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

Recommendations on the use of COVID-19 Vaccines

PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH

Public Health Agency of Canada   Agence de la santé publique du Canada

Canada

PREAMBLE

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

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

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

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

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TABLE OF UPDATES

This evergreen document will be updated as COVID-19 vaccines are authorized and become available for use in Canada, as evidence on these vaccines and COVID-19 evolves, and as recommendations from NACI evolve based on this evidence. This table summarizes the updated information provided in the current version of this document since the publication of the last version of the document on July 2, 2021.

A complete list of changes to this document can be found in the Table of updates: Recommendations on the use of COVID-19 vaccines web page. Complete previous versions of this document are archived and are available through the National Advisory Committee on Immunization (NACI): Statements and publications web page under COVID-19.

Section	Update	Date
Vaccines: Special populations	Updated summary of evidence on risk of re-infection and vaccination in individuals with prior SARS-CoV-2 infection.	2021-07-22
Recommendations	Summary of evidence and rationale for NACI recommendation (#4) on vaccination of individuals with prior SARS-CoV-2 has been updated to reflect latest evidence.	2021-07-22

SUMMARY OF INFORMATION CONTAINED IN THIS NACI STATEMENT

The following highlights key, current information for immunization providers on COVID-19 vaccines. The evidence on COVID-19 disease and vaccines is evolving. Evidence from clinical trial data is limited due to limitations in the size and duration of follow-up of trial populations. However, clinical trials and studies in the real-world setting are ongoing. NACI will continue to monitor the evidence and update its recommendations as needed. Please refer to the remainder of the Statement for details.

What

Disease
- Novel coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
- Genetic mutations in the SARS-CoV-2 virus have been identified ("variants"), some of which make the virus more infectious and transmissible. They may also affect the severity of disease and the level of protection offered by vaccines against them.
- Anyone can be infected with SARS-CoV-2. However, some populations are at increased risk of exposure to the virus (e.g., due to living or work settings), and some populations are at increased risk of severe disease and death due to biological (e.g., advanced age, pre-existing medical conditions) and social (e.g., low socioeconomic status, belonging to

a racialized population) factors that may intersect. Risk factors for exposure and severe disease may overlap, further increasing risk. Any combination of these factors, as well as varying access to health care services, has the potential for disproportionate consequences for specific populations.

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

- mRNA vaccines are authorized for use in Canada for individuals 12 years of age and older (Pfizer-BioNTech COVID-19 vaccine) 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 (Beta) variant of concern (VOC) and P.2 (Zeta) variant of interest (VOI) were circulating, respectively. There is currently limited evidence on the duration of protection and on the efficacy of these vaccines in reducing transmission of SARS-CoV-2, although studies are ongoing. Evidence of protection against asymptomatic SARS-CoV-2 infection is emerging for the mRNA and Janssen vaccines.
- Evidence of varying protection offered by COVID-19 vaccines against SARS-CoV-2 variants is evolving. To date, evidence has emerged that the Pfizer-BioNTech and AstraZeneca vaccines offer protection against the B.1.1.7 (Alpha) VOC . Furthermore, there is emerging evidence that both vaccines also offer good protection against infection with the B.1.617.2 (Delta) VOC after the second dose and good protection against hospitalization after the first dose. There is evidence that the Janssen vaccine offers some protection against the B.1.351 (Beta) VOC as well as the P.2 (Zeta) VOI. There is evidence that the AstraZeneca vaccine does not offer protection against the B.1.351 (Beta) VOC.
- For all vaccines, some solicited adverse events are reported to be very common (defined as 10% or more) among vaccine recipients. However, they are mild or moderate and transient, resolving within a few days. These include: pain at the injection site, fatigue, headache, muscle pain, chills, joint pain, and fever. In clinical trials of mRNA vaccines, some adverse events, including fever, are more frequent after the second dose; this was not the case with the AstraZeneca COVID-19 vaccine.
- Very rare cases of a specific syndrome that involves serious blood clots (at unusual sites such as cerebral venous sinus thrombosis) associated with thrombocytopenia have been reported after vaccination with viral vector vaccines. These cases often occur between 4 and 28 days after receipt of the vaccine. Early identification and appropriate treatment are critical. Investigations to better understand this syndrome, often referred to as Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT), are ongoing. Individuals who have experienced venous or arterial thrombosis with thrombocytopenia following vaccination with a viral vector COVID-19 vaccine should not receive a second dose of a viral vector COVID-19 vaccine.

- Very rare cases of myocarditis and pericarditis following vaccination with COVID-19 mRNA vaccines have been reported, most frequently in adolescents and younger adults under 30 years of age, more frequently in males compared to females, and more frequently after the second dose. The majority of reported cases were mild and the individuals tend to recover quickly. Investigations are ongoing. As a precautionary measure, individuals who have experienced myocarditis or pericarditis following vaccination with a first dose of an mRNA COVID-19 vaccine should defer the second dose in the vaccination series until more information is available. NACI will continue to monitor the evidence and update recommendations as needed.
- Very rare cases of capillary leak syndrome (CLS) have been reported following immunization with the AstraZeneca COVID-19 vaccine [1-3]. Some affected patients had a previous diagnosis of CLS. CLS is a serious, potentially fatal condition characterized by acute episodes of limb edema, hypotension, hemoconcentration and hypoalbuminemia. Individuals with a history of CLS should not receive the AstraZeneca/COVISHIELD COVID-19 vaccine.
- There is currently minimal evidence to inform on differences in vaccine efficacy, effectiveness, or safety between individuals with and those without prior evidence of SARS-CoV-2 infection at the time of vaccination.

Who

NACI makes the following recommendations:

A complete series with an mRNA COVID-19 vaccine should be preferentially offered to individuals in the authorized age group without contraindications to the vaccine.

A viral vector COVID-19 vaccine may be offered to individuals in the authorized age group without contraindications to the vaccine to initiate a series when other authorized COVID-19 vaccines are contraindicated or inaccessible. Informed consent should include discussion about the risk and symptoms of VITT, as well as the need to seek immediate medical care should symptoms develop.

A complete vaccine series with a currently authorized COVID-19 vaccine may be offered to:
- Individuals in the authorized age group without contraindications to the vaccine who have had previously polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection. Testing for previous SARS-CoV-2 infection is not needed prior to COVID-19 vaccination.

NACI also recommends that:

- Routine immunization programs and immunization with other vaccines recommended by NACI should continue during the COVID-19 pandemic with mitigation of risks of COVID-19 transmission during the immunization process as outlined in the Interim guidance on continuity of immunization programs during the COVID-19 pandemic.
- Clinical trials assessing COVID-19 vaccines should continue to be encouraged to include individuals with potential vulnerabilities to disease related to biological (e.g., pre-existing medical conditions, frailty, pregnancy and breastfeeding, immunocompromised), and social (e.g., residence in long term care facilities or crowded or remote locations, belonging to a racialized population, occupation) factors to ensure that vaccine options are informed by robust safety, immunogenicity, and efficacy data as outlined in NACI's guidance on Research Priorities for COVID-19 Vaccines to Support Public Health

Decisions. Furthermore, NACI recommends the continuation of clinical trials and ongoing follow-up of participants for as long as it is ethically feasible to determine the level of immunity needed to prevent disease, duration of protection, efficacy in different sub-populations, and medium- and long-term safety.

- In addition to ongoing vaccine pharmacovigilance activities in Canada with Phase 4 clinical trials and post-marketing studies, additional research and surveillance of COVID-19 vaccination, particularly in populations not currently included in clinical trials (e.g., pregnant, breastfeeding, immunosuppressed, and seniors living in congregate care settings) is recommended.

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

➢ Efforts should be made to increase access to immunization services to reduce health inequities without further stigmatization or discrimination, and to engage systemically marginalized populations and racialized populations in immunization program planning.

➢ Jurisdictions should ensure close and rapid monitoring of safety, coverage and effectiveness of the vaccines in different key populations, as well as effective and efficient immunization of populations in hardly reached, remote and isolated communities.

➢ Efforts should be made to improve knowledge about the benefits of vaccines in general and of COVID-19 vaccines as each becomes available, address misinformation, and communicate transparently about COVID-19 vaccine allocation decisions.

How
- Currently authorized and available COVID-19 vaccines are administered intramuscularly in a two-dose schedule (Pfizer-BioNTech, Moderna, and AstraZeneca) or in a one-dose schedule (Janssen).
- When the first dose in a COVID-19 vaccine series is an mRNA vaccine, the same mRNA vaccine product should be offered for the subsequent dose if readily available. When the same mRNA vaccine product is not readily available, or is unknown, another mRNA COVID-19 vaccine product recommended in that age group can be considered interchangeable and should be offered to complete the series.
- When the first dose in a COVID-19 vaccine series is the AstraZeneca/COVISHIELD vaccine, either the AstraZeneca/COVISHIELD vaccine or an mRNA vaccine product may be offered for the subsequent dose to complete the series; however an mRNA vaccine product is preferred as a subsequent dose due to emerging evidence including the possibility of better immune response, and the safety of heterologous schedules. Individuals who have already received two doses of the AstraZeneca/COVISHIELD vaccine are considered protected and do not require further vaccination.
- 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 for those ages 18 and above on December 23, 2020.
3. The AstraZeneca COVID-19 vaccine was authorized for use in Canada for those ages 18 and above 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 for those ages 18 and above 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 (archived) to inform clinical trials of candidate COVID-19 vaccines to protect against infection, serious illness, and deaths caused by SARS-CoV-2.

2. Preliminary guidance on key populations for early COVID-19 immunization 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 (archived) to maximize the number of individuals benefiting from the first dose of vaccine by extending the interval for the second dose up to four months after the first. This was followed by a more comprehensive NACI statement (archived) providing a detailed overview of the evidence and considerations leading to NACI's recommendation.
6. Rapid response: Recommended use of AstraZeneca COVID-19 vaccine in younger adults (archived) guidance developed in response to the investigation of Vaccine-Induced Prothrombotic Immune Thrombocytopenia (VIPIT) [hereafter referred to as Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)] following vaccination with AstraZeneca COVID-19 vaccine is investigated further.
7. Recommendation on the use of the Pfizer-BioNTech COVID-19 vaccine in adolescents 12 to 18 years of age (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. Rapid response: Interchangeability of authorized COVID-19 vaccines (archived) to provide advice on the interchangeability of authorized COVID-19 vaccines in a two-dose primary series schedule for COVID-19 immunization in Canada.
9. Recommendations on the use of COVID-19 vaccines (archived) initially published on December 12, 2020 and updated iteratively as new evidence becomes available and with the authorization of additional COVID-19 vaccines. This statement reflects the most up to date guidance.

Guidance Objective

The objective of this advisory committee statement is to provide evidence-informed guidance on the effective and equitable use of COVID-19 vaccines authorized 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 [4, 5].

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 [5]. The NACI Secretariat applied this framework with accompanying evidence-informed tools (Ethics Integrated Filters, Equity Matrix, Feasibility Matrix, and Acceptability Matrix) to systematically consider these programmatic factors for the development of clear, comprehensive, appropriate recommendations for timely, transparent decision-making. For details on the development and application of NACI's EEFA Framework and evidence-informed tools (including the Ethics Integrated Filters, Equity Matrix, Feasibility Matrix, and Acceptability Matrix), please see https://doi.org/10.1016/j.vaccine.2020.05.051.

For this advisory committee statement, NACI used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework to develop population-focused recommendations. Further information on this framework can be found in the GRADE handbook, available at: https://training.cochrane.org/resource/grade-handbook

NACI reviewed and approved the key policy questions used to guide recommendation development on November 25, 2020 and rated the outcomes for their importance for decision-making. With evolving evidence, NACI rated outcomes again on March 21, 2021. The Canadian Immunization Committee (CIC) provided feedback on the key policy questions to ensure alignment with program needs. Important ethical considerations relating to the key policy questions were presented on November 26, 2020, December 15, 2020, January 26, 2021 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.
- Evidence on mixed COVID-19 vaccine schedules was presented and reviewed by NACI on May 26, 2021 and related recommendations were approved on May 30, 2021. Emerging evidence was reviewed on June 9 and the related recommendation on interchangeability in a vaccine series when the first dose is an AstraZeneca/COVISHIELD COVID-19 vaccine was revised and approved on June 11, 2021.
- NACI reviewed its recommendation on simultaneous administration of COVID-19 vaccines with other vaccines and updated its recommendation on June 9, 2021.
- Evidence on myocarditis and pericarditis was presented and reviewed by NACI on May 18, June 1, June 15, June 21, and June 24, 2021. NACI approved updated information for inclusion in NACI's guidance on June 27, 2021.

III. EPIDEMIOLOGY

Information on COVID-19 is continually evolving. The following section will describe the current basis of knowledge, with an emphasis on the best available Canadian data where possible. To access the most recent updates to specific elements, please refer to the links below.

Disease description

Infectious agent

COVID-19 is caused by the SARS-CoV-2, which was first recognized in Wuhan, China in December 2019.

Transmission

Current evidence suggests that SARS-CoV-2 is spread through respiratory droplets and aerosols created when an infected person coughs, sneezes, sings, shouts, or talks. A person may be infectious for up to three days before showing symptoms.

More information on the transmission of SARS-CoV-2 can be found on the PHAC webpages for COVID-19: Main modes of transmission and COVID-19 signs, symptoms and severity of disease: A clinician guide

Variants of concern

Genetic mutations in the SARS-CoV-2 virus have been identified, some of which make the virus more infectious and transmissible. They may also affect the severity of disease and the level of protection offered by vaccines against them.

More information on the variants of concern (VOC) reported in Canada is available in the COVID-19 epidemiology update. The COVID-19 Weekly Epidemiological Update by the World Health Organization provides a summary on the global distribution and emerging evidence on VOC and variants of interest (VOI). Differences between VOC and VOI are available from SARS-CoV-2 variants: National definitions, classifications and public health actions.

NACI will continue to monitor the epidemiology and evidence pertaining to VOC and COVID-19 vaccines.

Risk factors

Anyone can be infected with SARS-CoV-2. However, some populations are at increased risk of exposure to the virus (e.g., due to living or occupational settings), and some populations are at increased risk of severe disease and outcomes (e.g., hospitalization and death) due to various biological (e.g., advanced age, pre-existing medical conditions) and social (e.g., socioeconomic status, belonging to a racialized population) factors that may intersect. Exposure and risk of severe disease factors may overlap, further increasing risk. Any combination of these factors, as well as varying access to health care services, has the potential for disproportionate consequences for specific populations characterized by increased rates of infection and disease, severe illness, hospitalizations, and/or deaths.

Please see NACI's Advisory Committee Statement on Key Populations for Early COVID-19 Immunization and the Equity Matrix [6] 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 [7] 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 [7]. 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) [8]. 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) [7].

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) [7]. The review found a low certainty of evidence for at least a 2-fold increase in mortality from COVID-19, and/or a low or moderate certainty of evidence for at least a 2-fold increase in hospitalization for a longer list of medical conditions (classified as Level 2). Individuals with two or more medical conditions were found to have at least a 2-fold increase in hospitalization and mortality from COVID-19 (moderate certainty of evidence). Similarly, in populations 21 years of age and younger, individuals with two or more medical conditions were found to have at least a 2-fold increase in hospitalizations from COVID-19 (moderate certainty of evidence). However, there is no direct evidence on which combination of medical conditions increase this risk [7].

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 [9] found low certainty evidence for at least a 2-fold increase in hospitalization or mortality for males, people with liver disease, and people with heart failure. As evidence has accumulated, there is now stronger evidence for little-to-no increased association of severe outcomes in these populations. The list of medical conditions included in Table 1 may not be comprehensive as it is based only on evidence from published studies included in the ARCHE review.

Table 1. Summary of risk factors for severe outcomes from COVID-19 and increased risk of exposure to COVID-19

Increased risk of severe outcomes from COVID-19 (hospitalization/mortality) [a]	Increased risk of exposure to COVID-19 [7] (e.g., due to inability to physically distance/reduced access to IPC) [b]
Increasing age (strong evidence) (based on moderate certainty of evidence of ≥2-fold increase in mortality) • ≥60 years (particularly ≥ 70 years) [7]	• 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)
Medical conditions – Level 1 (strong evidence) [7] (based on moderate or high certainty evidence of ≥2-fold increase in mortality) • Down syndrome • End-stage kidney disease • Epilepsy • Motor neuron disease, multiple sclerosis, myasthenia gravis, Huntington's disease [d]	

• Type 1 and 2 diabetes	• Frontline essential workers who cannot work virtually
Medical conditions – Level 2 (limited evidence) [7] **Level 2a** (based on low certainty of evidence of ≥2-fold increase in mortality • Cerebral palsy • Major psychiatric disorder (schizophrenia, schizoaffective disorder, or bipolar disorder); in combination with prescription drug use for the condition in the past 6 months • Obesity class III (BMI ≥40 kg/m^2) • Parkinson's disease • Sickle cell disease or severe immunodeficiency, transplant (any type) • Solid organ transplant • Recent bone marrow or stem cell transplant • Metastatic cancer • Recent/current chemotherapy or radiotherapy **Level 2b** (based on low or moderate certainty of evidence of ≥2-fold increase in hospitalization) • Previous cerebrovascular accident • Pregnancy (any stage) • Frailty (among community and non-community dwelling people; measured on scales that include items such as weight loss, exhaustion, physical activity, walking speed, grip strength, overall health, disability, presence of disease, dementia, falls, mental wellbeing) • Vasculitis • Obesity – all classes (BMI >30 kg/m^2)	

Increased risk of severe outcomes (hospitalization/mortality)[c] and Increased risk of exposure [7]
• 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

Product Brand Name	Pfizer-BioNTech COVID-19 Vaccine	Moderna COVID-19 Vaccine	AstraZeneca COVID-19 / COVISHIELD Vaccine	Janssen COVID-19 Vaccine
Type of vaccine	mRNA	mRNA	Non-replicating viral vector (ChAd)	Non-replicating viral vector (Ad26)
Date of authorization in Canada	December 9, 2020 (16 years of age and older); May 5, 2021 (12 years of age and older)	December 23, 2020	February 26, 2021	March 5, 2021
Authorized ages for use	12 years of age and older	18 years of age and older	18 years of age and older	18 years of age and older
Dose	0.3 mL (30 mcg of mRNA)[a]	0.5 mL (100 mcg of mRNA)	0.5 mL (5 x 10^{10} viral particles)	0.5 mL (5 x 10^{10} viral particles)
Authorized Schedule [b]	2 Doses, 3 weeks apart	2 Doses, 4 weeks apart	2 Doses, 4 to 12 weeks apart	1 Dose
Route of administration	IM	IM	IM	IM
Nature of the antigen	Transmembrane prefusion spike protein	Transmembrane prefusion spike protein	Transmembrane spike protein	Transmembrane prefusion spike protein
Adjuvant (if present)	None	None	None	None
Primary storage requirements pre-puncture[c]	-80°C to -60°C	-25°C to -15°C[d]	+2°C to +8°C	+2°C to +8°C
Additional storage options pre-puncture[c]	Frozen vials: -25°C to -15°C for up to 2 weeks[e] Thawed under frigeration: 1 month at +2°C to +8°C Thawed at room temperature: 2 hours up to +25°C	30 days at +2°C to +8°C AND/OR 24 hours at +8°C to +25°C	+2°C to +8°C	+2°C to +8°C
Diluent	Yes	No	No	No
Usage limit post-puncture	6 hours at +2°C to +25°C[f]	24 hours at +2°C to +25°C	6 hours at room temperature (up to +30°C) OR 48 hours at +2°C to +8°C.	3 hours at room temperature (up to +25°C) OR 6 hours at +2°C to +8°C
Formats available	Multi-dose vial (6 doses)[a], preservative-free	Multi-dose vial (10 doses), preservative-free	Multi-dose vial (8-and 10-dose presentations), preservative-free	Multi-dose vial (5 doses), preservative-free

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

[a] After dilution, one vial contains 6 doses of 0.3 mL each. 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) [10-12], Israel [13-15][16], the United States (US) [17], and Canada [18][19] suggests moderate to high vaccine effectiveness against severe COVID-19 outcomes after the first or second dose of mRNA COVID-19 vaccines in adults,[10-15, 17, 18][16], and after the first dose of AstraZeneca COVID-19 vaccine [10-12], including in older [10-12, 15] and frail [10] populations. COVID-19 related hospitalization was the most common severe COVID-19 outcome assessed [10-13, 17][16], while fewer studies provided estimates of effectiveness against severe disease [13, 14] and death [11, 13, 18]. Emerging evidence from Israeli studies suggest high vaccine effectiveness after the second dose of Pfizer-BioNTech COVID-19 vaccine against severe disease, [13, 14] COVID-19 related hospitalization [13][16] and death [16].

