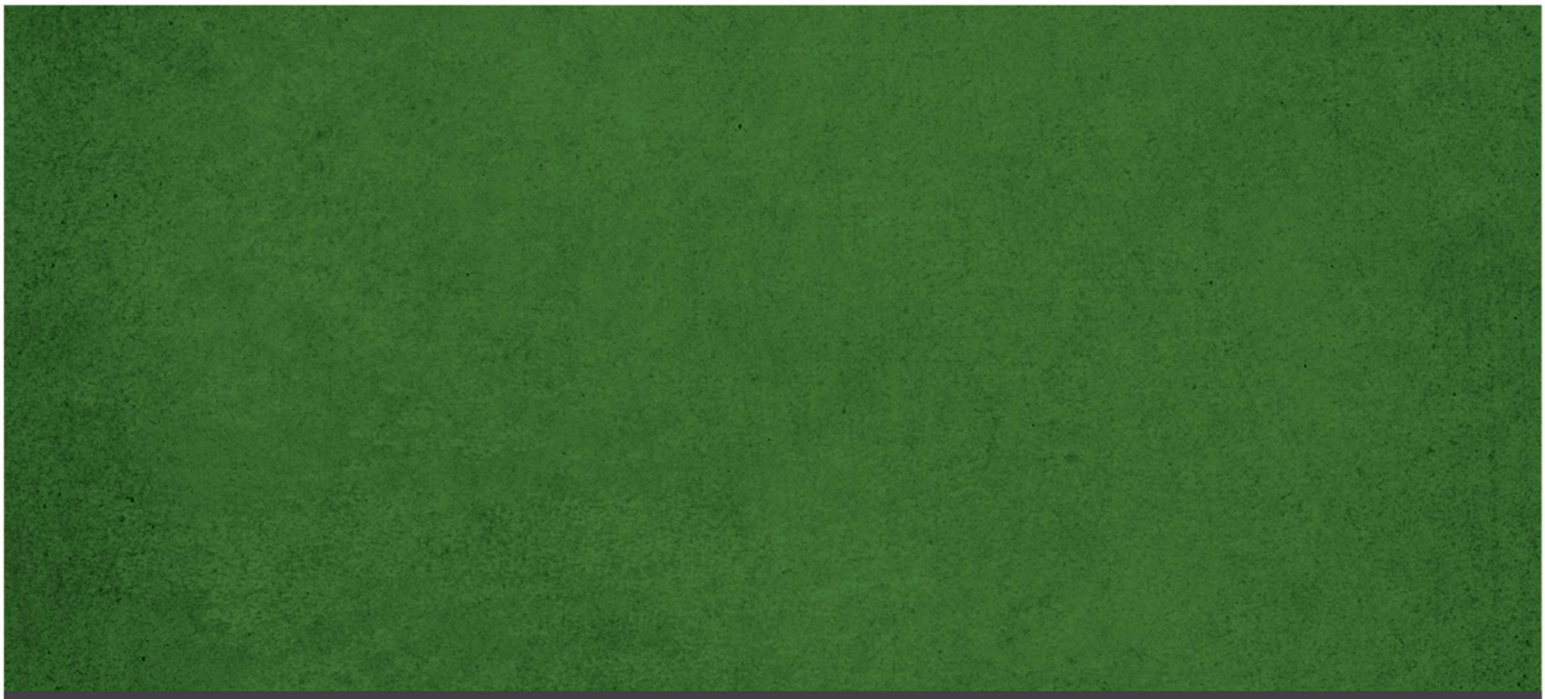
An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

Recommendations on the use of COVID-19 Vaccines



PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH

Public Health Agency of Canada
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Canada

PREAMBLE

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

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

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

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

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TABLE OF UPDATES

This evergreen document will be updated as COVID-19 vaccines are authorized for use in Canada, and as evidence on these vaccines and COVID-19 evolves. 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 January 12, 2020.

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	All sub-sections under Vaccines have been updated to include evidence or information from the product monograph related to the AstraZeneca COVID-19 vaccine. This includes: • Table 1. COVID-19 vaccines authorized for use in Canada • Dose, Route of administration, and Schedule • Efficacy and Immunogenicity • Storage requirements • Vaccine safety and adverse events following immunization	2021-03-01
Vaccines	Table 1. COVID-19 vaccines authorized for use in Canada has been updated to reflect the change in the Pfizer BioNTech COVID-19 product monograph stating one multi-dose vial contains 6 doses.	2021-03-01
Contraindications and Precautions	Tromethamine as an ingredient in the Moderna COVID-19 vaccine that has been associated with allergic reactions in other products has been added to Table 3. Clarification on the management of allergies and allergic reactions has been added, in consultation with NACI's Vaccine Safety Working Group.	2021-03-01
Contraindications and Precautions	Potential allergens for AstraZeneca COVID-19 vaccine have been added to Table 3.	2021-03-01
Drug Interactions	Guidance on the use of tuberculin skin tests and interferon gamma release assays before or after administration of COVID-19 vaccine has been added.	2021-03-01
Recommendations	Recommendations on COVID-19 vaccine now include use of the AstraZeneca COVID-19 vaccine, and the rationales have been updated	2021-03-01

Section	Update	Date
	with evidence from AstraZeneca COVID-19 vaccine clinical trials.	
Recommendations	A management options table for the use of different types of COVID-19 vaccines authorized for use in Canada has been added.	2021-03-01
Appendix C	Evidence on the efficacy, immunogenicity, and safety of the AstraZeneca COVID-19 vaccine has been added in a new appendix.	2021-03-01
Appendix D	Frequency of Solicited Adverse Events Following Immunization for COVID-19 vaccines has been updated to include information on the AstraZeneca COVID-19 vaccine.	2021-03-01

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, studies are ongoing. NACI will continue to monitor the data 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).
- Anyone can be infected with SARS-CoV-2. However, some populations are at increased risk of exposure to the virus (e.g., due to living or work settings), and some populations are at increased risk of severe disease and death due to biological (e.g., advanced age, pre-existing medical conditions) and social (e.g., low socioeconomic status, belonging to a racialized population) factors that may intersect. Risk factors for exposure and severe disease may overlap, further increasing risk. Any combination of these factors, as well as varying access to health care services, has the potential for disproportionate consequences for specific populations.

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

- mRNA vaccines are authorized for use in Canada for individuals 16 years of age and older (Pfizer-BioNTech COVID-19 vaccine) or 18 years of age and older (Moderna COVID-19 vaccine).
- A non-replicating viral vector vaccine is authorized for use in Canada for individuals 18 years of age and older (AstraZeneca COVID-19 vaccine). NACI does not recommend the use of this vaccine in individuals 65 years of age and older due to limited information on the efficacy of this vaccine in this age group at this time.
- In clinical trials, all COVID-19 vaccines are efficacious in the short-term against symptomatic, confirmed COVID-19 disease; trials are ongoing. mRNA COVID-19 vaccines have demonstrated high efficacy (approximately 94%). The AstraZeneca COVID-19 vaccine has demonstrated an average efficacy of approximately 62% in those 18-64 years of age.
- Protection offered by the first dose of mRNA vaccines is lower than the efficacy achieved after the second dose. The protection offered by the first dose of the viral vector vaccine is comparable to the efficacy observed after the second dose, with protection lasting until the second dose is administered (up to 12 weeks later).
- There is currently limited evidence on the duration of protection and on the efficacy of these vaccines in preventing death, hospitalization, asymptomatic infection and reducing transmission of SARS-CoV-2, although studies are ongoing.
- No serious safety concerns related to the vaccines have been identified to date in clinical trials; however, studies are ongoing. 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.
- There is currently minimal evidence to inform on differences in vaccine efficacy or safety between those with and those without prior evidence of SARS-CoV-2 infection at the time of vaccination.

Who

NACI makes the following recommendations:

A complete vaccine series with a currently authorized COVID-19 vaccine *should be* offered to:
- Individuals in the authorized age group without contraindications to the vaccine. In the context of limited vaccine supply, initial doses of mRNA COVID-19 vaccines should be prioritized for the key populations outlined in NACI's Guidance on the Prioritization of Initial Doses of COVID-19 Vaccine(s).
    - Due to suggested superior efficacy, mRNA COVID-19 vaccine is preferentially recommended for individuals in the authorized age group without contraindications, especially in those at highest risk of severe illness and death and highest risk of exposure to COVID-19 who are prioritized for early COVID-19 vaccination.
    - In the context of limited vaccine supply, AstraZeneca COVID-19 vaccine may be offered to individuals 18-64 years without contraindications if:
        i. The advantages of earlier vaccination outweigh the limitations of vaccinating with a less efficacious vaccine;
        ii. The ease of transport, storage and handling of this vaccine facilitates access to vaccination which may otherwise be challenging; and
        iii. Informed consent includes discussion about current vaccine options and the timing of future vaccine options.

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

For some specific populations who were either excluded from, or were represented by small numbers of participants in clinical trials, NACI recommends that a complete vaccine series with a currently authorized COVID-19 vaccine may be offered, if a risk assessment deems that the benefits of vaccination outweigh the potential risks for the individual (e.g., where the risk of severe outcomes of COVID-19 and/or risk of exposure to SARS-CoV-2 is high) or for the fetus/infant (in the case of pregnancy/breastfeeding) and if informed consent includes discussion about the insufficient evidence in these populations:
- Immunosuppressed due to disease or treatment
- Individuals with an autoimmune condition
- Pregnant or breastfeeding
- Adolescents 12 to 15 years of age (Only Pfizer-BioNTech COVID-19 vaccine may be offered)

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

NACI also recommends that:

- All individuals should continue to practice recommended public health measures for prevention and control of SARS-CoV-2 infection and transmission regardless of vaccination with COVID-19 vaccine, at this time, due to insufficient evidence on the duration of protection and effectiveness of COVID-19 vaccines in preventing asymptomatic infection and reducing transmission of SARS-CoV-2.

