Summary of available evidence and issues for consideration</th>
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<tbody>
<tr>
<td><strong>Efficacy and Effectiveness</strong></td>
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<tr>
<td><strong>Efficacy against symptomatic illness after a complete series</strong></td>
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<tr>
<td>- Pfizer-BioNTech vaccine is overall 94% efficacious ≥14 days after dose 2 in study participants 18 years of age and older. Data suggests the Pfizer/BioNTech vaccine is 95% efficacious in participants ≥65 years of age 7 or more days after dose 2.</td>
<td>- AstraZeneca SD/SD vaccine is 62% efficacious in participants 18 to 64 years of age.</td>
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<tr>
<td>- Moderna vaccine is overall 94% efficacious in participants 18 years of age and older ≥14 days after dose 2.</td>
<td>- Current data from clinical trials are insufficient to determine the efficacy of the AstraZeneca vaccine in individuals ≥65 years of age.</td>
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<tr>
<td>- Data suggests the Moderna vaccine is 86% efficacious in individuals ≥65 years of age ≥14 days after dose 2.</td>
<td>- 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.</td>
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<tr>
<td><strong>Effectiveness against symptomatic illness and hospitalization</strong></td>
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<td>- Current data from real-world studies suggests that mRNA COVID-19 vaccines provide good protection against COVID-19 hospitalization &gt;14 days after the first dose, including in older populations (≥65 years).</td>
<td>- 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.</td>
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<tr>
<td>- Data from real-world studies provide some evidence that the first dose of mRNA COVID-19 vaccines provide very good protection against COVID-19-related death.</td>
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<tr>
<td>- Limited data from real-world studies suggests the Pfizer-BioNTech COVID-19 vaccine has high vaccine effectiveness &gt;7 days after the second dose against severe disease and COVID-19 related hospitalization.</td>
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### Summary of available evidence and issues for consideration

<table>
<thead>
<tr>
<th>Factor for consideration</th>
<th>mRNA COVID-19 Vaccines</th>
<th>Non-replicating viral vector COVID-19 Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effectiveness data</strong></td>
<td>Effectiveness data on the Moderna COVID-19 vaccine alone is not currently available.</td>
<td>Efficacy against asymptomatic infection</td>
</tr>
<tr>
<td><strong>Efficacy against asymptomatic infection</strong></td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td><strong>Effectiveness against asymptomatic infection</strong></td>
<td>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 (9, 14). Similar results were reported for mRNA COVID-19 vaccines in general (15).</td>
<td></td>
</tr>
<tr>
<td><strong>Re-vaccination</strong></td>
<td>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 particular with the emergence of variants of concern.</td>
<td>Re-vaccination</td>
</tr>
<tr>
<td></td>
<td>Re-vaccinating those who initially received an mRNA vaccine with the same or another mRNA vaccine is currently being investigated.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>Humoral responses for both mRNA COVID-19 vaccines peaked after a second dose, including elicitation of neutralizing antibodies. However, as a correlate of protection is not known,</td>
<td>Humoral response</td>
</tr>
</tbody>
</table>
### Summary of available evidence and issues for consideration

<table>
<thead>
<tr>
<th>Factor for consideration</th>
<th>mRNA COVID-19 Vaccines</th>
<th>Non-replicating viral vector COVID-19 Vaccine</th>
</tr>
</thead>
</table>
| Humoral responses        | these humoral responses cannot be interpreted as corresponding with protection.  
- Humoral responses had similar trends in individuals 18 to 55 years of age and individuals 65 to 85 years of age. | responses peaked at the first dose and maintained or decreased at the second dose.  
- For the AstraZeneca vaccine, humoral responses 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.  
- 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.  
- As no immunological correlate of protection has been determined for SARS-CoV-2, these cellular responses cannot be interpreted as corresponding with vaccine protection. | 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.  
- 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

<table>
<thead>
<tr>
<th>Variant</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B.1.1.7 (identified in UK)</strong></td>
<td></td>
</tr>
</tbody>
</table>
- In countries where B.1.1.7 was the dominant circulating strain (>90% of sequenced samples), estimates of vaccine effectiveness of the Pfizer-BioNTech vaccine were comparable to vaccine efficacy against the parent strain.  
- Data suggest AstraZeneca vaccine has a vaccine efficacy against B.1.1.7 that is comparable to that against non-B.1.1.7 disease (74.6% vs. 84.1% respectively). |
| **B.1.351 (identified in South Africa)** |  
- There is emerging data on the efficacy or effectiveness of mRNA vaccines against B.1.351.  
- Data suggest AstraZeneca vaccine has a vaccine efficacy of 10.4% against B.1.351 against mild to moderate illness. |
| **P.1 and P.2 (identified in Brazil)** |  
- There is limited data on the efficacy or effectiveness of mRNA vaccines against P.1 (variant of concern) and P.2 (variant of interest).  
- There is limited data on the efficacy or effectiveness of viral vector vaccines against P.1. |
### Summary of available evidence and issues for consideration

<table>
<thead>
<tr>
<th>Factor for consideration</th>
<th>mRNA COVID-19 Vaccines</th>
<th>Non-replicating viral vector COVID-19 Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Technology</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Safety Signals</td>
<td>There have been no serious safety signals identified with either mRNA vaccine. Rare anaphylactic reactions have been reported following immunization with mRNA COVID-19 vaccines.</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>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.</td>
<td>For the AstraZeneca vaccine, rare cases of thrombosis and thrombocytopenia have been reported during post-licensure use. The mechanism of action appears to be a spontaneous form of heparin-induced thrombocytopenia (called VITT - Vaccine-Induced Immune Thrombotic Thrombocytopenia). The rate of this adverse event is still to be confirmed but is most commonly estimated to be between 1/100,000 and 1/250,000 people vaccinated with AstraZeneca vaccine. Case fatality of VITT depends on prompt detection, diagnoses and treatment and typically ranges between 25 and 40%.</td>
</tr>
<tr>
<td><strong>Ethics and Equity</strong></td>
<td>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.</td>
<td>Offering any COVID-19 vaccine to those who would otherwise have to wait to receive one could enhance equity.</td>
</tr>
<tr>
<td></td>
<td>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.</td>
<td>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 the AstraZeneca vaccine compared to mRNA vaccines, depending on which population groups received the AstraZeneca vaccine.</td>
</tr>
</tbody>
</table>
## RECOMMENDATIONS ON THE USE OF COVID-19 VACCINES