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[13], the UK [20], and the US [21] 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 [13, 20] (depending on time since vaccination) and high after the second dose [13, 20]. Similar results were reported for mRNA COVID-19 vaccines in general (i.e., Moderna and Pfizer-BioNTech) [21]. 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 [20]. There are no results specific to other COVID-19 vaccines yet, but studies are ongoing.

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

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

There is evidence that the Pfizer-BioNTech and AstraZeneca vaccines protect against the B.1.1.7 (Alpha) VOC. While there appears to be reduced protection against acquisition of B.1.617.2 (Delta) after the first dose for both Pfizer-BioNTech and AstraZeneca vaccines as compared with other strains, emerging data suggest that Pfizer-BioNTech offers very good protection and the AstraZeneca vaccine offers good protection against infection with the B.1.617.2 (Delta) VOC after the second dose. In addition, the vaccines offer good protection against hospitalization after the first doses. There are also emerging data on the efficacy or effectiveness of mRNA vaccines against B.1.351 (Beta) VOC. Evidence from the Janssen vaccine clinical trials indicate that it is protective against symptomatic moderate to severe/critical COVID-19 infection in areas where B.1.351 (Beta) VOC and P.2 (Zeta) VOI are circulating widely. The AstraZeneca clinical trial was conducted when the B.1.351 (Beta) lineage was the predominant strain in South Africa, and vaccine efficacy was not demonstrated against this strain.

NACI will continue to monitor the evidence and update recommendations as needed.

IV.3   Immunogenicity

No immunological correlate of protection has been determined for SARS-CoV-2; therefore, all immunological evidence in support of vaccine efficacy is indirect and cannot directly be used to estimate either vaccine efficacy or effectiveness.

There are several key knowledge gaps that affect the understanding of immune responses to COVID-19 vaccine:
- Which type of immune responses are important for protection from infection, severe disease, or transmission
- What level of humoral and cellular immune responses are necessary to confer protection
- The durability of immune responses and how they may change over time
- How immune responses to natural infection compare to responses elicited from a vaccine
- How immune responses differ across populations (e.g., 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 5×10^{10} particles of SARS-CoV-2 spike protein.

No dilution is required.

Janssen COVID-19 Vaccine

Each dose is 0.5 mL, containing 5×10^{10} particles of SARS-CoV-2 spike protein.

No dilution is required.

Route of administration

COVID-19 vaccines are given as an intramuscular (IM) injection into the deltoid muscle. The deltoid muscle of the arm is the preferred injection site in adolescents and adults (unless the muscle mass is not adequate or vaccination in that site is not possible, in which case the anterolateral thigh can be used).

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

Schedule

Refer to Table 3 for a summary of immunization schedules for authorized, available COVID-19 vaccines.

Table 3. Immunization schedule, by COVID-19 vaccine

Vaccine product	Immunization schedule	Minimum interval	Authorized interval	Extended interval[a]
Pfizer-BioNTech COVID-19 vaccine	2-dose schedule	19 days[b]	21 days	16 weeks
Moderna COVID-19 vaccine	2-dose schedule	21 days[c]	28 days	16 weeks
AstraZeneca COVID-19 vaccine	2-dose schedule	28 days	4 to 12 weeks[d]	16 weeks[d]
Janssen COVID-19 vaccine	1-dose schedule	N/A	N/A	N/A

[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.

For mixed COVID-19 vaccine schedules, the minimum interval between doses should be based on the minimum interval of the product used for the first dose (e.g., Pfizer-BioNTech COVID-19 vaccine should be offered a minimum of 28 days after AstraZeneca COVID-19 vaccine). Recommendations on extended intervals apply to mixed vaccine schedules.

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: <u>Extended dose intervals for COVID-19 vaccines to optimize early vaccine rollout and population protection in Canada in the context of limited vaccine supply</u> (archived) 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

Interchangeability of authorized COVID-19 vaccines in a vaccines series when the first dose is:

mRNA COVID-19 vaccine

NACI recommends that, if readily available*, the same mRNA COVID-19 vaccine product should be offered for the subsequent dose in a vaccine series started with an mRNA COVID-19 vaccine. However, when the same mRNA COVID-19 vaccine product is not readily available*, or is unknown, another mRNA COVID-19 vaccine product recommended for use in that age group can be considered interchangeable and should be offered to complete the vaccine series. The previous dose should be counted, and the series need not be restarted.

(Strong NACI Recommendation)

*readily available = easily available at the time of vaccination without delay or vaccine wastage

AstraZeneca/COVISHIELD COVID-19 vaccine

NACI recommends that while either an AstraZeneca/COVISHIELD COVID-19 vaccine or an mRNA COVID-19 vaccine product may be offered for the subsequent dose in a vaccine series started with an AstraZeneca/COVISHIELD COVID-19 vaccine, an mRNA COVID-19 product is preferred as a subsequent dose, due to emerging evidence, including the possibility of better immune response, and the safety of heterologous schedules. Regardless of which product is offered, a complete two-dose series is important for protection; the previous dose should be counted, and the series need not be restarted.

Individuals who receive two doses of the AstraZeneca/COVISHIELD vaccine are considered protected and do not require further vaccination.

(Discretionary NACI Recommendation)

No data currently exist on the interchangeability of COVID-19 mRNA vaccines. However, there is no reason to believe that mRNA vaccine series completion with a different authorized mRNA vaccine product will result in any additional safety issues or deficiency in protection.

Emerging evidence indicates that mixed COVID-19 viral vector and mRNA vaccine schedules with dosing intervals between 4 and 12 weeks have acceptable safety profiles that may be associated with short-term increased systemic reactogenicity, which is potentially increased with shorter intervals between vaccines. Current evidence indicates that humoral and cellular immune responses (including responses against VOCs) increase when the Pfizer-BioNTech vaccine is administered as the second dose after AstraZeneca vaccine with an interval of 8 to 12 weeks [22], and are equivalent to or greater than immune responses following a homologous two-dose schedule of the AstraZeneca or Pfizer-BioNTech vaccine.

Due to the risk of VITT associated with the second dose of AstraZeneca/COVISHIELD COVID-19 vaccine, offering an alternative product with a more acceptable safety profile and expected comparable immunogenicity profile, while enabling individuals to make an informed choice is ethically justifiable. This is expected to lead to increased accessibility and acceptability for those who were initially offered a first dose of the AstraZeneca/COVISHIELD vaccine, including those who are most at risk of COVID-19. Given the risk of VITT associated with the Janssen vaccine, it should not be offered to individuals who received a first dose of AstraZeneca/COVISHIELD vaccine and prefer to receive an alternative product for their second dose. For more details on VITT, please see Thrombosis with Thrombocytopenia following vaccination with viral vector COVID-19 vaccines.

For mixed COVID-19 vaccine schedules, the minimum interval between doses should be based on the minimum interval of the product used for the first dose (e.g., Pfizer-BioNTech COVID-19 vaccine should be offered a minimum of 28 days after AstraZeneca COVID-19 vaccine). Recommendations on extended intervals apply to mixed vaccine schedules. See Table 3 for information on recommended intervals for authorized COVID-19 vaccines.

Recommendations for the interchangeability of COVID-19 vaccines are consistent with the current NACI guidance on interchangeability for vaccines that are used for the same indication and contain comparable antigens. In line with basic principles of vaccinology [23], it is expected that combining different COVID-19 vaccines that induce an immune response against the SARS-CoV-2 spike protein will lead to a robust immune response. All currently authorized COVID-19 vaccines in Canada use the spike protein of the SARS-CoV-2 virus as the antigen. The spike protein produced by the mRNA (Pfizer-BioNTech, Moderna) and Janssen vaccines is stabilized in the prefusion conformation while the AstraZeneca vaccine produces a wild-type spike protein in various conformations, including prefusion.

Very rare cases of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining around the heart) following vaccination with COVID-19 mRNA vaccines have been reported in Canada and internationally, most frequently in adolescents and younger adults under

30 years of age, more frequently in males compared to females, and more frequently after the second dose in a two-dose homologous vaccination series compared to the first dose. The majority of cases are mild and individuals recover quickly. For more details on myocarditis/pericarditis, please see Myocarditis or pericarditis following vaccination with an mRNA COVID-19 vaccine.

Active surveillance of effectiveness and safety of a mixed schedule are important, and accurate recording of vaccines received will be critical. NACI will continue to monitor the evidence and update its recommendations as needed. For additional details on evidence related to mixed COVID-19 vaccine schedules, see NACI Rapid response: Interchangeability of authorized COVID-19 vaccines (archived).

IV.4.4 Post-vaccination counseling

NACI recommends that prophylactic oral analgesics or antipyretics (e.g., acetaminophen or ibuprofen) should not be routinely used before or at the time of vaccination, but their use is not a contraindication to vaccination. Oral analgesics or antipyretics may be considered for the management of adverse events (e.g., pain or fever, respectively), if they occur after vaccination.

Analgesics and antipyretics were used in clinical trials of COVID-19 vaccine for the management of pain and/or fever after vaccination. There is currently no evidence 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 [24]. 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 -80ºC to -60ºC and protected from light, in the original packaging, until ready to use.

Refer to the re-icing guidelines (available at CVDVaccine.ca) for instructions regarding the use of the manufacturer's original thermal container for temporary storage.

Vials may also be stored at -25°C to -15°C for up to 2 weeks. Vials must be kept frozen and protected from light, in the original cartons, until ready to use. Vials stored at -25°C to -15°C for up to 2 weeks may be returned one time to the recommended storage condition of -80°C to -60°C. Total cumulative time the vials are stored at -25°C to -15°C should be tracked and should not exceed 2 weeks.

Thawed, unpunctured vials (prior to dilution)
The Pfizer-BioNTech COVID-19 vaccine may be thawed and stored at +2°C to +8°C for up to 1 month or at room temperature (up to +25ºC) 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 +2ºC to +25ºC and used within 6 hours from the time of dilution. During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light. After dilution, the vaccine vials can be handled in room light conditions.

Moderna COVID-19 vaccine

Frozen vials prior to use
The Moderna COVID-19 vaccine should be stored at temperatures of -25ºC to -15ºC and protected from light in the original packaging. Do not store on dry ice or below -40ºC.

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 +25ºC for up to 24 hours.

Do not refreeze thawed vials.

Thawed, punctured vials
The Moderna COVID-19 vaccine can be stored between +2ºC to below +25ºC but must be discarded after 24 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 routinely be given simultaneously with other vaccines (live or inactivated). *(Strong NACI Recommendation)*

There are currently no data on the simultaneous administration of COVID-19 vaccine with other vaccines, although a number of studies are ongoing. In the absence of evidence, a precautionary approach is being recommended at this time. The potential for immune interference is not known. In addition, administering the COVID-19 vaccine alone assists with the assessment of any adverse event following immunization (AEFI). 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 any dose of a COVID-19 vaccine before the administration of another non-COVID-19 vaccine 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.

The minimum waiting period between vaccines is precautionary and there may be circumstances in which simultaneous administration or a shortened interval may be warranted on an individual basis. These circumstances may include:

- when another vaccine is required for post-exposure prophylaxis;
- when individuals require accelerated vaccination schedules prior to immunosuppressive therapy or transplant;
- when there is a risk of the individual being unable to complete an immunization series due to limited access to health services or being unlikely to return at a later date;
- when it will enable a pregnant person to receive the Tdap vaccine at 32 weeks gestation or earlier; and
- at the clinical discretion of the healthcare provider.

If a risk assessment deems that the benefits outweigh the potential risks for the individual, and if informed consent is provided, a shorter waiting period or simultaneous administration of COVID-19 vaccines with other vaccines (live or inactivated) may be considered.

If more than one type of vaccine is administered at a single visit, they should be administered at different injection sites using separate injection equipment.

NACI will continue to monitor the evidence and update recommendations as needed.

Refer to Timing of Vaccine Administration in the CIG, Part 1 – Key Immunization Information for additional general information on simultaneous administration of other vaccines.

IV.8   Vaccine safety and adverse events following immunization (AEFI)

Due to limitations in the number of participants and duration of follow-up from COVID-19 clinical trials, medium- and long-term evidence on vaccine safety is limited. However, post-licensure vaccine pharmacovigilance is ongoing and safety signals around the world are detected and communicated globally. Clinical trials of the authorized COVID-19 vaccines excluded individuals with a history of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine. However, studies are ongoing.

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

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

IV.8.1 Very common and common adverse events

Common adverse events are defined as those that occur in 1% to less than 10% of vaccine recipients; very common adverse events occur in 10% or more of vaccine recipients. Please see

Appendix E for a summary of adverse events identified in clinical trials of authorized, available COVID-19 vaccines.

Local

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

Systemic

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

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

Evidence on the safety of vaccine booster doses is available from observational[25] and clinical studies[26][27][28]. Occurrence of solicited and unsolicited systemic adverse events in individuals with prior SARS-CoV-2 infection was slightly higher compared to the SARS-CoV-2 naïve population, primarily in younger adults. However, there was no observed increase in the frequency of more severe adverse events in this population. Two observational studies included less than 100 patients with persistent symptoms from prior COVID-19 infections (long COVID). In this subgroup, receipt of COVID-19 vaccination with either an mRNA or viral vector vaccine was not associated with a worsening of long COVID symptoms or increased reactogenicity following immunization.

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

Uncommon adverse events occur in 0.1% to less than 1% of vaccine recipients. Rare and very rare adverse events occur in 0.01% to less than 0.1% and less than 0.01% of vaccine recipients,

respectively. The probability of detection of very rare adverse events in clinical trials is low given clinical trial population sizes; therefore, ongoing pharmacovigilance is essential.

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

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

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

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

Very rare cases of serious blood clots (at unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis) associated with thrombocytopenia have been reported globally following vaccination with viral vector COVID-19 vaccines. The terminology for this syndrome has been evolving since the safety signal was detected. The Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) uses the case definition for Thrombosis with Thrombocytopenia Syndrome (TTS) [29] 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 [30][31][32][33][2][34]. 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 [30]. Clots related to VITT can be very aggressive and challenging to treat [35]. 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 [36]. The rate of VITT is estimated to be between 1 per 26,000 and 1 per 100,000 persons vaccinated with a first dose of AstraZeneca/COVISHIELD COVID-19 vaccine. As of June 1, 2021, PHAC has estimated the rate of VITT in Canada to be 1 in 73,000 doses administered. However, as investigations continue, this rate could be as high as 1 in 50,000. For updates to the numbers of cases of TTS and VITT in Canada, please see the "Serious and non-serious adverse events reported" section of Reported

side effects following COVID-19 vaccination in Canada. The frequency of TTS following a second dose of AstraZeneca vaccine is currently reported between 1 per 600,000 and 1 per 750,000 individuals vaccinated with a second dose, based on vaccine safety surveillance data from the United Kingdom but this continues to evolve [2]. The case fatality rate of VITT also varies between countries, and ranges between 20 and 50%. Many cases have been reported to have serious long-term morbidity, including neurologic injury. Reports of TTS after administration of the Janssen vaccine are emerging from the United States. As of May 24, 2021, 32 cases have been confirmed after about 10.2 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.

Myocarditis or pericarditis following vaccination with an mRNA COVID-19 vaccine

Very rare cases of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining around the heart) following vaccination with COVID-19 mRNA vaccines[37], have been reported in Canada and internationally including from Israel [38], the United States[39], and Europe [38]. In Israel and the United States, cases of myocarditis and pericarditis have been reported most frequently in adolescents and younger adults under 30 years of age, more frequently in males compared to females, and more frequently after the second dose [40, 41]. Data in Canada are emerging and surveillance is ongoing [42].

There are many potential causes for myocarditis and pericarditis including both infectious and non-infectious causes. Disease severity can be variable. The cases of myocarditis and pericarditis that have been reported after vaccination with an mRNA COVID-19 vaccine to date have generally been mild, and individuals tend to recover quickly [43-46]. Symptoms can include shortness of breath, chest pain, or the feeling of a rapid or abnormal heart rhythm. Symptoms can be accompanied by abnormal tests (e.g., electrocardiogram, serum troponins, echocardiogram).