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

- Clinical trials assessing COVID-19 vaccines should continue to be encouraged to include individuals with potential vulnerabilities to disease related to biological (e.g., pre-existing medical conditions, frailty, pregnancy and breastfeeding, immunocompromised), and social (e.g., residence in long term care facilities or crowded/remote locations, belonging to a racialized population, occupation) factors to ensure that vaccine options are informed by robust safety, immunogenicity, and efficacy data as outlined in NACI's guidance on Research Priorities for COVID-19 Vaccines to Support Public Health Decisions Furthermore, NACI recommends the continuation of clinical trials and ongoing follow-up of participants for as long as it is ethically feasible to determine the level of immunity needed to prevent disease, duration of protection, efficacy in different sub-populations, and medium- and long-term safety.

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

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

- Efforts should be made to increase access to immunization services to reduce health inequities without further stigmatization or discrimination, and to engage 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 specifically once available, address misinformation, and communicate transparently about COVID-19 vaccine allocation decisions.

How

- Currently authorized COVID-19 vaccines are administered intramuscularly in a two-dose schedule.
- Attempts should be made to complete the vaccine series with the same vaccine product.
- Serologic testing is not needed before or after receipt of a COVID-19 vaccine to assess susceptibility to SARS-CoV-2 or immune response to the vaccine.
- COVID-19 vaccines should not be given simultaneously with other live or inactivated vaccines at this time, unless other vaccines are required for post-exposure prophylaxis.
- COVID-19 vaccines should not be given simultaneously with monoclonal antibodies or convalescent plasma.

Why

- The COVID-19 pandemic has caused significant morbidity and mortality, as well as social and economic disruption in Canada and worldwide.
- The authorized COVID-19 vaccines that are recommended for use by NACI in this Statement have been shown to be safe, as well as efficacious against symptomatic laboratory-confirmed COVID-19 disease.

I. INTRODUCTION

The 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. Safe and effective COVID-19 vaccines could help achieve this goal. Clinical trials of numerous candidate COVID-19 vaccines are currently underway.

This guidance document will provide recommendations on the use of authorized COVID-19 vaccines as they are approved for use in Canada, and as evidence on authorized vaccines evolves.

COVID-19 vaccines currently authorized for use in Canada:

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

The evidence on COVID-19 and COVID-19 vaccines has been rapidly evolving. To date, NACI has published the following evidence-informed guidance:

1. Research priorities for COVID-19 vaccines to support public health decisions to inform clinical trials of candidate COVID-19 vaccines to protect against infection, serious illness, and deaths caused by SARS-CoV-2.
2. Preliminary guidance on key populations for early COVID-19 immunization to plan for the efficient, effective, and equitable allocation of an eventual COVID-19 vaccine when limited initial vaccine supply will necessitate the immunization of some populations earlier than others.
3. Guidance on the prioritization of initial doses of COVID-19 vaccine(s) for the efficient and equitable prioritization of initial doses of COVID-19 vaccines to assist with the planning for allocation of the first COVID-19 immunization programs.
4. Guidance on the prioritization of key populations for COVID-19 immunization to provide guidance for the equitable, ethical, and efficient allocation of authorized COVID-19 vaccines in the context of staggered arrival of vaccine supply that will necessitate offering vaccines to some populations earlier than others.
5. Recommendations on the use of COVID-19 vaccine initially published on December 12, 2020 and updated iteratively as new evidence becomes available and with the authorization of additional COVID-19 vaccines.

Guidance Objective

The objective of this advisory committee statement is to provide guidance on the effective and equitable use of COVID-19 vaccines authorized for use in Canada in the context of staggered authorization of these vaccines. This evergreen document will be updated as COVID-19 vaccines are authorized for use in Canada, and as evidence on these vaccines evolves. In this guidance document, the evidence and rationale for recommendations as well as current knowledge gaps (e.g., due to the size and short-term follow up in ongoing clinical trials) will be summarized. Clinical trial details on vaccine characteristics for specific COVID-19 vaccines will be included in appendices.

II. METHODS

Details of NACI's recommendation development process can be found elsewhere [1, 2].

In brief, the broad stages in the preparation of this NACI advisory committee statement included:

1. Knowledge synthesis
2. Synthesis of the body of evidence of benefits and harms, considering the quality of the synthesized evidence and magnitude and certainty of effects observed across the studies
3. Translation of evidence into recommendations.

In order to develop comprehensive, appropriate immunization program recommendations, NACI considers a number of factors. In addition to critically appraising evidence on burden of disease and vaccine characteristics such as safety, efficacy, immunogenicity and effectiveness, NACI uses a published, peer-reviewed framework and evidence-informed tools to ensure that issues related to ethics, equity, feasibility, and acceptability (EEFA) are systematically assessed and integrated into its guidance [2]. The NACI Secretariat applied this framework with accompanying evidence-informed tools (Ethics Integrated Filters, Equity Matrix, Feasibility Matrix, Acceptability Matrix) to systematically consider these programmatic factors for the development of clear, comprehensive, appropriate recommendations for timely, transparent decision-making. For details on the development and application of NACI's EEFA Framework and evidence-informed tools (including the Ethics Integrated Filters, Equity Matrix, Feasibility Matrix, and Acceptability Matrix), please see https://doi.org/10.1016/j.vaccine.2020.05.051.

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. 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 and January 26, 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.

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 COVID-19 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 COVID-19 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

Risk factors

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

Please see NACI's Advisory Committee Statement on Key Populations for Early COVID-19 Immunization and the Equity Matrix [3] for a summary of inequities associated with COVID-19, potential reasons for and intersections between these inequities, and suggested interventions to reduce inequities and improve access to vaccines.

More information on the risk factors associated with COVID-19 can be found on PHAC webpages for People who are at high risk for severe illness from COVID-19 and Vulnerable populations and COVID-19.

Spectrum of clinical illness

The median incubation period for COVID-19 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.

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.

Non-replicating viral vector vaccines

COVID-19 vaccines based on viral vector platforms use a modified virus to carry genes that encode SARS-CoV-2 spike proteins into the host cells. The vector virus is a type of adenovirus that has been modified to carry COVID-19 genes and to prevent replication. These modifications are intended to prevent the viral vector from causing disease. (i.e., they are non-replicating). Once inside the cell, the SARS-CoV-2 spike protein genes are transcribed into mRNA in the nucleus and translated into proteins in the cytosol of the cell. The AstraZeneca vaccine uses a modified chimpanzee adenovirus vector (ChAd).

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

Table 1. COVID-19 vaccines authorized for use in Canada

Product Brand Name	Pfizer-BioNTech COVID-19 Vaccine	Moderna COVID-19 Vaccine	AstraZeneca COVID-19 Vaccine
Type of vaccine	mRNA	mRNA	Non-replicating viral vector (ChAd)
Date of authorization in Canada	December 9, 2020	December 23, 2020	February 26, 2021
Authorized ages for use	16 years of age and older	18 years of age and older	18 years of age and older
Dose	0.3 mL (30 mcg of mRNA)[a]	0.5 mL (100 mcg of mRNA)	0.5 mL (5×10^{10} viral particles)
Schedule[b]	2 Doses, 3 weeks apart	2 Doses, 4 weeks apart	2 Doses, 4 to 12 weeks apart
Route of administration	IM	IM	IM
Nature of the antigen	Transmembrane prefusion spike protein	Transmembrane prefusion spike protein	Transmembrane spike protein
Adjuvant (if present)	None	None	None
Primary storage requirements pre-puncture	-80°C to -60°C[c]	-25°C to -15°C[c, d]	+2ºC to +8ºC
Storage requirements pre-puncture[c]	120 hours (5 days) at +2°C to +8°C AND/OR 2 hours up to +25°C	30 days at +2°C to +8°C AND/OR 12 hours at +8°C to +25°C	+2ºC to +8ºC
Diluent	Yes	No	No
Usage limit post-puncture	6 hours at +2°C to +25°C[e]	6 hours at +2°C to +25°C	6 hours at room temperature (up to +30ºC)

Product Brand Name	Pfizer-BioNTech COVID-19 Vaccine	Moderna COVID-19 Vaccine	AstraZeneca COVID-19 Vaccine
			or 48 hours at +2ºC to +8ºC.
Formats available	Multi-dose vial (6 doses)[a], preservative-free	Multi-dose vial (10 doses), preservative-free	Multi-dose vial (8-and 10-dose presentations), preservative-free

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

[a] After dilution, one vial contains 6 doses of 0.3 mL each. However, vial labels and cartons may state that after dilution, a vial contains 5 doses of 0.3 mL. Information in the product monograph supersedes the number of doses stated on vial labels and cartons. Low dead-volume syringes and/or needles can be used to extract 6 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract a 6th dose from a single vial.Refer to the product monograph available through Health Canada's Drug Product Database for choice of diluent, dilution instructions and type of syringes which can be used to extract 6 doses from a single vial.

[b] Authorized schedule. For NACI recommendations on intervals between doses refer to Table 2 for details

[c] Protected from light during storage

[d] Do not store on dry ice or below -40ºC

[e] After dilution, vaccine must be used within 6 hours

IV.2 Efficacy

Due to the availability of only short-term clinical trial data, the duration of COVID-19 vaccine efficacy and vaccine effectiveness are currently unknown. However, studies are ongoing.

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

Efficacy against symptomatic COVID-19 disease

The currently authorized mRNA COVID-19 vaccines have been shown to be highly efficacious in the short term against confirmed symptomatic COVID-19 disease (presence of one or more symptoms plus laboratory confirmation of SARS-CoV-2 infection) from one to two weeks after receiving the full two-dose series. The authorized mRNA vaccines are similarly efficacious in adults with one or more comorbidities**,** as well as in younger adults and older adults. However, evidence in adults of a much more advanced age (e.g., 85 years and older) and in long-term care facilities is limited. In clinical trials, the currently authorized 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. At present, there are insufficient data in adults ≥65 years of age to conclude the vaccine is efficacious 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).

The clinical trial data demonstrates that the authorized mRNA COVID-19 vaccines are efficacious over the short-term in individuals with or without evidence of prior SARS-CoV-2 infection.

However, participants with laboratory-confirmed SARS-CoV-2 infection prior to enrollment were excluded from the trials and the number of trial participants with evidence of previous infection (as defined by trial protocol) who had confirmed symptomatic COVID-19 disease during the trials were small; therefore, the efficacy in this population and how it compares to those without evidence of previous infection is unknown at this time.

