Important Notice

Updated advice on mixed COVID-19 vaccine schedules is available in the NACI Rapid Response: Interchangeability of authorized COVID-19 vaccines.

Advice on interchangeability in the current COVID-19 vaccine statement has not yet been updated and is out of date.

Published May 28, 2021
An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

Recommendations on the use of COVID-19 Vaccines

Published May 28, 2021
PREAMBLE

The National Advisory Committee on Immunization (NACI) is an External Advisory Body that provides the Public Health Agency of Canada (PHAC) with independent, ongoing and timely medical, scientific, and public health advice in response to questions from PHAC relating to immunization.

In addition to burden of disease and vaccine characteristics, PHAC has expanded the mandate of NACI to include the systematic consideration of programmatic factors in developing evidence-based recommendations to facilitate timely decision-making for publicly funded vaccine programs at provincial and territorial levels.

The additional factors to be systematically considered by NACI include: economics, ethics, equity, feasibility, and acceptability. Not all NACI Statements will require in-depth analyses of all programmatic factors. While systematic consideration of programmatic factors will be conducted using evidence-informed tools to identify distinct issues that could impact decision-making for recommendation development, only distinct issues identified as being specific to the vaccine or vaccine-preventable disease will be included.

This statement contains NACI’s independent advice and recommendations, which are based upon the best current available scientific knowledge. This document is being disseminated for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph. Recommendations for use and other information set out herein may differ from that set out in the product monographs of the Canadian manufacturers of the vaccines. Manufacturer(s) have sought approval of the vaccines and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of PHAC’s Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.
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TABLE OF UPDATES

This evergreen document will be updated as COVID-19 vaccines are authorized and become available for use in Canada, as evidence on these vaccines and COVID-19 evolves, and as recommendations from NACI evolve based on this evidence. This table summarizes the updated information provided in the current version of this document since the publication of the last version of the document on May 21, 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.

<table>
<thead>
<tr>
<th>Section</th>
<th>Update</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>Table 1 has been updated with the results of an updated rapid review of risk factors for severe outcomes from COVID-19.</td>
<td>2021-05-28</td>
</tr>
<tr>
<td>Vaccines</td>
<td>Table 2 and “Storage Requirements” have been updated to reflect the revised product monograph for Pfizer-BioNTech COVID-19 vaccine allowing thawed undiluted vials to be stored in the refrigerator (2°C to 8°C [35°F to 46°F]) for up to 1 month.</td>
<td>2021-05-28</td>
</tr>
</tbody>
</table>
| Vaccines           | All sub-sections under the section “Vaccines” have been updated to include evidence or information from the revised product monograph related to the Pfizer-BioNTech COVID-19 vaccine in 12-15 year olds. This includes:  
  - Table 2. COVID-19 vaccines authorized for use in Canada  
  - Efficacy and effectiveness  
  - Vaccine safety and adverse events following immunization | 2021-05-28|
| Vaccines           | A section summarizing accumulating evidence on COVID-19 vaccination in populations who were excluded from clinical trials (or included in small numbers) has been added. These populations include: those previously infected with SARS-CoV-2; and those who are immunosuppressed, have an autoimmune condition, or are pregnant or breastfeeding. | 2021-05-28|
| Recommendations    | NACI’s recommendation on the use of COVID-19 vaccines in pediatric populations has been updated to acknowledge the NACI recommendation on the use of the Pfizer- | 2021-05-28|
### 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

- mRNA vaccines are authorized for use in Canada for individuals 12 years of age and older (Pfizer-BioNTech COVID-19 vaccine) or 18 years of age and older (Moderna COVID-19 vaccine).
- Non-replicating viral vector vaccines are authorized for use in Canada for individuals 18 years of age and older (AstraZeneca COVID-19 vaccine and Janssen COVID-19 vaccine).
- In clinical trials, all COVID-19 vaccines are efficacious in the short-term against symptomatic, confirmed COVID-19 disease; trials are ongoing. mRNA COVID-19 vaccines have demonstrated high efficacy (≥94%). The AstraZeneca COVID-19 vaccine has demonstrated an average efficacy of approximately 62% in those 18-64 years of age. In adults 65 years of age and older who received one dose of AstraZeneca, real-world observational data of vaccine effectiveness have shown a reduction in the risk of symptomatic disease and hospitalization. The Janssen COVID-19 vaccine has demonstrated efficacy of 67% against confirmed symptomatic moderate to severe/critical COVID-19 infection based on trials conducted in South Africa and Brazil while B.1.351 and P.2 were circulating, respectively. There is currently limited evidence on the duration of protection and on the efficacy of these vaccines in reducing transmission of SARS-CoV-2, although studies are ongoing. Evidence of protection against asymptomatic SARS-CoV-2 infection is emerging for the mRNA and Janssen vaccines.
- Evidence of varying protection offered by COVID-19 vaccines against SARS-CoV-2 variants is evolving. To date, evidence has emerged that the Pfizer-BioNTech and AstraZeneca vaccines offer protection against the B.1.1.7 variant first identified in the UK. There is also emerging evidence that both vaccines also protect against the B.1.167.2 variant first identified in India, but only after the second dose. There is evidence that the Janssen vaccine offers some protection against the B.1.351 variant of concern first identified in South Africa as well as the P.2 variant of interest first identified in Brazil. There is evidence that the AstraZeneca vaccine does not offer protection against the B.1.351 variant.
- 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.
- Rare cases of a specific syndrome that involves serious blood clots (at unusual sites such as cerebral venous sinus thrombosis) associated with thrombocytopenia have recently been reported after vaccination with viral vector vaccines. These cases often occur between 4 and 28 days after receipt of the vaccine. Early identification and appropriate treatment are critical. Investigations to better understand this syndrome, often referred to as Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT), are ongoing.
- 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 a viral vector COVID-19 vaccine *may be* offered to individuals 30 years of age and older without contraindications only if the individual prefers an earlier vaccine rather than wait for an mRNA vaccine AND all the following conditions apply:

a) The benefit-risk analysis* determines that the benefit of earlier vaccination with a viral vector 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 Tool](#) 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.

**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) is recommended.

NACI continues to recommend the following elements to guide ethical decision-making, as outlined in NACI’s guidance on Key Populations for Early COVID-19 Immunization:

- Efforts should be made to increase access to immunization services to reduce health inequities without further stigmatization or discrimination, and to engage systemically marginalized populations and racialized populations in immunization program planning.
- Jurisdictions should ensure close and rapid monitoring of safety, coverage and effectiveness of the vaccines in different key populations, as well as effective and efficient immunization of populations in hardly reached, remote and isolated communities.
- Efforts should be made to improve knowledge about the benefits of vaccines in general and of COVID-19 vaccines as each becomes available, address misinformation, and communicate transparently about COVID-19 vaccine allocation decisions.

**How**

- Currently authorized and available COVID-19 vaccines are administered intramuscularly in a two-dose schedule (Pfizer-BioNTech, Moderna, AstraZeneca) or in a one-dose schedule (Janssen).
- Attempts should be made to complete the vaccine series with the same vaccine product, when possible.
- 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 COVID-19 vaccines that are recommended for use by NACI in this Statement have been shown to be safe (although very rare cases of VITT reported following vaccination with the viral vector COVID-19 vaccines), efficacious against symptomatic laboratory confirmed COVID-19, and appear to protect against severe disease, hospitalization and death due to COVID-19.
I. INTRODUCTION

The **overall goal of Canada’s pandemic response** is to minimize serious illness and death while minimizing societal disruption as a result of the COVID-19 pandemic. The **goal of Canada’s COVID-19 immunization response** is: To enable as many Canadians as possible to be immunized against COVID-19 as quickly as possible, while ensuring that high risk populations are prioritized.

This guidance document will provide recommendations on the use of authorized COVID-19 vaccines as they are approved 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:

1. The Pfizer-BioNTech COVID-19 vaccine was authorized for use in Canada on December 9, 2020 for ages 16 and up. On May 5, 2021, Health Canada expanded the Interim Order authorization for the Pfizer-BioNTech COVID-19 vaccine to include 12 to 15 year olds.
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 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 guidance developed in response to the investigation 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. Recommendation on the use of the Pfizer-BioNTech COVID-19 vaccine in adolescents 12 to 18 years of age (recommending that a complete series with a Pfizer-BioNTech COVID-19 vaccine should be offered to individuals 12 to 18 years of age without contraindications to the vaccine).

8. Recommendations on the use of COVID-19 vaccines 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 appendices.

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](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](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 was first reviewed on March 24, 2021 and related recommendations were approved on March 28, 2021. New evidence, including the Health Canada’s safety assessment report issued on April 14, 2021, was formally reviewed on April 13, 15, 17 and 20, 2021. Updated recommendations were approved on April 20, 2021.
- The Janssen COVID-19 vaccine was discussed on March 16, 25 and April 13, 26, 2021, and recommendations were approved on April 30, 2021.
Evolving evidence on extended intervals was reviewed on May 11 and 13, 2021. NACI updated the related recommendation on May 13, 2021 in the context of increasing COVID-19 vaccine supplies.

Additional evidence in populations either excluded from, or included in small numbers, in clinical trials was reviewed on May 4 and 13, 2021. Related recommendations for COVID-19 vaccination in those who are immunosuppressed, have an autoimmune condition, are pregnant, or are breastfeeding were revised and approved on May 13, 2021.

NACI reviewed the available evidence on the use of the Pfizer-BioNTech COVID-19 vaccine in adolescents 12 to 15 years of age on May 9, 2021 and approved the related recommendation on May 11, 2021.

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 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 (4) 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). 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). As evidence accumulates, observed associations may change. For example, a previous rapid review by ARCHE (5) 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 (^{(4)}) (e.g., due to inability to physically distance/reduced access to IPC)</th>
</tr>
</thead>
</table>
| **Increasing age (strong evidence)** (based on moderate certainty of evidence of ≥2-fold increase in mortality)  
  • ≥60 years (particularly ≥ 70 years) \(^{(4)}\) | • Residents and staff of congregate living settings that provide care for seniors  
  • Frontline healthcare workers  
  • Adults in Indigenous communities  
  • Residents and staff of other congregate living settings (e.g., quarters for migrant workers, shelters, correctional facilities, group homes)  
  • Adults in racialized and marginalized communities  
  • First responders (e.g., police, firefighters)  
  • Frontline essential workers who cannot work virtually |
| **Medical conditions – Level 1 (strong evidence) \(^{(4)}\)** (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\(^{(4)}\)  
  • Type 1 and 2 diabetes | |
| **Medical conditions – Level 2 (limited evidence) \(^{(4)}\)** | |
| **Level 2a** (based on low certainty of evidence of ≥2-fold increase in mortality)  
  • Cerebral palsy  
  • Major psychiatric disorder (schizophrenia, schizoaffective disorder, or bipolar disorder); in combination with prescription drug use for the condition in the past 6 months  
  • Obesity class III (BMI ≥40 kg/m\(^2\) )  
  • Parkinson’s disease  
  • Sickle cell disease or severe immunodeficiency, transplant (any type)  
  • Solid organ transplant  
  • Recent bone marrow or stem cell transplant  
  • Metastatic cancer  
  • Recent/current chemotherapy or radiotherapy | |
| **Level 2b** (based on low or moderate certainty of evidence of ≥2-fold increase in hospitalization)  
  • Previous cerebrovascular accident  
  • Pregnancy (any stage)  
  • Frailty (among community and non-community dwelling people; measured on scales that include items such as weight loss, exhaustion, physical activity, walking speed, grip strength, overall health, disability, presence of disease, dementia, falls, mental wellbeing)  
  • Vasculitis  
  • Obesity – all classes (BMI >30 kg/m\(^2\)) | |
Increased risk of severe outcomes (hospitalization/mortality) and Increased risk of exposure

- Long-term care residents
- Visible minority groups (includes mainly South Asian, Chinese, Black, Filipino, Latin American, Arab, Southeast Asian, West Asian, Korean, Japanese)

a Identified through rapid review of evidence from OECD countries for an independent association with severe outcomes from COVID
b Identified, in part, through Canadian epidemiological reports
c Identified through rapid review of Canadian studies that may have an association with hospitalization and mortality from COVID-19. These studies may not have accounted for other covariates.
d These conditions were grouped within a single study; evidence for the individual conditions is either unavailable or of lower certainty.

The list of medical conditions in Table 1 may differ from those in other jurisdictions due to differences in local epidemiology and differing levels of evidence considered.

The evidence on risk factors for COVID-19 continues to evolve.

Spectrum of clinical illness

The median incubation period for non-variant SARS-CoV-2 has been estimated to be 5 to 6 days from exposure to symptom onset, with most individuals (97.5%) developing symptoms within 11.5 days of exposure. The incubation period ranges from 1 to 14 days.

Clinical presentation and symptoms of COVID-19 vary in frequency and severity. To date, there is no list of symptoms that has been validated to have high specificity or sensitivity for COVID-19.

More information on the spectrum of clinical illness is available on the PHAC webpage for COVID-19 signs, symptoms and severity of disease: A clinician guide.

Disease incidence

Global

Updated international data on COVID-19 cases and deaths is available at: https://health-infobase.canada.ca/covid-19/international/

Weekly epidemiological updates highlighting key global, regional and country-level data on COVID-19 cases and deaths are available from the World Health Organization (WHO) at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports

National

Updated national, provincial and territorial-level data on COVID-19 cases and deaths in Canada over time is available from the PHAC webpage on Coronavirus disease (COVID-19): Outbreak update.
IV. VACCINES

The following section summarizes information about COVID-19 vaccines authorized for use in Canada. More detailed vaccine-specific information is included in Appendices A through D. The current landscape of all candidate COVID-19 vaccines in clinical evaluation can be found on the WHO webpage Draft landscape of COVID-19 candidate vaccines. Under the Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19, Health Canada can make regulatory decisions for COVID-19 vaccines that have completed Phase 3 clinical trials for authorized use in Canada.

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). The Janssen vaccine uses a modified human adenovirus serotype 26 vector (Ad26).
IV.1 Preparations of COVID-19 vaccines authorized and available for use in Canada

Table 2. COVID-19 vaccines available for use in Canada

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of vaccine</td>
<td>mRNA</td>
<td>mRNA</td>
<td>Non-replicating viral vector (ChAd)</td>
<td>Non-replicating viral vector (Ad26)</td>
</tr>
<tr>
<td>Date of authorization in Canada</td>
<td>December 9, 2020 (16 years of age and older); May 5, 2021 (12 years of age and older)</td>
<td>December 23, 2020</td>
<td>February 26, 2021</td>
<td>March 5, 2021</td>
</tr>
<tr>
<td>Authorized ages for use</td>
<td>12 years of age and older</td>
<td>18 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>
<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>
<td>1 Dose</td>
</tr>
<tr>
<td>Route of administration</td>
<td>IM</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>
<td>Transmembrane prefusion spike protein</td>
</tr>
<tr>
<td>Adjuvant (if present)</td>
<td>None</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(^d)</td>
<td>+2°C to +8°C</td>
<td>+2°C to +8°C</td>
</tr>
<tr>
<td>Additional storage options pre-puncture(^e)</td>
<td>-25°C to -15°C for up to 2 weeks(^a) OR 1 month 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>
<td>+2°C to +8°C</td>
</tr>
<tr>
<td>Diluent</td>
<td>Yes</td>
<td>No</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>
<td>3 hours at room temperature (up to +25°C) OR 6 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>
<td>Multi-dose vial (5 doses), preservative-free</td>
</tr>
</tbody>
</table>

Abbreviations: ChAd: Chimpanzee adenovirus; Ad26: modified human adenovirus 26; IM: Intramuscular; mRNA: Messenger ribonucleic acid

\(^a\) After dilution, one vial contains 6 doses of 0.3 mL each. 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.
IV.2 Efficacy and Effectiveness

Due to the availability of only short-term clinical trial data, the duration of protection provided by COVID-19 vaccination is currently unknown. However, studies are ongoing.

The following section highlights key efficacy and effectiveness data for authorized mRNA COVID-19 vaccines (Pfizer-BioNTech COVID-19 vaccine, Moderna COVID-19 vaccine) and the authorized viral vector-based COVID-19 vaccines (AstraZeneca COVID-19 vaccine, Janssen COVID-19 vaccine) only. For additional details regarding trial design, including study population, length of follow-up, and efficacy for the authorized and available vaccines, refer to the evidence summaries in Appendix A (for the Pfizer-BioNTech COVID-19 vaccine), Appendix B (for the Moderna COVID-19 vaccine), Appendix C (for the AstraZeneca COVID-19 vaccine) and Appendix D (for the Janssen COVID-19 vaccine).

Efficacy against symptomatic COVID-19 disease

The currently authorized mRNA COVID-19 vaccines have been shown to be highly efficacious in the short term against confirmed symptomatic COVID-19 disease (presence of one or more symptoms plus laboratory confirmation of SARS-CoV-2 infection). The authorized two-dose mRNA vaccines schedules are similarly efficacious in adults with one or more comorbidities, as well as in adolescents (Pfizer-BioNTech COVID-19 vaccine), younger adults and older adults.

In clinical trials, AstraZeneca COVID-19 viral vector vaccine has shown moderate short-term efficacy against symptomatic COVID-19 disease (presence of at least one pre-defined COVID-19 symptom plus laboratory confirmation of SARS-CoV-2 infection) in adults 18–64 years of age, at least two weeks after receiving the full series of two standard doses of the vaccine. Clinical trial data show that efficacy increased as the interval between doses increased. At present, there are insufficient clinical trial data in adults ≥65 years of age to assess vaccine efficacy in this age group. The vaccine is similarly efficacious in adults ≥18 years of age with and without pre-defined comorbidities (presence of one or more mild to moderate and controlled cardiovascular disease, respiratory disease, diabetes or obesity). In the initial absence of sufficient data from clinical trials to date on the efficacy of the AstraZeneca COVID-19 vaccine in those 65 years of age and older, a review of three observational studies in the UK published as pre-prints on vaccine effectiveness in this age group has been conducted to inform NACI’s recommendations in this age group. The findings of this review are summarized in Appendix C. These studies provide effectiveness estimates following the first dose of AstraZeneca vaccine and have shown a reduction in the risk of symptomatic disease and hospitalization that appears to reach a comparable level to that observed among persons of similar age who received one dose of mRNA vaccine.

The Janssen COVID-19 vaccine demonstrates moderate efficacy against symptomatic confirmed moderate to severe/critical COVID-19 infection from 14 days and 28 days post-vaccination, where the definition of moderate disease includes the presence of one to two or more of a relatively broad range of COVID-19 compatible signs and symptoms plus laboratory confirmation of SARS-CoV-2 infection. The point estimates of vaccine efficacy at these two time points across a variety of age groups are similar to the overall estimate, including among study participants ≥65 years of age who comprised approximately 20% of the study population. Point estimates of vaccine efficacy at 14 days post-vaccination are comparable in study participants with and without one or more comorbidities. In contrast, the point estimate of efficacy in participants with comorbidities is somewhat lower at 28 days post-vaccination. Efficacy for Janssen vaccine was based on clinical trials that were conducted in countries with widely circulating VOCs (South Africa and Brazil),
which may have impacted its overall efficacy. This is in contrast to the clinical trials for other authorized COVID-19 vaccines.

The clinical trial data demonstrates that the authorized mRNA COVID-19 vaccines are efficacious over the short-term in individuals with or without evidence of prior SARS-CoV-2 infection. However, participants with laboratory-confirmed (using a nucleic acid amplification test, such as RT-PCR) SARS-CoV-2 infection prior to enrollment were excluded from the trials and the number of trial participants with evidence of previous infection (as defined by trial protocol) who had confirmed symptomatic COVID-19 disease during the trials were small; therefore, the efficacy in this population and how it compares to those without evidence of previous infection is unknown at this time. The efficacy of the Janssen COVID-19 vaccine in those with evidence of prior infection is inconclusive at this time due to small sample size, and this outcome has not been assessed for AstraZeneca COVID-19 vaccine.

The first dose of the authorized COVID-19 vaccines has been shown to offer at least short-term protection against confirmed COVID-19 disease. For mRNA vaccines, the highest efficacy is seen after the second dose is administered. There is currently no available evidence on medium- and long-term efficacy of the authorized COVID-19 vaccines, however trials are ongoing, and this Statement will be updated as evidence emerges.

**Efficacy and effectiveness against severe disease**

The clinical trials of the authorized and available COVID-19 vaccines assessed efficacy against severe COVID-19 disease, but not all provided sufficient data to be able to assess the efficacy against hospitalizations or deaths.

The authorized mRNA and the Janssen COVID-19 vaccines appear efficacious against severe COVID-19 outcomes based on clinical trial data used for authorization (severe outcomes were defined as laboratory-confirmed COVID-19 with one of the following additional features: clinical signs at rest that are indicative of severe systemic illness; respiratory failure; evidence of shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death). However, the number of severe cases that have been observed to date was small in the Pfizer-BioNTech clinical trial in participants 16 years of age and older, and was too small in the AstraZeneca clinical trials to assess efficacy. There were no severe cases identified in adolescents 12 to 15 years of age in the Pfizer-BioNTech clinical trial. Efficacy against hospitalization was not assessed in the clinical trials of the mRNA vaccines, but evidence from the clinical trials involving the viral vector vaccines is suggestive of a protective effect against hospitalization. To date there have been very few COVID-19 associated deaths identified in the clinical trials making it difficult to assess efficacy against this outcome. However, of the COVID-19 associated deaths identified in clinical trials, none have been in study participants receiving COVID-19 vaccines.

Emerging real world evidence from studies in the United Kingdom (UK) (6-8), Israel (9-11)(12), the United States (US) (13), and Canada (14) suggests moderate to high vaccine effectiveness against severe COVID-19 outcomes after the first or second dose of mRNA COVID-19 vaccines in adults (6-11, 13, 14)(12), 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, 13)(12), while fewer studies provided estimates of effectiveness against severe disease (9, 10) and death (7, 9, 14). Emerging evidence from Israeli studies suggest high vaccine effectiveness after the second dose of Pfizer-BioNTech COVID-19 vaccine against severe disease, (9, 10) COVID-19 related hospitalization(9)(12) and death (12). Studies
for COVID-19 vaccines are ongoing and new effectiveness data against severe COVID-19 outcomes will be assessed as it emerges.