<table>
<thead>
<tr>
<th>Factor for consideration</th>
<th>Summary of available evidence and issues for consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mRNA COVID-19 Vaccines</td>
</tr>
<tr>
<td></td>
<td>• 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 infection, should take into consideration trust, justice, and the risk of doing harm vs good.</td>
</tr>
<tr>
<td>Feasibility</td>
<td>Vaccine schedule</td>
</tr>
<tr>
<td></td>
<td>• Both mRNA vaccines are given as a two-dose series.</td>
</tr>
<tr>
<td></td>
<td>• 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. NACI has recommended an extended interval between the first and second dose of up to 4 months to maximize the number of individuals who can be vaccinated as quickly as possible with available vaccine supplies. This could allow for more individuals to receive one dose of the vaccine and have some protection against symptomatic COVID-19 disease.</td>
</tr>
<tr>
<td></td>
<td>Storage requirements</td>
</tr>
<tr>
<td></td>
<td>• 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.</td>
</tr>
<tr>
<td></td>
<td>• 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.</td>
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<tr>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor for consideration</td>
<td>Summary of available evidence and issues for consideration</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td><strong>mRNA COVID-19 Vaccines</strong></td>
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<td></td>
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<td></td>
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</tbody>
</table>

**Concerns about vaccine safety and effectiveness are the two most cited reasons for vaccine refusal** \(^{(21)}\)
- In a survey of Canadians conducted between February 9 and 16, 2021 \(^{(22)}\), 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 (late May-early June).
  - 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 \((n=691)\) \(^{(23)}\)
- In a survey of health care providers conducted on Dec 4-13, 2020 \(^{(24)}\), the most important factors reported to influence the decision to receive vaccine were vaccine safety \((95.5\%)\), followed by vaccine effectiveness \((86.7\%)\) \((n=14,336)\)
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 duration 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)?

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 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?

6. 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?

c. Are immunoglobulin (Ig)A/IgG/IgM antibodies protective against SARS-CoV-2 and what is the correlate of protection?

7. 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 herd immunity to protect non-vaccinated individuals, and remove PHM controls. What vaccine characteristics play the largest role on these milestones (i.e., efficacy, durability, uptake)?

8. 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?

9. 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?

10. Are any components of the COVID-19 vaccine at high risk of inducing an anaphylactic reaction?

11. 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? What is the trigger for the development of this adverse event following immunization and what can be done to mitigate its development?

12. 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?

13. 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?

14. Does vaccination have an impact on the transmissibility of SARS-CoV-2 in individuals with asymptomatic infection?

15. What is the role of seasonal attenuation of SARS-CoV-2?

16. How does vaccination impact individual-level variation in transmission (e.g., superspreaders)?

17. 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?
18. What are the epidemiological characteristics of breakthrough illness (e.g., vaccine recipient characteristics, SARS-CoV-2 VOC)?

**Vaccine Administration**

19. Are any COVID-19 vaccines interchangeable to complete a regular vaccine series? What is the efficacy, effectiveness, immunogenicity and safety of a mixed dose schedule or a mixed dose booster series?

20. 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?

21. Are any other vaccines (e.g., Bacillus Calmette-Guérin) protective against COVID-19 through off-target effects?

22. Can COVID-19 vaccine be simultaneously administered with other, non-COVID-19 vaccines (either live or inactivated vaccines)? If not, what is the minimum interval between administrations?

23. Can COVID-19 vaccines be given in individuals who have received convalescent plasma or anti-SARS-CoV-2 spike protein monoclonal antibodies? If so, what is the minimum interval required for vaccine administration following receipt of convalescent plasma or 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 directly targeted by vaccination and in populations not directly targeted by immunization?

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

<table>
<thead>
<tr>
<th>Strength of NACI Recommendation based on factors not isolated to strength of evidence (e.g., public health need)</th>
<th>STRONG</th>
<th>DISCRETIONARY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wording</strong></td>
<td>“should/should not be offered”</td>
<td>“may/may not be offered”</td>
</tr>
<tr>
<td><strong>Rationale</strong></td>
<td>Known/anticipated advantages outweigh known/anticipated disadvantages (“should”), OR Known/Anticipated disadvantages outweigh known/anticipated advantages (“should not”)</td>
<td>Known/anticipated advantages are closely balanced with known/anticipated disadvantages, OR uncertainty in the evidence of advantages and disadvantages exists</td>
</tr>
<tr>
<td><strong>Implication</strong></td>
<td>A strong recommendation applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present.</td>
<td>A discretionary recommendation may/may not be offered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.</td>
</tr>
</tbody>
</table>
### LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>AEFI</td>
<td>Adverse event following immunization</td>
</tr>
<tr>
<td>ARCHE</td>
<td>Alberta Research Center for Health Evidence</td>
</tr>
<tr>
<td>CDC</td>
<td>Centres for Disease Control and Prevention (United States)</td>
</tr>
<tr>
<td>ChAd</td>
<td>Chimpanzee Adenovirus</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CIC</td>
<td>Canadian Immunization Committee</td>
</tr>
<tr>
<td>CIG</td>
<td>Canadian Immunization Guide</td>
</tr>
<tr>
<td>COVID-19</td>
<td>Coronavirus disease 2019</td>
</tr>
<tr>
<td>CVST</td>
<td>Cerebral venous sinus thrombosis</td>
</tr>
<tr>
<td>DART</td>
<td>Developmental and Reproductive Toxicity</td>
</tr>
<tr>
<td>DIC</td>
<td>Disseminated intravascular coagulation</td>
</tr>
<tr>
<td>EEFA</td>
<td>Ethics, Equity, Feasibility, and Acceptability</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of Recommendations, Assessment, Development and Evaluation</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>IM</td>
<td>Intramuscular</td>
</tr>
<tr>
<td>Ig</td>
<td>Immunoglobulin</td>
</tr>
<tr>
<td>IGRA</td>
<td>Interferon gamma release assay</td>
</tr>
<tr>
<td>JCVI</td>
<td>Joint Committee on Vaccination and Immunisation (UK)</td>
</tr>
<tr>
<td>MAAE</td>
<td>Medically attended adverse event</td>
</tr>
<tr>
<td>MenACWY</td>
<td>Quadrivalent meningococcal vaccine</td>
</tr>
<tr>
<td>mRNA</td>
<td>messenger ribonucleic acid</td>
</tr>
<tr>
<td>NACI</td>
<td>National Advisory Committee on Immunization</td>
</tr>
<tr>
<td>NITAG</td>
<td>National Immunization Technical Advisory Group</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>PHAC</td>
<td>Public Health Agency of Canada</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse events</td>
</tr>
<tr>
<td>SAGE</td>
<td>Strategic Advisory Group of Experts on Immunization (WHO)</td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td>Severe acute respiratory syndrome coronavirus 2</td>
</tr>
<tr>
<td>SD</td>
<td>Standard dose</td>
</tr>
<tr>
<td>SII</td>
<td>Serum Institute of India</td>
</tr>
<tr>
<td>SOC</td>
<td>System organ class</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>--------------</td>
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<tr>
<td>TST</td>
<td>Tuberculin skin test</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>VIPIT</td>
<td>Vaccine-Induced Prothrombotic Immune Thrombocytopenia</td>
</tr>
<tr>
<td>VITT</td>
<td>Vaccine-Induced Thrombotic Thrombocytopenia</td>
</tr>
<tr>
<td>VOC</td>
<td>Variants of concern</td>
</tr>
<tr>
<td>VPD</td>
<td>Vaccine preventable disease</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
ACKNOWLEDGMENTS