The first dose of the authorized COVID-19 vaccines has been shown to offer at least short-term protection against confirmed COVID-19 disease. 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 against severe disease
There are limited data to be able to assess the efficacy of the authorized COVID-19 vaccines against hospitalizations or deaths specifically, but studies are ongoing and further evidence is expected.

The authorized COVID-19 vaccines appear to be efficacious 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). However, the follow-up time for this outcome was short in trials of both mRNA vaccines and the number of severe cases that have been observed to date in one of the vaccine trials (Pfizer-BioNTech COVID-19 vaccine) is small. At the present time, there are insufficient data to estimate the efficacy of the viral vector vaccine against severe COVID-19 disease.

Efficacy 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 (before Dose 2), and therefore viral shedding, in the group that received the vaccine compared to the placebo group. However, the current data is insufficient to draw conclusions. Exploratory analyses for the viral vector vaccine have not demonstrated efficacy against confirmed SARS-CoV-2 asymptomatic infection, however the number of asymptomatic infections was small. Studies are ongoing for these vaccines.

Efficacy against variants of concern
Data about the efficacy of authorized mRNA COVID-19 vaccines (Pfizer-BioNTech COVID-19 vaccine, Moderna COVID-19 vaccine) and viral vector-based COVID-19 vaccine (AstraZeneca COVID-19 vaccine) against VOC is evolving. 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 efficacy.

There are several key knowledge gaps that affect the understanding of immune responses to COVID-19 vaccine:

- Which type of immune responses are important for protection from infection, severe disease, or transmission
- The durability of immune responses and how they may change over time
- How immune responses to natural infection compare to responses elicited from a vaccine
- How immune responses differ across populations (e.g., in immunocompromised, children) or by SARS-CoV-2 serostatus (i.e., past COVID-19 infection)
- How immune responses differ based on previous infection with non-SARS-CoV-2 coronaviruses

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

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

Humoral immune responses
All authorized COVID-19 vaccines induce humoral immune responses, including binding and neutralizing antibody responses. Humoral responses peaked after the second dose of mRNA vaccine, and after the second dose of AstraZeneca COVID-19 vaccine in participants who were not previously infected. Some vaccines induce higher immune responses in younger populations, see Appendix A, Appendix B, and Appendix C for details.

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 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. Refer to Appendix A, Appendix B, and Appendix C for details.

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.

Route of administration

COVID-19 vaccines are given as an intramuscular (IM) injection into the deltoid muscle.

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

Schedule

Refer to Table 2 for a summary of immunization schedules for authorized COVID-19 vaccines.

Table 2. Recommended immunization schedule, by COVID-19 vaccine

Vaccine product (manufacturer)	**Immunization schedule**	**Minimum interval**	**Authorized interval**	**Alternate interval**
Pfizer-BioNTech COVID-19 (Pfizer-BioNTech)	2-dose schedule	19 days	21 days	>3 to 6 weeks[a]
Moderna COVID-19 (Moderna)	2-dose schedule	21 days	28 days	>4 to 6 weeks[a]
AstraZeneca COVID-19 (AstraZeneca)	2-dose schedule	28 days	4 to 12 weeks	12 weeks[b]

[a] While efforts should be made to vaccinate according to the recommended schedules, some jurisdictions considering vaccine delivery logistics, current epidemiological status and projections, and healthcare system capacity may

maximize the number of individuals benefiting from a first dose of mRNA vaccine by delaying the second dose, until further supplies of the vaccine become available, preferably within 6 weeks of receipt of the first dose
[b] A 12-week interval is preferred for the AstraZeneca COVID-19 vaccine based on vaccine principles, feasibility considerations for pandemic supply management, and available *ad hoc* analyses of clinical trial interval data from the manufacturer,

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

The authorized COVID-19 vaccines are efficacious against symptomatic laboratory-confirmed COVID-19 disease when provided as a two-dose schedule.

The majority of participants in the Pfizer-BioNTech COVID-19 vaccine clinical trial received the second dose 21 to 27 days apart. The per-protocol design was 19-23 days. An alternate interval of 28 days may be more feasible to implement. This interval is consistent with the minimum interval required for many other routine immunizations and the authorized interval for the Moderna COVID-19 vaccine. 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. A harmonized approach to the scheduling of COVID-19 vaccine doses 28 days apart could prevent erroneous administration of other vaccines at less than the recommended minimal interval.

For AstraZeneca COVID-19 vaccine, a secondary analysis of vaccine efficacy by interval between doses demonstrated a potential for higher efficacy with increasing duration between doses. Given the potential for higher efficacy, the longer interval within the range AstraZeneca COVID-19 vaccine is authorized for (i.e., 12 weeks) is preferred. Refer to Appendix C for details on these analyses.

Delay in receipt of dose 2 in a mRNA COVID-19 vaccine series
Currently, no data on a maximum interval between doses or on medium- or long-term efficacy of COVID-19 vaccines are available and peak humoral response occurs after a second dose. 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 vaccines represent a new vaccine technology. If administration of the second dose of a COVID-19 vaccine is delayed, the second dose should be provided as soon as possible.

Although not specified in the Phase 3 study protocol, a post-hoc analysis of the Pfizer-BioNTech clinical trial data suggests a vaccine efficacy of 52% (95% confidence interval [CI], 29.5 to 68.4%) between the first and second dose. This estimate of vaccine efficacy is likely an underestimate of the short-term efficacy as cases occurring immediately after dose 1 were included. It is presumed that there would be minimal efficacy in the first 14 days following dose 1, because the immune response usually requires 7 to 14 days to develop and because recipients who are already infected and incubating the virus upon vaccination are unlikely to be protected. A further post-hoc estimate of vaccine efficacy calculated from 14 days after dose 1 until dose 2 (a period of one week for the majority of study participants) was 92.3% (95% CI: 69 to 98%) [4, 5]. However, these estimates of vaccine efficacy are based on short periods of follow-up and therefore cannot predict the duration of protection offered by one dose of the vaccine.

An exploratory analysis of data from the Phase 3 Moderna clinical trial also suggests there may be protection against symptomatic COVID-19 disease starting as soon as 12 or 14 days after the first dose. An interim analysis in a small, non-random subgroup of study participants who had only received one dose of vaccine at the time of analysis (n=996 in the vaccine arm and n=1,079 in the placebo arm) was used to calculate an estimated vaccine efficacy of 80.2% (95% CI 55.2 to 92.5%) between the first and second dose. This estimate of vaccine efficacy is likely an underestimate as cases occurring immediately after dose one were included. Vaccine efficacy calculated in the same small subgroup of study participants from 14 days after dose 1 was 92.1% (95% CI, 68.8 to 99.1%) [6]. These estimates of vaccine efficacy after one dose should be interpreted with caution, given the short period of follow-up (median 28 days). In addition, the calculations after dose 1 are based on a small subset of the larger randomized cohort of study participants resulting in efficacy estimates with reduced precision, as indicated by the relatively wide confidence intervals.

Humoral responses for both mRNA COVID-19 vaccines peak one to two weeks after a second dose, and then decline but remain detectable over the period of assessment in the clinical trials (either 4 weeks in the Pfizer-BioNTech trial or 3 months in the Moderna trial). However, as a correlate of protection is not known, these humoral responses cannot be interpreted as corresponding with vaccine efficacy or effectiveness.

Efforts should be made to vaccinate with the second dose of COVID-19 vaccine following the schedules outlined in Table 2. If, due to logistical or epidemiological considerations, jurisdictions do not complete the two-dose COVID-19 vaccine series within these recommended schedules, they may refer to Section V.II of this statement for a summary of evidence and decision points for COVID-19 immunization program roll-out in the context of limited vaccine supply, as well as Appendix E for an ethics analysis using NACI's Core Ethical Dimensions Filter of the EEFA Framework [2].

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 variants of concern against which vaccine effectiveness may be decreased, additional vaccine doses may be necessary. NACI will continue to monitor the evidence and update recommendations as needed.

IV.4.3 Interchangeability

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

Currently, no data exist on the interchangeability of COVID-19 vaccines. However, the spike proteins encoded by either of the authorized mRNA vaccines have the same sequence and are

stabilized in the same manner to remain in the pre-fusion conformation, though other vaccine components like the lipid nanoparticle and the mRNA sequence may be different. The spike protein encoded by the authorized viral vector vaccine is not stabilized in any specific conformation. Vaccines of different types (e.g., mRNA, viral vector) should be considered different vaccines and should not be used in the same series.

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

At this time, it is not recommended that vaccines of different types (e.g., mRNA vaccine and viral vector vaccine) be used in the same series. Active surveillance of effectiveness and safety of a mixed schedule will be important and these recommendations may change as further evidence becomes available. Accurate recording of vaccines received will be critical. NACI will continue to monitor the evidence and update recommendations as needed.

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

IV.4.4 Post-vaccination counseling

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

Analgesics and antipyretics were used in clinical trials of COVID-19 vaccine for the management of pain and/or fever after vaccination. There is currently no evidence on the benefit from administration of oral analgesics for the prevention of immunization injection pain or systemic reactions.

All vaccine recipients should be instructed to seek medical care if they develop signs or symptoms of an allergic reaction after their observation period ends and they have left the immunization clinic/venue.

All vaccine recipients who develop symptoms compatible with COVID-19 should be tested for SARS-CoV-2 to document breakthrough illness, particularly in the context of the emergence of variants of concern.

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.

Thawed, unpunctured vials (prior to dilution)
The Pfizer-BioNTech COVID-19 vaccine may be thawed and stored at +2°C to +8°C for up to 120 hours (5 days) or at room temperature (up to +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 12 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 6 hours from the time of first puncture.

AstraZeneca COVID-19 vaccine

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

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

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

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

IV.7 Simultaneous administration with other vaccines

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

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

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

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

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

Due to limitations in the number of participants and duration of follow-up from COVID-19 clinical trials, medium- and long-term evidence on vaccine safety is limited. 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 for use in Canada, refer to the evidence summaries in Appendix A (for the Pfizer-BioNTech COVID-19 vaccine), Appendix B (for the Moderna COVID-

19 vaccine), and Appendix C (for the AstraZeneca COVID-19 vaccine). Refer to Appendix D for a summary of the frequency of AEFI for the different COVID-19 vaccine products.