Efficacy and effectiveness against asymptomatic infection and transmission

Preliminary data from the ongoing Moderna COVID-19 vaccine trial showed a lower prevalence of SARS-CoV-2 positivity by PCR in asymptomatic participants at one particular time point (after Dose one but before Dose 2), and therefore viral shedding, in the group that received the vaccine compared to the placebo group. However, the current data are insufficient to draw conclusions. Exploratory analyses for the AstraZeneca viral vector vaccine have not demonstrated efficacy against confirmed SARS-CoV-2 asymptomatic infection, however the number of asymptomatic infections was small. The clinical trial of the Janssen COVID-19 vaccine found the vaccine to have moderate protection against asymptomatic and undetected COVID-19 infection. Studies are ongoing for these vaccines.

Evidence has begun to emerge from post-marketing studies conducted in Israel, (9) the UK, (15) and the US (16) on the effectiveness of COVID-19 vaccines against asymptomatic infection in adults. Estimates of vaccine effectiveness for the Pfizer-BioNTech COVID-19 vaccine against SARS-CoV-2 infection with no reported symptoms was moderate to high after the first dose (9, 15) (depending on time since vaccination) and high after the second dose (9, 15). Similar results were reported for mRNA COVID-19 vaccines in general (i.e., Moderna and Pfizer-BioNTech) (16). 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 (15). There are no results specific to other COVID-19 vaccines yet, but studies are ongoing.

Efficacy and effectiveness against variants

Evidence of varying protection and effectiveness offered by authorized mRNA COVID-19 vaccines (Pfizer-BioNTech COVID-19 vaccine, Moderna COVID-19 vaccine) and viral vector-based COVID-19 vaccines (AstraZeneca COVID-19 vaccine, Janssen COVID-19 vaccine) against variants of SARS-CoV-2 is evolving. Please see Table 5 for a summary of this evidence.

The Janssen clinical trial was conducted during the time of emergence of SARS-CoV-2 VOC. As part of the testing conducted during the trial, a proportion of case isolates were genetically sequenced, and of the sequenced isolates, just over two-thirds of the isolates from Brazil were of the P.2 lineage and nearly all isolates from South Africa were of the B.1.351 lineage. Point estimates of vaccine efficacy against confirmed symptomatic moderate to severe/critical COVID-19 infection with onset from 28 days post-vaccine are comparable to the overall estimate of efficacy against this outcome in Brazil and South Africa.

There is evidence that both the Pfizer and AstraZeneca vaccines protect against the B.1.1.7 SARS-CoV-2 variant first identified in the UK, and emerging data suggesting both vaccines protect against the B.1.167.2 variant first identified in India but only after the second dose. There are also emerging data on the efficacy or effectiveness of mRNA vaccines against B.1.351. Evidence from the Janssen vaccine clinical trials indicate that it is protective against symptomatic moderate to severe/critical COVID-19 infection in areas where COVs B.1.351 and P.2 are circulating widely. 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 persons, children) or by SARS-CoV-2 serostatus (i.e., past COVID-19 infection)
- How immune responses differ based on previous infection with non-SARS-CoV-2 coronaviruses

Due to limitations in the number of participants evaluated for immunogenicity outcomes and duration of follow up from COVID-19 clinical trial data, long-term evidence on immunogenicity is unknown. However, studies are ongoing.

The following section highlights key immunogenicity data for the authorized mRNA COVID-19 vaccines (Pfizer-BioNTech COVID-19 vaccine and Moderna COVID-19 vaccine) and viral vector based COVID-19 vaccines (AstraZeneca COVID-19 vaccine and Janssen COVID-19 vaccine) only. For additional details regarding trial design, including study population and length of follow-up, and immunogenicity for these authorized vaccines, refer to the evidence summaries in Appendix A (for the Pfizer-BioNTech COVID-19 vaccine), Appendix B (for the Moderna COVID-19 vaccine), Appendix C (for the AstraZeneca COVID-19 vaccine) and Appendix D (for the Janssen COVID-19 vaccine).

Humoral immune responses

All authorized COVID-19 vaccines induce humoral immune responses, including binding and neutralizing antibody responses. Humoral responses peaked after the second dose of mRNA vaccine, and after the second dose of AstraZeneca COVID-19 vaccine in participants who were not previously infected. Humoral immune responses were elevated after the one dose of Janssen vaccine. Some vaccines induce higher immune responses in younger populations.

Viral vector-based vaccines may induce anti-vector immune responses, which may impact future vaccine efficacy and effectiveness and may vary by age, dose, and interval between doses.

Cellular immune responses

All authorized, available COVID-19 vaccines have been shown to produce cellular immune responses. Cellular immune responses increased after the second dose of mRNA COVID-19 vaccine, while responses for AstraZeneca COVID-19 vaccine were maintained or decreased after the second dose. Cellular immune responses were present following one dose of Janssen vaccine.
IV.4 Vaccine Administration

For additional vaccine product-specific information, consult the product leaflet or information contained within the product monograph available through Health Canada's Drug Product Database. Refer to Vaccine Administration Practices in the Canadian Immunization Guide (CIG), Part 1 - Key Immunization Information for additional general information.

As for the routine administration of all vaccines, COVID-19 vaccines should be administered in settings capable of managing anaphylaxis. Refer to Anaphylaxis and other Acute Reactions Following Vaccination in the CIG, Part 2 – Vaccine Safety for information on the management of anaphylaxis post-vaccination.

IV.4.1 Dose, route of administration, and schedule

Dose

Pfizer-BioNTech 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.

Janssen 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. The deltoid muscle of the arm is the preferred injection site in adolescents and adults (unless the muscle mass is not adequate or vaccination in that site is not possible, in which case the anterolateral thigh can be used).
Refer to Vaccine Administration Practices in the CIG, Part 1 - Key Immunization Information for additional general information.

Schedule

Refer to Table 3 for a summary of immunization schedules for authorized, 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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer-BioNTech COVID-19 vaccine</td>
<td>2-dose schedule</td>
<td>19 days(^b)</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(^c)</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(^d)</td>
</tr>
<tr>
<td>Janssen COVID-19 vaccine</td>
<td>1-dose schedule</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

\(^a\) 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.

\(^b\) 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.

\(^c\) 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.

\(^d\) 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, when possible.

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). The previous dose should be counted, and the series need not be restarted.

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. At this time there is no reason to believe that mRNA vaccine series completion with a different authorized mRNA vaccine product would result in any additional safety issues or deficiency in protection.

Similarly, no data exist on the interchangeability of COVID-19 viral vector vaccines. The authorized viral vector vaccines differ in three key ways: number of doses in a complete series, SARS-CoV-2 antigen, and virus used as the vector. The AstraZeneca vaccine is a two-dose vaccine based on ChAd that encodes a wild-type spike protein. The Janssen vaccine is a one-dose vaccine based on Ad26 that encodes a spike protein stabilized in the prefusion conformation. In the event that an individual receives one dose of the AstraZeneca vaccine and is unable to receive the AstraZeneca vaccine for the second dose, one dose of Janssen vaccine (if available) can be used as the second dose to complete the vaccine series if the individual still consents to receive another viral vector vaccine (understanding the risk for VITT is currently reported to be lower than with the first AstraZeneca dose). There is limited evidence that two COVID-19 viral vector vaccines that use different adenovirus platforms can be used in the same series.
Currently, data only exist on the reactogenicity of a mixed schedule with the AstraZeneca and Pfizer-BioNTech COVID-19 vaccines (17). Studies involving mixed schedules with vaccines using different platforms 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 forthcoming once further evidence on mixed COVID-19 vaccine schedules is available (expected early June 2021).

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.

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. Genetic sequencing should be strongly considered for those with SARS-CoV-2 infection after vaccination with either one or two doses of a COVID-19 vaccine.

Anyone receiving a viral vector COVID-19 vaccine should be informed of the recently recognized adverse event of thrombosis with thrombocytopenia syndrome and advised to seek immediate medical attention if they develop symptoms within 42 days of vaccination (18). Symptoms to be vigilant for include: shortness of breath, chest pain, leg swelling, persistent abdominal pain, neurological symptoms including sudden onset of severe or persistent worsening headaches or blurred vision, skin bruising (other than at the site of vaccination) or petechiae. In addition, healthcare professionals should be aware of VITT including how to diagnose and treat the condition (see national guidance from Thrombosis Canada).

Refer to Vaccine Administration Practices in the CIG, Part 1 - Key Immunization Information for additional information on pre- and post-vaccination counseling.

IV.5 Serological testing

Serologic testing is not needed before or after immunization with COVID-19 vaccine.
IV.6 Storage requirements

**Pfizer-BioNTech 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 not exceed 2 weeks.

**Thawed, unpunctured vials (prior to dilution)**
The Pfizer-BioNTech COVID-19 vaccine may be thawed and stored at +2°C to +8°C for up to 1 month or at room temperature (up to +25°C) for no more than 2 hours. During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light. Thawed vials can be handled in room light conditions.

Do not refreeze thawed vials.

**Thawed, punctured vials (after dilution)**
The Pfizer-BioNTech COVID-19 vaccine must be stored between +2°C to below +25°C but must be discarded after 6 hours from the time of first puncture.

**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 +2ºC to +8ºC and protected from light in the original packaging. Do not freeze.

Opened multidose vial
After first opening, chemical and physical in-use stability has been demonstrated from the time of vial puncture to administration for no more than 6 hours at room temperature (up to +30ºC) or 48 hours in a refrigerator (+2ºC to +8ºC).

After the first puncture, the vial can be re-refrigerated, but the cumulative storage time at room temperature must not exceed 6 hours, and the total cumulative storage time must not exceed 48 hours. After this time, the vial must be discarded.

Janssen COVID-19 vaccine

Unopened multidose vial
The Janssen COVID-19 vaccine can be stored between +2ºC to +8ºC and protected from light in the original packaging. Do not freeze.

Punctured multidose vial
After the first dose has been withdrawn, the vial/filled syringe can be held at 2°C to 8°C for up to 6 hours or at room temperature (maximally 25°C) for up to 3 hours, after the first puncturing of the vial. Discard if vaccine is not used within this time.

For more information, consult the product leaflet or information contained within the product monograph available through Health Canada’s Drug Product Database. Refer to Storage and Handling of Immunizing Agents in the CIG, Part 1 – Key Immunization Information for additional general information.

IV.7 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 COVID-19 vaccines. For additional details regarding trial design, including study population and length of follow-up, and safety for the vaccines authorized and available for use in Canada, refer to the evidence summaries in Appendix A (for the Pfizer-BioNTech COVID-19 vaccine), Appendix B (for the Moderna COVID-19 vaccine), Appendix C (for the AstraZeneca COVID-19 vaccine) and Appendix D (for the Janssen COVID-19 vaccine). Refer to Appendix E for a summary of the frequency of AEFI for the different COVID-19 vaccine products.

Refer to Part 2 - Vaccine Safety in the CIG for definitions of AEFIs and additional general information.

IV.8.1 Very common and common adverse events

Common adverse events are defined as those that occur in 1% to less than 10% of vaccine recipients; very common adverse events occur in 10% or more of vaccine recipients. Please see Appendix E for a summary of adverse events identified in clinical trials of authorized, available COVID-19 vaccines.

Local

Pain at the injection site is very common after administration of the currently authorized COVID-19 vaccines. More than 40% of recipients experienced injection site pain. Redness and swelling are common or very common after administration. Localized axillary swelling and tenderness was a solicited adverse event in the Moderna COVID-19 clinical trial and was very common after administration with that vaccine. Local adverse events are usually mild or moderate and resolve within a few days of vaccination. For the authorized mRNA COVID-19 vaccines, pain at the injection site was slightly more frequent in younger authorized age groups including adolescents 12-15 years of age (Pfizer-BioNTech COVID-19 vaccine) compared to older adults. For AstraZeneca COVID-19 vaccine, local reactions were milder and reported less frequently after the second vaccine dose in all age groups. Similar frequencies of local reactions were reported across age groups after administration of the Janssen vaccine.

Systemic

Fatigue, headache, muscle pain, chills, and joint pain are all either common or very common after the administration of the currently authorized COVID-19 vaccines. Fever was very common after administration of the second dose of the mRNA COVID-19 vaccines and common after any dose
of viral vector vaccines. More than a quarter of vaccine recipients experienced headache and/or fatigue after any dose. Systemic adverse events are usually mild or moderate intensity and resolve within a few days of vaccination. For the mRNA COVID-19 vaccines, systemic reactions are more frequent after the second vaccine dose and in younger authorized age groups including adolescents 12-15 years of age (Pfizer-BioNTech COVID-19 vaccine). For AstraZeneca COVID-19 vaccine, systemic reactions are milder and reported less frequently after the second vaccine dose than the first in all age groups. Similar frequencies of local reactions were reported across age groups after administration of the Janssen vaccine.

**Adverse events following the second dose of COVID-19 in individuals previously infected with SARS-CoV-2**

Evidence on the safety of vaccine booster doses is available from observational\(^{(19)}\) and clinical studies\(^{(20)(21)(22)}\). Occurrence of solicited and unsolicited systemic adverse events in individuals with prior SARS-CoV-2 infection was slightly higher compared to the SARS-CoV-2 naïve population, primarily in younger adults. However, there was no observed increase in the frequency of more severe adverse events in this population. Two observational studies included less than 100 patients with persistent symptoms from prior COVID-19 infections (long COVID). In this subgroup, receipt of COVID-19 vaccination with either an mRNA or viral vector vaccine was not associated with a worsening of long COVID symptoms or increased reactogenicity following immunization.

**IV.8.2 Uncommon, rare, and very rare adverse events**

Uncommon adverse events occur in 0.1% to less than 1% of vaccine recipients. Rare and very rare adverse events occur in 0.01% to less than 0.1% and less than 0.01% of vaccine recipients, respectively. The probability of detection of very rare adverse events in clinical trials is low given clinical trial population sizes; therefore, ongoing pharmacovigilance is essential.

To date, the available data does not indicate that vaccination of SARS-CoV-2 naïve individuals with authorized COVID-19 vaccines will elicit enhanced or altered disease upon subsequent infection by SARS-CoV-2 (e.g., vaccine-enhanced disease); however, further study is needed.

Lymphadenopathy was a solicited event in the Moderna clinical trials but not in other authorized COVID-19 vaccine trials see Appendix E). It was uncommonly reported after administration of the Pfizer-BioNTech, AstraZeneca and Janssen COVID-19 vaccines.

No other solicited uncommon, rare, or very rare adverse events were reported among vaccinated participants in the clinical trials at this time.

**Thrombosis with Thrombocytopenia following vaccination with viral vector COVID-19 vaccines**

Very rare cases of serious blood clots (at unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis) associated with thrombocytopenia have been reported globally following vaccination with viral vector COVID-19 vaccines. The terminology for this syndrome has been evolving since the safety signal was detected. In Canada, the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) uses the
case definition for Thrombosis with Thrombocytopenia Syndrome (TTS) \(^{(23)}\) to detect these rare events in Canada. Cases that test positive for a biomarker, anti-PF4 (antibodies to platelet factor 4-polyanion complexes), represent a subset of TTS events and are being referred to clinically as Vaccine-Induced Prothrombotic Immune Thrombocytopenia (VIPIT) or Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT).

International case reports and case series have raised the signal that those cases found to be positive for anti-PF4 could be associated with viral vector vaccines \(^{(24)(25)(26)(27)(28)(29)}\). Evidence on the association between TTS following vaccination with the viral vector COVID-19 vaccines is evolving; however, multiple international surveillance systems have early data that consistently point towards an association between adenovirus vector COVID-19 vaccines and TTS, including in the US, UK, and Europe. The exact mechanism by which the viral vector COVID-19 vaccines may trigger this syndrome is still under investigation but viral vector vaccines appear to trigger a presentation similar to spontaneous heparin-induced thrombosis (HIT) / autoimmune heparin-induced thrombosis, where antibodies to platelet factor 4 (PF4)-polyanion complexes induce platelet activation, which causes thrombosis and thrombocytopenia \(^{(26)}\). Clots related to VITT can be very aggressive and challenging to treat \(^{(30)}\). Please refer to Thrombosis Canada guidance for clinical management of VITT. They cannot be managed the same way as clots related to oral contraceptives, immobility, or long haul flights, and have an entirely different biologic mechanism of action.

Cases of VITT usually occur between 4 and 28 days after receipt of a viral vector COVID-19 vaccine, and patients should be monitored for symptoms up to 42 days \(^{(31)}\). The rate of VITT is estimated to be between 1 per 26,000 and 1 per 100,000 persons vaccinated with a first dose of AstraZeneca/COVISHIELD COVID-19 vaccine. As of May 12, 2021, PHAC has estimated the rate of VITT in Canada to be 1 in 83,000 doses administered. However, as investigations continue, this rate could be as high as 1 in 55,000. For updates to the numbers of cases of TTS and VITT in Canada, please see the "Serious and non-serious adverse events reported" section of Reported side effects following COVID-19 vaccination in Canada. The frequency of VITT following a second dose of AstraZeneca vaccine is currently reported as approximately 1 per 600,000 individuals vaccinated with a second dose, based on vaccine safety surveillance data from the United Kingdom but this continues to evolve \(^{(28)}\). The case fatality rate of VITT also varies between countries, and ranges between 20 and 50%. Many cases have been reported to have serious long-term morbidity, including neurologic injury. Reports of VITT after administration of the Janssen vaccine are emerging from the United States. As of May 18, 2021, 30 cases have been confirmed after 9.6 million doses of Janssen vaccine administered in the United States, and others are under investigation. For more information, see Appendix C, Appendix D, 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/](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 Special Populations

The following populations were either excluded from, or included in small numbers, in clinical trials for the COVID-19 vaccines. However, real-world data from the use of COVID-19 vaccines in these populations is accumulating. NACI will continue to monitor the evidence and update recommendations as needed.

Individuals previously infected with SARS-CoV-2

In studies that reported immune responses in individuals with previous SARS-CoV-2 infection anti-spike and anti-RBD IgG concentrations, neutralizing titres and B and T cell responses after dose 1 were comparable to those observed in SARS-CoV-2 naïve individuals following the administration of the second vaccine dose. Elevated binding and neutralizing antibody responses were seen for both symptomatic and asymptomatic people who were previously infected compared to vaccine recipients who weren’t previously infected. These findings were consistent with those reported by the RECOVER study investigators. However, in the absence of an established correlate of protection, it is not possible to determine the significance of these findings as they relate to the level of protection against reinfection.

Individuals who are immunosuppressed due to disease or treatment

Evidence on the safety of COVID-19 vaccination in these individuals is emerging. Safety data in immunocompromised individuals, including those receiving immunosuppressive therapy, were available from observational studies in solid organ transplant recipients, cancer patients and individuals with chronic inflammatory diseases who were taking immunosuppressive therapies. The frequency and severity of adverse events following vaccination with an mRNA COVID-19 vaccine in these populations were comparable to that of non-immunosuppressed individuals in these studies and what was reported in clinical trials. Safety data in these populations following vaccination with a viral vector vaccine is not available.

The efficacy and effectiveness of COVID-19 vaccines in immunosuppressed populations is currently unknown, but evidence of a diminished immune response is emerging. Immunogenicity data in immunocompromised individuals, including those receiving immunosuppressive therapy, were available from observational studies in solid organ transplant recipients, cancer patients and individuals with chronic inflammatory diseases who were taking immunosuppressive
Therapies\(^{(51)}\)(52)(44)(43)(45)(54)(55)(56)(57)(58)(48)(59)(60)(61)(62)(63)(64)(39)(65)(41)(42). Study participants showed diminished or delayed immune responses to mRNA or AstraZeneca COVID-19 vaccines. The type of immunosuppressive therapy or condition affected the immune response to COVID-19 vaccines, leading to a lack of humoral and cellular responses in some cases or diminished levels in those who did develop responses compared to healthy controls. Given the limited number of participants and the lack of an immunological correlate of protection against SARS-CoV-2 infection, there are limitations in interpreting the significance of these results. The same general principles may apply to those with chronic kidney disease receiving hemodialysis (for whom there is strong evidence of an increased risk of mortality for COVID-19), as individuals with impaired renal function have a less than optimal response to immunization \(^{(48)}(59)(50)(61)(62)(63)(64)(39)(65)(41)(42),\(^{(60)}\)(66).\)

**Individuals who have an autoimmune condition**

Emerging safety data from observational studies in individuals with autoimmune conditions indicates that the frequency and severity of adverse events in this population is comparable to that of individuals without autoimmune conditions and what was reported in clinical trials \(^{(37)}(38)(39)(40)(41),\(^{(42)}(78).\) The onset of new autoimmune disease or disease exacerbation following vaccination with mRNA COVID-19 vaccines was rare or comparable to the background incidence of these events in the general population. Safety data in this population following vaccination with a viral vector vaccine is not available.

The efficacy and effectiveness of COVID-19 vaccines in individuals with autoimmune conditions is unknown, but immunogenicity data is emerging. Data were available from observational studies in which participants received the mRNA or the AstraZeneca COVID-19 vaccines \(^{(64)}(39)(65)(41),\(^{(66)}(42).\) Immune responses were diminished only in participants who were also receiving immunosuppressive therapy. Given the limited number of participants and the lack of an immunological correlate of protection against SARS-CoV-2 infection, there are limitations in interpreting the significance of these results.