Based on cases reported internationally, available information indicates that cases of myocarditis and pericarditis after vaccination with an mRNA COVID-19 vaccine occur:
- More often after the second dose
- Usually within a week after vaccination
- More often in adolescents and young adults
- More often in males than females.

As part of ongoing COVID-19 vaccine safety efforts, PHAC and Health Canada are closely monitoring myocarditis and pericarditis through passive and active Canadian safety surveillance systems and collaboration with Canadian provincial and territorial health authorities, manufacturers and international regulators.

NACI continues to review information as it becomes available and will take appropriate action as needed.

Refer to the PHAC weekly AEFI report for information on numbers of cases reported in Canada. Refer to Reporting Adverse Events Following Immunization (AEFI) in Canada and to the recently developed Brighton Collaboration case definition of myocarditis for additional information on the completion and submission of AEFI reports.

Capillary leak syndrome following vaccination with AstraZeneca COVID-19 vaccine

Very rare cases of capillary leak syndrome (CLS) have been reported following immunization with the AstraZeneca COVID-19 vaccine [2, 3, 38]. CLS is a very rare, serious condition that causes fluid leakage from small blood vessels (capillaries), resulting in swelling mainly in the arms and legs, low blood pressure, thickening of the blood and low blood levels of albumin (an important blood protein). Symptoms are often associated with feeling faint (due to low blood pressure).

In Canada, as of June 18, 2021, one case of CLS had been confirmed [47] among more than 2,250,000 doses of AstraZeneca/COVISHIELD vaccines administered. As of May 27, 2021, six cases of CLS in individuals who had received the AstraZeneca COVID-19 vaccine had been reviewed by the European Medicine Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) among 78 million doses of AstraZeneca COVID-19 vaccine administered in the United Kingdom (UK) and European Economic Area/European Union (EU/EEA). Three of those affected had a previous history of CLS and one subsequently died. Following its review, the EMA's PRAC has concluded that individuals with a history of CLS should not be vaccinated with the AstraZeneca COVID-19 vaccine.

PHAC and Health Canada are closely monitoring CLS in relation to the AstraZeneca vaccine. Health Canada is working closely with the manufacturers to ensure the labelling reflects relevant information [42].

Cases of CLS following COVID-19 vaccination in Canada should be reported to assist with vaccine safety monitoring. Refer to Reporting Adverse Events Following Immunization (AEFI) in Canada for additional information on the completion and submission of AEFI reports.

Please see *Section IV.10 Contraindications and Precautions* for additional guidance on CLS as a contraindication for the Astra-Zeneca/COVISHIELD COVID-19 vaccine.

IV.8.3 Guidance on reporting adverse events following immunization (AEFI)

Vaccine providers are asked to report AEFIs through local public health departments and to follow AEFI reporting requirements that are specific to their province or territory. In general, any serious (defined as resulting in hospitalization, permanent disability or death) or unexpected adverse event that is temporally related to vaccination should be reported.

In addition to provincial or territorial reporting requirements, the Brighton Collaboration has developed a list of Adverse Events of Special Interest (AESI) that are of particular interest and should be reported. Refer to https://brightoncollaboration.us/covid-19/ for the list with definitions.

There may be additional very rare AEFIs that have not been detected through clinical trials to date.

Refer to Adverse Events Following Immunization (AEFI) in the CIG, Part 2 – Vaccine Safety for additional information on definitions, reporting, investigating and managing, and causality assessments for AEFIs.

Refer to Reporting Adverse Events Following Immunization (AEFI) in Canada for additional information on the completion and submission of AEFI reports.

Refer to the [PHAC weekly report for reported adverse events](#) following COVID-19 vaccination in Canada.

IV.9 Special Populations

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

Individuals previously infected with SARS-CoV-2
In studies looking at the immune response of individuals previously infected with SARS-CoV-2, binding and neutralizing antibodies have been shown to persist for at least 6 months post-infection [48], with only a small proportion of people becoming re-infected for potentially as long as 10 months [49]. Follow-up of cohorts of previously infected individuals have reported high levels of protection against reinfection and were more likely to be asymptomatic (~50%) than cases of primary infection (19%). The risk of re-infection due to VOCs is uncertain. Limited evidence assessing neutralizing activity against VOCs suggests that neutralizing activity is retained against B.1.1.7 (Alpha); correspondingly, the risk of re-infection is similar to the original SARS-CoV-2 strain. There appears to be a reduction in neutralizing activity against B.1.351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta) compared to the original strain, and the risk of reinfection may be higher [50].

Evidence on the safety of COVID-19 vaccination of individuals with prior SARS-CoV-2 infection is available from observational [25][51][52] and clinical studies [26][27][28]. The occurrence of solicited and unsolicited systemic adverse events after the first or second dose in individuals with prior SARS-CoV-2 infection was slightly higher compared to the SARS-CoV-2 naïve population. However, there was no observed increase in the frequency of more severe adverse events in this population. Two observational studies included less than 100 patients with persistent symptoms from prior COVID-19 infections (long COVID). In this subgroup, receipt of COVID-19 vaccination with either an mRNA or viral vector vaccine was not associated with a worsening of long COVID symptoms or increased reactogenicity following immunization.

A number of large observational studies have compared the incidence of reinfection in individuals previously infected, with or without prior infection, to the incidence of infection in those without prior infection [53][54][55]. A retrospective cohort of 52,238 health care system employees (5% with prior infection) in the US found that after 5 months of follow-up, no cases of reinfection were identified (Shrestha et al.). The cumulative incidence of SARS-CoV-2 infection among previously infected unvaccinated employees did not differ from that of previously infected fully vaccinated employees or from that of previously uninfected fully vaccinated employees (63% of total study population received Moderna and 37% received Pfizer-BioNTech) [53].

A prospective observational study capturing the entire adult (≥16 years) Israeli population provided estimates of protection against subsequent infection, hospitalization, and severe illness in previously infected unvaccinated individuals over 3 months of follow-up, when the B.1.1.7

(alpha) variant was the most prevalent variant (Goldberg et al.) [55]. In this unvaccinated population, the estimates of protection due to prior SARS-CoV-2 infection were 95% against subsequent infection, 94% against hospitalization, and 96% against severe illness compared to unvaccinated individuals without prior infection. These estimates of protection were comparable to those provided by two doses of Pfizer-BioNTech vaccine in the previously uninfected vaccinated cohort [55].

In a prospective cohort of 23,324 staff working in National Health Service hospitals in the UK (35% with prior infection), after a follow-up of approximately two months, previously infected unvaccinated individuals had 90% protection against infection when compared to unvaccinated individuals without prior infection [54]. Although there was insufficient data to assess the vaccine effectiveness for previously infected individuals, the estimates of protection for vaccinated individuals without prior infection were 72% after the first dose and 86% after the second dose [54]. (Hall et al., 2021).

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

In studies that reported immune responses after vaccination in individuals with previous SARS-CoV-2 infection[56][26][57][58][59][60][51], anti-spike binding and neutralizing antibody titres after Dose 1 were higher than those after Dose 1 in SARS-CoV-2 naïve individuals, and comparable to those observed after Dose 2 in SARS-CoV-2 naïve individuals. These trends were seen in both those who had previous symptomatic or asymptomatic infections; in some studies, antibody responses after Dose 1 were slightly higher in individuals with previous symptomatic infection compared to individuals with previous asymptomatic infection. In some studies of previously infected individuals, immune responses did not increase following Dose 2 and remained similar to those observed following Dose 1. Limited data on cellular immune responses were available. Two studies reported increased T cell responses in previously infected individuals compared to naïve individuals after Dose 1, but observed no differences in T cell responses between the two cohorts after Dose 2. However, in the absence of an established correlate of protection, it is not possible to determine the significance of differences in humoral and cellular immune responses in previously infected vaccinated individuals compared to SARS-CoV-2 naïve vaccinated individuals as they relate to the level and durability of protection against re-infection or breakthrough infections.

Individuals who are 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 [61]

(62)(63)(64)(65)(66)(67)(68)(69)(70)(71)(72)(73)(74). 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[75][76][77][68][67][69][78][79][80][81][82][72][83][74][84][85][86][87][88][63][89][65][66, 90]. 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 [91][92][72][93][85][84][94][95][96][97][98][99][100][101].

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 [61][62][63][64][65, 66][102]. The onset of new autoimmune disease or disease exacerbation following vaccination with mRNA COVID-19 vaccines was rare or comparable to the background incidence of these events in the general population. Safety data in this population following vaccination with a viral vector vaccine is not available.

The efficacy and effectiveness of COVID-19 vaccines in individuals with autoimmune conditions is unknown, but immunogenicity data is emerging. Data were available from observational studies in which participants received the mRNA or the AstraZeneca COVID-19 vaccines [88][63][89][65][90][66]. 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 [103]. 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 [104]. 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 [105]. 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 [106].

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 [107]. In one small cohort study, mRNA from COVID-19 vaccines was undetectable in breastmilk 4-48 hours post-vaccination [108].

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 [109][110][111]. 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 [112][109][113, 114]. 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 [115][116][117][118].

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.

Refer to https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-2-vaccine-safety/page-4-early-vaccine-reactions-including-anaphylaxis.html in the CIG, Part 2 – Vaccine Safety for information on the management of anaphylaxis post-vaccination.

Table 4. Ingredients of authorized, available COVID-19 vaccines that have been associated with allergic reactions in other products

Vaccine product	Potential allergen included in the vaccine or its container	Other products where the potential allergen may be found
Pfizer-BioNTech COVID-19 vaccine	polyethylene glycol (PEG) [a,b,c]	Over the counter (e.g., cough syrup, laxatives), and prescription medications, medical bowel preparation products for colonoscopy, skin care products, dermal fillers, cosmetics, contact lens care solutions, products such as ultrasound gel[d].
Moderna COVID-19 vaccine	PEG [a,b,c]	Over the counter (e.g., cough syrup, laxatives), and prescription medications, medical bowel preparation products for colonoscopy, skin care products, dermal fillers, cosmetics, contact lens care solutions, products such as ultrasound gel[d].
	tromethamine[e] (trometamol or Tris)	Component in contrast media, oral and parenteral medications.
AstraZeneca COVID-19 vaccine	polysorbate 80[c]	medical preparations (e.g., vitamin oils, tablets, and anticancer agents), cosmetics[d,f]
Janssen COVID-19 vaccine	polysorbate 80[c]	medical preparations (e.g., vitamin oils, tablets, and anticancer agents), cosmetics[d,f]

*N.B. This is not a complete list of products.

[a] Medications that contain PEG are described in Stone CA, et al., DOI:10.1016/j.jaip.2018.12.003

[b] A review of immediate type hypersensitivity reactions to PEG is available in Wenande et al, DOI: 10.1111/cea.12760

[c] There is a potential of cross-reactive hypersensitivity between PEG and polysorbates

[d] PEG is an additive in some food and drinks but allergic reactions to PEG in food or drinks have not been documented.

[e] One case report of anaphylaxis to tromethamine has been described (Lukawska et al, DOI: 10.1016/j.jaip.2018.08.035).

[f] Case reports of anaphylaxis to polysorbate 80 have been described (Badiu et al, DOI: 10.1136/bcr.02.2012.5797, Palacios Castaño et al, DOI: 10.18176/jiaci.0109).

Rare cases of VITT have been reported following immunization with viral vector COVID-19 vaccines. Investigations are ongoing and the recommendations will be updated as evidence becomes available. For more information, refer to Appendix C and Appendix D

Contraindications

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 a mRNA vaccine). If immunization with a different platform is offered, individuals should be observed for at least 30 minutes after immunization.

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

Thrombosis and Thrombocytopenia following vaccination

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

Capillary leak syndrome

As a precautionary measure following the international cases that have been reported, individuals with a history of capillary leak syndrome should not receive the AstraZeneca /COVISHIELD 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.

<u>Acute illness</u>

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

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

<u>Hematologic</u>

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

<u>Thrombosis and Thrombocytopenia</u>

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.

<u>Myocarditis and/or pericarditis</u>

Post-market safety surveillance on mRNA COVID-19 vaccines has identified an increased frequency of myocarditis and pericarditis internationally, reported very rarely but most frequently in adolescents and young adults under 30 years of age, more frequently in males compared to females, and more frequently after the second dose [40, 41]. The association of myocarditis and pericarditis with mRNA vaccination and a mechanism for inflammation remain under investigation.

As a precautionary measure, the second dose in the mRNA COVID-19 vaccination series should be deferred in individuals who experience myocarditis or pericarditis following the first dose of an mRNA COVID-19 vaccine until more information is available. NACI will continue to monitor the evidence and update recommendations as needed.Anyone receiving an authorized mRNA COVID-19 vaccine should be informed of the risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining around the heart) and advised to seek medical attention if they develop symptoms including chest pain, shortness of breath, or palpitations.

Healthcare providers should consider myocarditis and/or pericarditis in their evaluation if the patient presents with clinically compatible symptoms (chest pain, shortness of breath, palpitations) after the second dose of an mRNA COVID-19 vaccine but should be investigated regardless of timing from vaccination to onset. Investigations include electrocardiogram, serum troponins and echocardiogram with frequent abnormal electrocardiogram findings and elevated troponin levels. Consultation with a cardiologist, infectious disease specialist, internal medicine specialist and/or rheumatologist may be advisable to assist in this evaluation, particularly to investigate the many potential causes of myocarditis and pericarditis. Investigations may include diagnostic testing for acute COVID-19 infection (e.g., PCR testing), prior SARS-CoV-2 infection (e.g., detection of SARS-CoV-2 nucleocapsid antibodies), and consideration of other potential infectious or non-infectious etiologies including auto-immune conditions.

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 [5] 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.**
   (Strong NACI Recommendation)

2. **NACI recommends that a viral vector COVID-19 vaccine may be offered to individuals in the authorized age group without contraindications to the vaccine to initiate a series when other authorized COVID-19 vaccines are contraindicated or inaccessible. Informed consent should include discussion about the risk and symptoms of VITT, as well as the need to seek immediate medical care should symptoms develop.**
   (Discretionary NACI Recommendation)

Refer to the Table 5 for a summary of evidence and factors for jurisdictions to consider when implementing COVID-19 immunization programs.

Summary of evidence and rationale:
- The COVID-19 pandemic has caused significant morbidity and mortality, as well as social and economic disruption. The COVID-19 immunization program should be rolled out as efficiently, effectively and equitably as possible.
- mRNA COVID-19 vaccines are authorized in individuals 12 years of age and older (Pfizer-BioNTech COVID-19 vaccine) 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 (Alpha) VOC. Emerging evidence suggests the Pfizer-BioNTech vaccine is 33.2% effective after the first dose and 87.9% effective after the second dose against the B.1.617.2 (Delta) VOC.
- Local and systemic adverse events were generally less frequent in older adults (≥56 in the Pfizer-BioNTech clinical trial and ≥65 in the Moderna clinical trial).
- The authorized mRNA vaccines are similarly safe and efficacious in those with one or more comorbidities (e.g., body mass index ≥30 kg/m2, chronic pulmonary disease, diabetes mellitus, cardiac disease).

Informed consent for mRNA COVID-19 vaccines should include information about very rare reports of myocarditis or pericarditis in the week following an mRNA vaccine

- Post-market safety surveillance reports of myo/peri following mRNA vaccines have been reported most frequently in adolescents and younger adults under 30 years of age, more frequently in males compared to females, and more frequently after the second dose [40, 41].
- The majority of cases are mild and individuals tend to recover quickly.
- Anyone receiving an mRNA COVID-19 vaccine should be informed of the risk of myocarditis and pericarditis and advised to seek medical attention if they develop symptoms, which include shortness of breath, chest pain, or the feeling of a rapid or abnormal heart rhythm.
- As a precautionary measure, the second dose in the mRNA COVID-19 vaccination series should be deferred in individuals who experience myocarditis or pericarditis as an adverse event following the first dose of an mRNA COVID-19 vaccine until more information is available. NACI will continue to monitor the evidence and update recommendations as needed.
- Informed consent should also include discussion about the individual's personal risk of severe COVID-19 disease (see Table 1), risk of infection and local epidemiology (including circulation of VOC), complications of COVID-19 (which may include myocarditis and pericarditis), and protection offered by COVID-19 vaccination.
  - ➢ Vaccination for adolescents and young adults is recommended as the benefits of vaccination to prevent COVID-19 including variants of concern, outweigh very rare cases of myocarditits/pericarditis.
  - ➢ Individuals aged 12 to 24 years account for approximately 15% of the Canadian population [119], and similarly, this age group constitutes approximately 18% of cumulative COVID-19 cases reported nationally. However, with the increasing number of older adults who have been immunized against COVID-19, the relative proportion of COVID-19 cases has been increasing among younger age groups. In contrast to older populations, this age group accounts for less than 2% of COVID-19 cases resulting in hospitalization, less than 2% of COVID-19 cases admitted to ICU, and less than 0.1% of deaths from COVID-19 [120].
  - ➢ Some individuals are at increased risk of hospitalization and mortality from COVID-19 (see Table 1). An updated rapid review of risk factors for severe illness conducted by the Alberta Research Centre for Health Evidence (ARCHE) found a moderate certainty of evidence of ≥2-fold increase in hospitalizations in individuals 21 years of age and younger with 2 or more chronic conditions (versus no chronic conditions) [7].
  - ➢ There is emerging evidence that mRNA vaccines offer good protection against infection with the B.1.617.2 (Delta) VOC after the second dose and very good protection against hospitalization after the first dose.
  - ➢ In clinical trials, mRNA COVID-19 vaccines have been shown to be immunogenic and efficacious in preventing symptomatic disease in adolescents and young adults. Clinical trials demonstrated a similar safety profile to that observed in older age groups.