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

IV.8.1 Very common and common adverse events

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

Local

Pain at the injection site is very common after administration of the currently authorized COVID-19 vaccines. More than 50% of recipients experienced injection site pain. Redness and swelling are common or very common after administration. Localized axillary swelling and tenderness was a solicited adverse event in the Moderna COVID-19 clinical trial and was very common after administration with that vaccine. Local adverse events are usually mild or moderate and resolve within a few days of vaccination. For the authorized mRNA COVID-19 vaccines, pain at the injection site was slightly more frequent in younger adults compared to older adults. For AstraZeneca COVID-19 vaccine, local reactions were milder and reported less frequently after the second vaccine dose in all age groups.

Systemic

Fatigue, headache, muscle pain, chills, and joint pain are all either common or very common after the administration of the currently authorized COVID-19 vaccines. Fever was very common after administration of the second dose of the mRNA COVID-19 vaccines and common after any dose of AstraZeneca COVID-19 vaccine. More than a quarter of vaccine recipients experienced headache and/or fatigue after any dose. Systemic adverse events are usually mild or moderate intensity and resolve within a few days of vaccination. For the mRNA COVID-19 vaccines, systemic reactions are more frequent after the second vaccine dose and in younger adults. For AstraZeneca COVID-19 vaccine, systemic reactions are milder and reported less frequently after the second vaccine dose in all age groups.

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

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

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

Lymphadenopathy was not a solicited adverse event (unless indicated, see Appendix D) but was uncommonly reported after administration of the Pfizer-BioNTech and AstraZeneca COVID-19 vaccines.

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

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

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

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

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

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

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

IV.9 Contraindications and Precautions

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

Table 3 lists potential non-medicinal ingredients in authorized COVID-19 vaccines that have been associated with allergic reactions in other products. These reactions have occurred rarely, and ranged from mild cutaneous reactions to anaphylaxis. Anaphylaxis is typically a rare, severe, life-threatening allergic reaction typically with a rapid onset that involves multiple organ systems and can progress rapidly. Symptoms and signs of anaphylaxis may include, but are not limited to generalized urticaria; wheezing; swelling of the mouth, tongue, and throat; difficulty breathing; vomiting; diarrhea; hypotension; decreased level of consciousness; and shock. It is important to note that other, less serious reactions may mimic allergic reactions (e.g., vasovagal syncope) and vaccination is not contraindicated in these cases.

Refer to Anaphylaxis and other Acute Reactions Following Vaccination in the CIG, Part 2 – Vaccine Safety for information on the management of anaphylaxis post-vaccination.

Table 3. Ingredients of authorized COVID-19 vaccines that have been associated with allergic reactions in other products

Vaccine product (manufacturer)	**Potential allergen included in the vaccine or its container**	**Other products where the potential allergen may be found***
Pfizer-BioNTech COVID-19 (Pfizer-BioNTech)	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 (Moderna)	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 (AstraZeneca)	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).

Contraindications

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

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.

Precautions

If a risk assessment deems that the benefits outweigh the potential risks for the individual; and if informed consent is provided; vaccination may be considered in individuals with mild to moderate immediate allergic reactions (defined as limited in the scope of symptoms and involvement of organ systems or even localized to the site of administration) after a previous dose of authorized COVID-19 vaccines or any of its components. Assessment by a physician or nurse with expertise in immunization may be warranted prior to re-immunization. Most instances of anaphylaxis to a vaccine begin within 30 minutes after administration of the vaccine. Therefore, if vaccination is chosen, an extended period of observation post-vaccination of at least 30 minutes should be provided for the aforementioned individuals.

Individuals with proven severe allergic reaction (e.g., anaphylaxis) to injectable therapy not related to a component of authorized COVID-19 vaccines (e.g., intramuscular, intravenous, or subcutaneous vaccines or therapies) may be routinely vaccinated and do not need to be assessed. Most instances of anaphylaxis to a vaccine begin within 30 minutes after administration of the vaccine. Therefore, an extended period of observation post-vaccination of 30 minutes should be provided for the aforementioned individuals.

Individuals with a history of allergy not related to a component of authorized COVID-19 vaccines or other injectable therapy (e.g., foods, oral drugs, insect venom or environmental allergens) can receive COVID-19 vaccines without any special precautions. Individuals should be observed for a minimum of 15 minutes following vaccination.

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

Vaccination of individuals who may be currently infected with SARS-CoV-2 is not known to have a detrimental effect on the illness. However, vaccination should be deferred in symptomatic individuals with confirmed or suspected SARS-CoV-2 infection, or those with respiratory symptoms, in order to avoid attributing any complications resulting from SARS-CoV-2 infection to

vaccine-related AEFI and to minimize the risk of COVID-19 transmission at an immunization clinic/venue. If any persons are identified with symptoms on arrival at the venue, they should be instructed to follow current local public health measures.

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

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

IV.10 Drug Interactions

There have been no drug interactions studies performed to date.

For more information about potential interactions with products containing anti-SARS-CoV-2 antibodies, refer to section IV.11 Blood products, human immunoglobulin and timing of immunization, in this Statement.

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

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

IV.11 Blood Products, Human Immunoglobulin and Timing of Immunization

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

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

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

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

V. RECOMMENDATIONS

Following the thorough review of available evidence summarized above, as well as the systematic assessment of ethics, equity, feasibility and acceptability considerations with the EEFA Framework [2] as summarized in NACI's Guidance on Key Populations for Early COVID-19 Immunization, NACI makes the following recommendations for public health program level decision-making for the effective and equitable use of COVID-19 vaccines authorized for use in Canada.

NACI will continue to carefully monitor the scientific developments related to COVID-19 and COVID-19 vaccines, as well as ongoing vaccine pharmacovigilance, and will update recommendations as evidence evolves.

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 7 for a more detailed explanation of the strength of NACI recommendations.

RECOMMENDATIONS ON AUTHORIZED COVID-19 VACCINES FOR PUBLIC HEALTH PROGRAM LEVEL DECISION-MAKING
(i.e., Provinces/Territories making decisions for publicly funded immunization programs)

These recommendations apply only to COVID-19 vaccines currently authorized in Canada (Pfizer-BioNTech COVID-19 vaccine; Moderna COVID-19 vaccine; AstraZeneca COVID-19 vaccine). In considering these recommendations and for the purposes of publicly funded program implementation, provinces and territories may consider local programmatic factors (e.g., logistical and operational contexts, resources).

1. **NACI recommends that a complete COVID-19 vaccine series should be offered to individuals in the authorized age group without contraindications to the vaccine. In the context of limited vaccine supply, initial doses of mRNA COVID-19 vaccine should be prioritized for the key populations outlined in NACI's Guidance on the Prioritization of Key Populations for Early COVID-19 Immunization. (*Strong NACI Recommendation*)**
    a. **Due to suggested superior efficacy, mRNA COVID-19 vaccine is preferentially recommended for individuals in the authorized age group without**

contraindications, especially in those at highest risk of severe illness and death and highest risk of exposure to COVID-19 who are prioritized for early COVID-19 immunization.

b. In the context of limited vaccine supply, AstraZeneca COVID-19 vaccine may be offered to individuals 18 to 64 years without contraindications if:

i. the advantages of earlier vaccination outweigh the limitations of vaccinating with a less efficacious vaccine;

ii. the ease of transport, storage and handling of this vaccine facilitates access to vaccination which may otherwise be challenging; and

iii. informed consent includes discussion about current vaccine options and the timing of future vaccine options

(Discretionary NACI Recommendation)

When considering which groups to offer the AstraZeneca COVID-19 vaccine to when an authorized mRNA COVID-19 vaccine is unavailable or inaccessible, the advantages of earlier immunization should outweigh the limitations of immunizing with a less efficacious vaccine. This assessment may vary between jurisdictions and groups and will depend on:

- **Local COVID-19 epidemic conditions** (e.g., consider offering available AstraZeneca COVID-19 vaccine in regions of high epidemic transmission where immediate protection is needed to prevent symptomatic disease and preserve health system capacity; carefully considering the local transmission potential for viral variants of concern and anticipated effectiveness against them)
- **Local vaccine supply** (e.g., consider how long a group will need to wait to be offered an mRNA vaccine, based on available and expected vaccine supply)
- **Risk of severe illness and death** (e.g., consider offering available AstraZeneca COVID-19 vaccine to groups at lower risk of severe illness and death who will need to wait to receive mRNA vaccine while those at highest risk are offered a more efficacious vaccine)
- **Risk of exposure** (e.g., consider offering the available AstraZeneca COVID-19 vaccine to groups at lower risk of exposure who will need to wait to receive mRNA vaccine while those at highest risk of exposure with minimal ability to physically distance are offered a more efficacious vaccine)
- **Logistical considerations** (e.g., consider offering available AstraZeneca COVID-19 vaccine to those at lower risk of exposure or severe illness and death who would not otherwise get vaccinated due to personal barriers accessing mRNA vaccination sites despite jurisdictional efforts to increase access. Due to ease of transport, storage and handling of the AstraZeneca vaccine, a variety of alternate vaccination sites could increase convenience of vaccination and reduce vaccine hesitancy)

Refer to the Management Options Table for COVID-19 vaccines authorized for use in Canada (Section V.I) for a summary of evidence and factors for jurisdictions to consider when implementing COVID-19 immunization programs.

Summary of evidence and rationale:

- The COVID-19 pandemic has caused significant morbidity and mortality, as well as social and economic disruption. The COVID-19 immunization program should be rolled out as efficiently, effectively and equitably as possible.