**Individuals who are pregnant or breastfeeding**

Evidence regarding the safety and immunogenicity of COVID-19 vaccines in individuals who are pregnant or breastfeeding are emerging. Pre-clinical studies on the safety of COVID-19 vaccines from animal developmental and reproductive toxicity studies did not identify concerns regarding female reproduction, fetal/embryonal development, or postnatal development following the administration of the Moderna COVID-19 vaccine prior to or during gestation \(^{(79).}\) A report presented to the European Medicines Agency (EMA) also did not indicate adverse effects with respect to fertility, pregnancy, embryo/fetal development, or postnatal development (up to day 21) in studies in rats using a full dose of the Pfizer-BioNTech COVID-19 vaccine \(^{(80).}\) A US Food and Drug Administration (FDA) review of a study in rabbits that received the Janssen COVID-19 vaccine at two times the human dose prior to or during gestation similarly concluded there were no adverse effects on female reproduction, fetal/embryonal development, or postnatal development \(^{(81).}\) AstraZeneca performed a preliminary DART study in 32 female mice given the vaccine prior to or during gestation and found no effects of female reproduction, fetal or pup survival or development. Their main DART study in mice is ongoing \(^{(82).}\)

Analysis of data collected through international COVID-19 immunization registries to date have not revealed any maternal or neonatal safety signals, and preliminary analyses of over 35,000 pregnant women in the United States who received an mRNA COVID-19 vaccine did not reveal
any obvious safety signals (83) In one small cohort study, mRNA from COVID-19 vaccines was undetectable in breastmilk 4-48 hours post-vaccination (84).

Emerging evidence suggests that COVID-19 mRNA vaccination during pregnancy is also immunogenic and results in comparable antibody titres to those generated in non-pregnant women (85)(86)(87). Maternal IgG humoral response to mRNA COVID-19 vaccines transfers across the placenta to the fetus, leading to a significant and potentially protective, antibody titre in the neonatal bloodstream one week after the second dose (88)(89)(90). Observational studies consistently show that both anti-spike IgG and IgA are present in breastmilk for at least 6 weeks after maternal vaccination with mRNA vaccines (91)(92)(93)(94).

IV.10 Contraindications and Precautions

Rare anaphylactic reactions have been reported following immunization with mRNA COVID-19 vaccines.

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.

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>
<tr>
<td>Janssen 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>

\(^a\) Medications that contain PEG are described in Stone CA, et al., DOI:10.1016/j.jaip.2018.12.003
\(^b\) A review of immediate type hypersensitivity reactions to PEG is available in Wenande et al, DOI: 10.1111/cea.12760
\(^c\) There is a potential of cross-reactive hypersensitivity between PEG and polysorbates
\(^d\) PEG is an additive in some food and drinks but allergic reactions to PEG in food or drinks have not been documented.
\(^e\) One case report of anaphylaxis to tromethamine has been described (Lukawska et al, DOI: 10.1016/j.jaip.2018.08.035).
\(^f\) Case reports of anaphylaxis to polysorbate 80 have been described (Badiu et al, DOI: 10.1136/bcr.02.2012.5797, Palacios Castaño et al, DOI: 10.18176/jiaci.0109).

Rare cases of VITT have been reported following immunization with viral vector COVID-19 vaccines. Investigations are ongoing and the recommendations will be updated as evidence becomes available. For more information, refer to Appendix C, Appendix D, and NACI rapid response: Recommended use of AstraZeneca COVID-19 vaccine in younger adults.

Contraindications

Anaphylaxis and Allergies to a COVID-19 vaccine

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 an 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.

Thrombosis and Thrombocytopenia following vaccination

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

Precautions

Hypersensitivity and Allergies

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.
Acute illness

Vaccination of individuals who may be currently infected with SARS-CoV-2 is not known to have a detrimental effect on the illness. However, vaccination should be deferred in symptomatic individuals with confirmed or suspected SARS-CoV-2 infection, or those with respiratory symptoms, in order to avoid attributing any complications resulting from SARS-CoV-2 infection to vaccine-related AEFI and to minimize the risk of COVID-19 transmission at an immunization clinic/venue. If any persons are identified with symptoms on arrival at the venue, they should be instructed to follow current local public health measures.

As a precautionary measure and in light of the need to be able to monitor for COVID-19 vaccine adverse events without potential confounding from symptoms of COVID-19 or other co-existing illnesses, one should wait until all symptoms of an acute illness are resolved before vaccinating with an authorized COVID-19 vaccine.

Hematologic

In individuals with bleeding disorders, the condition should be managed prior to immunization to minimize the risk of bleeding. Individuals receiving long-term anticoagulation are not considered to be at higher risk of bleeding complications following immunization and may be safely immunized without discontinuation of their anticoagulation therapy.

Thrombosis and Thrombocytopenia

Individuals who have experienced a previous CVST with thrombocytopenia or heparin-induced thrombocytopenia (HIT) should only receive a viral vector COVID-19 vaccine if the potential benefits outweigh the potential risks. An alternate COVID-19 vaccine should be offered.

Anyone receiving any authorized viral vector COVID-19 vaccine should be informed of the risk of VITT and advised to seek immediate medical attention if they develop symptoms of VITT. These symptoms may include: shortness of breath, chest pain, leg swelling or pain, or persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms after vaccination including sudden onset of severe headaches, persistent or worsening headaches, blurred vision, confusion or seizures, or who experiences unusual skin bruising or petechiae beyond the site of vaccination after a few days, should seek prompt medical attention.

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

IV.11 Drug Interactions

There have been no drug interactions studies performed to date.

For more information about potential interactions with products containing anti-SARS-CoV-2 antibodies, refer to section IV.11 Blood products, human immunoglobulin and timing of immunization, in this Statement.
Tuberculin skin testing (TST) or Interferon Gamma Release Assay (IGRA)

There is a theoretical risk that mRNA or viral vector vaccines may temporarily affect cell-mediated immunity, resulting in false-negative TST or IGRA test results. If tuberculin skin testing or an IGRA test is required, it should be administered and read before immunization or delayed for at least 4 weeks after vaccination. Vaccination with COVID-19 vaccines may take place at any time after all steps of tuberculin skin testing have been completed.

In cases where an opportunity to perform the TST or IGRA test might be missed, the testing should not be delayed since these are theoretical considerations. However, re-testing (at least 4 weeks post immunization) of individuals with negative results for whom there is high suspicion of tuberculosis infection may be prudent in order to avoid missing cases due to potentially false-negative results.

IV. 12 Blood Products, Human Immunoglobulin and Timing of Immunization

NACI recommends that COVID-19 vaccines should not be given simultaneously with monoclonal antibodies or convalescent plasma.

To date, there is insufficient evidence on the receipt of both a COVID-19 vaccine and anti-SARS-CoV-2 monoclonal antibodies or convalescent plasma for treatment or prevention. Therefore, timing of administration and potential interference between these two products are currently unknown. Administration of these products close together may result in decreased effectiveness of a COVID-19 vaccine and/or anti-SARS-CoV-2 monoclonal antibodies because the monoclonal antibodies have high affinity for the spike protein expressed by the vaccines, which could prevent the production of antibodies stimulated by the vaccine.

In the post-exposure setting, expert clinical opinion should be sought on a case-by-case basis when deciding whether anti-SARS-CoV-2 monoclonal antibodies would be appropriate to administer after receipt of COVID-19 vaccine, taking into consideration the risk of exposure and the risk of severe COVID-19 disease in the individual.

To date, there is also insufficient evidence on the receipt of both a COVID-19 vaccine and any monoclonal antibodies or convalescent plasma for treatment or prevention of non-COVID-19 disease. Therefore, timing of administration and potential interference between these two products are currently unknown and expert clinical opinion should be sought on a case-by-case basis.

V. RECOMMENDATIONS

Following the thorough review of available evidence summarized above, as well as the systematic assessment of ethics, equity, feasibility and acceptability considerations with the EEFA Framework (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 for use in Canada (Pfizer-BioNTech COVID-19 vaccine; Moderna COVID-19 vaccine; AstraZeneca COVID-19 vaccine; and Janssen COVID-19 vaccine). In considering these recommendations and for the purposes of publicly funded program implementation, provinces and territories may consider local programmatic factors (e.g., logistical and operational contexts, resources) and local epidemiology (e.g., transmission of SARS-CoV-2 VOC).

1. **NACI preferentially recommends that a complete series with an mRNA COVID-19 vaccine should be offered to individuals in the authorized age group without contraindications to the vaccine.** 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 a viral vector COVID-19 vaccine may be offered to individuals 30 years of age and older without contraindications, only if the individual prefers an earlier vaccine rather than 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 viral vector 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.

   *(Discretionary NACI Recommendation)*

*See Risk Assessment Tool below and Management Options Table to assist with this determination*

*Risk Assessment Tool for the use of viral vector COVID-19 vaccines*

The benefit-risk analysis for vaccination with a viral vector COVID-19 vaccine while an authorized mRNA COVID-19 vaccine is temporarily unavailable or inaccessible may vary between jurisdictions and individuals and will depend on various factors, summarized in the table below.
<table>
<thead>
<tr>
<th>Factors that may vary between jurisdictions and individuals</th>
<th>Considerations¹</th>
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| Local COVID-19 epidemic conditions                          | • The benefit of viral vector COVID-19 vaccines increases 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.  
  • Consider local transmission potential for viral variants of concern and anticipated protection against them. |
| Local vaccine supply                                         | • Consider how long an individual will need to wait to be offered an mRNA vaccine, based on expected vaccine supply and priority group. |
| Risk of severe illness and death                             | • Consider offering available viral vector COVID-19 vaccines 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                                             | • Consider offering available viral vector COVID-19 vaccines 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                                    | • Although the viral vector COVID-19 vaccines are refrigerator-stable, which makes these vaccines easier to store and handle, infrastructure now exists to support the use of ultra-frozen and frozen mRNA vaccines.  
  • The Janssen COVID-19 vaccine is authorized as a single dose; however, the duration of protection of one dose is unknown. |
| Risk of VITT                                                 | • The rate of this adverse event has been estimated to be between 1/26,000 and 1/100,000 persons vaccinated with the first dose of AstraZeneca COVID-19 vaccine. The estimated rate of VITT in Canada as of May 12, 2021 is closer to 1/83,000. The rate of VITT after the second dose of AstraZeneca COVID-19 vaccine has been reported to be lower (than the first dose) but is increasing as new cases are identified. Rates of VITT are evolving as cases continue to be reported and investigated. The case fatality rate typically ranges between 20 and 50%. Predisposing factors for VITT are unclear.  
  • The frequency of this adverse event following the Janssen COVID-19 vaccine is emerging in the United States. As of May 18, 2021, 30 cases have been confirmed after 9.6 million doses of the Janssen vaccine administered. Most of these cases were in females between 18 and 49 years of age, however additional cases are under investigation. Initial cases of VITT after vaccination with AstraZeneca COVID-19 vaccine were also seen in younger females; however, reports of VITT in older adults and in males have more recently been confirmed. |
Vaccine characteristics

- Emerging data suggests that all authorized COVID-19 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 viral vector vaccines.
- There is evidence that both the Pfizer-BioNTech and AstraZeneca vaccines protect against the B.1.1.7 SARS-CoV-2 variant, and emerging evidence suggesting they protect against the B.1.617.2 SARS-CoV-2 variant but only after the second dose. In studies in South Africa, the Janssen vaccine was shown to offer protection against the B.1.351 SARS-CoV-2 variant, while the AstraZeneca vaccine was shown not to offer protection against that variant of concern. In studies in Brazil, the Janssen vaccine was shown to offer protection against the P.2 variant.
- Early evidence suggests that the Pfizer-BioNTech vaccine has moderate to high effectiveness against asymptomatic infection, with some evidence of protection available for Moderna and Janssen as well. Early evidence suggests that the AstraZeneca vaccine may not be efficacious against asymptomatic infections.

Access to diagnosis and treatment for COVID-19 and VITT

- Consider healthcare system capacity, access to tertiary and ICU care, as well as IVIG for treatment of VITT.

Risk of exacerbating inequities

- The use of viral vector COVID-19 vaccines 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 viral vector COVID-19 vaccines.
- Consider the impact of exacerbating inequities in these populations, many of whom belong to marginalized and disadvantaged groups disproportionately affected by the pandemic.

NACI is monitoring evolving evidence.

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 12 years of age and older (Pfizer-BioNTech COVID-19 vaccine) and in individuals 18 years of age and older (Moderna COVID-19 vaccine). Non-replicating viral vector vaccines are authorized for use in Canada for individuals 18 years of age and older (AstraZeneca COVID-19 vaccine, Janssen COVID-19 vaccine).
- A complete series for all currently authorized and available COVID-19 vaccines is two doses except for the Janssen COVID-19 vaccine which is authorized as a single dose.
• See Table 1 for risk factors associated with increased risk of severe outcomes from COVID-19 and increased risk of exposure to COVID-19. Please refer to NACI’s Guidance on the prioritization of key populations for COVID-19 immunization for additional details on sequencing of key populations, including a comprehensive analysis of ethical, equity, feasibility and acceptability considerations.

**mRNA COVID-19 vaccines**

• Clinical trial data available to date have shown that the currently authorized mRNA COVID-19 vaccines are highly efficacious (≥94%) in preventing confirmed symptomatic COVID-19 disease in the short term, starting at one to two weeks after receiving the full two-dose series.
• Highest efficacy and maximum immune response were observed after the second dose. Efficacy of a two-dose series was consistent across age groups.
• Estimates of vaccine effectiveness of the Pfizer-BioNTech vaccine were comparable in countries where the predominant circulating strain was the B.1.1.7 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 COVID-19 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, with concurrent thrombocytopenia have been reported globally following post-licensure use of
viral vector COVID-19 vaccines. The exact mechanism by which these vaccines may trigger thrombosis with thrombocytopenia is still under investigation. The case fatality rate typically ranges between 20 and 50%.

- 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$^2$).

**Janssen COVID-19 vaccine**

- Clinical trial data available to date have shown that the Janssen COVID-19 vaccine is 67% efficacious against moderate to severe/critical symptomatic COVID-19 disease at least two weeks after receiving one dose.
- Efficacy was consistent across age groups.
- Point estimates of vaccine efficacy against confirmed symptomatic moderate to severe/critical COVID-19 infection from 28 days post-vaccination were comparable in the trial conducted in Brazil (68%), where two-thirds of the isolates were of the P.2 lineage and in the one conducted in South Africa (64%), where almost all isolates were of the B.1.351 lineage.
- Local and systemic adverse events were typically mild and transient, and no safety signals were detected in clinical trials.
- As of May 18, 2021, 30 TTS cases were confirmed to have tested positive for anti-PF4 antibodies after 9.6 million doses of Janssen vaccine administered in the United States. Investigations regarding the association between Janssen and VITT are ongoing.
- The vaccine is similarly safe and efficacious in those with one or more comorbidities 14 days after vaccination, although efficacy is somewhat lower in participants with comorbidities at 28 days post-vaccination.

**mRNA COVID-19 vaccines versus viral vector COVID-19 vaccines**

NACI reviewed the recent epidemiology of COVID-19 in Canada (including circulation of variants), vaccine characteristics (including efficacy, effectiveness, safety), evidence and international guidance on VITT, anticipated vaccine supplies, Health Canada’s assessment of COVID-19 vaccines, as well as a comprehensive analysis of the implications on ethics, equity, feasibility and acceptability $^2$ 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, if one had to wait for an mRNA vaccine given Canada’s expected vaccine supply, compared to COVID-19 ICU admissions and deaths that could be prevented by an early dose of the AstraZeneca or Janssen COVID-19 vaccines, by age across various COVID-19 epidemiologic scenarios (very low, low, moderate, high, very high activity). Please refer to archived versions of the NACI statement to see the risk benefit analysis. However, given the increase in VITT rates observed, the decrease in COVID-19 disease incidence in Canada, and the shorter time to mRNA availability, provinces and territories have reassessed the use of the AstraZeneca vaccine. 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 viral vector COVID-19 vaccines 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.
At this time, NACI cautions that there is uncertainty in the evidence of advantages and disadvantages of the use of viral vector COVID-19 vaccines for all Canadians, because this will depend on local COVID-19 epidemiology, wait time for an mRNA vaccine, as well as other individual risk factors (such as risk of exposure) summarized in its Risk Assessment Tool. Therefore, NACI made a discretionary recommendation on the use of viral vector COVID-19 vaccines for individuals who prefer an earlier vaccine rather than wait for an mRNA vaccine, only if certain conditions are met (including a benefit-risk analysis, informed consent, and substantial delay for receipt of an mRNA vaccine). On the other hand, the advantages of highly efficacious mRNA COVID-19 vaccines, with no confirmed safety signals of concern to date, outweigh any possible disadvantages for eligible 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 a viral vector 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 a viral vector COVID-19 vaccine increases in regions of moderate, high, or very high epidemic transmission of SARS-CoV-2 strains for which these vaccines offer protection and in areas of increasing COVID-19 incidence rates.

- **Efficacy and Effectiveness:** Emerging data suggests that all authorized vaccines offer protection against hospitalization and likely also death from COVID-19. In clinical trials, mRNA COVID-19 vaccines demonstrated higher efficacy than was shown for the viral vector COVID-19 vaccines. There is evidence that both the Pfizer and AstraZeneca COVID-19 vaccines offer protection against the B.1.1.7 SARS-CoV-2 variant, and emerging evidence suggesting they protect against the B.1.617.2 SARS-CoV-2 variant but only after the second dose. Pfizer and Janssen COVID-19 vaccines seem to offer protection against the B.1.351 SARS-CoV-2 VOC, but the AstraZeneca COVID-19 vaccine does not. In studies in Brazil, the Janssen vaccine was shown to offer protection against the P2 variant. There is limited evidence on the protection of mRNA or viral vector COVID-19 vaccines against the P.1 variant.

- **Safety and VITT:** Evidence on the association between VITT following vaccination with the viral vector COVID-19 vaccines is evolving, however multiple international surveillance systems have early data that consistently point towards an association between adenovirus vector COVID-19 vaccines and TTS, including in the US, UK, and Europe. 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). The Janssen vaccination program in the United States was paused to investigate cases of VITT; however, this pause was lifted on April 23 after a review of the data. No clear pattern or predisposing risk factors have been identified to date among cases of VITT. Though most cases in the United States to date have been identified in females younger than 50 years of age who received the Janssen vaccine, cases in males are being investigated and the case that has now been linked to this syndrome in the clinical trial was a male. In Europe, initial cases of VITT after vaccination with
AstraZeneca COVID-19 vaccine were also seen in younger females; however, this is no longer the case as reports of VITT in older adults and in males have been confirmed.

- **Public health benefit-risk assessment:** Age-based benefit-risk analyses were conducted to determine if the benefit of earlier vaccination with a viral vector 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 analyses were conducted, when the estimated incidence rate of VITT was between 1/100,000 and 1/250,000, 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 under most conditions. The benefits of earlier vaccination with AstraZeneca COVID-19 vaccine in younger age groups and in areas with low COVID-19 activity were more sensitive to change, depending on the assumed rate of VITT, which continues to change rapidly as new cases are identified. A benefit-risk assessment was not completed for adults 70 years or older for either viral vector vaccine as mRNA vaccine is already available to this age group in Canada. Internationally, reported incidence rates of VITT now range between 1/26,000 and 1/100,000.

- **Ethics:** NACI consulted with the Public Health Ethics Consultative Group (PHECG) on the ethical considerations for restricting the use of a viral vector vaccine in the current and anticipated pandemic and vaccine supply context. The PHECG provided recommendations in the following areas: promoting well-being and minimizing risk of harm, maintaining trust, respect for persons and fostering autonomy, and promoting justice and equity. NACI integrated these recommendations into its guidance (e.g., enabling respect for persons and autonomy by incorporating informed consent into the discretionary recommendation for use of a viral vector vaccine; promoting justice and equity by specifically identifying risks to exacerbating inequities in the Risk Assessment Tool). NACI applied the precautionary principle in making its discretionary recommendation, and took into account the evolving evidence on VITT, the potential for harm, biologic plausibility for a class effect with the viral vector vaccine platform common to the AstraZeneca and Janssen COVID-19 vaccines, the availability of other effective vaccines without this safety signal, as well as evidence of the effectiveness of alternate infection prevention and control measures.

- **Equity:** NACI examined the implications of various recommendation options on the opportunity for all populations to have a fair opportunity to attain their full health potential (2). Populations that receive a viral vector 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 disproportionally 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 Tool 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 viral vector 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 viral vector COVID-19 vaccines, infrastructure now exists to support the use of ultra-frozen and frozen mRNA vaccines. The Janssen vaccine is authorized as a single dose vaccine; however, the duration of protection against COVID-19 is unknown.

Acceptability: NACI reviewed recent Canadian data to consider the potential impact of its recommendations on intention and behaviours toward COVID-19 vaccination. The desire to be vaccinated continues to rise. However, various populations who have been disproportionately affected by the pandemic are also more hesitant or experience barriers in receiving a COVID-19 vaccine (e.g., racialized populations, migrant or undocumented workers). While public opinion research conducted in March suggested 44-60% of Canadians had no preference on which vaccine they received, surveys conducted in early April found that Canadians who are planning to get vaccinated are far more comfortable with the mRNA vaccines (90-92%) than the Janssen (70%) or AstraZeneca (41%) vaccines. 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. NACI recommends that jurisdictions should maximize the number of individuals benefiting from the first dose of a COVID-19 vaccine by extending the second dose of COVID-19 vaccine up to four months after the first. With the expansion of COVID-19 vaccine supply in Canada, second doses should be offered as soon as possible, with priority given to those at highest risk of severe illness and death from COVID-19 disease after or concurrent with first doses for all remaining eligible populations. (Strong NACI Recommendation)

Summary of evidence and rationale:

- Morbidity and mortality from COVID-19 is ongoing. 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. The interval between first and second dose may be shortened based on increasing vaccine supply and should not be extended longer than needed to offer first doses of vaccine to eligible individuals.
- Because of ongoing disease transmission and less than complete individual protection from vaccination in particular after the first dose of vaccine, ongoing compliance with public health measures (masking, physical distancing and limiting social interactions as per public health guidance) should continue at this time. 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
c 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.
- The effectiveness of the extended dose strategy will be monitored on an ongoing basis.
  If indicated, recommendations will be revised.

This recommendation applies to all two-dose COVID-19 vaccines currently authorized for use
and available in Canada.