This statement was prepared by: SJ Ismail, K Young, MC Tunis, A Killikelly, R Stirling, O Baclic, J Zafack, M Salvadori, N Forbes, L Coward, C Jensen, R Krishnan, Y-E Chung, B Warshawsky, E Wong, K Farrah, A Nam, S Deeks, and C Quach on behalf of the High Consequence Infectious Disease Working Group (HCID WG) and was approved by NACI.


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PHAC Participants: N Abraham, P Doyon-Plourde, K Farrah, V Ferrante, N Forbes, SJ Ismail, C Jensen, A Killikelly, A Nam, M Patel, A Sinilaite, E Tice, MC Tunis, MW Yeung, K Young, and L Zhao.
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APPENDIX A: EVIDENCE SUMMARY FOR PFIZER-BIONTECH 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 adults 18 to 55 and 65 to 85 years of age. Evidence on the safety and efficacy of the vaccine is available for 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 44,000 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 were published recently, after NACI’s review of the evidence (25).

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 (26).

There may be a protective effect against severe COVID-19 outcomes 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).

Symptomatic COVID-19 disease
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 (25) 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 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 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

<table>
<thead>
<tr>
<th>Time period of interest</th>
<th>Events in vaccine group (N=21,669)</th>
<th>Events in placebo group (N=21,686)</th>
<th>Estimate of vaccine efficacy (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>After dose 1 to before dose 2</td>
<td>39</td>
<td>82</td>
<td>52.4% (29.5 to 68.4%)</td>
</tr>
<tr>
<td>&gt;14 days after dose 1 to before dose 2</td>
<td>2</td>
<td>27</td>
<td>92.3% (69 to 98%)</td>
</tr>
</tbody>
</table>

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 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 age groups studied (N=195). 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. At all time points and age groups, immune responses were higher than placebo.

**Cellular immune responses**
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 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.

Local Reactions

In vaccine recipients, frequency of local reactions was similar after Dose 1 and Dose 2. Pain at the injection site was very common (occurred in 66.1 to 83.1%, dependent on age and whether it was Dose 1 or Dose 2 administered). Most local reactions among vaccine recipients were mild or moderate in severity, with any severe reactions being reported by ≤0.6% of participants. No Grade 4 local reactions were reported. Across both 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 2 days.

Systemic Reactions

Systemic events were generally increased in frequency and severity in vaccine recipients compared to placebo recipients, and in the younger age group (16-55 years old) compared with the older age group (≥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 all age groups 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 all age groups (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 age groups (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.

Across age groups, the median onset day for most systemic events after either dose of vaccine was 1 to 2 days post-vaccination, with a median duration of 1 day. 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%. 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.

Severe or Serious Adverse Events

In total, 1.1% and 0.1% of participants in the vaccine group 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. There were no clinically meaningful differences in AEs by category observed by age, sex, or race/ethnicity.

The proportions of participants who reported at least 1 serious adverse event (SAE) were similar in the vaccine group (0.5%) and in the placebo group (0.4%). Three of the SAEs in the vaccine group and none in the placebo group were assessed by the investigator as related to study
intervention: 1 SAE each of shoulder injury related to vaccine administration, ventricular arrhythmia, and lymphadenopathy. 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 participants (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. Among the AEs of lymphadenopathy in the vaccine group, the majority (47 of 64) were judged by the investigator as related to the vaccine. 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.

Appendicitis
Among participants 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.

Death
There were 6 participants 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.
APPENDIX B: EVIDENCE SUMMARY FOR MODERNA 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.

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

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 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 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 8. Moderna vaccine efficacy against the first occurrence of symptomatic COVID-19 disease after dose 1

<table>
<thead>
<tr>
<th>Time period of interest</th>
<th>Events in vaccine group (N=996)</th>
<th>Events in placebo group (N=1,079)</th>
<th>Estimate of vaccine efficacy (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>After dose 1</td>
<td>7</td>
<td>39</td>
<td>80.2% (55.2 to 92.5%)</td>
</tr>
<tr>
<td>&gt;14 days after dose 1</td>
<td>2</td>
<td>28</td>
<td>92.1% (68.8 to 99.1%)</td>
</tr>
</tbody>
</table>

*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 weren’t 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.

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) \(^{(28)}\). 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 \(^{(28)}\). 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%) \(^{(28)}\).

**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 \(^{(28)}\). 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.

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 (28). 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**

**Facial swelling**

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.

**Death**

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: EVIDENCE SUMMARY FOR ASTRAZENECA 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) are 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 x 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 (29).

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.

Table 9. 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\(^a\))

<table>
<thead>
<tr>
<th>Dosing interval</th>
<th>Event in vaccine group (AZD1222) n/N (%)</th>
<th>Events in control group (MenACWY) n/N (%)</th>
<th>Vaccine efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4–12 weeks</td>
<td>67/5,473 (1.2)</td>
<td>162/5,422 (3.0)</td>
<td>59.6% (46.4 to 69.6%)</td>
</tr>
<tr>
<td>4 – 8 weeks</td>
<td>52/4,188 (1.2)</td>
<td>113/4,098 (2.8)</td>
<td>55.7% (38.5 to 68.1%)</td>
</tr>
<tr>
<td>9–12 weeks</td>
<td>15/1,285 (1.2)</td>
<td>49/1,324 (3.7)</td>
<td>69.0% (44.8 to 82.6%)</td>
</tr>
<tr>
<td>&gt;12 weeks</td>
<td>4/571 (0.7)</td>
<td>22/599 (3.7)</td>
<td>81.6% (47.0 to 93.6%)</td>
</tr>
</tbody>
</table>

\(^a\) 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 10).