- mRNA COVID-19 vaccines are authorized in individuals 16 years of age and older (Pfizer-BioNTech COVID-19 vaccine) and in individuals 18 years of age and older (Moderna COVID-19 vaccine). A non-replicating viral vector vaccine is authorized for use in Canada for individuals 18 years of age and older (AstraZeneca COVID-19 vaccine). NACI does not recommend the use of the AstraZeneca COVID-19 vaccine in individuals 65 years of age and older due to the insufficiency of evidence of efficacy in this age group at this time.
- A complete series for all currently authorized COVID-19 vaccines is two doses.
- Clinical trial data available to date has shown that the currently authorized mRNA COVID-19 vaccines are highly efficacious in preventing confirmed symptomatic COVID-19 disease in the short term from 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.
  - 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/m^2, chronic pulmonary disease, diabetes mellitus, cardiac disease).
- Clinical trial data available to date has shown that the currently authorized viral vector COVID-19 vaccine is efficacious in adults 18 to 64 years of age for preventing confirmed symptomatic COVID-19 disease after receiving the full two-dose series.
  - There is insufficient evidence of efficacy in adults 65 years of age and older at this time. In addition, there was a relatively small proportion of participants between 55 and 64 years of age included in the trial.
  - The highest efficacy with the authorized regimen was seen in clinical trial groups that had a longer interval between doses (e.g., 9 to 12 weeks). Only a small proportion of older adults received their second dose 9 to 12 weeks after the first.
  - The majority of local and systemic adverse events were mild and transient and did not differ by dose administered or age.
  - AstraZeneca COVID-19 vaccine is similarly safe and efficacious in those with one or more mild to moderate and controlled medical conditions (e.g., cardiovascular disease, respiratory disease, diabetes, body mass index ≥30 kg/m2).
- mRNA COVID-19 vaccines demonstrated higher efficacy in clinical trials than was shown in clinical trials for the authorized viral vector vaccine. In the context of limited supply, there are additional factors to consider when assessing options for COVID-19 immunization. Refer to Section V.I for further details.
  - Internal modelling reviewed by NACI based on Canadian supply projections indicated that a program including both mRNA vaccines and AstraZeneca COVID-19 vaccine could have short-term public health benefits (preventing symptomatic disease, hospitalisation, death) when the AstraZeneca COVID-19 vaccine can be offered earlier to adults 18 to 54 instead of waiting for mRNA vaccine, during periods of epidemic transmission. The public health benefits of offering the AstraZeneca vaccine earlier only to individuals 55 to 64 years were less certain given the shorter expected wait times of this population for mRNA vaccines. Modelling assumed no impact of vaccines on preventing transmission, as evidence on this is not yet available.
  - Populations that receive a lower efficacy COVID-19 vaccine will have protection against COVID-19 disease earlier than if they had waited for mRNA vaccines to be available. However, these populations may ultimately have lower protection depending on the duration of protection of both vaccines, as a larger proportion of the population will remain susceptible. 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 (e.g., poverty, homelessness, underlying medical conditions) and exposure (e.g., multigenerational housing, over-representation in jobs providing essential services such as food and healthcare).

- The mRNA COVID-19 vaccines have more challenging storage and transportation requirements than the AstraZeneca COVID-19 vaccine, which may limit the venues where the vaccine may be offered. Vaccine hesitancy may be reduced by offering the COVID-19 vaccine in more convenient locations.
- Individual intention to receive a vaccine is tied closely with safety and effectiveness of a vaccine. The acceptability of a vaccine may be lower if there are alternatives with higher efficacy. However, in the context of limited supply, receipt of any vaccine may be more acceptable than waiting for additional doses of a higher efficacy vaccine to some individuals.

- While efforts should be made to vaccinate according to the recommended schedules outlined in Table 2, some jurisdictions considering vaccine delivery logistics, current epidemiological status and projections, and healthcare system capacity may maximize the number of individuals benefiting from a first dose of mRNA vaccine by delaying the second dose, until further supplies of the mRNA vaccine become available,preferably within 42 days of receipt of the first dose.
  - In the context of limited, uncertain, and sequential shipments of vaccine supply; significant morbidity and mortality due to COVID-19 with overwhelmed healthcare system capacity and ongoing substantial community transmission, jurisdictions are faced with balancing the rapid roll-out of the COVID-19 immunization program to as many individuals as possible with ensuring the completion of a two-dose COVID-19 vaccine series as close as possible to recommended schedules. Options to maximize population health benefits are needed. The Management Options in Section V.II below summarizes evidence, considerations and guiding principles for jurisdictions to decide on how to roll out the immunization program as efficiently, effectively, and equitably as possible given their local epidemiological and vaccine supply contexts.
  - Model-based studies suggest population health benefits may be greater with a more balanced approach that does not withhold doses during early distribution in order to vaccinate more people as soon as possible, when early supplies of highly efficacious COVID-19 vaccines are constrained [7].
  - Currently, no data on a maximum interval between doses or on medium- or long-term efficacy of COVID-19 vaccines are available. However, efficacy analyses in the Pfizer-BioNTech clinical trial included participants that received their second dose 19-42 days after their first dose, and the majority of participants in the Moderna clinical trial received their second dose between 21 to 42 days after the first. As a general vaccination principle, interruption of a vaccine series resulting in a greater than recommended interval between doses does not require restarting the series. Principles of immunology, vaccine science, and historical examples demonstrate that delays between doses do not result in a reduction in final antibody concentrations nor a reduction in durability of memory response for most multi-dose products. However, the follow-up time in COVID-19 vaccine clinical trials is short and it is currently unknown whether maximum protection will be attained until the complete vaccine series has been administered, and the duration of protection after the first dose is not known as most individuals in the trials received a second dose.
  - 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 very important to inform future recommendations

and ensure completion of the vaccine series as soon as possible. NACI does not recommend a one-dose COVID-19 vaccine schedule.
  - NACI continues to recommend a complete two-dose COVID-19 vaccine series with the same vaccine product and will continue to monitor the evidence and update recommendations as needed.
- Key populations in whom initial doses are prioritized are at increased risk of exposure to SARS-CoV-2 (e.g., due to living or occupational settings), and/or increased risk of severe disease and outcomes due to various biological (e.g., advanced age, pre-existing medical conditions) and social (e.g., low socioeconomic status, belonging to a racialized population) factors that may overlap. Any combination of these factors, as well as varying access to health care services, has the potential for disproportionate outcomes [3]
- Expert stakeholders [8] and the general Canadian public [9] ranked the relative importance of COVID-19 immunization strategies in the context of limited vaccine supply as follows: 1) protect those most vulnerable, 2) protect healthcare capacity, 3) minimize spread, 4) protect critical infrastructure.
- Congregate living settings that provide care for seniors (e.g., long-term care facilities) have experienced a large number of outbreaks associated with a high number of fatalities in Canada. Residents in these settings are at an increased risk of exposure to SARS-CoV-2 and residents are more likely to experience a combination of risk factors for severe COVID-19, including advanced age and pre-existing medical conditions. Therefore, if vaccine supplies are limited such that not all populations in Stage 1 can be offered vaccine, jurisdictions may consider prioritizing this population first for initial doses if it is logistically feasible to do so. Distinguishing between vaccine adverse events and symptoms of COVID-19 or complications of co-morbidities will be especially important in this population and testing for COVID-19 after vaccination may be appropriate if residents develop symptoms that are compatible with both COVID-19 and an AEFI. Receipt of a vaccine will not interfere with the results of molecular testing or antigen detection test for SARS-CoV-2. SARS-CoV-2 PCR and rapid antigen detection tests can distinguish between SARS-CoV-2 infection and AEFIs.
- Immunization strategies aimed at protecting healthcare capacity and other services essential for the functioning of society help minimize risks for those who take on a disproportionate burden to protect and serve the public. The public also benefits from the ongoing work of those who provide these services.
- Given the ultra-low temperature storage and handling requirements for the Pfizer-BioNTech COVID-19 vaccine, vaccinating in centralized clinics such as in health care settings may be more feasible, although careful transportation of the product in the thawed state between +2 and 8^{0}C is now possible.
- Please refer to NACI's previous guidance on Key populations for early COVID-19 immunization and 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.

2. **NACI recommends that all individuals should continue to practice recommended public health measures for prevention and control of SARS-CoV-2 infection and transmission regardless of vaccination with COVID-19 vaccine, at this time.** ***(Strong NACI Recommendation)***

Summary of evidence and rationale

- Currently, there is insufficient evidence on the duration of protection of COVID-19 vaccines and the effectiveness of COVID-19 vaccines in preventing asymptomatic infection and reducing transmission of SARS-CoV-2. There is preliminary descriptive evidence suggesting the Moderna COVID-19 vaccine may reduce asymptomatic infection, but the evidence is insufficient at this time to recommend discontinuation of public health measures. NACI will continue to monitor, and this recommendation may change as more evidence becomes available.
- There is emerging evidence on the decreased efficacy of COVID-19 vaccines against variants of concern.
- There is evidence to support the effectiveness of other recommended public health measures in pre-exposure and post-exposure scenarios, including physical distancing, masking, hand hygiene, as well as isolation and quarantine.
- Currently, there is no evidence on the use of COVID-19 vaccine for post-exposure prophylaxis.
- Federal, provincial/territorial, and local public health measures for the prevention and control of SARS-CoV-2 should continue to be followed.

3. NACI recommends that a complete series with a COVID-19 vaccine may be offered to individuals in the authorized age group without contraindications to the vaccine who have had previously PCR-confirmed SARS-CoV-2 infection. In the context of limited vaccine supply, initial doses may be prioritized for those who have not had a previously PCR-confirmed SARS-CoV-2 infection. *(Discretionary NACI Recommendation)*

Summary of evidence and rationale:

- Testing for previous SARS-CoV-2 infection is not needed prior to COVID-19 vaccination.
- Currently, there is a lack of evidence on potential differences in vaccine efficacy or safety between those with and without prior evidence of SARS-CoV-2 infection. In COVID-19 vaccine clinical trials to date, individuals with PCR-confirmed SARS-CoV-2 were excluded and there were only a small number of trial participants with serologic evidence of previous infection (IgG+) who had confirmed symptomatic COVID-19 during the trials, therefore efficacy in this population is uncertain.
- The immune response to SARS-CoV-2, including duration of immunity, is not yet well-understood. Reinfections with SARS-CoV-2 have been reported and research to establish the severity, frequency, and risk factors of reinfection with SARS-CoV-2 is ongoing.
- In the context of limited supply, to allow for the protection of a larger number of at-risk individuals, vaccination with a COVID-19 vaccine may be delayed for 3 months following a PCR-confirmed infection, as reinfections reported to date have been rare within the first three months following infection. However, if challenging from a feasibility perspective, jurisdictions may elect to disregard prior PCR-confirmed SARS-CoV-2 infection status and vaccinate everyone in a given target group.
- As a precautionary measure and in light of the need to be able to monitor for COVID-19 vaccine adverse events without potential confounding from symptoms of COVID-19 or other co-existing illnesses, and to minimize the risk of transmission of COVID-19 at an immunization venue, NACI recommends that it is prudent to wait until all symptoms of an acute illness are completely resolved before vaccinating with COVID-19 vaccine, as well as ensuring that the individual is no longer considered infectious based on current criteria.