AstraZeneca COVID-19 vaccine

- Combined evidence from clinical trial and observational study data available to date have shown that the AstraZeneca COVID-19 vaccine offers protection against symptomatic COVID-19 disease and hospitalization in adults ≥18 years of age after receiving at least one dose.
  - ➤ Clinical trial data available to date have shown that the AstraZeneca COVID-19 vaccine has demonstrated moderate efficacy against symptomatic, confirmed COVID-19 of approximately 62% in those 18-64 years of age. Efficacy of a two-dose series increased to approximately 82% when the interval between doses was 12 weeks or more. In adults 65 years of age and over, observational data from the UK of vaccine effectiveness after one dose have shown a reduction in the risk of symptomatic disease and hospitalization.
  - ➤ The highest efficacy with the authorized regimen of AstraZeneca COVID-19 vaccine was seen in clinical trial groups that had a longer interval between doses. Clinical trials suggest that vaccine efficacy increases with extended intervals between the first and second dose of vaccine, with a maximum reduction in risk of symptomatic disease observed at 12 weeks or more following the priming dose.
- Data suggest AstraZeneca COVID-19 vaccine has a vaccine efficacy of 74.6% against the B.1.1.7 (Alpha) VOC (compared to 84.1% against the non-B.1.1.7 (Alpha) strain). Published data suggests a vaccine efficacy of 10.4% against mild to moderate illness from the B.1.351 (Beta) VOC. Emerging data suggest the AstraZeneca vaccine is 32.9% effective after one dose and 59.8% effective after the second dose against the B.1.617.2 (Delta) VOC.
- In clinical trials, the majority of local and systemic adverse events with the AstraZeneca COVID-19 vaccine were mild and transient and did not differ by dose administered or age.
- Very rare but serious cases of blood clots, including cerebral venous sinus thrombosis, with concurrent thrombocytopenia have been reported globally following post-licensure use of viral vector COVID-19 vaccines. The exact mechanism by which these vaccines may trigger thrombosis with thrombocytopenia is still under investigation. The case fatality rate typically ranges between 20 and 50%.
- 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 (Zeta) lineage and in the one conducted in South Africa (64%), where almost all isolates were of the B.1.351 (Beta) lineage.
- Local and systemic adverse events were typically mild and transient, and no safety signals were detected in clinical trials.

- As of May 24, 2021, 32 TTS cases were confirmed to have tested positive for anti-PF4 antibodies after about 10.2 million doses of Janssen vaccine administered in the United States.
- 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 [5] of its recommendations for the use of COVID-19 vaccines in Canada.

NACI concluded that the advantages of safe, highly efficacious mRNA COVID-19 vaccines outweigh any possible disadvantages for eligible populations. Therefore, NACI made a strong recommendation for the preferential use of mRNA COVID-19 vaccines in all authorized age groups. NACI cautions that there is uncertainty in the evidence of advantages and disadvantages of the use of viral vector COVID-19 vaccines for eligible populations in Canada due to the risk of a rare but serious adverse event (Vaccine Induced Thrombotic Thrombocytopenia, VITT); the availability of other safe, highly efficacious mRNA COVID-19 vaccines; as well as some evidence of lower protection against asymptomatic transmission and the B.1.351 (Beta) and B.1.617.2 (Delta) VOC with the AstraZeneca vaccine. Therefore, NACI made a discretionary recommendation on the use of viral vector COVID-19 vaccines.

NACI previously made a discretionary recommendation on the use of viral vector COVID-19 vaccines for individuals who prefer an earlier vaccine rather than wait for an mRNA vaccine, only if certain conditions were met (including a benefit-risk analysis, informed consent, and substantial delay for receipt of an mRNA vaccine). This recommendation was based on a public health benefit-risk analysis using rates of VITT reported at that time (this analysis is available in archived versions of this statement). However, with increasing reported rates of VITT following vaccination with viral vector vaccines and increasing mRNA vaccine supplies in Canada, NACI now recommends that viral vector vaccines may be offered only if mRNA vaccines are contraindicated or inaccessible.

A summary of the evidence and rationale for NACI's preferential recommendation for the use of mRNA COVID-19 vaccines in population-level programs and discretionary recommendation for the use of a viral vector COVID-19 vaccine for individuals when other authorized COVID-19 vaccines are contraindicated or inaccessible is below:
- **Epidemiology**: The epidemiology and risk of COVID-19 vary across Canada and between populations. The proportion of COVID-19 cases classified as a VOC is increasing in Canada. Cases classified with a VOC are hospitalized more often relative to those without a VOC in those aged 20 and over. NACI will continue to monitor the evolving epidemiology.
- **Efficacy and Effectiveness**: Emerging data suggest that all authorized vaccines offer protection against hospitalization and likely also death from COVID-19. In clinical trials, mRNA COVID-19 vaccines demonstrated higher efficacy than was shown for the viral vector COVID-19 vaccines. There is evidence that the mRNA COVID-19 vaccines and the AstraZeneca COVID-19 vaccine offer protection against the B.1.1.7 (Alpha) VOC.

There is also emerging vaccine effectiveness evidence that suggests the Pfizer-BioNTech vaccine offers very good protection (87.9%) and the AstraZeneca vaccine provides good protection (59.8%) against the B.1.617.2 (Delta) VOC after the second dose. Effectiveness is much lower after only one dose of either the Pfizer-BioNTech and AstraZeneca vaccines (33.2% and 32.9% respectively). The mRNA COVID-19 vaccines and Janssen COVID-19 vaccines seem to offer protection against the B.1.351 (Beta) VOC, but the AstraZeneca COVID-19 vaccine does not. In studies in Brazil, the Janssen vaccine was shown to offer protection against the P2 (Zeta) VOI. There is limited evidence on the protection of mRNA or viral vector COVID-19 vaccines against the P.1 (Gamma) VOC.

- **Safety**:
  - ➢ Very rare cases of serious blood clots associated with thrombocytopenia have been reported globally following vaccination with viral vector COVID-19 vaccines. The rate of VITT is estimated to be between 1 per 26,000 and 1 per 100,000 persons vaccinated with a first dose of AstraZeneca/COVISHIELD COVID-19 vaccine. As of June 1, 2021, PHAC has estimated the rate of VITT in Canada to be 1 in 73,000 doses administered. However, as investigations continue, this rate could be as high as 1 in 50,000. 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. As of May 24, 2021, 32 cases of this adverse event have been confirmed after about 10.2 million doses of Janssen vaccine administered in the United States, and others are under investigation.
  - ➢ Very rare cases of a serious condition called capillary leak syndrome (CLS) have been reported following immunization with the AstraZeneca COVID-19 vaccine.
  - ➢ Post-market safety surveillance on mRNA COVID-19 vaccines has found an increased frequency of myocarditis and pericarditis following a second dose of a COVID-19 mRNA vaccine and in younger males and adolescents. However the majority of cases reported were mild and individuals tended to recover quickly.
- **Ethics**: NACI consulted with the Public Health Ethics Consultative Group (PHECG) on the ethical considerations for restricting the use of a viral vector vaccine in the current and anticipated pandemic and vaccine supply context. The PHECG provided recommendations in the following areas: promoting well-being and minimizing risk of harm, maintaining trust, respect for persons and fostering autonomy, and promoting justice and equity. NACI integrated these recommendations into its guidance. NACI applied the precautionary principle in making its discretionary recommendation, and took into account the evolving evidence on VITT, the potential for harm, the availability of other effective vaccines without this safety signal, as well as evidence of the effectiveness of alternate infection prevention and control measures.
- **Equity**: NACI examined the implications of various recommendation options on the opportunity for all populations to have a fair opportunity to attain their full health potential [5]. Populations that received a viral vector COVID-19 vaccine when mRNA vaccine supplies were limited had protection against COVID-19 disease earlier than if they had waited for mRNA vaccines to be available. However, these populations may ultimately have lower protection, as a larger proportion of the vaccinated population will remain susceptible. NACI considered the impact of the provision of a less efficacious vaccine with a safety signal of concern to marginalized and disadvantaged populations who have been disproportionately affected by the pandemic, and whose lived experience may have led to distrust of governments. Depending on vaccination strategies, this could potentially exacerbate health inequities if this potential harm is not considered when

implementing the vaccine program in populations who experience intersecting risk factors for severe disease and exposure (e.g., racialized populations living in multigenerational housing with over-representation in jobs providing essential services such as food and healthcare). With increased supply of mRNA vaccines, inequities will be reduced if viral vector vaccines are offered only when mRNA vaccines are contraindicated or inaccessible.

- **Feasibility**: NACI considered the impact of its recommendations on the successful implementation of COVID-19 immunization programs in the local setting with available resources [5]. 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. Therefore, the anticipated waiting time to receive an mRNA vaccine is now reduced but may vary between populations and across jurisdictions. The Janssen vaccine is authorized as a single dose vaccine; however, the duration of protection against COVID-19 is unknown.

- **Acceptability**: NACI reviewed recent Canadian data to consider the potential impact of its recommendations on intention and behaviours toward COVID-19 vaccination. The desire to be vaccinated continues to rise. However, various populations who have been disproportionately affected by the pandemic are also more hesitant or experience barriers in receiving a COVID-19 vaccine (e.g., racialized populations, migrant or undocumented workers). While public opinion research conducted in March 2021 suggested 44-60% of Canadians had no preference on which vaccine they received, surveys conducted in early April 2021 found that Canadians who are planning to get vaccinated are far more comfortable with the mRNA vaccines (90-92%) than the Janssen (70%) or AstraZeneca (41%) vaccines [121]. A follow up survey conducted in late April 2021 found that while comfort with mRNA vaccines remained high (90-92%), comfort receiving the Janssen vaccine decreased to 54% and was similar to comfort with receiving the AstraZeneca vaccine (52%) [122]. A survey of Canadians conducted in early May 2021 found that among unvaccinated respondents, 65% indicated they had a vaccine preference, with most willing to receive mRNA vaccines (58-82%) compared to viral vector vaccines (7-16%) [123]. 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.
- Current evidence suggests very good vaccine efficacy against symptomatic COVID-19 from one dose of COVID-19 vaccines, with good effectiveness shown in observational studies (generally between 60 and 80%, with some lower and higher estimates) against symptomatic disease and/or asymptomatic infection, as well as very good effectiveness against hospitalization (approximately 80%) and death (approximately 85% based on one study from the UK). While two doses of mRNA vaccines have shown excellent efficacy and effectiveness, one dose of mRNA vaccines appear to perform similarly to one or two doses of the AstraZeneca vaccine. However, emerging evidence suggests reduced protection offered by one dose of Pfizer-BioNTech and AstraZeneca vaccines against B.1.617.2 (Delta) VOC.
- 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 (archived) in the context of limited vaccine supply for a summary of the evidence and further rationale for this recommendation.

4. **NACI recommends that a complete series with a COVID-19 vaccine may be offered to individuals in the authorized age group without contraindications to the vaccine who have had previously PCR-confirmed SARS-CoV-2 infection.** *(Discretionary NACI Recommendation)*

Summary of evidence and rationale:
- Testing for previous SARS-CoV-2 infection is not needed prior to COVID-19 vaccination.
- On June 29, NACI reaffirmed its recommendation that those previously infected with SARS-CoV-2 may be offered a complete series with a COVID-19 vaccine, after considering evidence from rapid reviews that reported on the protective immunity of previous SARS-CoV-2 infection, the immunogenicity and safety of vaccination in previously infected individuals.
- In the absence of one-dose vaccine effectiveness data in previously infected individuals (particularly as it relates to the VOCs), no notable safety signals following a second-dose in this population, and the potential programmatic challenges associated with the implementation of a one-dose strategy, people with previous SARS-CoV-2 infection may

continue to be offered a complete vaccine series at the recommended intervals, regardless of the severity of their previous infection. Based on current immunogenicity evidence, it is possible that one dose of COVID-19 vaccine for individuals who have had a previous SARS-CoV-2 infection may adequately protect against COVID-19.

- In COVID-19 vaccine clinical trials to date, individuals with PCR-confirmed SARS-CoV-2 were excluded and there were only a small number of trial participants with serologic evidence of previous infection (IgG+) who had confirmed symptomatic COVID-19 during the trials. Therefore, efficacy based on clinical trials in this population is uncertain.

- A number of large observational studies have found the incidence of reinfection in individuals with prior SARS-CoV-2 infection, with and without subsequent mRNA COVID-19 vaccination, to be comparable to individuals without prior infection who have received two doses of mRNA vaccine. In addition, a prospective observational study of the Israeli adult (≥16 years) population estimated prior SARS-CoV-2 infection provided very high (94 to 96%) protection against subsequent infection, hospitalization, and severe illness, which were comparable to the estimates of protection provided by two doses of vaccine in the previously uninfected vaccinated cohort. However, both the protective effect of immunity induced by previous infection and the durability of this protection against VOCs are unknown. Emerging evidence indicates that sera from convalescent patients may have reduced capacity to neutralize some VOCs and the risk of reinfection with these strains could be higher [50].

- There are currently limited data on potential differences in COVID-19 vaccine reactogenicity between those with and without prior evidence of SARS-CoV-2 infection. Due to the small sample sizes of the studies that report these data, the incidence of very rare adverse events such as myocarditis and pericarditis in previously infected individuals who receive one or two doses of COVID-19 vaccines is unknown. There is also a lack of evidence regarding the impact of the severity of the previous infection and the impact of the interval between a previous infection and the first dose of a COVID-19 vaccine on reactogenicity and rare adverse events.

- There is a growing body of evidence demonstrating that individuals with previous infection who receive a single dose of vaccine generate a comparable immune response compared to SARS-CoV-2 naïve individuals who receive two doses. Thus, it could be inferred that previously infected individuals who receive a single dose of vaccine may have similar levels of protection against infection as SARS-CoV-2 naïve individuals vaccinated with two doses, although comparative vaccine effectiveness data between these two groups are lacking and protection against most VOCs in this scenario is unknown.

- There is also limited evidence that individuals with previous symptomatic infections may generate a greater immune response after vaccination compared to individuals with previous asymptomatic infections. Research on the immune response to SARS-CoV-2 and VOCs, including duration of immunity and cross-protection, is ongoing. There is a lack of evidence comparing the immune responses against VOCs in unvaccinated, previously infected persons to immune responses against VOCs in vaccinated individuals.

- While previously infected individuals may be able to obtain a similar level of protection from a single dose of vaccine compared to naïve individuals receiving two doses, previously infected individuals may choose to complete their vaccination series in order to

meet vaccination-related requirements/guidelines to engage in activities, such as those related to travel.

- It was previously recommended in the context of limited supply that vaccination with a COVID-19 vaccine may be delayed for 3 months following a PCR-confirmed infection, due to available evidence on the risk of re-infection at the time. Research to establish the severity, frequency and risk factors for re-infection is ongoing. While binding and neutralizing antibodies have been shown in multiple studies to persist 6 months post-infection, and protection against re-infection could potentially be for as long as 10 months, the risk of re-infection over time in a given individual with previous infection is difficult to determine, as is the protection offered by previous infection against VOC. Therefore, if a delay in administering vaccination following infection is being considered, risk factors for exposure (including local epidemiology and circulation of VOCs) and risk of severe disease should also be taken into account.

- As a precautionary measure and in light of the need to be able to monitor for COVID-19 vaccine adverse events without potential confounding from symptoms of COVID-19 or other co-existing illnesses, and to minimize the risk of transmission of COVID-19 at an immunization venue, NACI recommends that, at a minimum, before vaccinating with COVID-19 vaccine, the person should no longer be considered infectious based on current criteria, and symptoms of an acute illness should be completely resolved.

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

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

Immunosuppressed persons

5. **NACI preferentially recommends that a complete COVID-19 vaccine series with an mRNA COVID-19 vaccine should be offered to individuals in the authorized age group who are immunosuppressed due to disease or treatment. 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*)**

6. **NACI recommends that a viral vector COVID-19 vaccine may be offered to individuals in the authorized age group who are immunosuppressed due to disease or treatment to initiate a series when other authorized COVID-19 vaccines are contraindicated or inaccessible. Informed consent should include discussion about the risk and symptoms of VITT, the need to seek immediate medical care should symptoms**

develop, as well as the limited evidence on the use of viral vector COVID-19 vaccines in this population. *(Discretionary NACI Recommendation)*

Summary of evidence and rationale

- 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 [61][62][63][64][65][66][67][68][69][70][71][72][73][74]. 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 [75][76][77][67][68][69][78][79][80][81][82][72][83][74][84][85][86][87][88][63][89][65][90][66]. 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 [66][85][82][79][88][81][69][87]. 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 [124][125][126].

- 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 [7]. 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 [7][9].

- 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

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

8. **NACI recommends that a viral vector COVID-19 vaccine may be offered to individuals in the authorized age group with an autoimmune condition to initiate a series when other authorized COVID-19 vaccines are contraindicated or inaccessible. Informed consent should include discussion about the risk and symptoms of VITT, the need to seek immediate medical care should symptoms develop, as well as the limited evidence on the use of viral vector COVID-19 vaccines in this population.** (*Discretionary NACI Recommendation*)

Summary of evidence and rationale
- Although participants with autoimmune conditions who were not immunosuppressed were not excluded from trials, they constitute a very small proportion of trial participants and represent a very narrow range of autoimmune conditions. However, real-world evidence (mostly with mRNA vaccination) has become available.
- Other applications of mRNA technologies have been for the treatment of cancer, which requires an immune response directed against an individual's cancer cells. This raised the theoretical concern that mRNA vaccines for infectious diseases would behave similarly, eliciting inflammation and possibly exacerbating existing autoimmune diseases. Current applications of mRNA technology for COVID-19 vaccines have been optimized to reduce this risk; however, further evaluation is needed. The theoretical concern is similar for viral vector vaccines. However, evidence on the safety of COVID-19 vaccination in individuals with an autoimmune condition is emerging.

- Observational studies in individuals with autoimmune conditions indicates that the frequency and severity of adverse events in this population is comparable to that of individuals without autoimmune conditions and what was reported in clinical trials [61][62][63][64][65][66][102]. The onset of new autoimmune disease or disease exacerbation following vaccination with mRNA COVID-19 vaccines was rare or comparable to the background incidence of these events in the general population. Safety data in these populations following vaccination with a viral vector vaccine is not available.
- Observational studies in individuals with autoimmune conditions who were taking immunosuppressive therapies showed diminished or delayed immune responses to the mRNA or AstraZeneca vaccines. Given the limited number of participants and the lack of an immunological correlate of protection against SARS-CoV-2 infection, there are limitations in interpreting the significance of these observational studies [88][63][89][65][90][66].
- The spectrum of autoimmune conditions is diverse. The relative degree of autoimmunity in individuals with autoimmune conditions is variable depending on the underlying condition, the severity and progression of disease, and use of medications that impact immune function.
- The evidence about autoimmune conditions as an independent risk factor for severe COVID-19 is evolving. A rapid review of evidence from OECD member countries found strong evidence (of moderate certainty) for at least a 2-fold increase in mortality from COVID-19 with type 1 diabetes, as well as with a group of neurological disorders including multiple sclerosis and myasthenia gravis. The review also found low certainty evidence for a large increase in hospitalization with vasculitis [7]. 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 [7]. 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 [7][9].
- Active surveillance in these vaccine recipients is strongly encouraged. NACI will monitor the evidence as it evolves, and update recommendations as needed.