Table 10. 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)*

<table>
<thead>
<tr>
<th>Dosing interval and age group</th>
<th>Event in vaccine group (AZD1222) n/N (%)</th>
<th>Events in control group (MenACWY) n/N (%)</th>
<th>Vaccine efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4–12 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–64 years</td>
<td>63/4,790 (1.2)</td>
<td>156/4,760 (3.0)</td>
<td>60.5% (47.1 to 70.5%)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>4/683 (0.6)</td>
<td>6/662 (0.9)</td>
<td>43.2% (-99.3 to 83.8%)</td>
</tr>
<tr>
<td>4 – 8 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–64 years</td>
<td>48/3,506 (1.4)</td>
<td>107/3,439 (3.1)</td>
<td>56.6% (39.1 to 69.1%)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>4/682 (0.6)</td>
<td>6/659 (0.9)</td>
<td>43.4% (-98.5 to 83.9%)</td>
</tr>
<tr>
<td>9–12 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–64 years</td>
<td>15/1,284 (1.2)</td>
<td>49/1,321 (3.7)</td>
<td>69.0% (44.8 to 82.6%)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>0/1 (0)</td>
<td>0/3 (0)</td>
<td>No estimate</td>
</tr>
<tr>
<td>&gt;12 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–64 years</td>
<td>4/571 (0.7)</td>
<td>22/599 (3.7)</td>
<td>81.6% (47.0 to 93.6%)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>0/0 (0)</td>
<td>0/0 (0)</td>
<td>No estimate</td>
</tr>
</tbody>
</table>

*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/m²) 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 11). 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 11. Estimates of vaccine efficacy against the first occurrence of confirmed COVID-19 beginning after Dose 1, (SD/SD seronegative baseline efficacy set\( ^a \))

<table>
<thead>
<tr>
<th>Time period of interest</th>
<th>Events in vaccine group (AZD1222)</th>
<th>Events in control group (MenACWY)</th>
<th>Estimate of vaccine efficacy (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>After Dose 1</td>
<td>92 (N=8,008)</td>
<td>185 (N=8,013)</td>
<td>50.5% (36.5 to 61.5%)</td>
</tr>
<tr>
<td>≥22 days after Dose 1</td>
<td>51 (N=6,307)</td>
<td>141 (N=6,297)</td>
<td>64.1% (50.5 to 73.9%).</td>
</tr>
<tr>
<td>≥22 after Dose 1 but before Dose 2</td>
<td>15 (N=6,310)</td>
<td>52 (N=6,296)</td>
<td>71.3% (49.0 to 83.8%)</td>
</tr>
</tbody>
</table>

\( ^a \) 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 12). 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 12. Estimates of vaccine efficacy against hospitalization, by dosing interval (SD/SD seronegative baseline efficacy set)**

<table>
<thead>
<tr>
<th>Time period of interest</th>
<th>Event in vaccine group (AZD1222) n/N (%)</th>
<th>Events in control group (MenACWY) n/N (%)</th>
<th>Vaccine efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥22 days after Dose 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0/6,307 (0.0)</td>
<td>9/6,297 (0.1)</td>
<td>100% (95% CI: 49.6 to 100%)</td>
</tr>
<tr>
<td>≥15 days after Dose 2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0/6,085 (0.0)</td>
<td>7/6,073 (0.1)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

* Participants without prior evidence of SARS-CoV-2 infection at baseline; all SD/SD vaccine recipients (or respective controls)

<sup>b</sup> Based on data as of November 4, 2020
<sup>c</sup> 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 13. Estimates of vaccine efficacy against asymptomatic infection, by dosing interval (SD/SD seronegative baseline efficacy set)**

<table>
<thead>
<tr>
<th>Dosing interval</th>
<th>Event in vaccine group (AZD1222) n/N (%)</th>
<th>Events in control group (MenACWY) n/N (%)</th>
<th>Vaccine efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥22 days after Dose 1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>14/3,060 (0.5%)</td>
<td>15/3,064 (0.5%)</td>
<td>6.6% (-93.5 to 54.9%)</td>
</tr>
<tr>
<td>≥15 days after Dose 2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Any interval 8/2,377 (0.3%)</td>
<td>11/2,340 (0.5%)</td>
<td>26.9% (-81.5 to 70.6%)</td>
</tr>
<tr>
<td>4–12 weeks</td>
<td>N/A</td>
<td>N/A</td>
<td>37.7% (-90.1 to 79.6%)</td>
</tr>
<tr>
<td>&gt;12 weeks</td>
<td>N/A</td>
<td>N/A</td>
<td>-4.3% (-416.5 to 79.0%)</td>
</tr>
</tbody>
</table>

* Participants without prior evidence of SARS-CoV-2 infection at baseline; all SD/SD vaccine recipients (or respective controls)

<sup>b</sup> Based on data as of November 4, 2020
<sup>c</sup> 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 (18).

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 (30). 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 12021 received at least one dose of the AZ COVID-19 vaccine and 11724 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 <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°) 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 recently reported globally following post-licensure use of AstraZeneca COVID-19 vaccine. The majority of cases identified so far have been in women under the age of 55 years - although cases in men and individuals between 55 and 80 years of age have also been reported- and have mostly occurred between 4 and 14 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 AstraZeneca COVID-19 vaccine 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 is most commonly estimated to be between 1 in 100,000 and 1 in 250,000 persons vaccinated. 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 25 and 40%. 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 SARS-CoV-2 B.1.1.7 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 variant in early December, 2020 in England, and 43% in Scotland in early January, 2021. By mid to late February, the SARS-CoV-2 B.1.1.7 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:**


   **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.

   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.