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

Immunosuppressed persons

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

Summary of evidence and rationale

- Currently, there is limited evidence that immunosuppression is an independent risk factor for severe COVID-19, though evidence is evolving.
- Currently, there are no data on COVID-19 vaccination in individuals who are immunosuppressed. Participants in the COVID-19 vaccine clinical trials only included individuals who were not immunosuppressed, such as those with stable infection with human immunodeficiency virus (HIV), and those not receiving immunosuppressive therapy during the trial.
- No safety signals of concern have been noted to date in non-immunosuppressed participants with an immunocompromising condition (e.g., stable HIV infection) included in the clinical trials.
- The relative degree of immunodeficiency in individuals who are immunocompromised is variable depending on the underlying condition, the progression of disease and use of medications that suppress immune function. Therefore, the balance of benefits and risks must be made on a case-by-case basis.
- Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the vaccine.
- In general, non-replicating vaccines may be administered to immunocompromised people because the antigens in the vaccine cannot replicate. However, the magnitude and duration of vaccine-induced immunity are often reduced. It is currently unknown whether immunocompromised individuals will be able to mount an immune response to the authorized COVID-19 vaccines.
- People living with HIV who are considered immunocompetent may be vaccinated.
- Active surveillance in these vaccine recipients is strongly encouraged. NACI will monitor the evidence as it evolves, and update recommendations as needed.

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

Persons with an autoimmune condition

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

Summary of evidence and rationale

- Currently, there is limited evidence that having an autoimmune condition is an independent risk factor for severe COVID-19, though evidence is evolving.
- Currently, there are very limited data on COVID-19 vaccination in individuals who have an autoimmune condition. Although participants with autoimmune conditions who were not immunosuppressed were not excluded from trials, they constitute a very small proportion of trial participants and represent a very narrow range of autoimmune conditions.
- The spectrum of autoimmune conditions is diverse. The relative degree of autoimmunity in individuals with autoimmune conditions is variable depending on the underlying condition, the severity and progression of disease, and use of medications that impact immune function. Therefore, the balance of benefits and risks must be made on a case-by-case basis.
- Other applications of mRNA technologies have been for the treatment of cancer, which requires an immune response directed against an individual's cancer cells. This raised the theoretical concern that mRNA vaccines for infectious diseases would behave similarly, eliciting inflammation and possibly exacerbating existing autoimmune diseases. Current applications of mRNA technology for COVID-19 vaccines have been optimized to reduce this risk; however, further evaluation is needed.
- Active surveillance in these vaccine recipients is strongly encouraged. NACI will monitor the evidence as it evolves, and update recommendations as needed.

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

Pregnancy and Breastfeeding

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

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

Summary of evidence and rationale

- The evidence of pregnancy as an independent risk factor for severe COVID-19 is evolving.
- Currently, there are no data on the safety and efficacy of COVID-19 vaccines in pregnancy or during breastfeeding. Pregnant or breastfeeding individuals were excluded from the mRNA and viral vector COVID-19 vaccine clinical trials.
- Currently, there are no data to inform outcomes of inadvertent administration of COVID-19 vaccine to pregnant individuals or their developing fetus in clinical trials. Outcomes in participants who became pregnant during the clinical trials and fetal outcomes will be reported through registries and NACI will reconsider recommendations when these data become available.
- It is unknown whether the vaccines are excreted in human milk, but there are no data on outcomes in breastfeeding individuals or their breastfed infants. There have been no theoretical concerns about these vaccines in breastfeeding individuals or their breastfed infants.
- Currently, there are limited data on the safety of COVID-19 vaccine from animal developmental and reproductive toxicity studies. In rats that received the Moderna COVID-19 vaccine prior to or during gestation, no safety concerns regarding female reproduction, fetal/embryonal development, or postnatal development were demonstrated. Developmental and Reproductive Toxicity (DART) animal studies for the Pfizer-BioNTech COVID-19 vaccine and AstraZeneca COVID-19 vaccine are ongoing.
- Individuals who are pregnant, breastfeeding, or of reproductive age may be at increased risk of exposure to SARS-CoV-2 (e.g., healthcare or essential workers) and/or at increased risk of severe COVID-19 disease (e.g., due to pre-existing medical condition, body mass index of 40 or more) and may wish to be vaccinated despite the lack of evidence of COVID-19 vaccination in pregnancy or during breastfeeding in order to protect themselves. Therefore, the balance of benefits and risks must be made on a case-by-case basis.
- There is currently no evidence to guide the time interval between the completion of the COVID-19 vaccine series and conception. In the face of scientific uncertainty, it may be prudent to delay pregnancy by 28 days or more after the administration of the complete two-dose vaccine series of a COVID-19 vaccine. A COVID-19 vaccine may be administered anytime after pregnancy.
- Individuals who become pregnant during their vaccine series or shortly thereafter should not be counselled to terminate pregnancy based on having received a COVID-19 vaccine.
- If pregnancy is determined after initiation of the vaccination series, completion of the series may be delayed until after pregnancy, unless risk factors for increased exposure or severe COVID-19 are present and informed consent for vaccination is obtained as above. NACI also encourages additional research and surveillance of COVID-19 vaccination in pregnancy.
- Eligible individuals should be offered a complete vaccine series with an authorized COVID-19 vaccine post-partum and prior to attempting pregnancy so that the recommended interval between completion of the vaccine series and conception is maintained.
- Vaccine recipients and health care providers are encouraged to report COVID-19 vaccine during pregnancy or breastfeeding to the local public health authority as well as to the vaccine manufacturer for follow-up. Active surveillance in these vaccine recipients is strongly encouraged. NACI will monitor the evidence as it evolves, and update recommendations as needed.

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

Children and Adolescents

8. **NACI recommends that COVID-19 vaccines should not be offered routinely to individuals who are not in the authorized age group. *(Strong NACI Recommendation)*.**
    a. **However, a complete vaccine series with a Pfizer-BioNTech may be offered to individuals 12-15 years of age who are at very high risk of severe outcomes of COVID-19 (e.g., due to a pre-existing medical condition known to be associated with increased risk of hospitalization or mortality) or are at increased risk of exposure (e.g., due to living in a congregate care facility), if a risk assessment deems that the benefits outweigh the potential risks for the individual, and if informed consent with the individual and the parent or guardian includes discussion about the insufficiency of evidence on the use of COVID-19 vaccines in this population. *(Discretionary NACI Recommendation)***

Summary of evidence and rationale

- Evidence to date suggests that in general, children infected with SARS-CoV-2 are not at increased risk of severe disease.
- Evidence on COVID-19 vaccination in those less than 12 years of age is absent, and only limited clinical data on the safety and efficacy of the Pfizer-BioNTech COVID-19 vaccine in those aged 12 to 15 years is available. The Moderna COVID-19 vaccine and AstraZeneca COVID-19 vaccine clinical trials have to date only included adults 18 years of age and older.
- Evidence on the increased risk of severe COVID-19 disease in individuals with certain medical conditions (e.g., heart failure, diabetes, liver disease, chronic kidney disease) exists [10] and the list of these medical conditions is evolving. For adolescents with certain pre-existing medical conditions compounded by an increased risk of exposure to SARS-CoV-2 (e.g., due to living in a congregate setting such as a group home), the balance of risks and benefits of vaccination with a COVID-19 vaccine must be made on a case-by-case basis.
- Active surveillance in these vaccine recipients is strongly encouraged. NACI will monitor the evidence as it evolves, and update recommendations as needed.

NACI continues to recommend the following:

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

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

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

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

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

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

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

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

V.I MANAGEMENT OPTIONS FOR COVID-19 VACCINES AUTHORIZED FOR USE IN CANADA

There are currently three authorized COVID-19 vaccines in Canada for the prevention of symptomatic COVID-19 that use two different vaccine platforms. To assist with the decision on which vaccine to offer to different populations or groups, a comparison of the relative merits of both have been summarized in Table 4 below.

Table 4. Management options for types of COVID-19 vaccines authorized for use in Canada

Factor for consideration	Considerations (Summary of available evidence and issues for consideration)	
	mRNA COVID-19 Vaccines	**Non-replicating viral vector COVID-19 Vaccine**
Efficacy	**Efficacy against symptomatic illness after dose 2** • Pfizer-BioNTech and Moderna mRNA vaccines have high short-term efficacy (approximately 94%). • Data suggests the Pfizer/BioNTech vaccine is 95% efficacious in individuals ≥65 years of age. • Data suggests the Moderna vaccine is 86% efficacious in individuals ≥65 years of age.	**Efficacy against symptomatic illness after dose 2** • AstraZeneca SD/SD vaccine is 62% efficacious in participants 18 to 64 years of age. • Data 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.
	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. There is no data on asymptomatic infection for Pfizer-BioNTech COVID-19 vaccine.	**Efficacy against asymptomatic infection** • An exploratory ad hoc analysis of limited data suggests the AstraZeneca vaccine may not be efficacious in preventing asymptomatic infection.
	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 thought to be safe and effective. • The efficacy and safety of re-vaccinating those who initially received mRNA vaccine with a different COVID-19 vaccine are unknown at this time.	**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 the AstraZeneca vaccine may reduce vaccine effectiveness. • The efficacy and safety of re-vaccinating those who initially received AstraZeneca vaccine with a different COVID-19 vaccine are unknown at this time.