Refer to Immunization in Persons with Chronic Diseases in the CIG, Part 3 – Vaccination of Specific Populations for additional general information on autoimmune conditions.

Pregnancy and Breastfeeding

9. **NACI preferentially recommends that a complete vaccine series with an mRNA COVID-19 vaccine should be offered to individuals in the authorized age group who are pregnant or breastfeeding. Informed consent should include discussion about emerging evidence on the safety of mRNA COVID-19 vaccines in these populations. (*Strong NACI Recommendation*)**

10. **NACI recommends that a viral vector COVID-19 vaccine may be offered to individuals in the authorized age group who are pregnant or breastfeeding to initiate a series when other authorized COVID-19 vaccines are contraindicated or inaccessible. Informed consent should include discussion about the risk and symptoms of VITT, the need to seek immediate medical care should symptoms develop, as well as the limited evidence on the use of viral vector COVID-19 vaccines in these populations. (*Discretionary NACI Recommendation*)**

Summary of evidence and rationale

- Pregnant or breastfeeding individuals were excluded from the mRNA and viral vector COVID-19 clinical trials. However, outcomes in participants who became pregnant during the clinical trials and fetal outcomes are reported through registries, and real-world evidence (mostly with mRNA vaccination) has become available.

- An mRNA vaccine is preferred due to published safety data. Recently published preliminary analyses of 35,691 pregnant women in the United States who received an mRNA COVID-19 vaccine did not reveal any obvious safety signals [107]. 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 [107]. 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[104], Moderna[103], Janssen[127], and AstraZeneca vaccines [106].

- Emerging evidence suggests that COVID-19 mRNA vaccination during pregnancy results in comparable antibody titres to those generated in non-pregnant women [109] [110] [111]. 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 [112] [109] [113] [114].

- 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 [115][116][117][118][128][129][108][130].

- 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 [108].

- The evidence of pregnancy as an independent risk factor for severe COVID-19 is evolving. A rapid review of evidence from Organisation for Economic Co-operation and Development (OECD) member countries found a low certainty of evidence of at least a two-fold increase in hospitalization due to COVID-19 for pregnancy (any stage) and a low certainty of evidence for little to no increase in mortality. Caution should be taken when interpreting low certainty evidence. However, the review found a moderate certainty of evidence of at least a two-fold increase in hospitalization and mortality if an individual had two or more underlying medical conditions, compared to individuals with no comorbidities. No direct evidence on the combination of medical conditions associated with increased risk was found [7, 9].

- Compared to non-pregnant persons, SARS-CoV-2 infection in pregnancy may increase the risk of complications requiring hospitalization and intensive care, premature birth and caesarean delivery. A review of 438,548 pregnant individuals found pregnancy is a risk factor for poorer pregnancy outcomes, such as preeclampsia, pre-term birth, and stillbirth, and that these risks are much greater with severe infection [131]. 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 [132]. Ventilatory support in pregnancy is more challenging and the risks are greater to both mother and child.

- Vaccine recipients and health care providers are encouraged to enroll patients who have received a COVID-19 vaccine during pregnancy in COVID-19 vaccine pregnancy registries (refer to Appendix F for a list of COVID-19 vaccine pregnancy registries). Timely reporting on adverse events following immunization to the local public health authority, as well as to the vaccine manufacturer, for follow up in these vaccine recipients is strongly encouraged.
- NACI encourages research on COVID-19 vaccination in pregnancy and during breastfeeding.
- NACI will monitor the evidence as it evolves, and update recommendations as needed.

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

Children and Adolescents

11. NACI recommends that a complete series with a Pfizer-BioNTech COVID-19 vaccine should be offered to individuals 12 to 15 years of age without contraindications to the vaccine. Informed consent should include discussion about very rare reports of myocarditis and/or pericarditis in the week following an mRNA vaccine dose. *(Strong NACI Recommendation)*

Internationally, cases of myocarditis and/or pericarditis following vaccination with mRNA vaccines have been reported most frequently in adolescents and younger adults under 30 years of age, more frequently in males compared to females, and more frequently after the second dose.

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

- Adolescents 12 to 15 years of age and younger represent 4% of the Canadian population and constitute less than 4% of COVID-19 cases reported in Canada up to June 8, 2021. Adolescents account for less than 0.5% of COVID-19 associated hospitalizations, less than 0.5% of COVID-19 cases admitted to ICU, and less than 0.01% of deaths from COVID-19.
- However, there have been recent reports of COVID-19 outbreaks affecting children, specifically related to the B.1.617.2 (Delta) variant, in areas of relatively high rates of vaccination in the adult population. Evidence on whether specific SARS-CoV-2 variants of concern, such as the B.1.617.2 (Delta) variant, may be more infectious due to increased transmissibility or reduced indirect protection conferred by mRNA vaccination of adults is still emerging.
- In Canada, 25% of individuals 17 years of age and younger hospitalized or admitted to intensive care for COVID-19 had one or more underlying health conditions[120].
- 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 [133].
- Post-market safety surveillance of mRNA COVID-19 vaccines has found an increased frequency of myocarditis and pericarditis most frequently in adolescents and younger

adults under 30 years of age, more frequently in males compared to females, and more frequently after the second dose. However the majority of cases have been mild and have resolved.

Please see *Informed consent for mRNA COVID-19 vaccines should include information about very rare reports of myocarditis or pericarditis in the week following an mRNA vaccine* for additional guidance.

- Active surveillance in adolescent vaccine recipients is strongly encouraged. NACI will monitor the evidence as it evolves, and update recommendations as needed.
- Evidence on COVID-19 vaccination in those less than 12 years of age is not available at this time. NACI is monitoring the evidence and will update recommendations when results become available.

NACI continues to recommend the following:

- Routine immunization programs and immunization with other vaccines recommended by NACI should continue during the COVID-19 pandemic with mitigation of risks of COVID-19 transmission during the immunization process as outlined in the Interim guidance on continuity of immunization programs during the COVID-19 pandemic.

- Clinical trials assessing COVID-19 vaccines should continue to be encouraged to include individuals with potential vulnerabilities to disease related to biological (e.g., pre-existing medical conditions, frailty, pregnancy and breastfeeding, immunocompromised), and social (e.g., residence in long term care facilities or crowded/remote locations, belonging to a racialized population, occupation) factors to ensure that vaccine options are informed by robust safety, immunogenicity, and efficacy data as outlined in NACI's guidance on Research Priorities for COVID-19 Vaccines to Support Public Health Decisions.

- In addition to ongoing vaccine pharmacovigilance activities in Canada with Phase 4 clinical trials and post-marketing studies, additional research and surveillance of COVID-19 vaccination, particularly in populations not currently included in clinical trials (e.g., pregnant, breastfeeding, immunosuppressed, seniors living in congregate care settings, children and adolescents) is recommended. Furthermore, NACI recommends the continuation of clinical trials and ongoing follow-up of participants for as long as it is ethically feasible to determine the level of immunity needed to prevent disease, duration of protection, efficacy in different sub-populations, and medium- and long-term safety.

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

- ➢ Efforts should be made to increase access to immunization services to reduce health inequities without further stigmatization or discrimination, and to engage systemically marginalized populations and racialized populations in immunization program planning.

- ➢ Jurisdictions should ensure close and rapid monitoring of safety, effectiveness, and coverage of the vaccines in different key populations, as well as effective and efficient immunization of populations in hardly reached, remote and isolated communities.

➢ Efforts should be made to improve knowledge about the benefits of vaccines in general and of COVID-19 vaccines as each becomes available, address misinformation, and communicate transparently about COVID-19 vaccine allocation decisions.

V.I SUMMARY OF CONSIDERATIONS FOR COVID-19 VACCINES AUTHORIZED FOR USE IN CANADA

There are currently four authorized COVID-19 vaccines in Canada for the prevention of symptomatic COVID-19 that use two different vaccine platforms. The merits of both vaccine platforms have been summarized in Table 5 below. 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. Vaccination considerations for types of COVID-19 vaccines authorized for use in Canada

Factor for consideration	Summary of available evidence and issues for consideration	
	mRNA COVID-19 Vaccines	**Non-replicating viral vector COVID-19 Vaccines**
Efficacy and Effectiveness	**Efficacy against symptomatic illness after a complete series** • Pfizer-BioNTech vaccine is overall 94% efficacious ≥14 days after dose 2 in study participants 16 years of age and older. Data suggest the Pfizer/BioNTech vaccine is 95% efficacious in participants ≥65 years of age, and 100% efficacious in participants 12-15 years of age, 7 or more days after dose 2. • Moderna vaccine is overall 94% efficacious in participants 18 years of age and older ≥14 days after dose 2. • Data suggest the Moderna vaccine is 86% efficacious in individuals ≥65 years of age ≥14 days after dose 2. **Effectiveness against severe disease, hospitalization and death from mRNA vaccines (with more data available for Pfizer-BioNTech than Moderna)** • Current data from real-world studies indicate that mRNA COVID-19 vaccines provide very good protection against COVID-19 hospitalization in adults following response to the first dose, including in older populations (≥65 years). • Data from real-world studies in adults provide some evidence that mRNA COVID-19 vaccines provide very good protection against COVID-19-related death following response to the first dose. • Real-world studies in adults indicate that mRNA COVID-19 vaccines provide excellent protection against severe disease,	**Efficacy against symptomatic illness after a complete series** • AstraZeneca SD/SD vaccine is 62% efficacious in participants 18 to 64 years of age. • Current data from clinical trials are insufficient to determine the efficacy of the AstraZeneca vaccine in individuals ≥65 years of age. • The interval between the first and second dose of the AstraZeneca vaccine may impact efficacy of the vaccine, with lower efficacy if the interval is less than 12 weeks. • The Janssen COVID-19 vaccine (1 dose) is 66.9% and 66.1% efficacious against confirmed symptomatic moderate to severe/critical COVID-19 infection at ≥14 days and ≥28 days post-vaccination, respectively. • The Janssen COVID-19 vaccine is 76.7% and 85.4% efficacious against confirmed symptomatic severe/critical COVID-19 infection at ≥14 days and ≥28 days post-vaccination, respectively. **Effectiveness against symptomatic illness and hospitalization** • Observational data in individuals ≥65 years of age have shown a reduction in the risk of symptomatic disease and hospitalization with one dose of AstraZeneca vaccine.

Factor for consideration	Summary of available evidence and issues for consideration	
	mRNA COVID-19 Vaccines	**Non-replicating viral vector COVID-19 Vaccines**
	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.	• Real-world effectiveness data on the Janssen COVID-19 vaccine indicate good protection against SARS-CoV-2 infection [134].
	Efficacy against asymptomatic infection • A preliminary analysis of limited data in an ongoing trial suggests the Moderna COVID-19 vaccine may be efficacious in preventing asymptomatic infection, however data is still being collected and the final analysis is not complete. **Effectiveness against asymptomatic infection** • Estimates of vaccine effectiveness for the Pfizer-BioNTech COVID-19 vaccine against SARS-CoV-2 infection with no reported symptoms was moderate to high after the first dose (depending on time since vaccination) and high after the second dose [13, 20] in adults. Similar results were reported for mRNA COVID-19 vaccines in general [21].	**Efficacy against asymptomatic infection** • An exploratory ad hoc analysis of limited data suggests the AstraZeneca vaccine may not be efficacious in preventing asymptomatic infection. • Preliminary analyses of limited data suggests that the Janssen COVID-19 vaccine has an estimated efficacy of 59.7% against asymptomatic or undetected SARS-CoV-2 infection with onset ≥28 days post-vaccination.

Factor for consideration	Summary of available evidence and issues for consideration	
	mRNA COVID-19 Vaccines	**Non-replicating viral vector COVID-19 Vaccines**
	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.
Immunogenicity	**Humoral response** • 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 [56][26][57, 58][59][60].	**Humoral response** • For the AstraZeneca vaccine, humoral responses in clinical trials peaked after a second dose, including elicitation of neutralizing antibodies, for seronegative vaccine recipients. For seropositive 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 [135]. • 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.

Factor for consideration	Summary of available evidence and issues for consideration	
	mRNA COVID-19 Vaccines	**Non-replicating viral vector COVID-19 Vaccines**
		• 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.	**Cellular response** • The AstraZeneca vaccine has been shown to produce cellular immune responses that did not appear to increase after the second dose. • Cellular immune responses do not appear to differ between age groups. • For the Janssen vaccine, cellular immune responses were elicited after one dose of vaccine. • As no immunological correlate of protection has been determined for SARS-CoV-2, these cellular responses cannot be interpreted as corresponding with vaccine protection.
Protection against variants, including Variants of concern	**B.1.1.7 (Alpha)** • Data suggest comparable vaccine effectiveness of mRNA COVID-19 vaccines against symptomatic and severe illness due to the B.1.1.7 (Alpha) VOC. **B.1.351 (Beta)** • Emerging data suggest that mRNA COVID-19 vaccines are 43% effective against symptomatic illness due to the B.1.351 (Beta) VOC after one dose, and 88% effective after two doses [19]. **P.1 (Gamma) and P.2 (Zeta)** • There are limited data on the efficacy or effectiveness of mRNA vaccines against the P.1 (Gamma) VOC and P.2 (Zeta) VOI. **B.1.617.2 (Delta)** • Emerging data suggest the Pfizer-BioNTech vaccine is 33.2% effective against symptomatic illness due to B.1.617.2 (Delta) after one dose, and 87.9% effective after two doses [136].	**B.1.1.7 (Alpha)** • Data suggest AstraZeneca COVID-19 vaccine has a vaccine efficacy of 70.4% against the B.1.1.7 (Alpha) VOC first identified in the UK, compared to 81.5% against non-B.1.1.7 strains (where cases were predominantly due to B.1.177, a non-VOI/VOC strain). [139] **B.1.351 (Beta)** • Data suggest AstraZeneca **vaccine** has a vaccine efficacy of 10.4% against the B.1.351 (Beta) VOC against mild to moderate illness [140]. • In South Africa, where the B.1.351 (Beta) VOC was the dominant strain (approximately 95% of preliminary sequenced samples), the Janssen vaccine was 64% efficacious against moderate to severe/critical COVID-19 as of Day 29. **P.1 (Gamma) and P.2 (Zeta)**

Factor for consideration	Summary of available evidence and issues for consideration	
	mRNA COVID-19 Vaccines	**Non-replicating viral vector COVID-19 Vaccines**
	- Against any infection (symptomatic or asymptomatic) due to B.1.617.2 (Delta) emerging data suggest the Pfizer-BioNTech vaccines is 30% effective after one dose, and 79% effective after two doses [137]. - Emerging data suggests the Pfizer-BioNTech vaccine is 94% effective against hospitalization due to B.1.617.2 (Delta) after one dose, and 96% effective after two doses [138].	- There are limited data on the efficacy or effectiveness of viral vector vaccines against the P.1 (Gamma) VOC. - In Brazil, where P.2 (Zeta) was detected in approximately 70% of sequenced samples of COVID-19 cases, the Janssen vaccine was 68% efficacious against moderate to severe/critical COVID-19 as of Day 29. **B.1.617.2 (Delta)** - Emerging data suggest the AstraZeneca vaccine is 32.9% effective against symptomatic illness due to B.1.617.2 (Delta) after one dose, and 59.8% effective after two doses [136]. - Against any infection (symptomatic or asymptomatic) due to B.1.617.2 (Delta) emerging data suggest the AstraZeneca vaccine is 18% effective after one dose, and 60% effective after two doses [137]. - Emerging data suggests the AstraZeneca vaccine is 71% effective against hospitalization due to B.1.617.2 (Delta) after one dose, and 92% effective after two doses [138].
Safety	**Technology** mRNA vaccines use a new technology (which has been studied in experimental vaccines); however, all COVID-19 vaccines undergo the same rigorous review and approval process as routine vaccines.	**Technology** Viral vector vaccines use a relatively new technology (the authorized Ebola vaccine uses this technology); however, all COVID-19 vaccines undergo the same rigorous review and approval process as routine vaccines.
	Safety Signals - Rare anaphylactic reactions have been reported following immunization with mRNA COVID-19 vaccines. - For both vaccines, some solicited adverse events are reported to be very common (defined as 10% or more) among vaccine recipients; however, they are mild or moderate and transient, resolving within a few days. These include: pain at the injection site, fatigue, headache, muscle pain, chills, joint pain, and fever.	**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.