Please see NACI’s Statement on 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 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 and Janssen 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.
• On March 30, NACI reaffirmed its recommendation that those previously infected with SARS-CoV-2 be offered a complete series with a COVID-19 vaccine, after considering evidence from observational studies that reported on the immunogenicity and safety of vaccination in previously infected individuals, safety data from pivotal clinical trials of vaccines approved for use in Canada, as well as presentations from the Canadian National Vaccine Safety Network and the University of Montreal RECOVER study.
• In the absence of one-dose vaccine effectiveness data in previously infected individuals (particularly as it relates to the variants of concern), limited second-dose safety data (i.e. impact of disease severity and the interval since previous infection on reactogenicity), and the potential programmatic challenges associated with the communication and implementation of a one-dose strategy, people with previous SARS-CoV-2 infection should continue to receive a complete vaccine series at the recommended intervals, regardless of the severity of their previous infection.
• Currently, there is a lack of evidence on potential differences in vaccine efficacy 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.
• There is currently limited data on potential differences in reactogenicity between those with and without prior evidence of SARS-CoV-2 infection. There is a lack of evidence regarding the impact of the severity of the previous infection and the impact of the interval between a previous infection and timing of the first dose on reactogenicity.
• The immune response to SARS-CoV-2 and variants of concern, including duration of immunity and cross-protection, is not yet well understood. Reinfections with SARS-CoV-2 and variants have been reported and research to establish the severity, frequency, and risk factors of reinfection is ongoing. There is limited data suggesting individuals with previous infection may generate a comparable or greater immune response to a single dose of vaccine compared to SARS-CoV-2 naïve individuals after receiving 2 doses.
• 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 key population.
• 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 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.

The following populations were either excluded from or were represented by small numbers of participants in the original pivotal clinical trials. NACI has updated recommendations for these populations as real-world evidence (mostly with mRNA vaccination) has become available. The recommendations above on the use of mRNA COVID-19 vaccines (Recommendation #1) and the use of viral vector COVID-19 vaccines (Recommendation #2), now also apply to those who are immunosuppressed, have autoimmune conditions, are pregnant or are breastfeeding.

**Immunosuppressed persons**

6. NACI preferentially recommends that a complete COVID-19 vaccine series with an mRNA COVID-19 vaccine should be offered to individuals in the authorized age group who are immunosuppressed due to disease or treatment. If an mRNA vaccine is contraindicated, another authorized COVID-19 vaccine should be offered. Informed consent should include discussion about the possibility that individuals who are immunosuppressed may have a diminished immune response to any of the authorized COVID-19 vaccines. (**Strong NACI Recommendation**)  

7. NACI recommends that a complete series with a viral vector COVID-19 vaccine may be offered to individuals 30 years of age and older who are immunosuppressed if the conditions outlined in Recommendation #2 (above) are met. Informed consent should include discussion about the limited evidence on the use of viral vector COVID-19 vaccines in this population. (**Discretionary NACI Recommendation**)  

**Summary of evidence and rationale**

- Participants in the COVID-19 vaccine clinical trials only included individuals who were not immunosuppressed, such as those with stable infection with human immunodeficiency virus (HIV), and those not receiving immunosuppressive therapy during the trial. However, real-world evidence (mostly with mRNA vaccination) has become available.  
- The efficacy of COVID-19 vaccines in immunocompromised individuals is currently unknown. **Individuals should continue to follow recommended public health measures for prevention and control of SARS-CoV-2 infection and transmission.** Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the vaccine. **A vaccine series should ideally be completed at least two weeks before initiation of immunosuppressive therapies where possible.**  
- 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.  
- Safety data in immunocompromised individuals, including those receiving immunosuppressive therapy, were available from observational studies in solid organ transplant recipients, cancer patients and individuals with chronic inflammatory diseases who were taking immunosuppressive therapies (37)(38)(39)(40)(41)(42)(43)(44)(45)(46)(47)(48)(49)(50). The frequency and severity of adverse events following vaccination with an mRNA COVID-19
vaccine in these populations were comparable to that of non-immunosuppressed individuals in these studies and what was reported in clinical trials. Safety data in these populations following vaccination with a viral vector vaccine is not available.

- Observational studies in solid organ transplant recipients, cancer patients and individuals with chronic inflammatory diseases who are taking immunosuppressive therapies showed diminished or delayed immune responses to mRNA or AstraZeneca vaccines. There is limited evidence that immune responses improve after a second dose of vaccine and the degree of improvement varies according to the type of immunosuppressive therapy or condition. Given the limited number of participants and the lack of an immunological correlate of protection against SARS-CoV-2 infection, there are limitations in interpreting the significance of these observational studies.

- In general, non-replicating vaccines may be administered to immunocompromised people. 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 should be vaccinated. In observational studies and clinical trials, humoral and cellular immune responses were similar between fully vaccinated people living with HIV and those who were HIV-negative.

- 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.

- Currently, there is limited evidence about immunodeficiency or immunosuppression as an independent risk factor for severe COVID-19, though evidence is evolving. A rapid review of evidence from OECD member countries found a moderate certainty of evidence for little-to-no association with mortality due to COVID-19 in those with unspecified immunosuppression and little-to-no increase in hospitalization due to COVID-19 with malignancy. 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 (in people <70 years); 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. There was also low certainty evidence for at least a two-fold increase in hospitalization due to COVID-19 in transplants of any type. 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.

- Recent Canadian surveillance data indicates that compared to the general population, a higher proportion of the immunocompromised population or those with malignancy are hospitalized or admitted to the ICU due to COVID-19.

- 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

8. NACI preferentially recommends that a complete vaccine series with an mRNA COVID-19 vaccine should be offered to individuals in the authorized age group with an autoimmune condition. If an mRNA vaccine is contraindicated, another authorized COVID-19 vaccine should be offered. Informed consent should include discussion about the emerging evidence on the safety of mRNA COVID-19 vaccines in these populations. (*Strong NACI Recommendation*)

9. NACI recommends that a complete series with a viral vector COVID-19 vaccine may be offered to individuals 30 years of age and older who have an autoimmune condition if the conditions outlined in Recommendation #2 (above) are met. Informed consent should include discussion about the limited evidence on the use of viral vector COVID-19 vaccines in this population. (*Discretionary NACI Recommendation*)

Summary of evidence and rationale

- Although participants with autoimmune conditions who were not immunosuppressed were not excluded from trials, they constitute a very small proportion of trial participants and represent a very narrow range of autoimmune conditions. However, real-world evidence (mostly with mRNA vaccination) has become available.
- Other applications of mRNA technologies have been for the treatment of cancer, which requires an immune response directed against an individual’s cancer cells. This raised the theoretical concern that mRNA vaccines for infectious diseases would behave similarly, eliciting inflammation and possibly exacerbating existing autoimmune diseases. Current applications of mRNA technology for COVID-19 vaccines have been optimized to reduce this risk; however, further evaluation is needed. The theoretical concern is similar for viral vector vaccines. However, evidence on the safety of COVID-19 vaccination in individuals with an autoimmune condition is emerging.
- Observational studies in individuals with autoimmune conditions indicates that the frequency and severity of adverse events in this population is comparable to that of individuals without autoimmune conditions and what was reported in clinical trials (37)(38)(39)(40)(41)(42)(78). The onset of new autoimmune disease or disease exacerbation following vaccination with mRNA COVID-19 vaccines was rare or comparable to the background incidence of these events in the general population. Safety data in these populations following vaccination with a viral vector vaccine is not available.
- Observational studies in individuals with autoimmune conditions who were taking immunosuppressive therapies showed diminished or delayed immune responses to the mRNA or AstraZeneca vaccines. Given the limited number of participants and the lack of an immunological correlate of protection against SARS-CoV-2 infection, there are limitations in interpreting the significance of these observational studies (64)(39)(65)(41)(66)(42).
- The spectrum of autoimmune conditions is diverse. The relative degree of autoimmunity in individuals with autoimmune conditions is variable depending on the underlying condition, the severity and progression of disease, and use of medications that impact immune function.
- The evidence about autoimmune conditions as an independent risk factor for severe COVID-19 is evolving. A rapid review of evidence from OECD member countries found strong evidence (of moderate certainty) for at least a 2-fold increase in mortality from COVID-19 with type 1 diabetes, as well as with a group of neurological disorders including multiple sclerosis and myasthenia gravis. The review also found low certainty evidence
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for a large increase in hospitalization with vasculitis (4). The review found a moderate certainty of evidence of little or no association with mortality or hospitalization from COVID-19 in those with rheumatoid arthritis, rheumatic or connective tissue disease, or systemic lupus erythematosus (4). 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 (4)(5).

- 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

10. NACI preferentially recommends that a complete vaccine series with an mRNA COVID-19 vaccine should be offered to individuals in the authorized age group who are pregnant. If an mRNA vaccine is contraindicated, another authorized COVID-19 vaccine should be offered. Informed consent should include discussion about emerging evidence on the safety of mRNA COVID-19 vaccines in this population. (Strong NACI Recommendation)

11. NACI recommends that a complete series with a viral vector COVID-19 vaccine may be offered to individuals 30 years of age and older who are pregnant if the conditions outlined in Recommendation #2 (above) are met AND a risk assessment deems the benefits outweigh the potential risks for the individual and the fetus (considering concerns about possible complexities of treatment of VITT in pregnancy, should it occur). Informed consent should include discussion about limited evidence on the use of viral vector vaccines in this population. (Discretionary NACI Recommendation)

12. NACI recommends that a complete vaccine series with an mRNA COVID-19 vaccine should be offered to individuals in the authorized age group who are breastfeeding. If an mRNA vaccine is contraindicated, another authorized COVID-19 vaccine should be offered. Informed consent should include discussion about the emerging evidence on the safety of mRNA COVID-19 vaccines in this population. (Strong NACI Recommendation)

13. NACI recommends that a complete series with a viral vector COVID-19 vaccine may be offered to individuals 30 years of age and older who are breastfeeding if the conditions outlined in Recommendation #2 (above) are met. Informed consent should include discussion about the limited evidence on the use of viral vector vaccines in this population. (Discretionary NACI Recommendation)

Summary of evidence and rationale

- Pregnant or breastfeeding individuals were excluded from the mRNA and viral vector COVID-19 clinical trials. However, outcomes in participants who became pregnant during the clinical trials and fetal outcomes are reported through registries, and real-world evidence (mostly with mRNA vaccination) has become available.
- An mRNA vaccine is preferred due to published safety data. Recently published preliminary analyses of 35,691 pregnant women in the United States who received an
mRNA COVID-19 vaccine did not reveal any obvious safety signals\(^{(83)}\). If VITT were to occur after receipt of a viral vector vaccine in a pregnant person, there might be complexity in the medical care. The US safety data suggests mRNA vaccine administration within 30 days of conception is safe\(^{(83)}\). Those who are trying to become pregnant do not need to avoid pregnancy after vaccination with an mRNA vaccine.

- Analysis of data collected through international COVID-19 immunization registries to date have not revealed any maternal or neonatal safety signals.
- To date, no safety signals have been detected in Development and Reproductive Toxicity (DART) animal studies for Pfizer\(^{(80)}\), Moderna\(^{(79)}\), Janssen\(^{(99)}\), and AstraZeneca vaccines\(^{(82)}\).
- Emerging evidence suggests that COVID-19 mRNA vaccination during pregnancy results in comparable antibody titres to those generated in non-pregnant women\(^{(85)}\)\(^{(86)}\)\(^{(87)}\). Maternal IgG humoral response to mRNA COVID-19 vaccines transfers across the placenta to the fetus, leading to a significant and potentially protective, antibody titre in the neonatal bloodstream one week after the second dose\(^{(88)}\)\(^{(85)}\)\(^{(89)}\)\(^{(90)}\).
- Observational studies consistently show that both anti-spike IgG and IgA are present in breastmilk at least for 6 weeks after maternal vaccination with mRNA vaccines\(^{(91)}\)\(^{(92)}\)\(^{(93)}\)\(^{(94)}\)\(^{(100)}\)\(^{(101)}\)\(^{(84)}\)\(^{(102)}\).
- In one small cohort study, mRNA from COVID-19 vaccines was undetectable in breastmilk 4–48 hours post-vaccination. No safety signals have been detected with mRNA vaccination during breastfeeding and individuals should continue to breastfeed after vaccination\(^{(84)}\).
- 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) and a low certainty of evidence for little to no increase in mortality. Caution should be taken when interpreting low certainty evidence. However, the review found a moderate certainty of evidence of at least a two-fold increase in hospitalization and mortality if an individual had two or more underlying medical conditions, compared to individuals with no comorbidities. No direct evidence on the combination of medical conditions associated with increased risk was found\(^{(4,5)}\).
- Compared to non-pregnant persons, SARS-CoV-2 infection in pregnancy may increase the risk of complications requiring hospitalization and intensive care, premature birth and cesarean delivery. A review of 438,548 pregnant individuals found pregnancy is a risk factor for poorer pregnancy outcomes, such as preeclampsia, pre-term birth, and stillbirth, and that these risks are much greater with severe infection\(^{(103)}\). Canadian-based surveillance of COVID-19 in pregnancy in five provinces from March 1st-December 21st, 2020 with a sample of 1880 pregnant positive cases, saw an increased risk of being hospitalized (RR=5.33, 95% CI: 4.51-6.20) and an increased risk of being admitted to the ICU (RR=5.88, 95% CI: 3.80 to 8.22) compared to non-pregnant counterparts\(^{(104)}\).
- Ventilatory support in pregnancy is more challenging and the risks are greater to both mother and child.
- Vaccine recipients and health care providers are encouraged to enroll patients who have received a COVID-19 vaccine during pregnancy in COVID-19 vaccine pregnancy registries (refer to Appendix F for a list of COVID-19 vaccine pregnancy registries). Timely reporting on adverse events following immunization to the local public health authority, as well as to the vaccine manufacturer, for follow up in these vaccine recipients is strongly encouraged.
- NACI encourages research on COVID-19 vaccination in pregnancy and during breastfeeding.
NACI will monitor the evidence as it evolves, and update recommendations as needed.

Refer to Immunization in Pregnancy and Breastfeeding, Part 3 – Vaccination of Specific Populations of the CIG for additional general information.

**Children and Adolescents**

14. NACI recommends that a complete series with a Pfizer-BioNTech COVID-19 vaccine should be offered to individuals 12 to 15 years of age without contraindications to the vaccine. *(Strong NACI Recommendation)*

Refer to NACI recommendation on the use of the Pfizer-BioNTech COVID-19 vaccine in adolescents 12 to 18 years of age.

**Summary of evidence and rationale**

- Evidence to date suggests that in general, the majority of cases of COVID-19 in children are mild with low incidence of severe outcomes. A rapid review found a moderate certainty of evidence of ≥2-fold increase in hospitalization in individuals 21 years of age and younger with two or more chronic medical conditions compared to those with no chronic conditions (105). In Canada, the majority of individuals 17 years of age and younger hospitalized or admitted to intensive care for COVID-19 had one or more underlying health conditions, most frequently asthma, immunodeficiency disease, and cancer (106).
- Evidence from a pivotal clinical trial of the Pfizer-BioNTech COVID-19 vaccine in adolescents 12-15 years of age has demonstrated a safety, immunogenicity and efficacy profile similar to that previously reported in individuals 16 to 25 years of age and older.
- 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 are ongoing. Evidence on COVID-19 vaccination in those less than 12 years of age is not available at this time. NACI is monitoring the evidence and will update recommendations when results become available.
- 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.

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 FOR USE IN CANADA

There are currently four authorized COVID-19 vaccines in Canada for the prevention of symptomatic COVID-19 that use two different vaccine platforms. 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 for use in Canada

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<tr>
<th>Factor for consideration</th>
<th>Summary of available evidence and issues for consideration</th>
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<td></td>
<td>mRNA COVID-19 Vaccines</td>
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<tr>
<td>Efficacy and Effectiveness</td>
<td>Efficacy against symptomatic illness after a complete series</td>
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<td>• Pfizer-BioNTech vaccine is overall 94% efficacious ≥14 days after dose 2 in study participants 16 years of age and older. Data suggest the Pfizer/BioNTech vaccine is 95% efficacious in participants ≥65 years of age, and 100% efficacious in participants 12-15 years of age, 7 or more days after dose 2.</td>
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<td>• Moderna vaccine is overall 94% efficacious in participants 18 years of age and older ≥14 days after dose 2.</td>
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<td>• Data suggest the Moderna vaccine is 86% efficacious in individuals ≥65 years of age ≥14 days after dose 2.</td>
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<td>Effectiveness against severe disease, hospitalization and death from mRNA vaccines (with more data available for Pfizer-BioNTech than Moderna)</td>
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<td>• Current data from real-world studies indicate that mRNA COVID-19 vaccines provide very good protection against COVID-19 hospitalization in adults following response to the first dose, including in older populations (≥65 years).</td>
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<td>• Data from real-world studies in adults provide some evidence that mRNA COVID-19 vaccines provide very good protection against COVID-19-related death following response to the first dose.</td>
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<tr>
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<td>• Real-world studies in adults indicate that mRNA COVID-19 vaccines provide excellent protection against severe disease,</td>
</tr>
<tr>
<td></td>
<td>Effectiveness against symptomatic illness and hospitalization</td>
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<tr>
<td></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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### Summary of available evidence and issues for consideration

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<tr>
<th>Factor for consideration</th>
<th>mRNA COVID-19 Vaccines</th>
<th>Non-replicating viral vector COVID-19 Vaccines</th>
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|                          | including COVID-19 related hospitalization and death following response to the second dose.  
  • Effectiveness data in adolescents 12 to 15 years of age (Pfizer-BioNTech COVID-19 Vaccine) or the Moderna COVID-19 vaccine alone is not currently available. | Efficacy against asymptomatic infection  
  • A preliminary analysis of limited data in an ongoing trial suggests the Moderna COVID-19 vaccine may be efficacious in preventing asymptomatic infection, however data is still being collected and the final analysis is not complete.  
  Efficacy against asymptomatic infection  
  • Estimates of vaccine effectiveness for the Pfizer-BioNTech COVID-19 vaccine against SARS-CoV-2 infection with no reported symptoms was moderate to high after the first dose (depending on time since vaccination) and high after the second dose (9,15) in adults. Similar results were reported for mRNA COVID-19 vaccines in general (16).  
| Re-vaccination | • It is not yet clear if booster doses (e.g., annual vaccination) will be required to provide long-term protection against symptomatic COVID-19 disease, in particular with the emergence of variants of concern.  
  • Re-vaccinating those who initially received an mRNA vaccine with the same or another mRNA vaccine is currently being investigated.  
  • The efficacy and safety of re-vaccinating those who initially received mRNA vaccine with a different COVID-19 vaccine are unknown at this time but are being investigated. | Re-vaccination  
  • It is not yet clear if booster doses (e.g., annual vaccination) will be required to provide long-term protection against symptomatic COVID-19 disease, in particular with the emergence of variants of concern  
  • Re-vaccination with a booster dose of viral vector vaccines may reduce vaccine effectiveness due to the possible development of immunity to the viral vector which may interfere with the immune response to subsequent doses. However, this is still being investigated.  
  • The efficacy and safety of re-vaccinating those who initially received a viral vector vaccine with a different COVID-19 vaccine are unknown at this time. |