Factor for consideration	Considerations (Summary of available evidence and issues for consideration)	
	mRNA COVID-19 Vaccines	**Non-replicating viral vector COVID-19 Vaccine**
Immunogenicity	**Humoral response** • Humoral responses for both mRNA COVID-19 vaccines peaked after a second dose, including elicitation of neutralizing antibodies. However, as a correlate of protection is not known, these humoral responses cannot be interpreted as corresponding with protection. • Humoral responses had similar trends in individuals 18 to 55 years of age and individuals 65 to 85 years of age.	**Humoral response** • Humoral responses 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 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[11]. • However, as a correlate of protection is not known, these humoral responses cannot be interpreted as corresponding with vaccine protection.
	Cellular response • Both mRNA vaccines have been shown to produce a cellular immune response by one to two weeks after administration of a second dose. • Increases in cellular immune responses response were seen in both younger and older adults. • As no immunological correlate of protection has been determined for SARS-CoV-2, these cellular responses cannot be interpreted as corresponding with vaccine protection.	**Cellular response** • AstraZeneca vaccine has been shown to produce cellular immunes responses that did not appear to increase after the second dose. • Cellular immune responses do not appear to differ between age groups. • As no immunological correlate of protection has been determined for SARS-CoV-2, these cellular responses cannot be interpreted as corresponding with vaccine protection.
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	**Safety Signals**

Factor for consideration	Considerations (Summary of available evidence and issues for consideration)	
	mRNA COVID-19 Vaccines	**Non-replicating viral vector COVID-19 Vaccine**
	• There have been no serious safety signals identified with either mRNA vaccine. • For both vaccines, some solicited adverse events are reported to be very common (defined as 10% or more) among vaccine recipients; however, they are mild or moderate and transient, resolving within a few days. These include: pain at the injection site, fatigue, headache, muscle pain, chills, joint pain, and fever. Some adverse events, including fever, are more frequent after the second dose.	• There have been no serious safety signals identified with the AstraZeneca vaccine. • Some solicited adverse events are reported to be very common (defined as 10% or more) among vaccine; 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.
Ethics and Equity	• mRNA vaccines have high short-term efficacy in all authorized age groups and Canada anticipates to have enough doses of mRNA vaccines for every individual in Canada in 2021. • Vaccines that are more efficacious may be directed to those who are most at risk of severe disease and exposure to limit the exacerbation of existing inequities. • The impact of not offering a less efficacious vaccine earlier to populations who would otherwise have to wait to receive an mRNA vaccine in areas with a high risk of transmission and infection, should take into consideration trust, justice, and the risk of doing harm vs good.	• 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 the AstraZeneca vaccine compared to mRNA vaccines, depending on which population groups received the AstraZeneca vaccine. • The AstraZeneca 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 or 28 days between dose one and dose two. NACI recommends a complete vaccine series be administered according to these schedules, but the interval between doses can be extended, preferably within 6 weeks, under exceptional circumstances of reduced vaccine supply and ongoing transmission. This could allow for more individuals to receive one dose of the vaccine and have some protection against symptomatic COVID-19 disease.	**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. • A longer interval could allow for more individuals to receive one dose of the vaccine and have some protection against symptomatic COVID-19 disease.
	Storage requirements	**Storage requirements**

Factor for consideration	Considerations (Summary of available evidence and issues for consideration)	
	mRNA COVID-19 Vaccines	**Non-replicating viral vector COVID-19 Vaccine**
	• The mRNA vaccines have more challenging transport and storage requirements, requiring frozen or ultra-frozen cold chains. Efforts are underway 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.	• The AZ vaccine is 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 AstraZeneca vaccine requires storage and transport at +2 to +8°C, which uses standard cold chain infrastructure widely available in provinces and territories. • The storage requirements for this vaccine could increase access to the vaccine for some populations.
Acceptability	• It is possible that individuals will favor mRNA vaccines since they have higher proven efficacy. • Fewer cases of COVID-19 are expected after vaccination with a vaccine with high efficacy. The relatively low incidence of cases post-vaccination could positively affect acceptability of COVID-19 vaccines and vaccines in general.	• It is possible that individuals will favor the AstraZeneca vaccine if it offers an earlier opportunity to receive a COVID-19 vaccine and is more convenient to access if it is 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.

	Concerns about vaccine safety and effectiveness are the two most cited reasons for vaccine refusal[12]
	• In a survey of Canadians conducted between December 16 and 22, 2020 [13], the following results were reported:
	  ○ Intention to get vaccinated when it becomes available and recommended is similar for a safe vaccine vs. an effective vaccine (65% vs 63% agreed, n=2,125)
	  ○ 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)
	• In a survey of health care providers conducted on Dec 4-13, 2020 [14], 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)	

V.II MANAGEMENT OPTIONS FOR COVID-19 IMMUNIZATION PROGRAM ROLL-OUT IN THE CONTEXT OF LIMITED SUPPLY

In the context of limited, uncertain, sequential shipments of COVID-19 vaccine supply; significant morbidity and mortality due to COVID-19 with overwhelmed healthcare system capacity and ongoing substantial community transmission of SARS-CoV-2, jurisdictions are faced with balancing logistical considerations for the rapid roll-out of the immunization program to as many individuals as possible with ensuring the completion of the two-dose COVID-19 vaccine series as close as possible to the recommended immunization schedules. Options to maximize population health benefits are needed. Strategies and recommendations of other countries and national immunization technical advisory groups (NITAGs) to date in this context are summarized in Table 5.

Table 5. International strategies and recommendations for COVID-19 immunization program roll-out in the context of limited vaccine supply

Organization	Strategy or Recommendation
Strategic Advisory Group of Experts on Immunization [15] (SAGE, World Health Organization)	-COVID-19 vaccines should be given according to recommended intervals unless exceptional circumstances of vaccine supply constraints and epidemiologic settings warrant a delay in the second dose. -"Countries experiencing exceptional epidemiological circumstances may consider delaying for a short period the administration of the second dose as a pragmatic approach to maximizing the number of individuals benefiting from a first dose while vaccine supply continues to increase. WHO's recommendation at present is that the interval between doses may be extended up to 42 days on the basis of currently available clinical trial data."
Joint Committee on Vaccination and Immunisation [16] (JCVI, United Kingdom)	-"…vaccinating more people with the first dose is prioritised above offering others their second dose, to maximise benefits from the vaccination programme in the short term." -"For the Pfizer-BioNTech vaccine, the second vaccine dose can be offered between 3 to 12 weeks after the first dose." -"There are some data from the AstraZeneca vaccine trials suggesting that extending the time to the second dose may be better than having the second dose earlier." -"Skipping the second dose is not advised, as the second dose may be important for longer lasting protection, however exact durations of protection are currently unknown."
-Centers for Disease Control [17] (CDC, United States)	-The second dose of authorized COVID-19 mRNA vaccines should be administered as close as possible to the recommended interval within a grace period of ≤4 days from the recommended date for the second dose to be considered valid. "However, there is no maximum interval between the first and second dose for either vaccine."
Food and Drug Administration [18] (FDA, United States)	-Changes to the authorized dosing or schedules of COVID-19 vaccines at this time is "premature and not rooted solidly in the available evidence. Without appropriate data supporting such changes…we run a significant risk of placing public health at risk."

The following Management Options Table summarizes the considerations for mRNA COVID-19 vaccines (including available evidence) with decision points below to guide provinces and territories in the roll out of an effective, efficient, and equitable COVID-19 immunization program in their local epidemiological and vaccine supply contexts.

Table 6. Management Options Table for mRNA COVID-19 immunization program roll-out in the context of limited mRNA vaccine supply

Options to distribute initial doses of mRNA COVID-19 vaccine	**Considerations** *(Summary of available evidence and issues for consideration)*
Distribute all of the initial doses of mRNA COVID-19 vaccine without assurance that initial vaccine recipients can receive both doses in accordance with the recommended interval. This will maximize the number of individuals receiving a first dose of vaccine, but the administration of a second dose may be delayed depending on subsequent shipments of vaccine.	**Epidemiology** -The epidemiology of COVID-19 and healthcare capacity varies across the country, with significant morbidity and mortality and ongoing community transmission in some jurisdictions, including increasing numbers of cases and outbreaks in high-risk settings and overwhelmed healthcare systems. -There is currently insufficient evidence to support the efficacy of authorized vaccines to prevent asymptomatic infection or transmission. -There is a theoretical risk of increased pressure that would allow for the development of a vaccine resistant strain in people who are partially immunized (i.e., where individuals do not receive a second dose for a prolonged period of time), especially in the context of high transmission. However, this risk is reduced by a high short-term efficacy of a single dose of vaccine. -There is no conclusive evidence on the protection of either one or two doses of currently authorized vaccines against potential new variants of the virus. **Efficacy/Effectiveness** -Vaccine efficacy of one dose against symptomatic COVID-19 disease calculated from 14 days after dose 1 (excluding the 14 days after dose 1 while the immune response is being generated or when the virus may be incubating) has been found to be 92.3% for the Pfizer-BioNTech vaccine (95% CI: 69 to 98%) and 92.1% for the Moderna vaccine (95% CI, 68.8 to 99.1%). However, these analyses should be interpreted with caution due to limited numbers and narrow window of follow-up time (as small as one week). -Duration of protection of the first dose is unknown, so breakthrough disease may begin to occur before the second dose is given, as the interval between doses is extended. - Efficacy analyses in the Pfizer-BioNTech clinical trial included participants that received their second dose within 19-42 days after their first dose, and the majority of participants in the Moderna clinical trial received their second dose between 21 to 42 days after the first. **Immunogenicity** **-**Two-dose series of authorized vaccines demonstrate a higher response following the 2nd dose (prime-boost phenomenon). -The immune response of a delayed second dose for the authorized vaccines is unknown.