Factor for consideration	Summary of available evidence and issues for consideration	
	mRNA COVID-19 Vaccines	**Non-replicating viral vector COVID-19 Vaccines**
	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. • Cases of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining around the heart) following vaccination with COVID-19 mRNA vaccines, have been reported in Canada and internationally. In Canada, we are not currently seeing higher rates than would be expected in the general population; however, the number of second doses administered to younger ages is small to-date. The evidence on this phenomenon is evolving and investigations into the association between myocarditis/ pericarditis and mRNA vaccines continue in Canada and abroad. Based on cases reported internationally, available information indicates that they occur more often after the second dose, usually within a week after vaccination, more often in adolescents and young adults and adolescents. Cases that have been reported after receipt of COVID-19 mRNA vaccines have been generally mild and resolved well with medical treatment.	The mechanism of action appears to be similar to spontaneous heparin-induced thrombocytopenia (called VITT-Vaccine-Induced Immune Thrombotic Thrombocytopenia). Internationally, the rate of this adverse event is still to be confirmed but had been most commonly estimated to be between 1/26,000 and 1/100,000 people vaccinated with AstraZeneca vaccine. Based on available evidence as of June 1, 2021, PHAC has estimated the rate of VITT in Canada as 1 in 73,000 doses administered. However, as investigations continue, this rate could be as high as 1 in 50,000 The case fatality rate typically ranges between 20 and 50%. Other predisposing factors for VITT are unclear. • For the Janssen vaccine, in the clinical trial, one case of cerebral venous thrombosis was reported among 21,895 vaccine recipients. As of May 24, 2021, 32 cases of TTS have been confirmed out of about 10.2 million doses of Janssen vaccine administered in the United States. Investigations are ongoing. • Very rare cases of capillary leak syndrome (CLS) have been reported following immunization with the AstraZeneca COVID-19 vaccine. Some affected patients had a previous diagnosis of CLS. CLS is a serious, potentially fatal condition characterized by acute episodes of limb edema, hypotension, hemoconcentration and hypoalbuminemia. Individuals with a history of CLS should not receive the AstraZeneca/COVISHIELD COVID-19 vaccine.
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.	• 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

Factor for consideration	Summary of available evidence and issues for consideration	
	mRNA COVID-19 Vaccines	**Non-replicating viral vector COVID-19 Vaccines**
	• Vaccines that are more efficacious may be directed to those who are most at risk of severe disease and exposure to limit the exacerbation of existing inequities. • The impact of not offering a less efficacious vaccine earlier to populations who would otherwise have to wait to receive an mRNA vaccine in areas with a high risk of transmission and infection, should take into consideration trust, justice, and the risk of doing harm vs. good.	vaccine compared to an mRNA vaccine, depending on which population groups received the viral vector vaccine. • The viral vector vaccines may offer an option for individuals who are allergic to mRNA vaccine ingredients or their containers. The impact of offering a less efficacious vaccine earlier to some populations should take into consideration trust, justice and the risk of doing harm vs. good.
Feasibility	**Vaccine schedule** • Both mRNA vaccines are given as a two-dose series. • 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. Although NACI currently recommends up to a 4 month extended interval between first and second doses of COVID-19 vaccines for all authorized age groups to maximize the number of individuals benefitting from the first dose, current supplies of COVID-19 vaccines now support shorter intervals between doses.	**Vaccine schedule** • The AstraZeneca vaccine is given as a two-dose series. The interval between the first and second dose of the AstraZeneca vaccine seems to impact efficacy of the vaccine, with lower efficacy if the interval is less than 12 weeks. Although NACI currently recommends up to a 4 month extended interval between first and second doses of COVID-19 vaccines for all authorized age groups to maximize the number of individuals benefitting from the first dose, current supplies of COVID-19 vaccines now support shorter intervals between doses. • The Janssen vaccine is authorized as a single dose. This may increase the feasibility of the completion of a vaccine series. • Vaccine recipients need to be advised of the VITT safety signal and the symptoms to watch for after vaccination.
	Storage requirements • The mRNA vaccines have more challenging transport and storage requirements, requiring frozen or ultra-frozen cold chains. Significant efforts have been undertaken to address these logistical complexities. The storage requirements for these vaccines increase the logistical complexity of offering these vaccines in some venues to increase access for various populations.	**Storage requirements** • The viral vector vaccines are easier to transport, store and handle than mRNA vaccines, and as a result, could be easier to use for wider distribution via pharmacies and primary healthcare providers. • The viral vector vaccines require storage and transport at +2 to +8°C, which uses standard cold chain infrastructure widely available in provinces and territories. • The storage requirements for these vaccines could increase access to the vaccine for various populations.

Factor for consideration	Summary of available evidence and issues for consideration	
	mRNA COVID-19 Vaccines	**Non-replicating viral vector COVID-19 Vaccines**
Acceptability	- It is possible that individuals will favor mRNA vaccines since they have higher proven efficacy. - Fewer cases of COVID-19 are expected after vaccination with a vaccine with high efficacy. The relatively low incidence of cases post-vaccination could positively affect acceptability of COVID-19 vaccines and vaccines in general.	- It is possible that individuals will favor the viral vector vaccines if it offers an earlier opportunity to receive a COVID-19 vaccine and is more convenient to access if they are available at more convenient locations due to ease of transport, storage and handling. - A greater number of COVID-19 cases are expected after vaccination with a vaccine that has lower efficacy. The relatively higher incidence of cases post-vaccination could negatively affect the public's acceptability of COVID-19 vaccines and vaccines in general. - The Janssen vaccine is given as a single dose. This may increase acceptability of vaccination. - Recent cases of VITT detected after administration with the viral vector vaccines have impacted their acceptability.
	Concerns about vaccine safety and effectiveness are the two most cited reasons for vaccine refusal [141] - In a survey of Canadians conducted between February 9 and 16, 2021 [142], 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) [143] - In a survey of health care providers conducted on Dec 4-13, 2020 [144], 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 durability of protection of a single dose or a complete series of each COVID-19 vaccine approved in Canada?

2. What is the efficacy, effectiveness, immunogenicity, and safety of COVID-19 vaccines across diverse population groups (e.g., adults of advanced age, those with high-risk medical conditions including autoimmune conditions and transplant recipients, individuals with social or occupational vulnerabilities, individuals who are pregnant or breastfeeding, children/adolescents, frailty)? Is a third booster dose of vaccine or a higher dose of vaccine needed to elicit an appropriate immune response in these individuals?

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

4. What is the efficacy, effectiveness, immunogenicity and safety of COVID-19 vaccines (including potential boosters) against SARS-CoV-2 VOC?

5. What is the 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? What is the minimum magnitude of antibody response needed for protection?

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

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. Is there an association between myocarditis/pericarditis and mRNA COVID-19 vaccines? If so, what is the biological mechanism by which mRNA vaccines may trigger myocarditis/pericarditis? How do age, sex, other patient characteristics, or vaccine schedule affect the incidence of myocarditis/pericarditis following immunization with COVID-19 vaccines?

13. 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?

14. 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?

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

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

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

18. 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?

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

Vaccine Administration

20. What is the efficacy, effectiveness, immunogenicity and safety of a mixed dose schedule or a mixed dose booster series?

21. 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?

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

23. Can COVID-19 vaccine be simultaneously administered with other, non-COVID-19 vaccines (either live or inactivated vaccines)? What is the minimum interval between administration of a COVID-19 vaccine and other, non-COVID-19 vaccines (either live or inactivated vaccines)? What are the immunological and clinical outcomes if COVID-19 vaccines were simultaneously administered with other, non-COVID-19 vaccines?

24. What is the minimum interval required for vaccine administration following receipt of convalescent plasma or anti-SARS-CoV-2 spike protein monoclonal antibodies?

Standing Research Priorities

COVID-19 infection and disease

1. What is the epidemiological profile of COVID-19 (e.g., communicable period, all risk groups)?

    a. What is the disease distribution and spectrum of clinical illness for COVID-19, including burden of illness and risk by age, sex and other demographic variables associated with higher risk?

    b. What are the transmission dynamics of COVID-19, including degree of asymptomatic transmission, role of children in transmission, vertical transmissibility, onset and duration of viral shedding and communicable period, impact of changing weather conditions, and trends over time?

    c. What are the rates of COVID-19 co-infections with other respiratory pathogens and what is the impact on pathogenesis and clinical outcomes?

2. Can COVID-19 vaccine be used to protect household contacts of a case from infection? Does COVID-19 vaccination decrease infectiousness and clinical illness in individuals that have already acquired infection? Is COVID-19 vaccination effective in interrupting transmission?

Ethics, Equity, Feasibility and Acceptability

3. What is the acceptability of (a) publicly funded COVID-19 vaccines and (b) other vaccines over time and over different epidemiological contexts among key populations, marginalized populations, providers and policy-makers in different epidemiological contexts across the country?
   a. What factors affect acceptability of immunization with a COVID-19 vaccine in these groups?
   b. What factors affect acceptability of immunization in general?
   c. How will acceptability of prioritized key populations for early immunization with COVID-19 vaccines evolve in different epidemiological contexts across the country?
   d. What strategies can improve acceptability of a COVID-19 vaccine in these groups?

4. How can vaccine allocation decisions be communicated to individuals and communities in order to maintain trust in public health authorities?

5. What COVID-19 vaccination strategies or implementation strategies can reduce health inequities in populations for whom the vaccination program is directly intended, and in populations for whom the vaccination program is not intended, but who are still impacted by it (e.g., impacted by the disease, spillover effects such as for caregivers, or externalities such as with 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

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

LIST OF ABBREVIATIONS

Abbreviation	Term
Ad26	Modified human adenovirus 26
AE	Adverse event
AEFI	Adverse event following immunization
ARCHE	Alberta Research Center for Health Evidence
CDC	Centres for Disease Control and Prevention (United States)
ChAd	Chimpanzee Adenovirus
CI	Confidence interval
CIC	Canadian Immunization Committee
CIG	Canadian Immunization Guide
CLS	Capillary leak syndrome
COVID-19	Coronavirus disease 2019
CVST	Cerebral venous sinus thrombosis
DART	Developmental and Reproductive Toxicity
DIC	Disseminated intravascular coagulation
EEFA	Ethics, Equity, Feasibility, and Acceptability
EMA	European Medicines Agency
FDA	Food and Drug Administration (US)
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HIV	Human immunodeficiency virus
ICU	Intensive care unit
IM	Intramuscular
Ig	Immunoglobulin
IGRA	Interferon gamma release assay
JCVI	Joint Committee on Vaccination and Immunisation (UK)
MAAE	Medically attended adverse event
MenACWY	Quadrivalent meningococcal vaccine
mRNA	messenger ribonucleic acid
OECD	Organisation for Economic Co-operation and Development
PF4	Platelet Factor 4
NACI	National Advisory Committee on Immunization
NITAG	National Immunization Technical Advisory Group
PCR	Polymerase chain reaction

PHAC	Public Health Agency of Canada
SAE	Serious adverse events
SAGE	Strategic Advisory Group of Experts on Immunization (WHO)
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard dose
SII	Serum Institute of India
SOC	System organ class
TST	Tuberculin skin test
TTS	Thrombosis with Thrombocytopenia Syndrome
UK	United Kingdom
US	United States
VIPIT	Vaccine-Induced Prothrombotic Immune Thrombocytopenia
VITT	Vaccine-Induced Thrombotic Thrombocytopenia
VOC	Variant of concern
VOI	Variant of interest
VPD	Vaccine preventable disease
WHO	World Health Organization

ACKNOWLEDGMENTS

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APPENDIX A: CLINICAL TRIAL 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 [126] and in adolescents 12 to 15 years of age [133]) were published in December 2020 and May 2021, respectively, after NACI's review of the evidence. Evidence from post-marketing surveillance and studies is found in the main body of this statement.

Efficacy

Severe outcomes due to COVID-19
There are no efficacy data for hospitalizations and deaths specifically, however data exists for efficacy against severe COVID-19 outcomes, defined as laboratory-confirmed COVID-19 with one of the following additional features: clinical signs at rest that are indicative of severe systemic illness; respiratory failure; evidence of shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death [146].

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 [133].

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 [145] identified among vaccine recipients (N=19,965) compared to 169 cases among placebo recipients (N=20,172). The vaccine efficacy at least 14 days after Dose 2 in this population was comparable (94.4%,

95% CI: 89.1 to 97.3%). Results were similar when estimating the efficacy specifically in individuals without evidence of prior SARS-CoV-2 infection at 95.0% (95% CI: 90.3 to 97.6%) with 8 confirmed cases among vaccine recipients (N=18,198) compared to 162 cases among placebo recipients (N=18,325).

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

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

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

Time period of interest	Events in vaccine group (N=21,669)	Events in placebo group (N=21,686)	Estimate of vaccine efficacy (95% confidence interval)
After dose 1 to before dose 2	39	82	52.4% (29.5 to 68.4%)
>14 days after dose 1 to before dose 2[b]	2	27	92.3% (69 to 98%)

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

[b] Comité sur l'immunisation du Québec. Stratégie de vaccination contre la COVID-19 : report de la 2e dose en contexte de pénurie. Institut national de Santé Publique du Québec, 18 décembre 2020

In adolescents 12 to 15 years of age:
In study participants without prior evidence of SARS-CoV-2 infection, there were no confirmed COVID-19 cases occurring at least 7 days after Dose 2 among vaccine recipients (n=1,005) compared to 16 cases among placebo recipients (n=978) for an estimated vaccine efficacy against confirmed COVID-19 of 100.0% (95% CI: 75.3 to 100%) [133].

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

Table 8. Pfizer-BioNTech vaccine efficacy against the first occurrence of symptomatic COVID-19 disease after dose 1 and before dose 2 in adolescents 12 to 15 years of age[a]

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

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

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

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

Immunogenicity

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

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

Vaccine Safety and Adverse Events Following Immunization

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

years of age is based on interim analyses of 2,260 participants. Approximately 1,300 participants had at least 2 months of follow-up after Dose 2, of which 660 in this group received the vaccine.

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

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

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

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

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

Severe or Serious Adverse Events
Among adult participants 16 years of age and older in the vaccine group, 1.1% and 0.1% of participants experienced at least one severe AE and one life-threatening adverse events (AE), respectively, compared to 0.7% and 0.1% of participants in the placebo group. Among non-

serious unsolicited adverse events, there was a numerical imbalance of four reports of Bell's palsy in the vaccine group compared with no report in the placebo group. These cases of Bell's palsy occurred 3, 9, 37, and 48 days following vaccination. Among adolescents 12 to 15 years of age in the vaccine group, 0.8% and 0.1% of participants experienced at least one severe AE and one life-threatening AE, compared to 0.3% and 0.1% of participants in the placebo group. In adolescents, no clinically meaningful differences were observed in AEs by age, sex, or race/ethnicity.

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

Other serious adverse events

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

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

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

APPENDIX B: CLINICAL TRIAL EVIDENCE SUMMARY FOR MODERNA COVID-19 VACCINE

Pivotal Phase 1, 2, and 3 trials are being conducted for the Moderna COVID-19 vaccine. Evidence on efficacy, immunogenicity, and safety is available for adults ≥18 years of age. Studies did not include participants from long term care facilities. The Phase 3 portion of the trial involved 30,413 study participants randomized (1:1) to receive either the vaccine (2 doses of 100 mcg) or placebo. The data presented below are for an interim analysis, therefore the time of follow-up is not consistent but was a median of two months after the second dose (maximum of 14 weeks) for all participants. Evidence from post-marketing surveillance and studies is found in the main body of this statement.

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 [147].

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

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

In study participants 18 to <65 years, there were 156 confirmed COVID-19 cases occurring at least 14 days after the second injection among placebo recipients compared to 7 cases among mRNA-1273 vaccine recipients, for an estimated vaccine efficacy of 95.6% (95% CI: 90.6 to 97.9%). The corresponding incidence rate per 1,000 person-years (total time at risk in each treatment group) was 64.63 in the placebo group and 2.88 in the Moderna COVID-19 vaccine group. In study participants ≥65 years of age there were 29 confirmed COVID-19 cases among

placebo recipients compared to 4 cases among Moderna COVID-19 vaccine recipients, corresponding to a somewhat lower point estimate of vaccine efficacy of 86.4% (95% CI: 61.4 to 95.2%). The corresponding incidence rate per 1,000 person-years was 33.73 in the placebo group and 4.60 in the Moderna COVID-19 vaccine group. In the subgroup of study participants ≥75 years of age there were 7 confirmed COVID-19 cases among placebo recipients compared to 0 cases among Moderna COVID-19 vaccine recipients, for a corresponding vaccine efficacy of 100.0% (95% CI: not evaluable to 100.0%), but this must be interpreted with caution as there were few events identified in this age group.

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

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

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

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

Time period of interest	Events in vaccine group (N=996)	Events in placebo group (N=1,079)	Estimate of vaccine efficacy (95% confidence interval)
After dose 1	7	39	80.2% (55.2 to 92.5%)
>14 days after dose 1	2	28	92.1% (68.8 to 99.1%)

[a] In the modified intention-to-treat population consisting of randomized study participants who had received only one dose of their assigned intervention (i.e., vaccine or placebo) at the time of analysis

Asymptomatic infection and transmission

Nasopharyngeal swabs for SARS-CoV-2 virus were collected for all participants at specified intervals before Dose 1 and before Dose 2. There were 14 participants in the vaccine arm who were previously seronegative before administration of Dose 1 who had asymptomatic infection at the second time point, compared to 38 participants in the placebo arm. No formal efficacy data are available; however, assessment of this outcome is ongoing.

Immunogenicity

Humoral immune responses

Antibodies that bind the spike protein were induced in vaccine recipients by day 15 (15 days after dose 1) and reach maximum levels on day 43 (15 days after dose 2). Maximal binding antibody responses approximate the levels of the highest affinity samples of convalescent sera. Binding antibodies reached elevated levels on day 36 (7 days after dose 2) and persisted but decreased through day 119 (90 days after dose 2), the last day for which data is available.

Binding antibodies induced by 1 dose of the vaccine (i.e., on day 29) were 10-20% of the elevated responses seen on day 36. It is unknown how binding antibody responses change over time. Binding antibody responses through day 36 seems to be approximately equivalent across age groups. The data may suggest an age-dependent binding antibody durability. Antibody responses for age 70 or below decreased more slowly than for those above 70.

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

Immunogenicity data from the Phase 1 trial of the Moderna COVID-19 vaccine in a small number of subjects (n=33) demonstrate antibody persistence for 6 months [149].

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) [148]. 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 [148]. 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%) [148].

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 [148]. After Dose 2, Grade 3 fever (1.3%), headache (4.3%), fatigue (9.4%), myalgia (8.7%), arthralgia (5.1%), and chills (1.3%) were common. The proportion of vaccine recipients that experience Grade 3 fever (>38.9°C to 40.0°C) increased between Dose 1 (<0.1%; n=11) and Dose 2 (1.3%; n=202). Among placebo recipients only 2.7% reported Grade 3 adverse events after either dose.

The incidence of any Grade 4 events was <0.1% after both doses in both vaccine (6 to 12 events) and placebo (2 to 4 events) recipients. Grade 4 fever (>40.0°C) was reported for 4 placebo recipients and 4 vaccine recipients after Dose 1, and 2 placebo recipients and 12 vaccine recipients after Dose 2. The majority of systemic reactions after either dose occurred within the first 1 to 2 days post-vaccination and had a median duration of 1 to 2 days.

Unsolicited Severe or Serious Adverse Events

During the first 28 days after any dose, 1.5% and 0.5% of participants in the vaccine group (Dose 1 and Dose 2, respectively) reported unsolicited severe and serious AEs (SAEs), compared to 1.3% and 0.6% of participants in the placebo group. There was no apparent effect of age on the relative incidence of SAEs in the vaccinated or placebo group. There were three

reports of Bell's palsy in the vaccine group which occurred 22, 29, and 32 days after the second dose and one in the placebo group which occurred 17 days post injection. One case of Bell's palsy in the vaccine group was considered a SAE (67-year-old female with diabetes who was hospitalized for stroke due to new facial paralysis 32 days after vaccination).