### Humoral response
## Summary of available evidence and issues for consideration

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<th>Factor for consideration</th>
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| Immunogenicity           | • Humoral responses for both mRNA COVID-19 vaccines in clinical trials peaked after a second dose, including elicitation of neutralizing antibodies. However, as a correlate of protection is not known, these humoral responses cannot be interpreted as corresponding with protection.  
• Humoral responses in clinical trials had similar trends in individuals 18 to 55 years of age and individuals 65 to 85 years of age.  
• Humoral responses for the Pfizer-BioNTech vaccine in adolescents 12 to 15 years of age met and surpassed levels observed in young adults 16 to 25 years of age.  
• In observational studies, humoral responses in seropositive vaccine recipients after the first dose were comparable to those observed in SARS-CoV-2 naïve individuals following administration of the second dose. However, as a correlate of protection is not known, the significance of these findings as they relate to the level of protection against reinfection is unknown.  
(32)(20)(33, 34)(35)(36) | • For the AstraZeneca vaccine, humoral responses in clinical trials peaked after a second dose, including elicitation of neutralizing antibodies, for seronegative vaccine recipients. For seropositive vaccine recipients, humoral responses peaked at the first dose and maintained or decreased at the second dose.  
• For the AstraZeneca vaccine, humoral responses in clinical trials were lower in individuals ≥65 years of age and older, compared to individuals 18 to 64 years of age in unpublished data presented to NACI. Conflicting results have been shown for other age groups in recently published data.  
• For the Janssen vaccine, humoral responses in clinical trials, including binding antibodies, neutralizing antibodies and antibodies with Fc effector functions, were seen by day 29 after one dose.  
• For the Janssen vaccine, somewhat lower humoral immune responses were seen in older age cohorts (>65) compared to younger cohorts (18 to 55) in clinical trials.  
• However, as a correlate of protection is not known, these humoral responses cannot be interpreted as corresponding with vaccine protection. |
| Cellular response        | • Both mRNA vaccines have been shown to produce a cellular immune response by one to two weeks after administration of a second dose.  
• Increases in cellular immune responses response were seen in both younger and older adults. No data exists on cellular immune responses in adolescents 12-15 years of age.  
• As no immunological correlate of protection has been determined for SARS-CoV-2, these cellular responses cannot be interpreted as corresponding with vaccine protection. | • The AstraZeneca vaccine has been shown to produce cellular immune responses that did not appear to increase after the second dose.  
• Cellular immune responses do not appear to differ between age groups.  
• For the Janssen vaccine, cellular immune responses were elicited after one dose of vaccine.  
• As no immunological correlate of protection has been determined for SARS-CoV-2, these cellular responses cannot be interpreted as corresponding with vaccine protection. |
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| Protection against variants, including Variants of concern | **mRNA COVID-19 Vaccines**  
- B.1.1.7 (identified in UK)  
  - 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.  
- B.1.351 (identified in South Africa)  
  - There are emerging data on the efficacy or effectiveness of mRNA vaccines against B.1.351.  
- P.1 and P.2 (identified in Brazil)  
  - There are limited data on the efficacy or effectiveness of mRNA vaccines against P.1 (variant of concern) and P.2 (variant of interest).  
- B.167 (identified in India)  
  - Emerging data suggest the Pfizer-BioNTech vaccine is 33.2% effective against symptomatic illness due to B.167.2 after one dose, and 87.9% effective after two doses. | **Non-replicating viral vector COVID-19 Vaccines**  
- B.1.1.7 (identified in UK)  
  - Data suggest AstraZeneca COVID-19 vaccine has a vaccine efficacy of 70.4% against the B.1.1.7 VOC first identified in the UK, compared to 81.5% against non-B.1.1.7 strains (where cases were predominantly due to B.1.177, a non-VOI/VOC strain).  
- B.1.351 (identified in South Africa)  
  - Data suggest AstraZeneca vaccine has a vaccine efficacy of 10.4% against B.1.351 against mild to moderate illness.  
  - In South Africa, where B.1.351 was the dominant strain (approximately 95% of preliminary sequenced samples), the Janssen vaccine was 64% efficacious against moderate to severe/critical COVID-19 as of Day 29.  
- P.1 and P.2 (identified in Brazil)  
  - There are limited data on the efficacy or effectiveness of viral vector vaccines against P.1.  
  - In Brazil, where P.2 was detected in approximately 70% of sequenced samples of COVID-19 cases, the Janssen vaccine was 68% efficacious against moderate to severe/critical COVID-19 as of Day 29.  
- B.167 (identified in India)  
  - Emerging data suggest the AstraZeneca vaccine is 32.9% effective against symptomatic illness due to B.1.167.2 after one dose, and 59.8% effective after two doses. |
| Safety | **Technology**  
- mRNA vaccines use a new technology (which has been studied in experimental vaccines); however, all COVID-19 vaccines undergo the same rigorous review and approval process as routine vaccines. | **Technology**  
- Viral vector vaccines use a relatively new technology (the authorized Ebola vaccine uses this technology); however, all COVID-19 vaccines undergo the same rigorous review and approval process as routine vaccines. |
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| Safety Signals           | • There have been no confirmed serious safety signals identified with either mRNA vaccine. Rare anaphylactic reactions have been reported following immunization with mRNA COVID-19 vaccines.  
  • For both vaccines, some solicited adverse events are reported to be very common (defined as 10% or more) among vaccine recipients; however, they are mild or moderate and transient, resolving within a few days. These include: pain at the injection site, fatigue, headache, muscle pain, chills, joint pain, and fever. Some adverse events, including fever, are more frequent after the second dose.  
  • For the Pfizer-BioNTech COVID-19 vaccine, compared to individuals 16 to 55 years of age, adolescents 12 to 15 years of age demonstrated increased frequency of headache, chills, and fever. Up to 65% of adolescent participants had headaches, up to 42% of adolescent participants had chills, and up to 20% of adolescent participants had fever. Lymphadenopathy in adolescents occurred in 0.8% of vaccine recipients, (0.6% had vaccination-related lymphadenopathy), and no serious adverse events related to the vaccine and no deaths were reported.  |
|                          | Safety Signals                                           |
|                          | • For both vaccines, some solicited adverse events are reported to be very common (defined as 10% or more) among vaccine recipients; however, they are mild or moderate and transient, resolving within a few days. These include: pain at the injection site, fatigue, headache, muscle pain, chills, joint pain, and fever. Some adverse events are less frequent after the second dose.  
  • For the AstraZeneca vaccine, rare cases of thrombosis and thrombocytopenia have been reported during post-licensure use. The mechanism of action appears to be similar to spontaneous heparin-induced thrombocytopenia (called VITT-Vaccine-Induced Immune Thrombotic Thrombocytopenia). Internationally, the rate of this adverse event is still to be confirmed but had been most commonly estimated to be between 1/26,000 and 1/100,000 people vaccinated with AstraZeneca vaccine. Based on available evidence as of May 12, 2021, PHAC has estimated the rate of VITT in Canada as 1 in 83,000 doses administered. However, as investigations continue, this rate could be as high as 1 in 55,000. The case fatality rate typically ranges between 20 and 50%. Other predisposing factors for VITT are unclear.  
  • For the Janssen vaccine, in the clinical trial, one case of cerebral venous thrombosis was reported among 21,895 vaccine recipients. As of May 18, 2021, 30 cases of VITT have been confirmed out of 9.6 million doses of Janssen vaccine administered in the United States. Investigations are ongoing.  |
| Ethics and Equity        | • mRNA vaccines have high short-term efficacy in all authorized age groups and Canada anticipates having enough doses of mRNA vaccines for every individual in Canada in 2021.  
  • Vaccines that are more efficacious may be directed to those who are most at risk of severe disease and exposure to limit the exacerbation of existing inequities.  |
|                          | • Offering any COVID-19 vaccine to those who would otherwise have to wait to receive one could enhance equity.  
  • If protection against COVID-19 disease cannot be boosted for those that received a lower efficacy vaccine first, significant inequities could be created for those who receive a viral vector vaccine compared to an mRNA vaccine, depending on which population groups received the viral vector vaccine.  |
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<tr>
<td>Feasibility</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>
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<tr>
<td>Vaccine schedule</td>
<td>• Both mRNA vaccines are given as a two-dose series.</td>
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<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>
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<tr>
<td>Storage requirements</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>
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<td>• The viral vector vaccines are easier to transport, store and handle than mRNA vaccines, and as a result, could be easier to use for wider distribution via pharmacies and primary healthcare providers.</td>
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<td>Acceptability</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</td>
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<td>Factor for consideration</td>
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<td>mRNA COVID-19 Vaccines</td>
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<td>post-vaccination could positively affect acceptability of COVID-19 vaccines and vaccines in general.</td>
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Concerns about vaccine safety and effectiveness are the two most cited reasons for vaccine refusal \(^{(111)}\)

- In a survey of Canadians conducted between February 9 and 16, 2021 \(^{(112)}\), the following results were reported:
  - Of those who indicated they have not yet been vaccinated (n=1954), more respondents ‘Agreed’ or ‘Strongly Agreed’ with items stating intention to get a ‘safe vaccine’ (69%) and an ‘effective vaccine’ (67%) since Wave 4 of the survey (late May-early June 2020).
  - When respondents who were willing or neutral towards getting vaccinated were asked what is most important with respect to selecting a COVID-19 vaccine to receive (n=1595), 46% selected “Receiving the most effective vaccine”, 15% selected “Receiving any vaccine as soon as possible” and 12% selected “Receiving the vaccine with the fewest reported side effects”. The number of doses and type of vaccine technology were not important factors, and 14% of respondents indicated they have no preference on what COVID-19 vaccine they receive.
  - For those who will wait to get the vaccine once it is available: 80% will wait to ensure the safety of the vaccine, 64% will wait to ensure the effectiveness of the vaccine (n=691) \(^{(113)}\)

- In a survey of health care providers conducted on Dec 4-13, 2020 \(^{(114)}\), 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 public health measures (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 and after infection with SARS-CoV-2? What is the trigger for the development of this adverse event following immunization and what can be done to mitigate its development?

   b. What is the exact biological mechanism by which viral vector vaccines may trigger VITT? Are VITTs a class effect of the adenovirus vector vaccines or are there separate mechanisms that are product-specific (e.g., due to differing dose and magnitude of immune response based on the nature of the vaccines)?

   c. How do age, sex, or other patient characteristics (e.g., pregnancy, health-seeking behaviours) affect the incidence of VITT and the complications of VITT?

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 for whom the vaccination program is directly intended, and in populations for whom the vaccination program is not intended, but who are still impacted by it (e.g., impacted by the disease, spillover effects such as for caregivers, or externalities such as with herd immunity)?

6. Can a different COVID-19 vaccine be used to complete a primary series or as a booster dose? How are returning travellers managed if they have initiated but not completed a COVID-19 vaccine series abroad?

Health-Related Quality of Life and Well-being

7. What is the health-related quality of life or well-being of COVID-19 patients and caregivers over time (e.g., health utilities, patient-reported outcomes, patient-reported experiences measures)?

8. What is the impact of COVID-19 vaccination on health-related quality of life or well-being on individuals?

VII. SURVEILLANCE ISSUES

Ongoing and systematic data collection, analysis, interpretation and timely dissemination is fundamental to planning, implementation, evaluation, and evidence-informed decision-making. To support such efforts, NACI encourages surveillance improvements in the following areas:

1. Epidemiology
   - Enhance social and socioeconomic data collected and made available to understand and address health inequities related to COVID-19
   - Systematic examination of the Canadian burden and epidemiology of COVID-19 outbreaks by setting and severity, identifying high-risk activities, settings and populations
- Evaluation of the success of public health interventions to minimize or prevent COVID-19 outbreak events, especially in vulnerable or high-risk communities

2. **Laboratory (e.g., strain characterization)**
   - Enhance laboratory surveillance in order to provide early warning of increasing or decreasing activity by age, sex, and presence of symptoms, and help interpret case data based on changes to testing algorithms
   - Conduct genomic surveillance to identify international and inter-provincial transmission and new strains/variants with differing severity, transmissibility, or vaccine comparability
   - Explore other SARS-CoV-2 detection kits at point of care with immediate results

3. **Vaccine (coverage, effectiveness, safety)**
   - Reliably monitor coverage rates for each authorized COVID-19 vaccine in different key populations, ensuring data on series completion
   - Ensure existing mechanisms for the evaluation of adverse events are positioned to generate data for each authorized COVID-19 vaccine

### TABLES

**Table 6. Strength of NACI Recommendations**

<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>Ad26</td>
<td>Modified human adenovirus 26</td>
</tr>
<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>FDA</td>
<td>Food and Drug Administration (US)</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>ICU</td>
<td>Intensive care unit</td>
</tr>
<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>PF4</td>
<td>Platelet Factor 4</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>Acronym</td>
<td>Definition</td>
</tr>
<tr>
<td>---------</td>
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</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>TST</td>
<td>Tuberculin skin test</td>
</tr>
<tr>
<td>TTS</td>
<td>Thrombosis with Thrombocytopenia Syndrome</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>
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</table>
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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 participants aged 12 to 15, 16 to 55, and 65 to 85. Evidence on the safety and efficacy of the vaccine is available for adolescents 12-15 years of age and adults 16 years of age and older. Studies did not include participants from long term care facilities. The Phase 2/3 portion of the trial involved approximately 46,000 study participants randomized (1:1) to receive either the vaccine or placebo. The data presented below are for an interim analysis, therefore the time of follow-up is not consistent but was less than four months after the second dose (maximum of 14 weeks) for all participants.

Evidence from the ongoing Phase 2/3 trial (participants 16 years of age and older) were published in December 2020, after NACI’s review of the evidence (115).

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 (116).

There may be a protective effect against severe COVID-19 outcomes for individuals 16 years of age and older when receiving at least one dose of vaccine (overall vaccine efficacy of 88.9%, 95% CI: 20.1 to 99.7%), based on one case identified in the vaccine group (N=21,669) and nine cases in the placebo group (N=21,686). Vaccine efficacy against severe COVID-19 disease was also examined after receipt of Dose 2 (from 7 days and 14 days after Dose 2), but there were an insufficient number of events reported (one severe outcome in the vaccine group and three in the placebo group for each outcome) to determine whether the vaccine was efficacious in reducing severe outcomes with any precision (i.e., the resulting point estimates had wide confidence intervals that included zero).

In adolescents 12 to 15 years of age, vaccine efficacy could not be assessed against severe outcomes as there were no confirmed cases of severe COVID-19 identified as of the date of data cut-off for the efficacy analysis. There were also no deaths identified in adolescent study participants during the clinical trial.

Symptomatic COVID-19 disease

In adults 16 years of age and older:

The estimated vaccine efficacy at least 7 days after Dose 2 was 94.6% (95% CI: 89.9 to 97.3%), with 9 confirmed symptomatic COVID-19 cases, as defined in trial protocol (115) identified among vaccine recipients (N=19,965) compared to 169 cases among placebo recipients (N=20,172). The vaccine efficacy at least 14 days after Dose 2 in this population was comparable (94.4%, 95% CI: 89.1 to 97.3%). Results were similar when estimating the efficacy specifically in individuals without evidence of prior SARS-CoV-2 infection at 95.0% (95% CI: 90.3 to 97.6%).
with 8 confirmed cases among vaccine recipients (N=18,198) compared to 162 cases among placebo recipients (N=18,325).

When adult study participants without evidence of prior SARS-CoV-2 infection were stratified by age, vaccine efficacy against COVID-19 from 7 days after Dose 2 was between 93.7% (>55 years) and 95.6% (16 to 55 years). In individuals ≥65 years of age, vaccine efficacy was 94.7% (95% CI: 66.7 to 99.9%), while in participants ≥75 years of age, the observed vaccine efficacy was 100% compared to placebo, but with a wide confidence interval including zero which resulted from an insufficient number of events reported (0 vs 5 cases, 95% CI: −13.1 to 100.0%). The estimated vaccine efficacy against confirmed COVID-19 from 7 days after Dose 2 was greater than 91% (between 91.7% and 100.0%) in all subgroups stratified by “at risk” status (e.g., presence of a 1 or more comorbidities). The estimated vaccine efficacy against confirmed COVID-19 from 7 days after Dose 2 was greater than 89% for all races (89.3 to 100%) and 94% for all ethnicities included in the sub-analysis (94.4 to 95.4%).

After Dose 1, but prior to administration of Dose 2, 39 COVID-19 cases were identified in the vaccine group (n=21,669) compared to 82 in the placebo group (n=21,686) for an overall estimated vaccine efficacy in participants 16 years of age and older of 52.4% (95% CI: 29.5 to 68.4%). If the analysis was restricted to cases identified only in the time period >14 days after Dose 1 to before Dose 2 the estimated vaccine efficacy increased to 92.3% (95% CI: 69 to 98%).

Table 7. Pfizer-BioNTech vaccine efficacy against the first occurrence of symptomatic COVID-19 disease after dose 1 and before dose 2 in participants 16 years of age and older

<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>

In adolescents 12 to 15 years of age:
In study participants without prior evidence of SARS-CoV-2 infection, there were no confirmed COVID-19 cases occurring at least 7 days after Dose 2 among vaccine recipients (n=1,005) compared to 16 cases among placebo recipients (n=978) for an estimated vaccine efficacy against confirmed COVID-19 of 100.0% (95% CI: 75.3 to 100%).

In adolescents 12 to 15 years of age:
In study participants without prior evidence of SARS-CoV-2 infection, there were no confirmed COVID-19 cases occurring at least 7 days after Dose 2 among vaccine recipients (n=1,005) compared to 16 cases among placebo recipients (n=978) for an estimated vaccine efficacy against confirmed COVID-19 of 100.0% (95% CI: 75.3 to 100%).

After Dose 1, but prior to administration of Dose 2, 3 COVID-19 cases were identified in the vaccine group (n=1,131) compared to 12 in the placebo group (n=1,129) for an overall estimated vaccine efficacy in adolescents 12 to 15 years of age of 75.0% (95% CI: 7.4 to 95.5%). If the analysis was restricted to case identified only in the time period ≥11 days after Dose 1 to before Dose 2, the estimated vaccine efficacy increased to 100% (95% CI: 41.4 to 100%).
Table 8. Pfizer-BioNTech vaccine efficacy against the first occurrence of symptomatic COVID-19 disease after dose 1 and before dose 2 in adolescents 12 to 15 years of age

<table>
<thead>
<tr>
<th>Time period of interest</th>
<th>Events in vaccine group (N=1,131)</th>
<th>Events in placebo group (N=1,129)</th>
<th>Estimate of vaccine efficacy (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>After dose 1 to before dose 2</td>
<td>3</td>
<td>12</td>
<td>75% (7.4 to 95.5%)</td>
</tr>
<tr>
<td>≥11 days after dose 1 to before dose 2</td>
<td>0</td>
<td>8</td>
<td>100% (41.4 to 100%)</td>
</tr>
</tbody>
</table>

In the all-available efficacy population consisting of randomized study participants who received at least one dose of the study intervention (i.e., vaccine or placebo).

There is no analysis provided for efficacy specifically in individuals (any age range) with prior evidence of SARS-CoV-2 infection.

Asymptomatic infection and transmission
There are no efficacy data for these outcomes at this time.

Immunogenicity

Humoral immune responses
Both SARS-CoV-2 binding and neutralizing antibodies induced by this vaccine had similar trends across both adult age groups (18 to 55 and 65 to 85 years of age N=195). In adults, maximal immune responses were seen on day 28, 7 days after the second dose. Binding and neutralizing antibodies were both induced by one dose of vaccine and boosted by the second dose of vaccine. The immune response elicited by one dose accounted for 10-20% of the maximal immune response. Up to day 35, older adults (65-85 years of age) had a lower immune response compared to younger adults (18-55 years of age). After the peak on day 28, immune responses decreased until the final evaluation point on day 52, 30 days after dose 2 in younger adults, while no decrease was observed in older adults. SARS-CoV-2 neutralizing antibody responses one month following dose 2 were consistent, if not slightly higher, in adolescents 12-15 years of age compared to young adults 16-25 years of age. At every time point tested and across all included age groups, immune responses were higher than placebo.

Cellular immune responses
Cellular immune responses were assessed in the adult age groups (18 to 55 and 65 to 85 years of age). Both CD4+ and CD8+ T-cells specific to SARS-CoV-2 were induced by the vaccine, as demonstrated by the increase in these cell population percentages from day 1 to day 28. Increases were seen in both younger adults (18-55 years of age) and older adults (65-85 years of age). The characterization of these cells indicates a Th-1 biased cellular immune response. Intermediate time points were not reported.

Vaccine Safety and Adverse Events Following Immunization
Safety evidence for participants 16 years and older is based on interim analyses of 37,586 participants with a median of two months of follow-up (range: <2 weeks to <14 weeks) after Dose 2. About 19,000 participants had at least 2 months of follow-up, including about 9,500 who received the vaccine. Participants who inadvertently received the vaccine (n=12) or placebo
(n=11) while pregnant are being followed. Safety evidence for adolescent participants 12 to 15 years of age is based on interim analyses of 2,260 participants. Approximately 1,300 participants had at least 2 months of follow-up after Dose 2, of which 660 in this group received the vaccine.

Local Reactions
In vaccine recipients 12 years of age and older, the frequency of local reactions was similar after Dose 1 and Dose 2. Pain at the injection site was very common (occurring in up to 86% of adolescents 12 to 15 years of age after dose 1). Most local reactions among vaccine recipients were mild or moderate in severity, with any severe reactions being reported by ≤1% of participants. No Grade 4 local reactions were reported. Across all adolescent and adult age groups, local reactions after either dose had a median onset between zero and 2 days post-vaccination and a median duration of 1 to 3 days.

Systemic Reactions
Systemic events were generally increased in frequency and severity in vaccine recipients compared to placebo recipients, and in younger adults (16-55 years old) compared to older adults (≥56 years old), with frequencies and severity increasing with the number of doses (Dose 2 compared to Dose 1). Fatigue (34.1 to 59.4%), headache (25.2 to 51.7%), and muscle pain (13.9 to 37.3%) were very common in both younger and older adults and after Dose 1 and Dose 2, respectively. Fever was common after the first dose (3.7% of 16-55 year olds, 1.4% of >55 year olds) but was very common after the second dose (15.8% of 16-55 year olds, 10.9% of >55 year olds). Joint pain was very common or common in both younger and older adults (11.0 to 21.9% of 16-55 year olds, 8.6 to 18.9% of >55 year olds). Diarrhea was very common or common in both younger and older adults (10.0 to 11.0% of 16-55 year olds, 8.0% of >55 year olds), but was similar to rates seen in the placebo group and did not appear to differ between Dose 1 and Dose 2.

Systemic events were more frequent in adolescents compared to adults. In the adolescent group, fatigue (60.1 to 66.0%), headache (55.3% to 64.5%), chills (27.6 to 41.5%), muscle pain (24.1 to 32.4%) and fever (10.1 to 19.6%) were very common after Dose 1 and Dose 2, respectively. Joint pain was common after Dose 1 (9.7%) and very common after Dose 2 (15.8%). Vomiting (2.8 to 2.6%) and diarrhea (8.0 to 5.9%) were common after both Dose 1 and Dose 2, respectively.

For adolescents and adults, the median onset day for most systemic events after either dose of vaccine was 1 to 3 days post-vaccination, with a median duration of 1 day, except for fatigue and chills, which had median durations of 1 to 2 days. The majority of systemic events were mild or moderate in severity.

Overall, the frequency of any severe systemic event after Dose 1 was ≤0.9% in individuals 16 years of age and older. After Dose 2, severe systemic events had frequencies of <2% with the exception of fatigue (3.8%) and headache (2.0%). The proportion of participants that experience severe fever (>38.9°C to 40.0°C) increased between Dose 1 (0.2%) and Dose 2 (0.8%). Grade 4 fever (>40.0°C) was reported for 2 participants in each of the vaccine and placebo groups. In adolescents 12 to 15 years of age, the frequency of severe systemic events was ≤3.5%. Grade 4 fever (40.4 °C) was reported for 1 participant in the vaccine group.

Severe or Serious Adverse Events
Among adult participants 16 years of age and older in the vaccine group, 1.1% and 0.1% of participants experienced at least one severe AE and one life-threatening adverse events (AE),
respectively, compared to 0.7% and 0.1% of participants in the placebo group. Among adolescents 12 to 15 years of age in the vaccine group, 0.8% and 0.1% of participants experienced at least one severe AE and one life-threatening AE, compared to 0.3% and 0.1% of participants in the placebo group. In adolescents, no clinically meaningful differences were observed in AEs by age, sex, or race/ethnicity.

The proportions of adult participants 16 years of age and older who reported at least 1 serious adverse event (SAE) were similar in the vaccine group (0.5%) and in the placebo group (0.4%), and was lower in adolescents 12 to 15 years of age (0.4% in the vaccine group and 0.2% in the placebo group). In adults 16 years of age and older, three of the SAEs in the vaccine group and none in the placebo group were assessed by the investigator as related to the study intervention: 1 SAE each of shoulder injury related to vaccine administration, ventricular arrhythmia, and lymphadenopathy. No SAEs reported in adolescents 12 to 15 years of age were assessed by the investigator as related to the study intervention. No clinically meaningful differences in SAEs were observed by age, sex, or race/ethnicity. After either vaccine dose, no participant reported an immediate allergic reaction to vaccine.