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.
RECOMMENDATIONS ON THE USE OF COVID-19 VACCINES

- 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 initially targeted 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: FREQUENCY OF SOLICITED ADVERSE EVENTS FOLLOWING IMMUNIZATION FOR COVID-19 VACCINES IN CLINICAL TRIALS

Table 14. Frequency of solicited local adverse events in authorized populations for mRNA COVID-19 vaccines

<table>
<thead>
<tr>
<th>AEFI</th>
<th>Pfizer-BioNTech COVID-19 Vaccine</th>
<th>Moderna COVID-19 Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaccine</td>
<td>Placebo control</td>
</tr>
<tr>
<td></td>
<td>Dose 1</td>
<td>Dose 2</td>
</tr>
<tr>
<td>Pain at injection site</td>
<td>Very</td>
<td>Common</td>
</tr>
<tr>
<td>Tenderness</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Redness/erythema</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Swelling</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Lymphadenopathy/axillary swelling</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>and tenderness</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Warmth</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Pruritis</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Induration</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

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 15. Frequency of solicited local adverse events in authorized populations for AstraZeneca COVID-19 vaccine

<table>
<thead>
<tr>
<th>AEFI</th>
<th>AstraZeneca COVID-19 Vaccine</th>
<th>MenACWY control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaccine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose 1</td>
<td>Dose 2</td>
</tr>
<tr>
<td>Pain at injection site</td>
<td>Very Common</td>
<td>Very Common</td>
</tr>
<tr>
<td>Tenderness</td>
<td>Very Common</td>
<td>Very Common</td>
</tr>
<tr>
<td>Redness/erythema</td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td>Swelling</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Lymphadenopathy(^b)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Axillary swelling and tenderness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warmth</td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td>Pruritis</td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td>Induration</td>
<td>Common</td>
<td>Common</td>
</tr>
</tbody>
</table>

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 AstraZeneca COVID-19 vaccine and was reported as an unsolicited adverse event. Please see Appendix C for more details.

Table 16. Frequency of solicited systemic adverse events in authorized populations for mRNA COVID-19 vaccines

<table>
<thead>
<tr>
<th>AEFI</th>
<th>Pfizer-BioNTech COVID-19 Vaccine</th>
<th>Moderna COVID-19 Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaccine</td>
<td>Placebo control</td>
</tr>
<tr>
<td></td>
<td>Dose 1</td>
<td>Dose 2</td>
</tr>
</tbody>
</table>
### Table 17. Frequency of solicited systemic adverse events in authorized populations for AstraZeneca COVID-19 vaccine

<table>
<thead>
<tr>
<th>AEFI</th>
<th>AstraZeneca COVID-19 Vaccine</th>
<th>MenACWY control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fatigue</td>
<td>Headache</td>
</tr>
</tbody>
</table>

**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.
APPENDIX E: BENEFIT-RISK ASSESSMENT FOR THE USE OF ASTRazeneca COVID-19 VACCINE IN A PUBLIC HEALTH CONTEXT

A benefit-risk analysis was conducted to determine whether the benefit of earlier vaccination with the AstraZeneca COVID-19 vaccine (instead of waiting for a later age-based mRNA vaccine) outweighs the risk of harms from Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT). In this analysis, the possible benefits were defined as potential ICU admissions and deaths due to COVID-19 that could be prevented with the use of AstraZeneca COVID-19 vaccine, instead of waiting for a later mRNA vaccine. The potential harm was the development of VITT events requiring ICU admission and/or resulting in death. An age-based analysis was conducted to account for differences in risk for COVID-19 disease and development of severe outcomes by age.

Methodology
The approach to the benefit-risk analysis was based on the analysis conducted by the UK Winton Centre for Risk and Evidence Communication, using Canadian-based data where available.

Calculation of potentially prevented COVID-19 ICU admissions and death
Five scenarios were considered, with daily COVID-19 case incidence rates per 10,000 corresponding to very low to high activity levels in the national COVID-19 Activity Levels Framework. These daily rates were then converted to weekly incidence rates (see Table 18). A very high activity level was assumed to be double the high activity level. Analysis was completed between April 16 and 21, 2021.

The weekly number of expected cases (per 100,000) of ICU admission and deaths due to COVID-19 were calculated by applying the age distribution of cases that were reported in Canadian surveillance data (cumulative to April 9, 2021) in 10-year age bands from 20 to 69 years of age against the weekly COVID-19 incidence defined by the five scenarios in Table 18. We applied the reported age-specific proportion of cases that were hospitalized, hospitalized cases that were admitted to ICU, and cases who died (see Table 19) to the weekly incidence rates. We assumed a single dose vaccine effectiveness of 80% against severe outcomes for the AstraZeneca vaccine.

In the context of the anticipated vaccine supply in Canada, the total number of events potentially prevented were calculated by multiplying the number of weekly events by the number of weeks each age group was estimated to have to wait before being able to receive an mRNA vaccine (see Table 20).

Calculation of potential VITT cases
To assess the potential harm of receiving the AstraZeneca COVID-19 vaccine, we assumed a fixed rate of VITT events across age groups due to limited available information on age-based risk. Given the uncertainty on the incidence of VITT events, we assessed scenarios with a rate of 1 case per 250,000 AstraZeneca doses administered and 1 case per 100,000 doses administered, where 100%
of cases would require ICU admission. When comparing mortality due to COVID-19 and mortality due to VITT, we considered two scenarios, assuming that 25% or 40% of VITT cases died to account for the current uncertainty.

Table 18. Daily and weekly incidence rates of infection under five different scenarios used for benefit-risk analysis

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Daily incidence per 10,000</th>
<th>Weekly incidence per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>0.06</td>
<td>4.20</td>
</tr>
<tr>
<td>Low</td>
<td>0.30</td>
<td>21.00</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.75</td>
<td>52.50</td>
</tr>
<tr>
<td>High</td>
<td>3.00</td>
<td>210.00</td>
</tr>
<tr>
<td>Very high*</td>
<td>6.00</td>
<td>420.00</td>
</tr>
</tbody>
</table>

*The very high scenario was considered for the purposes of this benefit-risk analysis only, and is not based on a category of activity within the COVID-19 Activity Levels Framework

Table 19. Proportion of COVID-19 events of interest by age group based on Canadian surveillance data

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Distribution of cases</th>
<th>Proportion of cases who are hospitalized</th>
<th>Proportion of hospitalized who require ICU</th>
<th>Proportion of cases who die</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 to 29</td>
<td>18.80%</td>
<td>0.94%</td>
<td>13.83%</td>
<td>0.02%</td>
</tr>
<tr>
<td>30 to 39</td>
<td>16.10%</td>
<td>1.79%</td>
<td>15.61%</td>
<td>0.05%</td>
</tr>
<tr>
<td>40 to 49</td>
<td>14.65%</td>
<td>2.69%</td>
<td>20.91%</td>
<td>0.13%</td>
</tr>
<tr>
<td>50 to 59</td>
<td>13.33%</td>
<td>4.99%</td>
<td>25.06%</td>
<td>0.47%</td>
</tr>
<tr>
<td>60 to 69</td>
<td>8.40%</td>
<td>10.62%</td>
<td>27.17%</td>
<td>2.15%</td>
</tr>
</tbody>
</table>