Three SAEs in vaccinated individuals were considered by the study sponsor to be related to the trial intervention: two cases of facial swelling and one case of nausea and vomiting with headaches and fever.
Four additional SAEs in vaccine recipients and five SAEs in placebo recipients were considered to be related to the trial intervention by trial investigators [148]. 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: CLINICAL TRIAL 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) were not available at time of writing. Evidence on efficacy, immunogenicity, and safety is available for adults ≥18 years of age. The Phase 2/3 trial (COV002) trial and Phase 3 trial (COV003) assessed efficacy, safety and immunogenicity of the vaccine. The Phase 2/3 trial was based in the United Kingdom, (UK) while the Phase 3 trial was based in Brazil. These two studies underwent a series of protocol amendments and logistical challenges during the conduct of the trials that resulted in significant changes to the trials' methodology. There were changes from a single to a two-dose vaccine regimen, the use of both a low dose/standard dose (LD/SD) (in COV002 only, due to dosing error) and standard dose/standard dose (SD/SD) vaccine regimen, and the recruitment of progressively older study participants (56–69 and then ≥70 years of age) after the initial focus on adults 18–55 years of age. In the SD/SD vaccine regimen, study participants were randomized (1:1) to receive either the AstraZeneca COVID-19 vaccine, AZD1222 (5×10^{10} viral particles per 0.5 mL dose) or control injection. The participants randomized to the control group were administered two doses of quadrivalent meningococcal vaccine (MenACWY) (COV002) or MenACWY for Dose 1 and placebo for Dose 2 (COV003).

There were significant differences in the baseline characteristics of participants in the Phase 2/3 and Phase 3 trials. In addition, the clinical trials prioritized the recruitment of health care professionals and other adults with high potential for exposure to SARS-CoV-2, including health care and social setting workers.

Evidence from the AstraZeneca COVID-19 vaccine trials has been published [150]. Evidence from post-marketing surveillance and studies is found in the main body of this statement.

Efficacy

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

Symptomatic COVID-19 disease
The primary efficacy outcome assessed in the two trials was prevention of the first occurrence of confirmed COVID-19 beginning ≥15 days after Dose 2, based on assessments of cases by an Adjudication Committee blinded to participant group assignment, and analysed in the combined LD/SD and SD/SD regimen population. Assessment in the subgroup that only received SD/SD was a pre-specified secondary analysis in the clinical trial. Symptomatic

COVID-19 was defined as having at least one of the following symptoms (objective fever ≥37.8 C, cough, shortness of breath, and anosmia or ageusia) AND a swab positive for SARS-CoV-2 by RT-PCR AND confirmed by an Adjudication Committee.

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

Symptomatic COVID-19 by interval
As of December 7, 2020, the majority of study participants in the COV002 (UK) and COV003 (Brazil) clinical trials received the two doses of the SD/SD regimen within a 4–8 week (UK: 45.6%, Brazil: 87.2%) or a 9–12-week interval (UK: 34.4%; Brazil: 10.5%). About 1 in 5 study participants in the UK clinical trial (18.9%) received the SD/SD regimen with a >12-week interval between vaccine doses, and in the Brazil trial it was less than 1 in 50 study participants (1.8%). A very small proportion of study participants received the SD/SD regimen with a <4-week interval between doses (UK: 1.0%, Brazil: 0.4%).

An exploratory analysis examined the potential effect of the interval between the administration of the first and second vaccine doses on vaccine efficacy in study participants receiving the SD/SD vaccine regimen. Table 10 summarizes the estimates of vaccine efficacy against confirmed COVID-19 cases occurring at ≥15 days after dose 2 by dosing interval. There is a suggestion of an increase in the point estimate of vaccine efficacy with increasing intervals between the first and second dose of vaccine. However, it is important to note that the confidence intervals around these point estimates overlap.

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

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

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

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

who received the SD/SD regimen (from COV002 and COV003), dichotomized into groups 18–64 years and ≥65 years of age.

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

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

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

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

Symptomatic COVID-19 by presence of co-morbidity
Efficacy was also assessed based on the presence of comorbidity, which was defined as the presence of one or more of the following mild to moderate and controlled medical conditions at baseline: cardiovascular disease, respiratory disease, diabetes, or obesity (BMI ≥30 kg/m^2) based on a data cut-off date of November 4, 2020. For this exploratory analysis, included study participants who were SARS-CoV-2 seronegative at baseline and received the SD/SD regimen. The estimated vaccine efficacy against confirmed COVID-19 cases occurring at ≥15 days after Dose 2 in study participants without comorbidities was 58.0% (95% CI: 25.8 to 76.2%), based on 17/2,825 (0.6%) cases identified in the vaccine group compared to 39/2,774 (1.4%) cases in the control group. The corresponding estimate of vaccine efficacy in study participants with comorbidities was 67.1% (95% CI: 33.2 to 83.8%), based on the identification of 10/1,611 (0.6%) cases in the vaccine group compared to 32/1,670 (1.9%) cases in the control group.

Symptomatic COVID-19 after one dose

Efficacy at various time points after one dose of AstraZeneca COVID-19 vaccine was assessed as a secondary/exploratory analysis based on data as of the interim analysis cut-off date of November 4, 2020 (Table 12). The analysis involved study participants who were SARS-CoV-2 seronegative at baseline and received SD vaccine as their initial vaccine dose. The median duration of follow-up after Dose 1 was 115 days (range: 41–149 days). Note that approximately 80% of study participants in the vaccine arm received the second dose of the vaccine; therefore, several estimates of vaccine efficacy are not solely due to the one dose of SD vaccine.

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

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

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

Severe outcomes due to COVID-19

Severe COVID-19 disease

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

Hospitalizations

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

The 2 hospitalizations in the vaccine group were 1 and 10 days post vaccination (median follow up: 115 days, range: 41–149).

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

Time period of interest	Event in vaccine group (AZD1222) n/N (%)	Events in control group (MenACWY) n/N (%)	Vaccine efficacy (95% CI)
≥22 days after Dose 1[b]	0/6,307 (0.0)	9/6,297 (0.1)	100% (95% CI: 49.6 to NE)
≥15 days after Dose 2[c]	0/6,085 (0.0)	7/6,073 (0.1)	N/A

[a] Participants without prior evidence of SARS-CoV-2 infection at baseline; all SD/SD vaccine recipients (or respective controls)
[b] Based on data as of November 4, 2020
[c] Based on data as of December 7, 2020

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

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

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

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

[a] Participants without prior evidence of SARS-CoV-2 infection at baseline; all SD/SD vaccine recipients (or respective controls)
[b] Based on data as of November 4, 2020
[c] Based on data as of December 7, 2020

An additional ad-hoc analysis combining study participants with SARS-CoV-2 asymptomatic infection or associated with unknown symptoms also failed to demonstrate the efficacy of the SD/SD regimen (3.9%, 95% CI: -72.1 to 46.4%), based on the identification of 22 cases in the vaccine group and 23 cases in the control group ≥15 days after Dose 2.

Immunogenicity

Approximately 15% of the overall safety analysis set was targeted for inclusion in the immunogenicity analysis set. These analyses combined evidence from SD/SD and LD/SD dosing regimens, and may not completely align with the data from individual studies.

Humoral immune responses
Antibody responses, both binding and neutralizing, differed for seronegative and seropositive vaccine recipients. Vaccine recipients who were seropositive at baseline demonstrated high antibody titres 28 days after Dose 1 compared to seronegative recipients. Seronegative recipients demonstrated an increase in their immune responses 28 days after Dose 2. By contrast, seropositive recipients had decreased immune responses after Dose 2 compared to responses after Dose 1. However, immune responses for seropositive recipients at all time points were higher than those for seronegative recipients. The mechanism behind these differences, and their potential impact on vaccine efficacy and effectiveness remains unclear. A recently published article contains additional evidence on humoral responses [135].

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

Vaccine Safety and Adverse Events Following Immunization

Safety evidence is based on interim analyses of 23,745 participants of which 12,021 received at least one dose of the AZ COVID-19 vaccine and 11,724 received a control. The safety analyses were conducted in different analysis sets. Solicited adverse events occurring within 7 days after any dose were assessed among 2648 vaccine recipients who received at least one

dose (SD) and 2497 control recipients. Approximately one third of study participants received their second vaccine dose within 6 weeks of receiving Dose 1. The majority (~90%) of study participants in the safety cohort were less than 65 years of age. The median duration of follow-up was 105 days post-Dose 1 and 62 days post-Dose 2.

Solicited Local Reactions

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

Solicited Systemic Reactions

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

Unsolicited Serious Adverse Events

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

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

Other serious adverse events

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

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

Vaccine-Induced Immune Thrombotic Thrombocytopenia
Rare cases of serious blood clots, including cerebral venous sinus thrombosis, associated with thrombocytopenia have been reported in Canada and globally following post-licensure use of AstraZeneca COVID-19 vaccine. Cases have usually occurred between 4 and 28 days after receipt of vaccine. This adverse event is being referred to as Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT). The mechanism of action is similar to heparin-induced thrombocytopenia (HIT). The exact mechanism by which the viral vector COVID-19 vaccines may trigger VITT is still under investigation. At this time, no other predisposing factors have consistently been identified in patients who develop VITT. The rate of this adverse event is still to be confirmed but had been most commonly estimated to be between 1 in 26,000 and 1 in 100,000 persons vaccinated with a first dose of AstraZeneca COVID-19 vaccine although this continues to evolve and may increase. Based on available evidence as of June 1st, 2021, PHAC has estimated the rate of VITT in Canada to be 1 in 73,000 doses administered. However, as investigations continue, this rate could be as high as 1 in 50,000 persons vaccinated with the COVISHIELD COVID-19 vaccine. The frequency of TTS following a second dose of AstraZeneca vaccine is currently reported as approximately 1 in 600,00 to 1 in 750,000 individuals vaccinated with a second dose, based on vaccine safety surveillance data from the United Kingdom but this continues to evolve [2]. Additional information is currently being gathered to characterize the rate of VITT more accurately. Based on available information, the case fatality of VITT typically ranges between 20 and 50%. Case fatality may vary with increased awareness of the adverse event and appropriate early treatment.

Effectiveness in individuals ≥65 years of age

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

All three observational studies assessed one dose of either the Pfizer-BioNTech or the AstraZeneca vaccines in the United Kingdom. The results below pertain only to the AstraZeneca portion of the studies. The studies were conducted during the period when the B.1.1.7 (Alpha) variant was rapidly becoming the dominant circulating strain in their respective geographic regions. Approximately 50% of laboratory samples were found to have a profile consistent with the B.1.1.7 (Alpha) variant in early December, 2020 in England, and 43% in

Scotland in early January, 2021. By mid to late February, the B.1.1.7 (Alpha) variant represented almost 100% of circulating strains in England, and was considered the dominant strain in Scotland.

Overall summary of evidence:

In adults 65 years of age and over, observational data available from pre-prints from the United Kingdom have shown a reduction in the risk of symptomatic disease and hospitalization starting from two weeks following one dose of AstraZeneca vaccine.

Detailed summary of each study:

1. Hyams et al., Assessing the Effectiveness of BNT162b2 and ChAdOx1nCoV-19 COVID-19 Vaccination in Prevention of Hospitalisations in Elderly and Frail Adults: A Single Centre Test Negative Case-Control Study. SSRN-Lancet **preprint.** March 3, 2021. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3796835

Description: Test-negative case control study of hospitalized people ≥80 years of age (many of whom were frail with comorbidities) in two hospitals in Bristol, United Kingdom. Vaccination was determined by record linkage and adjustment was conducted for a number of factors. Vaccine effectiveness against hospitalization was assessed in those who had been vaccinated ≥14 days before symptom onset.

Results: One-dose vaccine effectiveness of 80.4% (95% CI: 36.4 – 94.5%) against hospitalization occurring within 14 or more days (maximum 53 days) after one dose of AstraZeneca COVID-19 vaccine among patients ≥80 years of age.

Review:
- Vaccination was determined by record linkage and clinical information was obtained from records by individuals who are blinded to the participants SARS-CoV-2 results. These are methodological strengths of this study.
- The authors performed a sensitivity analysis of those with symptom onset < 14 days after vaccination and did not find an effect, which is expected as this is too early for the vaccine to work, and adds strength to differences they note 14 days or more after vaccination.
- Eligible cases and controls were selected from the medical admission list, and it is unclear how this was done.
- Separate analyses seemed to have been conducted for AstraZeneca and Pfizer-BioNTech but it is unclear how the study subjects for each analysis were assigned.

2. Lopez Bernal et al., Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England. medRxiv. **Preprint** March 2, 2021. https://www.medrxiv.org/content/10.1101/2021.03.01.21252652v1

Description: Test negative-case control study using linked surveillance data in the United Kingdom among patients ≥70 years of age. PCR tests were within 10 days of onset of symptoms. For those who were vaccinated, cases and controls were assessed by time since vaccination to onset of symptoms, controlling for a number of factors. The impact of vaccination on hospitalization in individuals ≥80 years of age was also assessed in those who tested positive.

Results: One-dose vaccine effectiveness against symptomatic PCR confirmed SARS-CoV-2 infection in the adjusted analysis was 22% (95% CI: 11 – 32) 14 to 20 days after vaccination and gradually rose up to 73% (95% CI: 27 – 90) 35 or more days (maximum 48 days) after vaccination. As well as the effect against symptomatic disease, in individuals who were ≥80 years of age there was an additional 37% protection against hospitalization within 14 days of a positive test in those 14 or more days from their first dose of vaccine compared to those who were unvaccinated.

Review:
- Record linkage using large data sets is a strength of this study.
- A relatively small number of subjects were included in the AstraZeneca COVID-19 vaccine analysis at later time periods, particularly in the time period of 35 or more days after vaccination when the vaccine effectiveness was the highest.
- The unadjusted and adjusted odds ratio are considerably different in the AstraZeneca COVID-19 analysis reflecting differences between study groups.
- Demographic and clinical information for cases and controls and vaccinated and unvaccinated individuals were not provided.

3. Vasileiou et al. Effectiveness of first dose COVID-19 vaccines against hospital admissions in Scotland effectiveness findings from Scotland: national prospective cohort study of 5.4 million people. SSRN-Lancet **preprint.** February 19, 2021. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3789264

Description: A prospective observational cohort study using record linkage between databases, including vaccination, hospitalization and laboratory records for the population in Scotland, with adjustment for a number of factors. Although the study included those ≥18 years of age, the AstraZeneca vaccine was mostly administered to participants aged 65 years and older. Age-specific vaccine effectiveness is provided but did not distinguish between the Pfizer-BioNTech and AstraZeneca vaccines, which were both studied, although those ≥80 years of age mainly received the AstraZeneca vaccine.

Results: The effectiveness of one dose of the AstraZeneca vaccine against hospitalization was 74% (95% CI: 66 – 81) 14 to 20 days after vaccination and rose up to 94% (95% CI: 73 – 99) 28 to 34 days after vaccination. In patients ≥80 years of age, the authors found a peak vaccine effectiveness (VE) of 81% (95% CI: 65 – 90) against hospitalization within 28 to 34 days after one dose of vaccine that was mainly the AstraZeneca vaccine.

Review:

Due to concerns with methodological weaknesses in this study, NACI did not use these results to inform its recommendations. Methodological weaknesses include:
- AstraZeneca COVID-19 vaccine effectiveness against hospitalization was high (70%) 7 to 13 days after vaccination, which is biologically implausible, as 7 to 13 days would be too early to expect protection from infection or hospitalization as a result of vaccination, suggesting methodological concerns and making the high vaccine effectiveness results at later time periods (94% at 28 to 34 days) challenging to interpret.
- The number of people vaccinated with the AstraZeneca COVID-19 vaccine is small in the period 28 days and more from vaccination.

- As vaccine roll out was initially tailored to priority groups at higher risk of severe disease or exposure, adjustments for potential confounding factors conducted during the statistical analyses might not have adequately controlled for all the differences between vaccinated and unvaccinated individuals. Demographic and risk factor comparisons between vaccinated and unvaccinated groups were not provided separately for each vaccine.
- Hospital admission was defined as: COVID-19 as the main cause of admission or hospitalization within 28 days of a positive PCR SARS-CoV-2 test. Hospital admission for COVID-19 is a less specific criteria for determining COVID-19 hospitalization and the proportion of cases defined using that criteria are not provided.
- Although product specific vaccine effectiveness and age specific vaccine effectiveness are both provided separately, product specific vaccine effectiveness by age was not provided.
- Record linkage using large data sets is a strength of this study.

APPENDIX D: CLINICAL TRIAL EVIDENCE SUMMARY FOR JANSSEN COVID-19 VACCINE

Data from Phase 1, 2, and 3 trials were available at the time of authorization for the Janssen vaccine. Evidence on efficacy, immunogenicity, and safety is available for adults ≥18 years of age. The Phase 3 trial involved 44,325 study participants randomized (1:1) to receive either the vaccine (1 dose of 5 x 10^{10} viral particles) or placebo. The data presented below was a median of two months after the completion of the series (one dose). Evidence from post-marketing surveillance and studies is found in the main body of this statement.

Efficacy

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

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

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

in the per-protocol set of study participants based on a January 22, 2021 data cut-off date.