**Other serious adverse events**

**Lymphadenopathy**
Lymphadenopathy was not a solicited AE. Among adult participants 16 years of age and older (n=37,586) who were followed for <2 weeks to <14 weeks after Dose 2, AEs of lymphadenopathy were reported in 0.3% (n=64) participants (0.5% [n=54] in the younger age group and 0.1% [n=10] in the older age group) in the vaccine group and 6 participants (0.0%) in the placebo group. Most lymphadenopathy events were reported within 2 to 4 days after vaccination. The average duration of these events was approximately 10 days, with 11 events ongoing at the time of the data cut-off. Vaccination-related lymphadenopathy in adolescents 12 to 15 years of age occurred in 0.6% of vaccine recipients (0.8% related and not related), and in 0.1% of placebo recipients (0.2% related and not related). Most cases were reported within 2 to 10 days after vaccination and approximately half resolved within 1 to 10 days, with others ongoing at the time of the data cut-off.

**Appendicitis**
Among adult participants 16 years of age and older who were followed <2 weeks to <14 weeks after Dose 2, there were a total of 12 participants with SAEs of appendicitis; 8 of which were in the vaccine group. Six of those 8 occurred in younger adults and 2 occurred in older adults. None of the cases were assessed as related to the vaccine by the investigators. The rate in either age group was not estimated to be greater than expected compared to baseline rates. Among adolescents 12 to 15 years of age, 1 participant in the vaccine group and 2 participants in the placebo group reported appendicitis. None were assessed as related to the vaccine by investigators.

**Death**
There were 6 adult participants (16 years of age and older) who died as of 14 November 2020, the data cut-off date for the interim analysis. This included 2 participants in the vaccine group and 4 participants in the placebo group. None of these deaths in the vaccinated group were assessed by the investigator as related to the vaccine. No deaths were reported in adolescents aged 12 to 15.
APPENDIX B: 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 (117).

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 (118) occurring at least 14 days after the second injection among placebo recipients compared to 11 cases among Moderna COVID-19 vaccine recipients, for an estimated vaccine efficacy of 94.1% (95% confidence interval, CI: 89.3 to 96.8%).

A subgroup analysis of the interim primary efficacy outcome was conducted in three age groups: 18 to <65 years of age (10,521 participants in the placebo group and 10,551 participants in the Moderna COVID-19 vaccine group), ≥65 years of age (3,552 participants in the placebo group and 3,583 participants in the Moderna COVID-19 vaccine group), and a further subgroup of study participants ≥75 years of age (688 participants in the placebo group and 630 participants in the Moderna COVID-19 vaccine group).

In study participants 18 to <65 years, there were 156 confirmed COVID-19 cases occurring at least 14 days after the second injection among placebo recipients compared to 7 cases among mRNA-1273 vaccine recipients, for an estimated vaccine efficacy of 95.6% (95% CI: 90.6 to 97.9%). The corresponding incidence rate per 1,000 person-years (total time at risk in each treatment group) was 64.63 in the placebo group and 2.88 in the Moderna COVID-19 vaccine group. In study participants ≥65 years of age there were 29 confirmed COVID-19 cases among placebo recipients compared to 4 cases among Moderna COVID-19 vaccine recipients,
corresponding to a somewhat lower point estimate of vaccine efficacy of 86.4% (95% CI: 61.4 to 95.2%). The corresponding incidence rate per 1,000 person-years was 33.73 in the placebo group and 4.60 in the Moderna COVID-19 vaccine group. In the subgroup of study participants ≥75 years of age there were 7 confirmed COVID-19 cases among placebo recipients compared to 0 cases among Moderna COVID-19 vaccine recipients, for a corresponding vaccine efficacy of 100.0% (95% CI: not evaluable to 100.0%), but this must be interpreted with caution as there were few events identified in this age group.

The efficacy of the Moderna COVID-19 vaccine to protect against confirmed COVID-19 cases occurring at least 14 days after the second injection was also assessed in participants most at risk for severe complications of COVID-19. In study participants 18 to <65 years of age and at risk for severe complications of COVID-19 (2,118 participants in the placebo group and 2,155 participants in the Moderna COVID-19 vaccine group) there were 35 confirmed COVID-19 cases in the placebo group compared to 2 cases among Moderna COVID-19 vaccine recipients, for an estimated vaccine efficacy of 94.4% (95% CI: 76.9 to 98.7%). In study participants 18 to <65 years of age, but not at risk for severe complications of COVID-19 (8,403 participants in the placebo group and 8,396 participants in the Moderna COVID-19 vaccine group) the estimated vaccine efficacy was 95.9% (95% CI: 90.0 to 98.3%) based on 121 confirmed COVID-19 cases in the placebo group and 5 cases among Moderna COVID-19 vaccine recipients. Vaccine efficacy estimates were also calculated for select individual co-morbid conditions; however, as of November 7, 2020 the number of identified events in these subgroups (n=0 to 11) were too small for meaningful analysis.

A secondary analysis of vaccine efficacy to protect against the first occurrence of confirmed COVID-19 starting 14 days after Dose 2 regardless of prior SARS-CoV-2 infection, as determined by serologic titre, involved the full analysis set (randomly assigned study participants who received at least one injection). There were 30,351 study participants 18 years of age or older (15,170 participants in the placebo group and 15,181 participants in the Moderna COVID-19 vaccine group). There were 187 confirmed COVID-19 cases among placebo recipients compared to 12 cases among Moderna COVID-19 vaccine recipients, for an estimated vaccine efficacy of 93.6% (95% CI: 88.6 to 96.5%). However, there was a small proportion of study participants enrolled (n=679/29,148; 2.3%) with positive SARS-CoV-2 infection status at baseline.

In participants who had only received one dose of vaccine at the time of data analysis (placebo group: n=1,079; vaccine group: n=996), vaccine efficacy was 80.2% (95% CI: 55.2 to 92.5%). Limiting the analysis to 14 or more days after Dose 1, efficacy rose to 92.1% (95% CI: 68.8 to 99.1%). However, there are limited data on the efficacy of Dose 1 alone beyond 28 days post-vaccination.

Table 9. Moderna vaccine efficacy against the first occurrence of symptomatic COVID-19 disease after dose 1

<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 were not induced to the level of convalescent sera until day 36, 7 days after dose 2 for all age groups. Neutralizing antibody responses through day 36 seems to be approximately equivalent across age groups. Neutralizing antibody responses on Day 119 represent a larger proportion of the maximum on day 43, compared to binding antibody responses. This may indicate increased durability of neutralizing antibody responses compared to binding antibody responses. These neutralizing data may also suggest an age-dependent neutralizing antibody durability as antibody responses on day 119 for each cohort were inversely proportional to the age of the cohort.

Immunogenicity data from the Phase 1 trial of the Moderna COVID-19 vaccine in a small number of subjects (n=33) demonstrate antibody persistence for 6 months (119).

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) (118). 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 (118). 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%) (118).

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 (118). 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 (118). 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 healthcare and social setting workers.

Evidence from the AstraZeneca COVID-19 vaccine trials has been published (120).

Efficacy

The estimates of vaccine efficacy for the AstraZeneca COVID-19 vaccine (AZD1222) come from the Phase 2/3 and Phase 3 trials. As of a data cut-off date of November 4, 2020 the primary analysis population (study participants who received either the LD/SD or SD/SD regimens) for the primary outcome included 11,636 participants seronegative at baseline (5,807 in the vaccine group, 5,829 in the control group). Of this population, 8,895 study participants (4,440 vaccine recipients and 4,455 controls) received the SD/SD regimen. As of a data cut-off date of December 7, 2020, the SD/SD population had increased to include 12,158 study participants (6,085 vaccine recipients and 6,073 controls). Unless otherwise noted, all data presented in this summary is based on the SD/SD vaccine regimen and as of a data cut-off date of December 7, 2020.

Symptomatic COVID-19 disease

The primary efficacy outcome assessed in the two trials was prevention of the first occurrence of confirmed COVID-19 beginning ≥15 days after Dose 2, based on assessments of cases by an Adjudication Committee blinded to participant group assignment, and analysed in the combined LD/SD and SD/SD regimen population. Assessment in the subgroup that only received SD/SD was a pre-specified secondary analysis in the clinical trial. Symptomatic COVID-19 was defined as having at least one of the following symptoms (objective fever ≥37.8
C, cough, shortness of breath, and anosmia or ageusia) AND a swab positive for SARS-CoV-2 by RT-PCR AND confirmed by an Adjudication Committee.

Based on data as of December 7, 2020, there were 12,158 study participants 18 years of age or older without prior evidence of SARS-CoV-2 infection at baseline (6,085 vaccine recipients and 6,073 controls) included as part of the SD/SD regimen analysis. The estimated vaccine efficacy against confirmed COVID-19 cases occurring at ≥15 days after Dose 2 in study participants receiving the SD/SD vaccine regimen was 62.5% (95% CI: 50.7 to 71.4%), based on identification of 71/6,085 (1.2%) cases in vaccine recipients and 186/6,073 (3.1%) in controls. The estimated vaccine efficacy by age was 63.1% (51.1 to 72.1%) in study participants 18-64 years of age and 50.7% (-65.8 to 85.4%) in participants ≥65 years of age. An ad-hoc subgroup analysis performed to examine the potential confounding effect of age and dosing interval on estimates of vaccine efficacy in the COV002 (UK) clinical trial generated an estimate of vaccine efficacy in study participants 18–55 years of age who received the SD/SD dosing regimen. Based on the interim data as of November 4, 2020, this subgroup analysis found an estimated vaccine efficacy of 59.3% (95% CI: 25.1 to 77.9%) in this age group. This analysis included study participants with any interval duration between doses.

Symptomatic COVID-19 by interval
As of December 7, 2020, the majority of study participants in the COV002 (UK) and COV003 (Brazil) clinical trials received the two doses of the SD/SD regimen within a 4–8 week (UK: 45.6%, Brazil: 87.2%) or a 9–12-week interval (UK: 34.4%; Brazil: 10.5%). About 1 in 5 study participants in the UK clinical trial (18.9%) received the SD/SD regimen with a >12-week interval between vaccine doses, and in the Brazil trial it was less than 1 in 50 study participants (1.8%). A very small proportion of study participants received the SD/SD regimen with a <4-week interval between doses (UK: 1.0%, Brazil: 0.4%). An exploratory analysis examined the potential effect of the interval between the administration of the first and second vaccine doses on vaccine efficacy in study participants receiving the SD/SD vaccine regimen. Table 10 summarizes the estimates of vaccine efficacy against confirmed COVID-19 cases occurring at ≥15 days after dose 2 by dosing interval. There is a suggestion of an increase in the point estimate of vaccine efficacy with increasing intervals between the first and second dose of vaccine. However, it is important to note that the confidence intervals around these point estimates overlap.

Table 10. Estimates of vaccine efficacy against the first occurrence of confirmed COVID-19 beginning ≥15 days after Dose 2 in all participants, by dosing interval (SD/SD seronegative baseline efficacy set)*

<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>

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

In a subgroup analysis in study participants who received the SD/SD vaccine regimen, vaccine efficacy against confirmed COVID-19 cases occurring at ≥15 days after dose 2 was estimated by dosing interval and age group. These ad-hoc subgroup analyses were performed in participants 18-55 years of age from the COV002 (UK) clinical trial and in all study participants...
who received the SD/SD regimen (from COV002 and COV003), dichotomized into groups 18–64 years and ≥65 years of age.

The ad-hoc subgroup analysis performed to examine the potential confounding effect of age and dosing interval on estimates of vaccine efficacy in the COV002 (UK) clinical trial generated an estimate of vaccine efficacy in study participants 18–55 years of age who received the SD/SD regimen at an interval of >8 weeks between doses. Based on the interim data as of November 4, 2020, this subgroup analysis found an estimated vaccine efficacy of 65.6% (95% CI: 24.5 to 84.4%). In the updated dataset as of December 7, 2020, there were 1,375 study participants ≥65 years of age (699 in the vaccine group and 676 in the control group). Efficacy estimates for participants ≥65 years for the overall 4–12-week dosing interval and the 4–8-week interval have wide confidence intervals that include zero. Estimates of vaccine efficacy could not be calculated for participants ≥65 years for the 9–12-week and >12-week dosing intervals due to a lack of older study participants who received the SD/SD regimen during these dosing intervals (Table 11).

Table 11. Estimates of vaccine efficacy against the first occurrence of confirmed COVID-19 beginning ≥15 days after dose 2, by dosing interval and age group (SD/SD seronegative baseline efficacy seta)

<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>

aParticipants 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 12). The analysis involved study participants who were SARS-CoV-2 seronegative at baseline and received SD vaccine as their initial vaccine dose. The median duration of follow-up after Dose 1 was 115 days (range: 41–149 days). Note that approximately 80% of study participants in the vaccine arm received the second dose of the vaccine; therefore, several estimates of vaccine efficacy are not solely due to the one dose of SD vaccine.

Table 12. Estimates of vaccine efficacy against the first occurrence of confirmed COVID-19 beginning after Dose 1, (SD/SD seronegative baseline efficacy set*)

<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% CI)</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</td>
<td>15 (N=6,310)</td>
<td>52 (N=6,296)</td>
<td>71.3% (49.0 to 83.8%)</td>
</tr>
<tr>
<td>before Dose 2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Severe outcomes due to COVID-19

Severe COVID-19 disease
Severe COVID-19 disease, defined as study participants who met the confirmed COVID-19 case definition and were assigned a severity score of ≥6 on the World Health Organization Clinical Progression Scale (e.g., clinical severity requiring hospitalization, and may include intubation and mechanical ventilation, and death), was assessed as a secondary analysis of vaccine efficacy. Analysis included study participants who had been followed for ≥15 days since Dose 2, who were seronegative for SARS-CoV-2 at baseline, and received both doses of the SD/SD regimen. As of December 7, 2020, there were 6,085 study participants in the vaccine group and 6,073 participants in the control group. There was 1 case of severe COVID-19 disease identified in a study participant in the control group who received the control intervention within the 4–12-week dosing interval. This participant also required ICU admission and eventually died. An additional severe case occurred >21 days after the first dose and ≤14 days after the second dose in a study participant in the control group.

Hospitalizations
Vaccine efficacy against COVID-19 associated hospitalizations was assessed at multiple time points (Table 13). Assessment included study participants who were seronegative for SARS-CoV-2 at baseline and received both doses of the SD/SD regimen. After Dose 2 (median follow-up duration: 36 days, range: 1–79 days, based on data as of November 4, 2020), there were 7 hospitalizations due to COVID-19 identified in study participants who received the SD/SD regimen within the 4–12-week dosing interval, all in participants in the control group. There were no hospitalizations in the vaccine group ≥22 days after Dose 1; however, there were 2 cases hospitalized due to COVID-19 identified in the vaccine group and 16 in the control group ≥15 days after Dose 1, resulting in an estimate of vaccine efficacy of 87.6% (95% CI: 46.0 to 97.2%).
The 2 hospitalizations in the vaccine group were 1 and 10 days post vaccination (median follow up: 115 days, range: 41–149).

Table 13. Estimates of vaccine efficacy against hospitalization, by dosing interval (SD/SD seronegative baseline efficacy set)*

<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 1⁠ª</td>
<td>0/6,307 (0.0)</td>
<td>9/6,297 (0.1)</td>
<td>100% (95% CI: 49.6 to NE)</td>
</tr>
<tr>
<td>≥15 days after Dose 2⁠ª</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)

¹ Based on data as of November 4, 2020

² Based on data as of December 7, 2020

Deaths
As of the updated data cut-off date of December 7, 2020, there has been a single death due to COVID-19 identified in a study participant in the control group.

Asymptomatic infection and transmission
This was an exploratory analysis conducted only in clinical trial COV002 (UK). As part of the study protocol, beginning one week after receipt of Dose 1, study participants were asked to provide weekly self-administered nose or throat swabs for RT-PCR testing. Participants were asked to report symptoms when they appeared; however, the presence or absence of symptoms at the time of sample collection was not routinely collected. An asymptomatic infection was defined as a study participant with a swab virologically confirmed for SARS-CoV-2 and who reported no clinical trial–defined symptoms of confirmed COVID-19. Study participants with virologically confirmed SARS-CoV-2 infection, but who did not report whether or not they had symptoms were classified as “unknown symptoms”.

Table 14. Estimates of vaccine efficacy against asymptomatic infection, by dosing interval (SD/SD seronegative baseline efficacy set)*

<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 1⁠ª</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 2⁠ª</td>
<td>N/A</td>
<td>N/A</td>
<td>-4.3% (-416.5 to 79.0%)</td>
</tr>
</tbody>
</table>

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 (107).

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 (121). The AstraZeneca COVID-19 vaccine uses a modified chimpanzee adenovirus vector (ChAd). AstraZeneca found no correlation between anti-ChAd neutralizing antibody responses and anti-SARS-CoV-2 immune responses. It also found that neutralizing antibody levels were not boosted after receiving the second dose. However, neutralization is not the only anti-vector immune response that could impact vaccine-induced immunity. It remains unclear if immune responses to the ChAd vector will impact the efficacy or effectiveness of this vaccine.

Vaccine Safety and Adverse Events Following Immunization

Safety evidence is based on interim analyses of 23,745 participants of which 12,021 received at least one dose of the AZ COVID-19 vaccine and 11,724 received a control. The safety analyses were conducted in different analysis sets. Solicited adverse events occurring within 7 days after any dose were assessed among 2648 vaccine recipients who received at least one dose (SD) and 2497 control recipients. Approximately one third of study participants received
their second vaccine dose within 6 weeks of receiving Dose 1. The majority (~90%) of study participants in the safety cohort were less than 65 years of age. The median duration of follow-up was 105 days post-Dose 1 and 62 days post-Dose 2.

**Solicited Local Reactions**
Solicited local injection site AEs were reported by 74.7% of evaluated participants within the first 7 days following any vaccine dose. Pain and tenderness were most frequently reported (54.2% and 63.7%, respectively) followed by warmth (17.7%), bruising (17.3%), redness (14.0%), pruritus (12.7%), and swelling (10.0%). The majority of solicited local reactions among vaccine recipients were mild or moderate in severity, with any grade 3 or 4 reactions being reported by ≤9.5% of participants. No Grade 4 AEs were reported. Local reactions were generally milder and reported less frequently after the second dose of the vaccine. By dose interval, the reactogenicity of the vaccine was lower in participants who received the second dose within 6 weeks following Dose 1 (38.0% versus 58.3% to 74.3% when Dose 2 was provided after ≥6 weeks).

**Solicited Systemic Reactions**
Solicited systemic AEs were reported by 73.0% of evaluated participants within the first 7 days following any vaccine dose. The most common systemic solicited systemic AEs were fatigue (53.1%) and headache (52.6%). Other frequently reported systemic solicited AEs were muscle pain (44.0%), malaise (44.2%), feverishness (33.6%), chills (31.9%), joint pain (26.4%), nausea (21.9%) and fever ≥38.0°C (7.9%). Overall, the frequency of any grade 3 or 4 reaction was ≤8.3%. The single reported Grade 4 event was fever > 40°C. Across study groups, AEs were milder and reported less frequently after the second vaccine dose. By dose interval, the reactogenicity of the vaccine was lower in participants who received the second dose at <6 weeks following Dose 1 (37.6% versus 49.2% to 67.1% when Dose 2 was provided after at ≥6 weeks).

**Unsolicited Serious Adverse Events**
SAE were reported by less than 1% of study participants and was similar between the vaccine and control groups (0.7% and 0.8%, respectively). There were no clear imbalances by System Organ Class (SOC). The most frequently reported SAEs by SOC were ‘Infections and Infestations’ (0.1% vs 0.2%) and ‘Injury, poisoning and procedural complications’ (<0.1% vs 0.1%).

Two SAEs (pyrexia, transverse myelitis) in the vaccine recipients were considered related to the vaccine by the study investigators. The case of pyrexia (40.5°C) occurred 2 days after dose 1 and resolved the same day following the administration of acetaminophen. The event of transverse myelitis occurred in a 37-year-old female with a family history of Charcot-Marie-Tooth type 1a (mother and brother). The participant received two doses of study intervention 77 days apart. Two weeks after the second dose, the participant developed sensory changes and clumsiness. Magnetic resonance imaging showed a lesion consistent with transverse myelitis or anterior spinal infarction. A third SAE was originally identified (C-reactive protein increase); however, after the cut-off date, causality for the SAE of C-reactive protein increase was updated by the investigator to be not treatment related.

**Other serious adverse events**

**Demyelinating events**
An event of multiple sclerosis occurred in a 37-year-old female who developed sensory symptoms about 10 days after first (and only) vaccination. The clinical episode had a duration
of 3 weeks. Further follow up with MRI of spine and brain showed an acute spinal lesion and older cerebral lesions, revealing pre-existing, but previously unrecognized, multiple sclerosis.

Death
A total of 6 deaths were reported among study participants (2 in the vaccine group and 4 in the control group). The cause of death among vaccine recipients included malignant neoplasm and fungal pneumonia, with neither considered to be related to the study intervention by the investigators.

Vaccine-Induced Immune Thrombotic Thrombocytopenia
Rare cases of serious blood clots, including cerebral venous sinus thrombosis, associated with thrombocytopenia have been reported in Canada and globally following post-licensure use of AstraZeneca COVID-19 vaccine. Cases have usually occurred between 4 and 28 days after receipt of vaccine. This adverse event is being referred to as Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT). The mechanism of action is similar to heparin-induced thrombocytopenia (HIT). The exact mechanism by which the viral vector COVID-19 vaccines may trigger VITT is still under investigation. At this time, no other predisposing factors have consistently been identified in patients who develop VITT. The rate of this adverse event is still to be confirmed but had been most commonly estimated to be between 1 in 26,000 and 1 in 100,000 persons vaccinated with a first dose and around 1 in 600,000 persons vaccinated with a second dose of AstraZeneca COVID-19 vaccine although this continues to evolve and may increase. Based on available evidence as of May 12, 2021, PHAC has estimated the rate of VITT in Canada to be 1 in 83,000 doses administered. However, as investigations continue, this rate could be as high as 1 in 55,000 persons vaccinated with the COVISHIELD COVID-19 vaccine. 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 50%. Case fatality may vary with increased awareness of the adverse event and appropriate early treatment.