Table 20: Projected wait time to mRNA vaccines from mid-April 2021 based on anticipated supply of mRNA vaccines

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Projected wait time (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 to 29</td>
<td>7</td>
</tr>
<tr>
<td>30 to 39</td>
<td>6</td>
</tr>
<tr>
<td>40 to 49</td>
<td>4</td>
</tr>
<tr>
<td>50 to 59</td>
<td>3</td>
</tr>
<tr>
<td>60 to 69</td>
<td>1</td>
</tr>
</tbody>
</table>
Results

Table 21. Expected VITT cases by age group (based on VITT incidence rate of 1 per 250,000) compared to expected COVID-19 ICU admissions prevented by early AstraZeneca vaccination under five different COVID-19 activity scenarios

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Expected ICU admissions due to VITT per 100,000</th>
<th>Scenario activity level (daily incidence of COVID-19 infection)</th>
<th>Potentially prevented ICU admissions due to COVID-19 per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 to 29</td>
<td>0.40</td>
<td>Very low (0.06 per 10,000) Low (0.30 per 10,000) Moderate (0.75 per 10,000) High (3 per 10,000) Very high (6 per 10,000)</td>
<td>0.04 0.21 0.53&lt;sup&gt;a&lt;/sup&gt; 2.12&lt;sup&gt;a&lt;/sup&gt; 4.24&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>30 to 39</td>
<td>0.40</td>
<td>Very low (0.06 per 10,000) Low (0.30 per 10,000) Moderate (0.75 per 10,000) High (3 per 10,000) Very high (6 per 10,000)</td>
<td>0.07 0.33 0.82&lt;sup&gt;a&lt;/sup&gt; 3.29&lt;sup&gt;a&lt;/sup&gt; 6.58&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>40 to 49</td>
<td>0.40</td>
<td>Very low (0.06 per 10,000) Low (0.30 per 10,000) Moderate (0.75 per 10,000) High (3 per 10,000) Very high (6 per 10,000)</td>
<td>0.09 0.43&lt;sup&gt;a&lt;/sup&gt; 1.08&lt;sup&gt;a&lt;/sup&gt; 4.32&lt;sup&gt;a&lt;/sup&gt; 8.64&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>50 to 59</td>
<td>0.40</td>
<td>Very low (0.06 per 10,000) Low (0.30 per 10,000) Moderate (0.75 per 10,000) High (3 per 10,000) Very high (6 per 10,000)</td>
<td>0.12 0.60&lt;sup&gt;a&lt;/sup&gt; 1.50&lt;sup&gt;a&lt;/sup&gt; 6.01&lt;sup&gt;a&lt;/sup&gt; 12.03&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>60 to 69</td>
<td>0.40</td>
<td>Very low (0.06 per 10,000) Low (0.30 per 10,000) Moderate (0.75 per 10,000) High (3 per 10,000) Very high (6 per 10,000)</td>
<td>0.07 0.33 0.83&lt;sup&gt;a&lt;/sup&gt; 3.32&lt;sup&gt;a&lt;/sup&gt; 6.64&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

N.B. Unless noted, the potential event of interest prevented by earlier AstraZeneca vaccination compared to waiting for mRNA vaccine is lower than the event of interest due to VITT.

*Potentially prevented ICU admissions due to COVID-19 exceeds expected ICU admissions due to VITT*

Table 22. Expected VITT cases by age group (based on VITT incidence rate of 1 per 100,000) compared to expected COVID-19 ICU admissions prevented by early AstraZeneca vaccination under five different COVID-19 activity scenarios

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Expected ICU admissions due to VITT per 100,000</th>
<th>Scenario activity level (daily incidence of COVID-19 infection)</th>
<th>Potentially prevented ICU admissions due to COVID-19 per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 to 29</td>
<td>1.00</td>
<td>Very low (0.06 per 10,000) Low (0.30 per 10,000) Moderate (0.75 per 10,000) High (3 per 10,000) Very high (6 per 10,000)</td>
<td>0.04 0.21 0.53 2.12&lt;sup&gt;a&lt;/sup&gt; 4.24&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>30 to 39</td>
<td>1.00</td>
<td>Very low (0.06 per 10,000) Low (0.30 per 10,000) Moderate (0.75 per 10,000) High (3 per 10,000) Very high (6 per 10,000)</td>
<td>0.07 0.33 0.82 3.29&lt;sup&gt;a&lt;/sup&gt; 6.58&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>40 to 49</td>
<td>1.00</td>
<td>Very low (0.06 per 10,000) Low (0.30 per 10,000) Moderate (0.75 per 10,000) High (3 per 10,000) Very high (6 per 10,000)</td>
<td>0.09 0.43 1.08&lt;sup&gt;a&lt;/sup&gt; 4.32&lt;sup&gt;a&lt;/sup&gt; 8.64&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>50 to 59</td>
<td>1.00</td>
<td>Very low (0.06 per 10,000) Low (0.30 per 10,000) Moderate (0.75 per 10,000) High (3 per 10,000) Very high (6 per 10,000)</td>
<td>0.12 0.60 1.50&lt;sup&gt;a&lt;/sup&gt; 6.01&lt;sup&gt;a&lt;/sup&gt; 12.03&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>60 to 69</td>
<td>1.00</td>
<td>Very low (0.06 per 10,000) Low (0.30 per 10,000) Moderate (0.75 per 10,000) High (3 per 10,000) Very high (6 per 10,000)</td>
<td>0.07 0.33 0.83 3.32&lt;sup&gt;a&lt;/sup&gt; 6.64&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

N.B. Unless noted, the potential event of interest prevented by earlier AstraZeneca vaccination compared to waiting for mRNA vaccine is lower than the event of interest due to VITT.