Confirmed symptomatic moderate to severe/critical COVID-19 infection

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

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

Co-Primary outcomes	Vaccine group		Placebo group		Vaccine efficacy (95% CI)
	Cases (n/N)	Person years	Cases (n/N)	Person years	
≥14 days post-vaccination					
Moderate and severe/critical COVID-19 infection	116/19,514	3,116.6	348/19,544	3,096.1	66.9% (59.0 to 73.4)
≥28 days post-vaccination					
Moderate and severe/critical COVID-19 infection	66/19,306	3,102.0	193/19,178	3,070.7	66.1% (55.0 to 74.8)

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

Confirmed symptomatic severe/critical COVID-19 infection

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

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

Co-Primary outcomes	Vaccine group		Placebo group		Vaccine efficacy (95% CI)
	Cases (n/N)	Person years	Cases (n/N)	Person years	
≥14 days post-vaccination					
Severe/critical COVID-19 infection	14/19,514	3,125.1	60/19,544	3,122.0	76.7% (54.6 to 89.1)
≥28 days post-vaccination					
Severe/critical COVID-19 infection	5/19,306	3,106.2	34/19,178	3,082.6	85.4% (54.2 to 96.9)

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

Subgroup analyses

<u>By study country</u>

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

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

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

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

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

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

Country	Onset post-vaccination	COVID-19 severity	
		Moderate to severe/critical Efficacy (95% CI)	Severe/critical Efficacy (95% CI)
US	≥14 days	74.4% (65.0 to 81.6)	78.0% (33.1 to 94.6)
	≥28 days	72.0% (58.2 to 81.7)	85.9% (-9.4 to 99.7)
Brazil	≥14 days	66.2% (51.0 to 77.1)	81.9% (17.0 to 98.1)
	≥28 days	68.1% (48.8 to 80.7)	87.6% (7.8 to 99.7)
South Africa	≥14 days	52.0% (30.3 to 67.4)	73.1% (40.0 to 89.4)
	≥28 days	64.0% (41.2 to 78.7)	81.7% (46.2 to 95.4)

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

By age group

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

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

Age group (years)	Vaccine group		Placebo group		Vaccine efficacy (95% CI)
	Cases (n/N)	Person years	Cases (n/N)	Person years	
≥14 days post-vaccination					
18–39	47/4,356	775.3	122/4,330	762.1	62.1% (46.6 to 73.6)
40–59	48/8,394	1,331.5	138/8,452	1,332.9	65.2% (51.3 to 75.5)
60–69	19/4,800	722.9	65/4,907	732.2	70.4% (50.0 to 83.2)
70–79	2/1,768	259.5	23/1,650	239.2	92.0% (67.6 to 99.1)
≥80	0/196	27.42	0/205	29.8	N/A*
<60 (i.e., 18–59)	95/12,750	2,106.8	260/12,782	2,095.0	63.7% (53.9 to 71.6)
<65 (i.e., 18–64)	107/15,544	2,530.3	297/15,552	2,511.2	64.2% (55.3 to 71.6)
≥60	21/6,764	1,009.8	88/6,762	1,001.2	76.3% (61.6 to 86.0)
≥65	9/3,970	586.3	51/3,992	584.9	82.4% (63.9 to 92.4)
≥75	0/751	88.4	8/690	99.2	100.0% (45.9 to 100.0)
≥28 days post-vaccination					
18–39	29/4,316	772.4	84/4,254	756.6	66.2% (47.9 to 78.6)
40–59	23/8,301	1,325.2	68/8,273	1,320.4	66.3% (45.2 to 80.0)
60–69	12/4,749	719.3	32/4,833	727.1	62.1% (24.4 to 82.2)
70–79	2/1,746	257.8	9/1,620	237.2	79.6% (1.2 to 97.9)
≥80	0/194	27.3	0/198	29.3	N/A
<60 (i.e., 18–59)	52/12,617	2,097.6	152/12,527	2,077.0	66.1% (53.3 to 75.8)
<65 (i.e., 18–64)	60/15,378	2,518.7	170/15,253	2,490.1	65.1% (52.9 to 74.5)
≥60	14/6,689	1,004.4	41/6,651	993.6	66.2% (36.7 to 83.0)
≥65	6/3,928	583.3	23/3,925	580.5	74.0% (34.4 to 91.4)
≥75	0/740	106.4	3/673	98.1	N/A

*N/A = Not available; estimates of vaccine efficacy not calculated when there were fewer than 6 events identified.
Source: Janssen manufacturer submission to Health Canada, Module 2.5: Clinical overview, Figures 30 and 31

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

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

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

Age group (years)	Vaccine group		Placebo group		Vaccine efficacy (95% CI)
	Cases (n/N)	Person years	Cases (n/N)	Person years	
≥14 days post-vaccination					
18–59	8/12,750	2,114.3	41/12,782	2,115.1	80.5% (57.8 to 92.1)
18–64	11/15,544	2,538.5	50/15,552	2,533.8	78.0% (57.3 to 89.7)
≥60	6/6,764	1,010.7	19/6,762	1,006.9	68.5% (18.1 to 89.7)
≥65	3/3,970	586.6	10/3,992	588.3	69.9% (-16.8 to 94.7)
≥28 days post-vaccination					
18–59	2/12,617	2,101.0	24/12,527	2,086.7	91.7% (66.7 to 99.1)
18–64	2/15,378	2,522.8	28/15,253	2,500.9	92.9% (71.9 to 99.2)
≥60	3/6,689	1,005.1	10/6,651	995.9	70.3% (-15.5 to 94.7)
≥65	3/3,928	583.4	6/3,925	581.7	50.1% (-133.4 to 91.9)

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

By comorbidity

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

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

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

Presence of comorbidities (yes/no)	Vaccine group		Placebo group		Vaccine efficacy (95% CI)
	Cases (n/N)	Person years	Cases (n/N)	Person years	
(a) Moderate to severe/critical COVID-19 infection					
≥14 days post-vaccination					
Yes	47/7,777	1,140.0	126/7,798	1,133.7	62.9% (47.8 to 74.1)
No	69/11,737	1976.6	222/11,746	1,962.5	69.1% (59.4 to 76.8)
≥28 days post-vaccination					
Yes	27/7,684	1,133.6	52/7,626	1,121.7	48.6% (16.7 to 69.0)
No	39/11,622	1,968.4	141/11,552	1,949.0	72.6% (60.7 to 81.3)
(b) Severe/critical COVID-19 infection					
≥14 days post-vaccination					
Yes	8/7,777	1,142.9	29/7,798	1,141.7	72.4% (38.2 to 89.1)
No	6/11,737	1,982.1	31/11,746	1,980.3	80.7% (53.0 to 93.4)
≥28 days post-vaccination					
Yes	4/7,684	1,135.0	12/7,626	1,124.2	67.0% (-8.9 to 92.2)
No	1/11,622	1,971.1	22/11,552	1,958.3	95.5% (72.1 to 99.9)

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

By serostatus

This analysis was conducted using the expanded dataset of both centrally and locally confirmed COVID-19 cases and estimated vaccine efficacy against confirmed symptomatic moderate to severe/critical COVID-19 infection in study participants based on serostatus at baseline (Table 22).

Table 22. Efficacy against confirmed symptomatic moderate to severe/critical COVID-19 infection with onset ≥14 days and ≥28 days post-vaccination, including confirmed and non-centrally confirmed cases, by serostatus, per-protocol set

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

*N/A = Not available; estimates of vaccine efficacy not calculated when there were fewer than 6 events identified.
Source: Table 14, FDA Briefing document for Vaccines and Related Biological Products Advisory Committee meeting (February 26, 2021)

Hospitalizations

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

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

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

FAS-SN = Full analysis set, all randomized study participants with documented study vaccine administration, seronegative at baseline; PP = per-protocol set
Source: Janssen manufacturer submission to Health Canada, Module 2.5: Clinical overview, Table 10

Deaths

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

Asymptomatic or undetected SARS-CoV-2 infection

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

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

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

Outcomes	Vaccine group		Placebo group		Vaccine efficacy (95% CI)
	Cases (n/N)	Person years	Cases (n/N)	Person years	
Full analysis set, seronegative at baseline					
Asymptomatic or undetected SARS-CoV-2 infection	22/19,301	3,099.7	54/19,162	3,064.2	59.7% (32.8 to 76.6)
Asymptomatic or undetected SARS-CoV-2 infection *without previous symptoms*	10/19,301	3,098.0	38/19,162	3,061.5	74.0% (46.8 to 88.4)
Serology risk set*					
Seroconverted	18/1,346	312.2	50/1,304	298.2	65.5% (39.9 to 81.1)
Seroconverted *without previous symptoms*	10/1,346	310.9	37/1,304	296.6	74.2% (47.1 to 88.6)

*Serology risk set = study participants with a serology result available at Day 71 post-vaccination
Source: Janssen manufacturer submission to Health Canada, Module 2.5: Clinical overview, Table 12

Immunogenicity

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

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

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

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

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

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

Anti-vector immune responses
It is unclear to what extent pre-existing immunity to any adenovirus-based vaccine vector exists in the Canadian population and what impact that could have on adenovirus based vaccine safety and efficacy. It is also unclear as to what extent immunization with adenovirus-based vaccines elicits anti-vector immune responses and what impact that could have on homologous or heterologous booster doses with adenovirus-based vaccines. Evidence for a COVID-19 viral vector vaccine based on human adenovirus 5 (not authorized in Canada) indicated that vaccine recipients with high pre-existing immunity to the adenovirus vector had lower anti-SARS-CoV-2 immune responses [151]. The Janssen COVID-19 vaccine uses a modified Ad26. Janssen found no correlation between anti-Ad26 neutralizing antibody responses and anti-SARS-CoV-2 immune responses. However, neutralization is not the only anti-vector immune response that could impact vaccine-induced immunity. It remains unclear if immune responses to the Ad26 vector will impact the efficacy or effectiveness of this vaccine.

Vaccine safety and adverse events following immunization

Safety evidence is based on interim analyses of 21,895 participants (of whom 7,331 were ≥60 years of age) who received at least one dose of the vaccine. A safety subset included 3,356 participants in the vaccine group who were followed for solicited reactions within 7 days following vaccination and unsolicited reactions within 28 days following vaccination. Medically attended adverse events (MAAEs), SAEs and AEs leading to discontinuation from study participation were assessed in all participants. Overall, the median duration of follow-up was 58 days after vaccination.

Solicited local reactions
Solicited local injection site AEs were reported by 50.3% of evaluated participants within the first 7 days following any vaccine dose. Injection site pain was the most frequently reported local AE (48.7%) followed by warmth (7.3%) and swelling (5.3%). In the vaccine group, the frequency of solicited local AEs was lower in participants aged ≥60 years compared to participants aged ≥18 to <60 years. The frequency of solicited local AEs was also similar in participants who were seronegative for SARS-CoV-2 at baseline compared to participants who were seropositive for SARS-CoV-2 at baseline (50.1% and 54.5%, respectively). The majority of solicited local reactions among vaccine recipients were mild or moderate in severity, with any Grade 3 reactions being reported by ≤0.7% of participants. No Grade 4 solicited local AEs were reported.

Solicited systemic reactions
Solicited systemic AEs were reported by 55.2% of evaluated participants within the first 7 days following vaccine administration. The most common systemic solicited AEs were headache (39.0%) and fatigue (38.3%). Other frequently reported systemic solicited AEs were muscle pain (33.2%), nausea (14.2%) and fever ≥38.0°C (9.0%). While AEs were lower in participants aged ≥60 years compared to participants aged ≥18 to <60 years, there were no clinically relevant differences in the frequency of solicited systemic AEs. AEs were similarly observed in participants who were seronegative for SARS-CoV-2 at baseline (55.4%) compared to participants who were seropositive for SARS-CoV-2 at baseline (50.6%). Overall, the frequency of any Grade 3 reactions was <2%, and no Grade 4 solicited systemic AEs were reported. Antipyretics were recommended post-vaccination for symptom relief as needed. Analgesics or antipyretics were used by 26.4% of vaccinated 18 to 59 year olds and 9.8% of vaccinated individuals 60 years of age and older up to 7 days post vaccination in the full analysis. The majority of solicited systemic AEs were transient in nature and had a median duration of 1 to 2 days after vaccination.

Unsolicited serious adverse events
During the 28-day period post-vaccination, there were 19 (0.6%) participants with unsolicited AEs of at least Grade 3 in the vaccine group compared to 18 (0.6%) participants in the placebo group. Of these unsolicited AEs of at least Grade 3, 5 (0.1%) were considered to be related to the study vaccine. There were no clear imbalances by System Organ Class (SOC). No cases of anaphylaxis were identified in the clinical trials. However, the manufacturer announced receipt of preliminary reports of two cases of severe allergic reactions, including one case of anaphylaxis, in participants who had received the vaccine. Details on the reports have not been provided to date.
In total there were 7 (<0.1%) participants who reported SAEs that were considered to be related to the study vaccine by the investigator and lead to discontinuation from the study. These included:

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

Other serious adverse events

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

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

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

Vaccine-Induced Immune Thrombotic Thrombocytopenia
Rare cases of serious blood clots, including cerebral venous sinus thrombosis, associated with thrombocytopenia have been recently reported in the United States following post-licensure use

of Janssen COVID-19 vaccine. This adverse event is being referred to as Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) and has been associated with both the AstraZeneca and Janssen COVID-19 viral vector vaccines. The mechanism of action is similar to heparin-induced thrombocytopenia (HIT). The exact mechanism by which the viral vector COVID-19 vaccines may trigger VITT is still under investigation. As of May 24, 2021, 32 cases of TTS out of about 10.2 million doses of Janssen administered in the United States have been confirmed. Most of the cases to date have occurred in females between the ages of 18 and 49 years; however, investigations are ongoing and additional cases may be identified with increased awareness and current emphasis on the clinical recognition of this event. Reports indicated symptom onset between 6 and 15 days after vaccination. Investigations are ongoing.

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

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

Pregnancies
Eight pregnancies were reported through January 22, 2021 (4 vaccine, 4 placebo). Vaccination was within 30 days after last menstrual period in 7 participants (3 vaccine, 4 placebo) while in 1 vaccine recipient vaccination was prior to last menstrual period. Unsolicited AEs related to pregnancy included spontaneous abortion (1 vaccine, 0 placebo), incomplete abortion (0 vaccine, 1 placebo), elective abortion (0 vaccine, 2 placebo) and ectopic pregnancy (1 vaccine, 0 placebo). Two pregnancies are ongoing among participants in the vaccine group, with unknown outcomes at this time.

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

Table 25. Frequency of solicited local adverse events in authorized populations for mRNA COVID-19 vaccines[a]

AEFI	Pfizer-BioNTech COVID-19 Vaccine								Moderna COVID-19 Vaccine			
	Adults (≥16 years old)				Adolescents (12 -15 years old)							
	Vaccine		Placebo control		Vaccine		Placebo control		Vaccine		Placebo control	
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2
Pain at injection site	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common
Tenderness	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Redness/erythema	Common	Common	Common	Rare	Common	Common	Common	Uncommon	Common	Common	Uncommon	Uncommon
Swelling	Common	Common	Rare	Rare	Common	Common	Common	Uncommon	Common	Very Common	Uncommon	Uncommon
Lymphadenopathy[b]/ Axillary swelling and tenderness	NS	NS	NS	NS	NS	NS	NS	NS	Very Common	Very Common	Common	Common
Warmth	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Pruritis	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Induration	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

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

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

[b] Lymphadenopathy was not a solicited adverse event for the Pfizer BioNTech COVID-19 vaccine and was reported as an unsolicited adverse event. Please see Appendix A for more details.

Table 26. Frequency of solicited local adverse events in authorized populations for viral vector COVID-19 vaccines[a]

AEFI	AstraZeneca COVID-19 Vaccine				Janssen COVID-19 Vaccine[b]	
	Vaccine		MenACWY control		Vaccine	Placebo control
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 1
Pain at injection site	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common
Tenderness	Very Common	Very Common	Very Common	Very Common	NS	NS
Redness/erythema	Very Common	Common	Common	Uncommon	Common	Common
Swelling	Common	Common	Common	Common	Common	Common
Lymphadenopathy[c]/ Axillary swelling and tenderness	NS	NS	NS	NS	NS	NS
Warmth	Very Common	Common	Very Common	Common	NS	NS
Pruritis	Very Common	Common	Common	Common	NS	NS
Induration	Common	Common	Common	Common	NS	NS

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

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

[b] Single dose vaccine (dose 2 not applicable)

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

Table 27. Frequency of solicited systemic adverse events in authorized populations for mRNA COVID-19 vaccines[a]

AEFI	Pfizer-BioNTech COVID-19 Vaccine								Moderna COVID-19 Vaccine			
	Adults (≥16 years old)				Adolescents (12 -15 years old)							
	Vaccine		Placebo control		Vaccine		Placebo control		Vaccine		Placebo control	
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2
Fatigue	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common
Headache	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common
Muscle Pain	Very Common	Very Common	Common	Common	Very Common	Very Common	Very Common	Common	Very Common	Very Common	Very Common	Very Common
Chills	Very Common	Very Common	Common	Common	Very Common	Very Common	Common	Common	Common	Very Common	Common	Common
Joint Pain	Common	Very Common	Common	Common	Common	Very Common	Common	Common	Very Common	Very Common	Very Common	Very Common
Fever[b]	Common	Very Common	Uncommon	Uncommon	Very Common	Very Common	Common	Uncommon	Uncommon	Very Common	Uncommon	Uncommon
Feverishness[b]	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Diarrhea	Common	Common	Common	Common	Common	Common	Common	Common	NS	NS	NS	NS
Nausea and/or Vomiting[c]	Uncommon	Common	Uncommon	Uncommon	Common	Common	Uncommon	Common	Common	Very Common	Common	Common

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

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

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

[c] If two frequencies are reported the first reflects frequency of nausea and the second reflects the frequency of vomiting.

Table 28. Frequency of solicited systemic adverse events in authorized populations for viral vector COVID-19 vaccines[a]

AEFI	AstraZeneca COVID-19 Vaccine				Janssen COVID-19 Vaccine[b]	
	Vaccine		MenACWY control		Vaccine	Placebo control
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 1
Fatigue	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common
Headache	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common
Muscle Pain	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common
Chills	Very Common	Common	Common	Common	NS	NS
Joint Pain	Very Common	Very Common	Common	Common	NS	NS
Fever[c]	Common	Common	Uncommon	Uncommon	Common	Uncommon
Feverishness[c]	Very Common	Common	Common	Common	NS	NS
Diarrhea	NS	NS	NS	NS	NS	NS
Nausea and/or Vomiting[d]	Very Common/ Common	Common/ Uncommon	Very Common/ Uncommon	Common/ Uncommon	Very Common	Common

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

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

[b] Single dose vaccine (dose 2 not applicable)

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

[d] If two frequencies are reported the first reflects frequency of nausea and the second reflects the frequency of vomiting.

APPENDIX F: PREGNANCY, BREASTFEEDING AND COVID-19 VACCINE REGISTRIES

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

- Canadian COVID-19 Vaccine Registry for Pregnant and Lactating Individuals

Table 29: Pregnancy registry information by vaccine product

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