Effectiveness in individuals ≥65 years of age
In the absence of sufficient data from clinical trials to date on the efficacy of the AstraZeneca COVID-19 vaccine in those 65 years of age and older, a review of three observational studies in the UK published as pre-prints on real-world vaccine effectiveness in this age group has been conducted to inform NACI’s recommendations in this age group. The findings of this review are summarized below.

All three observational studies assessed one dose of either the Pfizer-BioNTech or the AstraZeneca vaccines in the United Kingdom. The results below pertain only to the AstraZeneca portion of the studies. The studies were conducted during the period when 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](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.
- The number of people vaccinated with the AstraZeneca COVID-19 vaccine is small in the period 28 days and more from vaccination.
- As vaccine roll out was initially tailored to priority groups at higher risk of severe disease or exposure, adjustments for potential confounding factors conducted during the statistical analyses might not have adequately controlled for all the differences between vaccinated and unvaccinated individuals. Demographic and risk factor comparisons
between vaccinated and unvaccinated groups were not provided separately for each vaccine.

- Hospital admission was defined as: COVID-19 as the main cause of admission or hospitalization within 28 days of a positive PCR SARS-CoV-2 test. Hospital admission for COVID-19 is a less specific criteria for determining COVID-19 hospitalization and the proportion of cases defined using that criteria are not provided.
- Although product specific vaccine effectiveness and age specific vaccine effectiveness are both provided separately, product specific vaccine effectiveness by age was not provided.
- Record linkage using large data sets is a strength of this study.
Data from Phase 1, 2, and 3 trials were available at the time of authorization for the Janssen vaccine. Evidence on efficacy, immunogenicity, and safety is available for adults ≥18 years of age. The Phase 3 trial involved 44,325 study participants randomized (1:1) to receive either the vaccine (1 dose of $5 \times 10^{10}$ viral particles) or placebo. The data presented below was a median of two months after the completion of the series (one dose).

**Efficacy**

**Symptomatic COVID-19 disease**

Estimates of efficacy against moderate to severe/critical COVID-19 disease was the primary outcome for the Phase 3 trial. Due to the relatively broad definition of moderate COVID-19 disease adopted for the clinical trial, less than 1% of identified cases met the mild COVID-19 case definition. Therefore, nearly all observed symptomatic COVID-19 cases are captured by the definition of moderate to severe/critical COVID-19.

The co-primary endpoints for the efficacy analysis of the vaccine are the prevention of the first occurrence of confirmed symptomatic moderate to severe/critical COVID-19 infection with onset ≥14 post-vaccination and with onset ≥28 days post-vaccination. The primary analysis is supported by subgroup analyses of the primary endpoints stratified by study country, age group, the presence of comorbidities associated with an increased risk of progression to severe COVID-19 disease, sex, and by race/ethnicity. Efficacy against confirmed symptomatic severe/critical COVID-19 infection with onset ≥14 and ≥28 days post-vaccination are secondary endpoints, also supported by analyses stratified by the same subgroups as the primary endpoint. Additional analyses of efficacy in cases with severe/critical COVID-19 include examinations by cases requiring medical intervention, hospitalizations and deaths. For both the primary and secondary endpoints, cumulative incidence curves are used to examine the potential onset and duration of vaccine efficacy. Exploratory analyses of vaccine efficacy against asymptomatic or undetected SARS-CoV-2 infection, symptom severity and viral load are also investigated. Select outcomes from these analyses are presented in this Appendix.

A number of the analyses are conducted in the full analysis set, defined as study participants who were randomized and received the study intervention (vaccine or placebo), regardless of the occurrence of protocol deviations or serostatus at baseline. However, most primary efficacy analyses are conducted in the per-protocol set, defined as study participants who were randomized, received the study intervention (vaccine or placebo), were seronegative at the time of vaccination, and had no major protocol deviations that were judged to possibly impact the efficacy of the vaccine. Many of the subgroup analyses are conducted in the per-protocol set using centrally confirmed COVID-19 cases, but repeated using a larger dataset consisting of both centrally confirmed cases and cases with a positive PCR result from a local testing site that had not yet been confirmed by the central clinical trial testing facility at the date of data cut-off for the analysis. The use of the locally confirmed cases is supported by the demonstration of a high concordance (90.3%) in PCR results between local and central clinical trial testing facilities. **Unless otherwise specified, all efficacy analyses presented in this summary are in the per-protocol set of study participants based on a January 22, 2021 data cut-off date.**
Confirmed symptomatic moderate to severe/critical COVID-19 infection

The definition of moderate COVID-19 disease used in the clinical trial was very broad and so cases meeting the moderate to severe/critical case definition constituted >99% of all identified symptomatic COVID-19 in the trial. The estimates of vaccine efficacy against confirmed symptomatic moderate to severe/critical COVID-19 infection with onsets ≥14 days and ≥28 days post-vaccination are 66.9% and 66.1%, respectively (Table 15).

Table 15. Efficacy against confirmed symptomatic moderate to severe/critical COVID-19 infection with onset ≥14 days and ≥28 days post-vaccination, per-protocol set

<table>
<thead>
<tr>
<th>Co-Primary outcomes</th>
<th>Vaccine group</th>
<th>Placebo group</th>
<th>Vaccine efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n/N)</td>
<td>Person years</td>
<td>Cases (n/N)</td>
</tr>
<tr>
<td>≥14 days post-vaccination</td>
<td>116/19,514</td>
<td>3,116.6</td>
<td>348/19,544</td>
</tr>
<tr>
<td>Moderate and severe/critical COVID-19 infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥28 days post-vaccination</td>
<td>66/19,306</td>
<td>3,102.0</td>
<td>193/19,178</td>
</tr>
<tr>
<td>Moderate and severe/critical COVID-19 infection</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Janssen manufacturer submission to Health Canada, Module 2.5: Clinical overview, Tables 5 and 6

Confirmed symptomatic severe/critical COVID-19 infection

The estimates of vaccine efficacy against confirmed symptomatic severe/critical COVID-19 infection are 76.7% with onset ≥14 days post-vaccination and 85.4% with onset ≥28 days post-vaccination (Table 16).

Table 16. Efficacy against confirmed symptomatic severe/critical COVID-19 infection with onset ≥14 days and ≥28 days post-vaccination, per-protocol set

<table>
<thead>
<tr>
<th>Co-Primary outcomes</th>
<th>Vaccine group</th>
<th>Placebo group</th>
<th>Vaccine efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n/N)</td>
<td>Person years</td>
<td>Cases (n/N)</td>
</tr>
<tr>
<td>≥14 days post-vaccination</td>
<td>14/19,514</td>
<td>3,125.1</td>
<td>60/19,544</td>
</tr>
<tr>
<td>Severe/critical COVID-19 infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥28 days post-vaccination</td>
<td>5/19,306</td>
<td>3,106.2</td>
<td>34/19,178</td>
</tr>
<tr>
<td>Severe/critical COVID-19 infection</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Janssen manufacturer submission to Health Canada, Module 2.5: Clinical overview, Tables 5 and 6

Subgroup analyses

By study country

The time period of the clinical trial was associated with the emergence of new SARS-CoV-2 VOC in some study countries. At the time of data cut-off for the primary analysis, preliminary
genetic sequencing data were available for a proportion of case isolates from Brazil, South Africa and the US (Table 17). No SARS-CoV-2 variants from the B.1.1.7 or P.1 lineages were detected in any of the sequenced isolates.

Table 17. Genetic sequencing results for VOC, September–December, 2020

<table>
<thead>
<tr>
<th>Country</th>
<th>Cases identified N</th>
<th>Cases sequenced n (%)</th>
<th>Sequencing Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>179</td>
<td>124 (69.2)</td>
<td>86/124 (69.4%) – variant 20J/501Y.V3 of the of the P.2 lineage 38/124 (30.6%) – Wuhan-Hu1 reference sequence+D614G</td>
</tr>
<tr>
<td>South Africa</td>
<td>136</td>
<td>91 (66.9)</td>
<td>86/91 (94.5%) – variant 20H/501Y.V2 of the B.1.351 lineage</td>
</tr>
<tr>
<td>United States</td>
<td>268</td>
<td>197 (73.5)</td>
<td>190/197 (96.4%) – Wuhan-Hu1 reference sequence+D614G</td>
</tr>
</tbody>
</table>

Source: Janssen manufacturer submission to Health Canada, Module 2.5: Clinical overview, Section 4.1.3.1. Epidemiologic Setting of the Study

Analyses of vaccine efficacy by country were conducted in countries with >100 identified cases (US, 247; Brazil, 153; and South Africa, 133) using a dataset consisting of both centrally PCR-confirmed COVID-19 cases and cases with a positive PCR result from in-country testing not yet confirmed by the central clinical trial testing facility at the data cut-off date for the analysis. The rationale for inclusion of the locally confirmed cases was demonstration of a high concordance (90.3%) in PCR results between local and central clinical trial testing facilities. The point estimates of vaccine efficacy by country against both confirmed symptomatic moderate to severe/critical COVID-19 and severe/critical COVID-19 with onset ≥14 days and ≥28 days post-vaccination are comparable to or greater than the overall estimates of efficacy at these time points (Table 18). The one exception is the point estimate of efficacy for South Africa at ≥14 days post-vaccination.

Table 18. Efficacy against confirmed symptomatic moderate to severe/critical and severe/critical COVID-19, by country for countries with greater than 100 moderate to severe/critical cases, centrally and in-country PCR-confirmed cases

<table>
<thead>
<tr>
<th>Country</th>
<th>Onset post-vaccination</th>
<th>COVID-19 severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Moderate to severe/critical Efficacy (95% CI)</td>
</tr>
<tr>
<td>US</td>
<td>≥14 days</td>
<td>74.4% (65.0 to 81.6)</td>
</tr>
<tr>
<td></td>
<td>≥28 days</td>
<td>72.0% (58.2 to 81.7)</td>
</tr>
<tr>
<td>Brazil</td>
<td>≥14 days</td>
<td>66.2% (51.0 to 77.1)</td>
</tr>
<tr>
<td></td>
<td>≥28 days</td>
<td>68.1% (48.8 to 80.7)</td>
</tr>
<tr>
<td>South Africa</td>
<td>≥14 days</td>
<td>52.0% (30.3 to 76.4)</td>
</tr>
<tr>
<td></td>
<td>≥28 days</td>
<td>64.0% (41.2 to 78.7)</td>
</tr>
</tbody>
</table>

Source: Janssen manufacturer submission to Health Canada, Module 2.5: Clinical overview, Table 11

By age group

Efficacy against confirmed symptomatic moderate to severe/critical COVID-19 infection with onset ≥14 days and ≥28 days post-vaccination was assessed in a variety of age groups (Table 19).
Table 19. Efficacy against confirmed symptomatic moderate to severe/critical COVID-19 infection with onset ≥14 days and ≥28 days post-vaccination, by age group, per-protocol set

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Vaccine group</th>
<th></th>
<th>Placebo group</th>
<th></th>
<th>Vaccine efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n/N)</td>
<td>Person years</td>
<td>Cases (n/N)</td>
<td>Person years</td>
<td></td>
</tr>
<tr>
<td>≥14 days post-vaccination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–39</td>
<td>47/4,356</td>
<td>775.3</td>
<td>122/4,330</td>
<td>762.1</td>
<td>62.1% (46.6 to 73.6)</td>
</tr>
<tr>
<td>40–59</td>
<td>48/8,394</td>
<td>1,331.5</td>
<td>138/8,452</td>
<td>1,332.9</td>
<td>65.2% (51.3 to 75.5)</td>
</tr>
<tr>
<td>60–69</td>
<td>19/4,800</td>
<td>722.9</td>
<td>65/4,907</td>
<td>732.2</td>
<td>70.4% (50.0 to 83.2)</td>
</tr>
<tr>
<td>70–79</td>
<td>2/1,768</td>
<td>259.5</td>
<td>23/1,650</td>
<td>239.2</td>
<td>92.0% (67.6 to 99.1)</td>
</tr>
<tr>
<td>≥80</td>
<td>0/196</td>
<td>27.42</td>
<td>0/205</td>
<td>29.8</td>
<td>N/A*</td>
</tr>
<tr>
<td>&lt;60 (i.e., 18–59)</td>
<td>95/12,750</td>
<td>2,106.8</td>
<td>260/12,782</td>
<td>2,095.0</td>
<td>63.7% (53.9 to 71.6)</td>
</tr>
<tr>
<td>&lt;65 (i.e., 18–64)</td>
<td>107/15,544</td>
<td>2,530.3</td>
<td>297/15,552</td>
<td>2,511.2</td>
<td>64.2% (55.3 to 73.6)</td>
</tr>
<tr>
<td>≥60</td>
<td>21/6,764</td>
<td>1,009.8</td>
<td>88/6,762</td>
<td>1,001.2</td>
<td>76.3% (61.6 to 86.0)</td>
</tr>
<tr>
<td>≥65</td>
<td>9/3,970</td>
<td>586.3</td>
<td>51/3,992</td>
<td>584.9</td>
<td>82.4% (63.9 to 92.4)</td>
</tr>
<tr>
<td>≥75</td>
<td>0/751</td>
<td>88.4</td>
<td>8/690</td>
<td>99.2</td>
<td>100.0% (45.9 to 100.0)</td>
</tr>
<tr>
<td>≥28 days post-vaccination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–39</td>
<td>29/4,316</td>
<td>772.4</td>
<td>84/4,254</td>
<td>756.6</td>
<td>66.2% (47.9 to 78.6)</td>
</tr>
<tr>
<td>40–59</td>
<td>23/8,301</td>
<td>1,325.2</td>
<td>69/8,273</td>
<td>1,320.4</td>
<td>66.3% (45.2 to 80.0)</td>
</tr>
<tr>
<td>60–69</td>
<td>12/4,749</td>
<td>719.3</td>
<td>32/4,833</td>
<td>727.1</td>
<td>62.1% (24.4 to 82.2)</td>
</tr>
<tr>
<td>70–79</td>
<td>2/1,746</td>
<td>257.8</td>
<td>9/1,620</td>
<td>237.2</td>
<td>79.6% (1.2 to 97.9)</td>
</tr>
<tr>
<td>≥80</td>
<td>0/194</td>
<td>27.3</td>
<td>0/198</td>
<td>29.3</td>
<td>N/A</td>
</tr>
<tr>
<td>&lt;60 (i.e., 18–59)</td>
<td>52/12,617</td>
<td>2,097.6</td>
<td>152/12,527</td>
<td>2,077.0</td>
<td>66.1% (53.3 to 75.8)</td>
</tr>
<tr>
<td>&lt;65 (i.e., 18–64)</td>
<td>60/15,378</td>
<td>2,518.7</td>
<td>170/15,253</td>
<td>2,490.1</td>
<td>65.1% (52.9 to 74.5)</td>
</tr>
<tr>
<td>≥60</td>
<td>14/6,689</td>
<td>1,004.4</td>
<td>41/6,651</td>
<td>993.6</td>
<td>66.2% (36.7 to 83.0)</td>
</tr>
<tr>
<td>≥65</td>
<td>6/3,928</td>
<td>583.3</td>
<td>23/3,925</td>
<td>580.5</td>
<td>74.0% (34.4 to 91.4)</td>
</tr>
<tr>
<td>≥75</td>
<td>0/740</td>
<td>106.4</td>
<td>3/673</td>
<td>98.1</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*N/A = Not available; estimates of vaccine efficacy not calculated when there were fewer than 6 events identified.

Source: Janssen manufacturer submission to Health Canada, Module 2:5: Clinical overview, Figures 30 and 31

The efficacy against confirmed symptomatic severe/critical COVID-19 infection with onset ≥14 days and ≥28 days post-vaccination was calculated for four age groups: 18–59, 18–64, ≥60, and ≥65 years of age (Table 20).

The analysis was repeated using the larger dataset of both confirmed COVID-19 cases and cases with a positive PCR result from a local, in-country testing site. The estimates of vaccine efficacy in participants ≥65 years of age at ≥14 days and ≥28 days post-vaccination increased to 71.4% and 70.1%, respectively.

Table 20. Efficacy against confirmed symptomatic severe/critical COVID-19 infection with onset ≥14 days and ≥28 days post-vaccination, by age group, per-protocol set

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Vaccine group</th>
<th></th>
<th>Placebo group</th>
<th></th>
<th>Vaccine efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n/N)</td>
<td>Person years</td>
<td>Cases (n/N)</td>
<td>Person years</td>
<td></td>
</tr>
<tr>
<td>≥14 days post-vaccination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–59</td>
<td>8/12,750</td>
<td>2,114.3</td>
<td>41/12,782</td>
<td>2,115.1</td>
<td>80.5% (57.8 to 92.1)</td>
</tr>
<tr>
<td>18–64</td>
<td>11/15,444</td>
<td>2,538.5</td>
<td>50/15,552</td>
<td>2,533.8</td>
<td>78.0% (57.3 to 89.7)</td>
</tr>
<tr>
<td>≥60</td>
<td>6/6,764</td>
<td>1,010.7</td>
<td>19/6,762</td>
<td>1,006.9</td>
<td>68.5% (18.1 to 89.7)</td>
</tr>
<tr>
<td>≥65</td>
<td>3/3,970</td>
<td>586.6</td>
<td>10/3,992</td>
<td>583.3</td>
<td>69.9% (-16.8 to 94.7)</td>
</tr>
<tr>
<td>≥28 days post-vaccination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–59</td>
<td>2/12,617</td>
<td>2,101.0</td>
<td>24/12,527</td>
<td>2,086.7</td>
<td>91.7% (66.7 to 99.1)</td>
</tr>
<tr>
<td>18–64</td>
<td>2/15,378</td>
<td>2,522.8</td>
<td>28/15,253</td>
<td>2,500.9</td>
<td>92.9% (71.9 to 99.2)</td>
</tr>
<tr>
<td>≥60</td>
<td>3/6,689</td>
<td>1,005.1</td>
<td>10/6,651</td>
<td>995.9</td>
<td>70.3% (-15.5 to 94.7)</td>
</tr>
<tr>
<td>≥65</td>
<td>3/3,928</td>
<td>583.4</td>
<td>6/3,925</td>
<td>581.7</td>
<td>50.1% (-133.4 to 91.9)</td>
</tr>
</tbody>
</table>

Source: Janssen manufacturer submission to Health Canada, Module 2:5: Clinical overview, Figures 32 and 33
By comorbidity

In the clinical trial, the presence of comorbidities was defined as a study participant with one or more medical conditions at baseline that were associated with an increased risk of progression to severe COVID-19 disease (e.g., asthma, cerebrovascular disease, hypertension, respiratory disease, liver disease, and obesity). In participants with and without comorbidities, efficacy was assessed against confirmed symptomatic moderate to severe/critical and against severe/critical COVID-19 infection with onset ≥14 days and ≥28 days post-vaccination (Table 21).

A repeat of the analysis using the larger dataset of both centrally and locally in-country confirmed COVID-19 cases estimated vaccine efficacy against (a) moderate to severe/critical COVID-19 infection and (b) against severe/critical COVID-19 infection in participants with comorbidities of 58.6% (95% CI: 40.6 to 71.6%) and 75.2% (95% CI: 32.0 to 92.7%) with onset ≥28 days post-vaccination.

Table 21. Efficacy against confirmed symptomatic (a) moderate to severe/critical and (b) severe/critical COVID-19 infection with onset ≥14 days and ≥28 days post-vaccination, by presence or absence of comorbidities, per-protocol set

<table>
<thead>
<tr>
<th>Presence of comorbidities (yes/no)</th>
<th>Vaccine group</th>
<th>Placebo group</th>
<th>Vaccine efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n/N)</td>
<td>Person years</td>
<td>Cases (n/N)</td>
</tr>
<tr>
<td>(a) Moderate to severe/critical COVID-19 infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥14 days post-vaccination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>47/7,777</td>
<td>1,140.0</td>
<td>126/7,798</td>
</tr>
<tr>
<td>No</td>
<td>69/11,737</td>
<td>1,976.6</td>
<td>222/11,746</td>
</tr>
<tr>
<td>≥28 days post-vaccination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>27/7,684</td>
<td>1,133.6</td>
<td>52/7,626</td>
</tr>
<tr>
<td>No</td>
<td>39/11,622</td>
<td>1,968.4</td>
<td>141/11,552</td>
</tr>
<tr>
<td>(b) Severe/critical COVID-19 infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥14 days post-vaccination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8/7,777</td>
<td>1,142.9</td>
<td>29/7,798</td>
</tr>
<tr>
<td>No</td>
<td>6/11,737</td>
<td>1,982.1</td>
<td>31/11,746</td>
</tr>
<tr>
<td>≥28 days post-vaccination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4/7,684</td>
<td>1,135.0</td>
<td>12/7,626</td>
</tr>
<tr>
<td>No</td>
<td>1/11,622</td>
<td>1,971.1</td>
<td>22/11,552</td>
</tr>
</tbody>
</table>

Source: Janssen manufacturer submission to Health Canada, Module 2.5: Clinical overview, Figures 30, 31, 32 and 33

By serostatus

This analysis was conducted using the expanded dataset of both centrally and locally confirmed COVID-19 cases and estimated vaccine efficacy against confirmed symptomatic moderate to severe/critical COVID-19 infection in study participants based on serostatus at baseline (Table 22).
Table 22. Efficacy against confirmed symptomatic moderate to severe/critical COVID-19 infection with onset ≥14 days and ≥28 days post-vaccination, including confirmed and non-centrally confirmed cases, by serostatus, per-protocol set

<table>
<thead>
<tr>
<th>Baseline SARS-CoV-2 serostatus</th>
<th>Vaccine group (Cases (n/N) Person years)</th>
<th>Placebo group (Cases (n/N) Person years)</th>
<th>Vaccine efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥14 days post-vaccination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regardless of baseline status</td>
<td>176/21,636 3,450.2</td>
<td>513/21,574 3,409.8</td>
<td>66.1% (59.7 to 71.6%)</td>
</tr>
<tr>
<td>Positive</td>
<td>3/2,122 336.3</td>
<td>4/2,030 320.8</td>
<td>28.5% (-322.8 to 89.5)</td>
</tr>
<tr>
<td>Negative</td>
<td>173/19,514 3,113.9</td>
<td>509/19,544 3,089.1</td>
<td>66.3% (59.9 to 71.8)</td>
</tr>
<tr>
<td>≥28 days post-vaccination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regardless of baseline status</td>
<td>114/21,424 3,436.3</td>
<td>326/21,199 3,385.9</td>
<td>65.5% (57.2 to 72.4)</td>
</tr>
<tr>
<td>Positive</td>
<td>1/2,118 336.1</td>
<td>2/2,021 320.0</td>
<td>N/A*</td>
</tr>
<tr>
<td>Negative</td>
<td>113/19,306 3,100.3</td>
<td>324/19,178 3,065.9</td>
<td>65.5% (57.2 to 72.4)</td>
</tr>
</tbody>
</table>

* N/A = Not available; estimates of vaccine efficacy not calculated when there were fewer than 6 events identified.