*Potentially prevented ICU admissions due to COVID-19 exceeds expected ICU admissions due to VITT*
Table 23. Expected VITT deaths by age group (based on VITT rate of 1 per 250,000) compared to expected deaths due to COVID-19 prevented by early AstraZeneca vaccination under five different COVID-19 activity scenarios

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Expected deaths due to VITT per 100,000</th>
<th>Scenario activity level (daily incidence of COVID-19 infection)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Very low (0.06 per 10,000) Low (0.30 per 10,000) Moderate (0.75 per 10,000) High (3 per 10,000) Very high (6 per 10,000)</td>
</tr>
<tr>
<td>20 to 29</td>
<td>0.10 0.16</td>
<td>0.01 0.03 0.08 0.33 b 0.65 b</td>
</tr>
<tr>
<td>30 to 39</td>
<td>0.10 0.16</td>
<td>0.01 0.06 0.15 a 0.59 b 1.18 b</td>
</tr>
<tr>
<td>40 to 49</td>
<td>0.10 0.16</td>
<td>0.02 0.10 a 0.25 b 1.00 b 2.00 b</td>
</tr>
<tr>
<td>50 to 59</td>
<td>0.10 0.16</td>
<td>0.05 0.23 b 0.57 b 2.26 b 4.52 b</td>
</tr>
<tr>
<td>60 to 69</td>
<td>0.10 0.16</td>
<td>0.05 0.25 b 0.62 b 2.47 b 4.95 b</td>
</tr>
</tbody>
</table>

N.B. Unless noted, the potential event of interest prevented by earlier AstraZeneca vaccination compared to waiting for mRNA vaccine is lower than the event of interest due to VITT.

\[\text{\textsuperscript{a}}\text{Potentially prevented deaths due to COVID-19 exceeds expected deaths due to VITT only for the lower case fatality estimate}\]

\[\text{\textsuperscript{b}}\text{Potentially prevented deaths due to COVID-19 exceeds expected deaths due to VITT for both case fatality estimates}\]

Table 24. Expected VITT deaths by age group (based on VITT rate of 1 per 100,000) compared to expected deaths due to COVID-19 prevented by early AstraZeneca vaccination under five different COVID-19 activity scenarios

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Expected deaths due to VITT per 100,000</th>
<th>Scenario activity level (daily incidence of COVID-19 infection)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Very low (0.06 per 10,000) Low (0.30 per 10,000) Moderate (0.75 per 10,000) High (3 per 10,000) Very high (6 per 10,000)</td>
</tr>
<tr>
<td>20 to 29</td>
<td>0.25 0.40</td>
<td>0.01 0.03 0.08 0.33 b 0.65 b</td>
</tr>
<tr>
<td>30 to 39</td>
<td>0.25 0.40</td>
<td>0.01 0.06 0.15 0.59 b 1.18 b</td>
</tr>
<tr>
<td>40 to 49</td>
<td>0.25 0.40</td>
<td>0.02 0.10 0.25 a 1.00 b 2.00 b</td>
</tr>
<tr>
<td>50 to 59</td>
<td>0.25 0.40</td>
<td>0.05 0.23 0.57 b 2.26 b 4.52 b</td>
</tr>
<tr>
<td>60 to 69</td>
<td>0.25 0.40</td>
<td>0.05 0.25 a 0.62 b 2.47 b 4.95 b</td>
</tr>
</tbody>
</table>

N.B. Unless noted, the potential event of interest prevented by earlier AstraZeneca vaccination compared to waiting for mRNA vaccine is lower than the event of interest due to VITT.

\[\text{\textsuperscript{a}}\text{Potentially prevented deaths due to COVID-19 exceeds expected deaths due to VITT only for the lower case fatality estimate}\]
There is uncertainty in the base case risk analysis for ICU admissions due to incomplete reporting in the surveillance data at the national level, with ICU admission status known for only one-third of cases. We, therefore, conducted sensitivity analyses to examine scenarios representing ICU admissions that may reflect more recent trends, including the increasing proportion of VOC cases, and account for underreporting and some right-censoring in surveillance data. We defined this scenario by estimating the proportion of ICU admissions by age group over the period February 1, 2021 to April 12, 2021 in a representative province and applying those proportions to the recent average overall ICU admission rate (approximately 0.43 per 100,000). We then apply the same scenarios for activity levels and assumptions for wait times for mRNA vaccines and vaccine effectiveness from our base case. We also applied this analysis to a range of daily rates of ICU admissions (per 100,000) (Table 33 and Table 34).

Table 25. Proportion of total ICU admissions by age group based on representative provincial data

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Proportion of total ICU admissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 to 29</td>
<td>2.17%</td>
</tr>
<tr>
<td>30 to 39</td>
<td>4.56%</td>
</tr>
<tr>
<td>40 to 49</td>
<td>8.18%</td>
</tr>
<tr>
<td>50 to 59</td>
<td>20.59%</td>
</tr>
<tr>
<td>60 to 69</td>
<td>24.78%</td>
</tr>
</tbody>
</table>

Table 26. Sensitivity analysis of expected VITT cases by age group (based on VITT incidence rate of 1 per 250,000) compared to expected COVID-19 ICU admissions prevented by early AstraZeneca vaccination under five different COVID-19 activity scenarios using a high ICU admission rate (0.43 per 100,000)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Expected ICU admissions due to VITT per 100,000</th>
<th>Scenario activity level (daily incidence of COVID-19 cases)</th>
<th>Potentially prevented ICU admissions due to COVID-19 per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Very low (0.06 per 10,000)</td>
<td>Low (0.30 per 10,000)</td>
</tr>
<tr>
<td>20 to 29</td>
<td>0.40</td>
<td>0.05</td>
<td>0.26</td>
</tr>
<tr>
<td>30 to 39</td>
<td>0.40</td>
<td>0.10</td>
<td>0.48a</td>
</tr>
<tr>
<td>40 to 49</td>
<td>0.40</td>
<td>0.12</td>
<td>0.62a</td>
</tr>
<tr>
<td>50 to 59</td>
<td>0.40</td>
<td>0.21</td>
<td>1.05a</td>
</tr>
<tr>
<td>60 to 69</td>
<td>0.40</td>
<td>0.10</td>
<td>0.50a</td>
</tr>
</tbody>
</table>

N.B. Unless noted, the potential event of interest prevented by earlier AstraZeneca vaccination compared to waiting for mRNA vaccine is lower than the event of interest due to VITT.

Potentially prevented ICU admissions due to COVID-19 exceeds expected ICU admissions due to VITT
RECOMMENDATIONS ON THE USE OF COVID-19 VACCINES

Table 27. Sensitivity analysis of expected VITT cases by age group (based on VITT incidence rate of 1 per 100,000) compared to expected COVID-19 ICU admissions prevented by early AstraZeneca vaccination under five different COVID-19 activity scenarios using a high ICU admission rate (0.43 per 100,000).