Source: Table 14, FDA Briefing document for Vaccines and Related Biological Products Advisory Committee meeting (February 26, 2021)

Hospitalizations

A post-hoc analysis assessed vaccine efficacy against COVID-19 associated hospitalizations. The analysis was performed for cases with onset ≥1 day, ≥14 days and ≥28 days post-vaccination in study participants seronegative at baseline (Table 23). At each time point, the analysis was performed using (a) centrally confirmed COVID-19 cases only, and (b) both centrally and locally confirmed cases (“Any positive PCR result”).

Table 23. Efficacy against COVID-19 associated hospitalizations with onset ≥1, ≥14 and ≥28 days post-vaccination

<table>
<thead>
<tr>
<th>Analysis population</th>
<th>Vaccine group (Cases (n/N) Person years)</th>
<th>Placebo group (Cases (n/N) Person years)</th>
<th>Vaccine efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 day post-vaccination (in FAS-SN)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmed cases</td>
<td>6 3,202.8</td>
<td>18 3,213.1</td>
<td>66.6% (12.1 to 89.1)</td>
</tr>
<tr>
<td>Any positive PCR result</td>
<td>6 3,202.8</td>
<td>42 3,211.6</td>
<td>85.7% (66.1 to 95.0)</td>
</tr>
<tr>
<td>≥14 days post-vaccination (PP)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmed cases</td>
<td>2 3,125.8</td>
<td>11 3,125.9</td>
<td>81.8% (16.7 to 98.0)</td>
</tr>
<tr>
<td>Any positive PCR result</td>
<td>2 3,125.8</td>
<td>29 3,125.1</td>
<td>93.1% (72.7 to 99.2)</td>
</tr>
<tr>
<td>≥28 days post-vaccination (PP)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmed cases</td>
<td>0 3,106.3</td>
<td>6 3,084.4</td>
<td>100.0% (15.7 to 100.0)</td>
</tr>
<tr>
<td>Any positive PCR result</td>
<td>0 3,106.3</td>
<td>16 3,083.9</td>
<td>100.0% (74.3 to 100.0)</td>
</tr>
</tbody>
</table>

FAS-SN = Full analysis set, all randomized study participants with documented study vaccine administration, seronegative at baseline; PP = per-protocol set

Source: Janssen manufacturer submission to Health Canada, Module 2.5: Clinical overview, Table 10

Deaths

There were 19 deaths reported during the clinical trial: 3 in the vaccine group and 16 in the placebo group. Of the 19 deaths, zero in the vaccine group were determined to be associated with COVID-19, based on WHO COVID-19 case classifications combined with a positive RT-PCR result, compared to 5 COVID-19 associated deaths in the placebo group. All 5 deaths in
the placebo group were in South African study participants with one or more comorbidities with an increased risk for progression to severe COVID-19 disease.

Asymptomatic or undetected SARS-CoV-2 infection

Analysis of vaccine efficacy against asymptomatic or undetected COVID-19 infection (study participants not meeting one of the case definitions for symptomatic COVID-19 and with a positive PCR or serology result) and against seroconversion were conducted at two time points: with onset 1 to 29 days and ≥28 days post-vaccination. A sensitivity analysis was also performed for each of these outcomes by removing participants with symptoms at any time since screening and prior to the positive PCR or serology result (“without previous symptoms”).

The point estimate of vaccine efficacy against asymptomatic or undetected COVID-19 infection with onset ≥28 days post-vaccination is 59.7% (and 74.0% after removal of participants with prior symptoms) and against seroconversion it is 66.5% (74.2% with removal of participants with prior symptoms) (Table 24). The seroconversion results should be interpreted with caution as this is a preliminary analysis based on a limited duration of follow-up in approximately 29% of study participants planned for the final analysis based on Day 71 serology.

Table 24. Efficacy against asymptomatic and undetected COVID-19 infection, and against seroconversion, with onset ≥28 days post-vaccination

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Vaccine group</th>
<th>Placebo group</th>
<th>Vaccine efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n/N)</td>
<td>Person years</td>
<td>Cases (n/N)</td>
</tr>
<tr>
<td>Full analysis set, seronegative at baseline</td>
<td>22/19,301</td>
<td>3,099.7</td>
<td>54/19,162</td>
</tr>
<tr>
<td>Asymptomatic or undetected SARS-CoV-2 infection</td>
<td>10/19,301</td>
<td>3,098.0</td>
<td>38/19,162</td>
</tr>
<tr>
<td>Asymptomatic or undetected SARS-CoV-2 infection without previous symptoms</td>
<td>18/1,346</td>
<td>312.2</td>
<td>50/1,304</td>
</tr>
<tr>
<td>Serology risk set*</td>
<td>10/1,346</td>
<td>310.9</td>
<td>37/1,304</td>
</tr>
</tbody>
</table>

*Serology risk set = study participants with a serology result available at Day 71 post-vaccination

Source: Janssen manufacturer submission to Health Canada, Module 2.5: Clinical overview, Table 12

Immunogenicity

The majority of the immunogenicity analysis is based on data from a Phase 1 trial that included 2 cohorts of healthy adults aged 18 to 55 and ≥65 years of age. Within each cohort, there were two dose levels given as one or two doses. The analysis below is from one dose of the lower dose, 5x10^10 viral particles.

Humoral immune responses

Antibody responses were elicited by one dose of the Janssen vaccine. Binding and neutralizing antibodies reached a maximum by day 29 and maintained through day 85 (last time point of
evaluation) in the younger cohort. In the older cohort, binding antibody responses were slightly lower than those in the younger cohort and were elicited more slowly, increasing from day 15 through day 57 (last time point of evaluation). Neutralizing antibody responses were similar levels to those in the younger cohort, elicited by day 15 and maintained an approximate plateau through day 57. Functional antibody responses as determined through Fc effector function were maximally elicited by day 29 (the last day of evaluation), at similar levels in both age cohorts.

Minimal data are available for seropositive vaccine recipients that may suggest that they respond strongly to one dose of vaccine.

Minimal data are also available demonstrating decreased neutralizing antibody responses to viral variant B.1.1.7.

Without a correlate of protection, the significance of these difference in antibody responses is unclear.

**Cellular immune responses**

Cellular immune responses were elicited by one dose of this vaccine and were similar in both age cohorts. Spike protein-specific CD4+ T cells responses were detected in 76% of younger vaccine recipients and 60% of older vaccine recipients. Th-1 biased CD4+ T cell responses were observed by day 15 post-vaccination and remained elevated until day 29 (last time point of evaluation). Spike protein-specific CD8+ T cells responses were detected in 51% of younger vaccine recipients and 36% of older vaccine recipients by day 15 post vaccination and remained elevated until day 29.

**Anti-vector immune responses**

It is unclear to what extent pre-existing immunity to any adenovirus-based vaccine vector exists in the Canadian population and what impact that could have on adenovirus based vaccine safety and efficacy. It is also unclear as to what extent immunization with adenovirus-based vaccines elicits anti-vector immune responses and what impact that could have on homologous or heterologous booster doses with adenovirus-based vaccines. Evidence for a COVID-19 viral vector vaccine based on human adenovirus 5 (not authorized in Canada) indicated that vaccine recipients with high pre-existing immunity to the adenovirus vector had lower anti-SARS-CoV-2 immune responses. The Janssen COVID-19 vaccine uses a modified Ad26. Janssen found no correlation between anti-Ad26 neutralizing antibody responses and anti-SARS-CoV-2 immune responses. However, neutralization is not the only anti-vector immune response that could impact vaccine-induced immunity. It remains unclear if immune responses to the Ad26 vector will impact the efficacy or effectiveness of this vaccine.

**Vaccine safety and adverse events following immunization**

Safety evidence is based on interim analyses of 21,895 participants (of whom 7,331 were ≥60 years of age) who received at least one dose of the vaccine. A safety subset included 3,356 participants in the vaccine group who were followed for solicited reactions within 7 days following vaccination and unsolicited reactions within 28 days following vaccination. Medically attended adverse events (MAAEs), SAEs and AEs leading to discontinuation from study participation were assessed in all participants. Overall, the median duration of follow-up was 58 days after vaccination.
Solicited local reactions
Solicited local injection site AEs were reported by 50.3% of evaluated participants within the first 7 days following any vaccine dose. Injection site pain was the most frequently reported local AE (48.7%) followed by warmth (7.3%) and swelling (5.3%). In the vaccine group, the frequency of solicited local AEs was lower in participants aged ≥60 years compared to participants aged ≥18 to <60 years. The frequency of solicited local AEs was also similar in participants who were seronegative for SARS-CoV-2 at baseline compared to participants who were seropositive for SARS-CoV-2 at baseline (50.1% and 54.5%, respectively). The majority of solicited local reactions among vaccine recipients were mild or moderate in severity, with any Grade 3 reactions being reported by ≤0.7% of participants. No Grade 4 solicited local AEs were reported.

Solicited systemic reactions
Solicited systemic AEs were reported by 55.2% of evaluated participants within the first 7 days following vaccine administration. The most common systemic solicited AEs were headache (39.0%) and fatigue (38.3%). Other frequently reported systemic solicited AEs were muscle pain (33.2%), nausea (14.2%) and fever ≥38.0°C (9.0%). While AEs were lower in participants aged ≥60 years compared to participants aged ≥18 to <60 years, there were no clinically relevant differences in the frequency of solicited systemic AEs. AEs were similarly observed in participants who were seronegative for SARS-CoV-2 at baseline (55.1%) compared to participants who were seropositive for SARS-CoV-2 at baseline (50.6%). Overall, the frequency of any Grade 3 reactions was <2%, and no Grade 4 solicited systemic AEs were reported. Antipyretics were recommended post-vaccination for symptom relief as needed. Analgesics or antipyretics were used by 26.4% of vaccinated 18 to 59 year olds and 9.8% of vaccinated individuals 60 years of age and older up to 7 days post vaccination in the full analysis. The majority of solicited systemic AEs were transient in nature and had a median duration of 1 to 2 days after vaccination.

Unsolicited serious adverse events
During the 28-day period post-vaccination, there were 19 (0.6%) participants with unsolicited AEs of at least Grade 3 in the vaccine group compared to 18 (0.6%) participants in the placebo group. Of these unsolicited AEs of at least Grade 3, 5 (0.1%) were considered to be related to the study vaccine. There were no clear imbalances by System Organ Class (SOC). No cases of anaphylaxis were identified in the clinical trials. However, the manufacturer announced receipt of preliminary reports of two cases of severe allergic reactions, including one case of anaphylaxis, in participants who had received the vaccine. Details on the reports have not been provided to date.

In total there were 7 (<0.1%) participants who reported SAEs that were considered to be related to the study vaccine by the investigator and lead to discontinuation from the study. These included:

- Grade 4 Guillain-Barré syndrome in a participant 16 days after vaccination. The case was considered indeterminate as per WHO AEFI criteria; however, due to close temporal association and lack of other explanatory factors, it was considered as possibly related to the vaccine for reporting purposes.
- Grade 4 pericarditis in a participant approximately 17 days following vaccination and resulted in hospitalization. The event was assessed as indeterminate as per WHO AEFI criteria; however, due to close temporal association and a lack of other explanatory factors it was assessed as possibly related to the vaccine for reporting purposes.
- Grade 3 brachial radiculitis in a participant with immediate onset following vaccination.
- Grade 3 post-vaccination syndrome 2 days following vaccination. Based on the symptoms, the event was assessed as vaccine reactogenicity (asthenia).
• Grade 3 Type IV hypersensitivity in a participant 3 days following vaccination. The case was considered likely related to vaccination due to close temporal association.
• Grade 2 facial paralysis (Bell’s Palsy) in two participants 3 and 16 days after vaccination. Both events were assessed to have an inconsistent causal association with immunization, per the WHO AEFI criteria.

Other serious adverse events

Tinnitus
Six cases of tinnitus were reported in the vaccine group and none in the placebo group. All cases were considered non-serious, and two cases were considered related by the investigator. All participants had underlying medical conditions (such as history of tinnitus and migraine, history of hypertension, seasonal allergies and hypothyroidism) or used medications that offered a more plausible alternative cause for the event compared to the vaccine.

Convulsions/seizures
Four cases were reported in the vaccine group (1 serious) and one case (non-serious) in the placebo group, all of which were considered not related to the study vaccine by the investigator. The serious case of convulsion/seizure was reported in a participant with a history of epilepsy and obsessive-compulsive disorder.

Thrombotic and thromboembolic events
The overall incidence of thrombotic and thromboembolic events (arterial and venous) was similar across the vaccine (n=15, 0.1%) and placebo groups (n=10, <0.1%). A numerical imbalance was observed for the deep vein thrombosis deep/pulmonary embolism subtypes, with a total of 9 cases in the vaccine group (4 serious) and 3 cases in the placebo group (2 serious). One case of transverse sinus thrombosis occurred on Day 21 following vaccination in a 25-year-old male participant with no past medical history. The participant also presented a seizure reported to be a consequence of a secondary bleed caused by elevated venous pressure from the venous flow obstruction. Two thrombectomy procedures were performed because of the participant’s hypercoagulable state. No clear cause of the event was identified and it was deemed unrelated to the vaccine as there were possible contributing factors (preceding infection and anatomical anomaly). One non-serious case with onset 27 days after vaccination in a participant with a medical history of obesity and cholecystectomy was considered to be related to the vaccine.

Vaccine-Induced Immune Thrombotic Thrombocytopenia
Rare cases of serious blood clots, including cerebral venous sinus thrombosis, associated with thrombocytopenia have been recently reported in the United States following post-licensure use of Janssen COVID-19 vaccine. This adverse event is being referred to as Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) and has been associated with both the AstraZeneca and Janssen COVID-19 viral vector vaccines. The mechanism of action is similar to heparin-induced thrombocytopenia (HIT). The exact mechanism by which the viral vector COVID-19 vaccines may trigger VITT is still under investigation. As of May 18, 2021, 30 cases of VITT out of 9.6 million doses of Janssen administered in the United States have been confirmed. Most of the cases to date have occurred in females between the ages of 18 and 49 years; however investigations are ongoing and additional cases may be identified with increased awareness and current emphasis on the clinical recognition of this event. Reports indicated symptom onset between 6 and 15 days after vaccination. Investigations are ongoing.
Demyelinating disorders

In total there were four cases of demyelinating disorders that were reported in the vaccine group (2 cases peripheral neuropathy, 1 benign monoclonal hypergammaglobulinemia, 1 Guillain-Barré syndrome) compared with 5 cases in the placebo group (2 cases peripheral neuropathy, 1 Guillain-Barré syndrome and 2 sensory loss).

Death

A total of 19 deaths were reported among study participants (3 in the vaccine group and 16 in the control group). In the vaccine group, causes of death by preferred term were lung abscess, non-COVID-19 pneumonia, and 1 of unknown cause at the time of data cut-off. None of these deaths were considered to be related to the study intervention by the investigators.

Pregnancies

Eight pregnancies were reported through January 22, 2021 (4 vaccine, 4 placebo). Vaccination was within 30 days after last menstrual period in 7 participants (3 vaccine, 4 placebo) while in 1 vaccine recipient vaccination was prior to last menstrual period. Unsolicited AEs related to pregnancy included spontaneous abortion (1 vaccine, 0 placebo), incomplete abortion (0 vaccine, 1 placebo), elective abortion (0 vaccine, 2 placebo) and ectopic pregnancy (1 vaccine, 0 placebo). Two pregnancies are ongoing among participants in the vaccine group, with unknown outcomes at this time.
# APPENDIX E: FREQUENCY OF SOLICITED ADVERSE EVENTS FOLLOWING IMMUNIZATION FOR COVID-19 VACCINES IN CLINICAL TRIALS

Table 25. Frequency of solicited local adverse events in authorized populations for mRNA COVID-19 vaccines\(^a\)

<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>Adults (≥16 years old)</td>
<td>Adolescents (12 -15 years old)</td>
</tr>
<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>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(^b) / Axillary swelling 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 26. Frequency of solicited local adverse events in authorized populations for viral vector COVID-19 vaccines

<table>
<thead>
<tr>
<th>AEFI</th>
<th>AstraZeneca COVID-19 Vaccine</th>
<th>Janssen COVID-19 Vaccine&lt;sup&gt;b&lt;/sup&gt;</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 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&lt;sup&gt;c&lt;/sup&gt; Axillary swelling and tenderness</td>
<td>NS</td>
<td>NS</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>

<sup>a</sup> 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

<sup>b</sup> Single dose vaccine (dose 2 not applicable)

<sup>c</sup> Lymphadenopathy was not a solicited adverse event for the AstraZeneca or Janssen COVID-19 vaccine and was reported as an unsolicited adverse event. Please see Appendix C for more details.

Abbreviations: AEFI: adverse event following immunization; MenACWY: Quadrivalent meningococcal vaccine; NS: not solicited
Table 27. 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>Adults (≥16 years old)</td>
<td>Adolescents (12-15 years old)</td>
</tr>
<tr>
<td></td>
<td>Dose 1</td>
<td>Dose 2</td>
</tr>
<tr>
<td>Feverishness&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Common</td>
<td>Common</td>
</tr>
</tbody>
</table>

**Abbreviations:** AEFI: adverse event following immunization; MenACWY: Quadrivalent meningococcal vaccine; NS: not solicited

<sup>a</sup> 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

<sup>b</sup> Fever was objectively reported as having a temperature ≥38°C/100.4°F. Feverishness was a subjective, self-reported feeling of having fever.

<sup>c</sup> If two frequencies are reported the first reflects frequency of nausea and the second reflects the frequency of vomiting.
Table 28. Frequency of solicited systemic adverse events in authorized populations for viral vector COVID-19 vaccines

<table>
<thead>
<tr>
<th>AEFI</th>
<th>AstraZeneca COVID-19 Vaccine</th>
<th>Janssen COVID-19 Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaccine</td>
<td>MenACWY control</td>
</tr>
<tr>
<td></td>
<td>Dose 1</td>
<td>Dose 2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Very Common</td>
<td>Very Common</td>
</tr>
<tr>
<td>Chills</td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td>Joint Pain</td>
<td>Very Common</td>
<td>Very Common</td>
</tr>
<tr>
<td>Fever</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Feverishness</td>
<td>Very Common</td>
<td>Common</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: AEFI: adverse event following immunization; MenACWY: Quadrivalent meningococcal vaccine; NS: not solicited

- **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

- **a** Very common = occur in 10% or more of vaccine recipients, common = occur in 1 to less than 10% of vaccine recipients, uncommon= occur in 0.1% to less than 1% of vaccine recipients

- **b** Single dose vaccine (dose 2 not applicable)

- **c** Fever was objectively reported as having a temperature ≥38°C/100.4°F. Feverishness was a subjective, self-reported feeling of having fever.

- **d** If two frequencies are reported the first reflects frequency of nausea and the second reflects the frequency of vomiting.
APPENDIX F: PREGNANCY, BREASTFEEDING AND COVID-19 VACCINE REGISTRIES

There is a Canadian COVID-19 vaccine registry for pregnant and breastfeeding individuals:

- [Canadian COVID-19 Vaccine Registry for Pregnant and Lactating Individuals](#)

Table 29: Pregnancy registry information by vaccine product

<table>
<thead>
<tr>
<th>Vaccine product</th>
<th>Registry information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer-BioNTech COVID-19 vaccine</td>
<td>Pfizer does not have a pregnancy exposure registry. Pfizer COVID-19 vaccine recipients and health care providers are encouraged to report any exposure to COVID-19 vaccine during pregnancy or breastfeeding to the vaccine manufacturer (1-866-723-7111).</td>
</tr>
<tr>
<td>Moderna COVID-19 vaccine</td>
<td>There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to the Moderna COVID-19 vaccine during pregnancy. Women who are vaccinated with the Moderna COVID-19 vaccine during pregnancy are encouraged to enroll in the registry by calling 1-866-MODERNA (1-866-663-3762).</td>
</tr>
<tr>
<td>AstraZeneca COVID-19 vaccine</td>
<td>There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to AstraZeneca COVID-19 vaccine during pregnancy. Women who are vaccinated with AstraZeneca COVID-19 Vaccine during pregnancy are encouraged to enroll in the registry by visiting <a href="https://c-viper.pregistry.com">https://c-viper.pregistry.com</a> or calling 1-800-616-3791.</td>
</tr>
<tr>
<td>Janssen COVID-19 vaccine</td>
<td>There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Janssen COVID-19 vaccine during pregnancy. Women who are vaccinated with Janssen COVID-19 vaccine during pregnancy are encouraged to enroll in the registry by visiting <a href="https://c-viper.pregistry.com">https://c-viper.pregistry.com</a></td>
</tr>
</tbody>
</table>