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Expected ICU admissions due to VITT per 100,000</th>
<th>Scenario activity level (daily incidence of COVID-19 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Very low (0.06 per 10,000)</td>
</tr>
<tr>
<td>20 to 29</td>
<td>1.00</td>
<td>0.05</td>
</tr>
<tr>
<td>30 to 39</td>
<td>1.00</td>
<td>0.10</td>
</tr>
<tr>
<td>40 to 49</td>
<td>1.00</td>
<td>0.12</td>
</tr>
<tr>
<td>50 to 59</td>
<td>1.00</td>
<td>0.21</td>
</tr>
<tr>
<td>60 to 69</td>
<td>1.00</td>
<td>0.10</td>
</tr>
</tbody>
</table>

N.B. Unless noted, the potential event of interest prevented by earlier AstraZeneca vaccination compared to waiting for mRNA vaccine is lower than the event of interest due to VITT.

^a Potentially prevented ICU admissions due to COVID-19 exceeds expected ICU admissions due to VITT.

Table 28. Sensitivity analysis of expected VITT cases by age group (based on VITT incidence rate of 1 per 250,000) compared to expected COVID-19 ICU admissions prevented by early AstraZeneca vaccination under five different COVID-19 activity scenarios using a lower ICU admission rate (0.22 per 100,000).

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Expected ICU admissions due to VITT per 100,000</th>
<th>Scenario activity level (daily incidence of COVID-19 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Very low (0.06 per 10,000)</td>
</tr>
<tr>
<td>20 to 29</td>
<td>0.40</td>
<td>0.03</td>
</tr>
<tr>
<td>30 to 39</td>
<td>0.40</td>
<td>0.05</td>
</tr>
<tr>
<td>40 to 49</td>
<td>0.40</td>
<td>0.06</td>
</tr>
<tr>
<td>50 to 59</td>
<td>0.40</td>
<td>0.10</td>
</tr>
<tr>
<td>60 to 69</td>
<td>0.40</td>
<td>0.05</td>
</tr>
</tbody>
</table>

N.B. Unless noted, the potential event of interest prevented by earlier AstraZeneca vaccination compared to waiting for mRNA vaccine is lower than the event of interest due to VITT.

^a Potentially prevented ICU admissions due to COVID-19 exceeds expected ICU admissions due to VITT.
Table 29. Sensitivity analysis of expected VITT cases by age group (based on VITT incidence rate of 1 per 100,000) compared to expected COVID-19 ICU admissions prevented by early AstraZeneca vaccination under five different COVID-19 activity scenarios using a lower ICU admission rate (0.22 per 100,000)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Expected ICU admissions due to VITT per 100,000</th>
<th>Scenario activity level (daily incidence of COVID-19 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Very low (0.06 per 10,000)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low (0.30 per 10,000)</td>
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<tr>
<td></td>
<td></td>
<td>Moderate (0.75 per 10,000)</td>
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<td>High (3 per 10,000)</td>
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<tr>
<td></td>
<td></td>
<td>Very high (6 per 10,000)</td>
</tr>
<tr>
<td>20 to 29</td>
<td>1.00</td>
<td>0.03</td>
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<tr>
<td></td>
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<tr>
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<td></td>
<td>0.32</td>
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<td></td>
<td></td>
<td>1.28&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.55&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>30 to 39</td>
<td>1.00</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.24</td>
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<td></td>
<td></td>
<td>0.60</td>
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<td></td>
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<td>2.42&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>4.84&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>40 to 49</td>
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<td>0.06</td>
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<tr>
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<td></td>
<td>3.09&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
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<td>6.18&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>50 to 59</td>
<td>1.00</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.52</td>
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<td></td>
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<td>1.31&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>5.24&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>10.48&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>60 to 69</td>
<td>1.00</td>
<td>0.05</td>
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<td>5.05&lt;sup&gt;a&lt;/sup&gt;</td>
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N.B. Unless noted, the potential event of interest prevented by earlier AstraZeneca vaccination compared to waiting for mRNA vaccine is lower than the event of interest due to VITT.

<sup>a</sup>Potentially prevented ICU admissions due to COVID-19 exceeds expected ICU admissions due to VITT

Limitations of analysis

There are some limitations to this analysis to consider when interpreting the benefit-risk estimates.

1) Each scenario is based on a constant incidence rate. However, the risk of COVID-19 is dynamic and difficult to predict. As a result, the estimated benefits of preventing COVID-19 outcomes with AstraZeneca COVID-19 vaccination compared to waiting for an mRNA vaccine will be more uncertain for age groups with the longer wait times for mRNA vaccines.

2) The risks of ICU admission and deaths were based on the age distribution of cases in surveillance data and unreported cases are not uniformly distributed across age groups. Moreover, ICU admission status in the data used for the base case analysis was only known for approximately 33% of submitted cases as of April 14, 2021. Thus, there is uncertainty in the relative benefits between age groups in preventing ICU admissions with AstraZeneca vaccination compared to waiting for an mRNA vaccine.

3) The rate of ICU admissions relative to daily reported cases may vary considerably across provinces and territories due to different epidemiology (e.g. variants of concern), demographics (e.g. age and comorbidity profile in the population), testing policies, hospital capacity and vaccination rollout strategies. The benefit-risk of AstraZeneca COVID-19 vaccination should be interpreted with caution in the scenarios provided.
4) This analysis did not account for ICU capacity limits. In scenarios where incidence rates result in overflow of ICU capacity this analysis will underestimate the benefits of preventing deaths with AstraZeneca COVID-19 vaccination. However, if such a scenario is considered likely, then the benefit-risk estimates from the high scenario may be most applicable.

5) Estimates of VITT incidence and mortality are still highly uncertain and may change as evidence continues to emerge.

6) Time to wait to receive an mRNA vaccine assumes vaccine administration to be 100% efficient (i.e., weekly supply is consumed by the end of the week). If vaccine uptake is delayed or slower than anticipated, the cumulative risks of COVID-19 outcomes will increase, particularly in age groups facing longer wait times for mRNA vaccines.

7) Administration of AstraZeneca COVID-19 vaccine, as described in these scenarios, is assumed to take place in mid-April 2021. Any delay in administering the vaccine to a particular age group shortens the time period to wait for mRNA and therefore reduces the benefit of AstraZeneca COVID-19 vaccine early administration.