Options to distribute initial doses of mRNA COVID-19 vaccine	Considerations *(Summary of available evidence and issues for consideration)*
	-With vaccines for other vaccine preventable diseases (VPDs), immune response is either similar or improved when the second dose is administered after a longer interval. - Principles of immunology, vaccine science, and historical examples demonstrate that delays between doses do not result in a reduction in final antibody concentrations nor a reduction in durability of memory response for most multi-dose products. **Ethics*** -An individual's ability to make an informed choice may be limited in the face of uncertainty in protection and supply with this option. -The balance of risks and benefits may favour this option if the certainty of evidence evolves to suggest comparative protection with a single dose, delayed second dose, or interchangeability of vaccines, especially in the context of high disease burden. This option could potentially achieve Canada's pandemic response goal to minimize serious illness and overall deaths while minimizing societal disruption as a result of the COVID-19 pandemic, more quickly, at least in the short-term. However, more research is encouraged. **Equity** -This option may provide greater access to vaccine for a greater number of individuals identified as high risk key populations, [19, 20] providing short-term protection, which could increase equity when local disease burden is high. However, if protection becomes inadequate while these individuals are awaiting a second dose and subsequent supply is delayed or insufficient, this puts key populations at risk of disease. **Feasibility** -If there is uncertainty in successive vaccine supply, jurisdictions may not feasibly be able to provide a second dose, may need to provide the second dose at an extended interval with the same vaccine product, or provide the second dose with another mRNA vaccine (assuming availability). No evidence on the interchangeability of vaccines exists. -It may be more feasible to distribute all vaccine doses due to storage requirements and security of reserved doses. However, follow up for vaccination with a second dose may be more challenging. **Acceptability** -Individuals who view holding vaccine doses in freezers to deliver a second dose on schedule to some people while others remain unvaccinated may find this option more acceptable. Given uncertainties around the impact of the extended interval, if the rationale for this option is not communicated clearly and transparently it may: -negatively impact public trust in the COVID-19 immunization program, the COVID-19 response, and vaccines in general -perpetuate perceptions that certain populations are exposed to an experimental approach

Options to distribute initial doses of mRNA COVID-19 vaccine	**Considerations** *(Summary of available evidence and issues for consideration)*
	-increase vaccine hesitancy for COVID-19 vaccines and vaccines in general, especially if individuals vaccinated with one dose get disease due to insufficient protection
Distribute initial doses of mRNA COVID-19 vaccine in a manner that ensures all initial vaccine recipients can receive both doses in accordance with the recommended interval (e.g., reserve or stagger doses). This may result in fewer individuals who will receive the first dose of vaccine early on in the roll out of the immunization program.	**Epidemiology** -The epidemiology of COVID-19 and healthcare capacity varies across the country, with significant morbidity and mortality and ongoing community transmission in some jurisdictions, including increasing numbers of cases and outbreaks in high-risk settings and overwhelmed healthcare systems. -There is currently insufficient evidence to support the efficacy of authorized vaccines to prevent asymptomatic infection or transmission. -There is no conclusive evidence on the protection of either one or two doses of currently authorized vaccines against potential new variants of the virus. **Efficacy/Effectiveness** -Published data show efficacy against symptomatic COVID-19 disease after 2 doses of vaccine in individuals without prior SARS-CoV-2 infection to be 95% (95% CI, 90.3 to 97.6%) at least 7 days after the second dose for the Pfizer-BioNTech vaccine and 94.1% (95% CI, 89.3 to 96.8%) beginning 14 days after the second dose for the Moderna vaccine. -The duration of protection for a two-dose vaccine series is known for up to 14 weeks after the second dose and studies in this population who received two doses are ongoing. -Efficacy analyses in the Pfizer-BioNTech clinical trial included participants that received their second dose within 19-42 days after their first dose, and the majority of participants in the Moderna clinical trial received their second dose between 21 to 42 days after the first. **Immunogenicity** -Two-dose series of authorized vaccines demonstrate a higher response following the second dose (prime/boost phenomenon). -Humoral responses for both mRNA COVID-19 vaccines peak after a second dose. However, as a correlate of protection is not known, these humoral responses cannot be interpreted as corresponding with vaccine efficacy or effectiveness. **Ethics[a]** -An individual's ability to make an informed choice is comparatively better with more certainty of evidence and ability to get vaccinated with a 2nd dose on schedule with this option. - However, it will take longer to vaccinate a larger number of individuals with at least one dose of vaccine and therefore the risk remains for morbidity and mortality of unvaccinated individuals in the short-term while they await the first dose of vaccine.

Options to distribute initial doses of mRNA COVID-19 vaccine	Considerations *(Summary of available evidence and issues for consideration)*
	Equity -Given the current state of evidence, this option is based on the best known evidence of achieving maximum protection for those vaccinated in the high-risk key populations and is consistent with the authorized schedule. However, if initial supply is not sufficient to vaccinate all individuals in these groups, health equity principles may be undermined especially when local disease burden is high and there is some evidence of short-term protection with one dose of vaccine. **Feasibility** -Reserving doses may be less feasible initially due to storage and concerns regarding security of reserved doses. However, follow-up for a scheduled second dose may be more feasible. **Acceptability** **-**Individuals who are expecting a complete two-dose vaccine series according to the recommended schedule will find this option more acceptable. -If the rationale for this option is not communicated clearly and transparently, it may have a negative impact on public trust due to a perception that only a small number of individuals are getting preferential access despite availability of additional doses.

[a] Please see Appendix C for a thorough ethical analysis of options for the delivery of a second dose of COVID-19 vaccine in the context of a limited vaccine supply, with the application of the EEFA Framework [2].

Decision points

For either option presented in Table 6, various decision points will need to be assessed.

- Jurisdictions will need to determine the best course of action for the most effective, efficient, and equitable COVID-19 immunization program roll-out in the context of limited vaccine supply based on their:
  - local epidemiology
  - healthcare capacity
  - logistical contexts and ability to appropriately implement the chosen option
  - security of vaccine supply (including certainty and timeliness of subsequent vaccine supply, weather implications for delivery etc.)
  - ability to vaccinate high risk key populations identified by NACI to receive initial doses of COVID-19 vaccine [19, 20]
  - ability to clearly communicate the immunization roll-out plan to individuals being vaccinated and the population as a whole

  - ability to evaluate the chosen option, detect issues, and modify strategies quickly to ensure maximum effectiveness
  - legal implications.
- Transparency in decision-making and communication of rationale for all stakeholders including vaccine recipients will be vital to foster continued trust.
- 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 vaccination appointment) will be very important to inform future recommendations and ensure completion of the vaccine series as soon as possible.
- Research and evaluation is needed for the option chosen.
- Options and recommendations may change as more evidence (e.g., effectiveness and duration of protection from the first dose of COVID-19 vaccine) emerges and certainty and quantity of vaccine supply increase.

VI. RESEARCH PRIORITIES

COVID-19 disease and associated vaccines are novel; therefore, research is warranted in many areas. Research to address the following outstanding questions (not ordered in terms of importance) is encouraged, drawing from both short-term and long-term data, where available:

New and Emerging Research Priorities

Efficacy, Effectiveness, Immunogenicity and Safety

1. What is the population effectiveness (against infection/transmission, hospitalization and death) and medium and long-term duration of protection of a single dose or a complete series of each COVID-19 vaccine approved in Canada?

2. What is the efficacy, effectiveness, immunogenicity, and safety of COVID-19 vaccines across diverse population groups (e.g., adults of advanced age, those with high-risk medical conditions including autoimmune conditions and transplant recipients, individuals with social or occupational vulnerabilities, individuals who are pregnant or breastfeeding, children/adolescents, frailty)?

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

4. What is the 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?

5. Further immunological evidence is needed in the following areas to inform efficacy predictions:
    a. How do immune responses change over time; what is the durability of immune responses against SARS-COV-2 over the long-term? What is the impact of vaccine dose or interval on durability?
    b. Which immune responses are most important for protection from infection (adaptive or innate immunity), severe disease or transmissibility? What is the role of humoral vs. cellular immunity in preventing immune escape of viral variants?

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

6. What level of COVID-19 vaccination coverage is required to achieve various public health milestones, including: coverage to reduce the burden on the health care system to a manageable degree, achieve herd immunity to protect non-vaccinated individuals, and remove PHM controls. What vaccine characteristics play the largest role on these milestones (i.e., efficacy, durability, uptake)?
7. 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?
8. 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?
9. Are any components of the COVID-19 vaccine at high risk of inducing an anaphylactic reaction?
10. What is the incidence of rare, serious adverse events following immunization with COVID-19 vaccines?
11. 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?
12. 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?
13. Does vaccination have an impact on the transmissibility of SARS-CoV-2 in individuals with asymptomatic infection?
14. What is the role of seasonal attenuation of SARS-CoV-2?
15. How does vaccination impact individual-level variation in transmission (e.g., superspreaders)?

Vaccine Administration

16. Are any COVID-19 vaccines interchangeable to complete a regular vaccine series? What is the efficacy, effectiveness, immunogenicity and safety of a mixed dose schedule or a mixed dose booster series?
17. 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?
18. Are any other vaccines (e.g., Bacillus Calmette-Guérin) protective against COVID-19 through off-target effects?

19. Can COVID-19 vaccine be simultaneously administered with other, non-COVID-19 vaccines (either live or inactivated vaccines)? If not, what is the minimum interval between administrations?
20. Can COVID-19 vaccines be given in individuals who have received convalescent plasma or anti-SARS-CoV-2 spike protein monoclonal antibodies? If so, what is the minimum interval required for vaccine administration following receipt of convalescent plasma or monoclonal antibodies?

Standing Research Priorities

COVID-19 infection and disease

1. What is the epidemiological profile of COVID-19 (e.g., communicable period, all risk groups)?
    a. What is the disease distribution and spectrum of clinical illness for COVID-19, including burden of illness and risk by age, sex and other demographic variables associated with higher risk?
    b. What are the transmission dynamics of COVID-19, including degree of asymptomatic transmission, role of children in transmission, vertical transmissibility, onset and duration of viral shedding and communicable period, impact of changing weather conditions, and trends over time?
    c. What are the rates of COVID-19 co-infections with other respiratory pathogens and what is the impact on pathogenesis and clinical outcomes?
2. Can COVID-19 vaccine be used to protect household contacts of a case from infection? Does COVID-19 vaccination decrease infectiousness and clinical illness in individuals that have already acquired infection? Is COVID-19 vaccination effective in interrupting transmission?

Ethics, Equity, Feasibility and Acceptability

3. What is the acceptability of (a) publicly funded COVID-19 vaccines and (b) other vaccines over time and over different epidemiological contexts among key populations, marginalized populations, providers and policy-makers in different epidemiological contexts across the country?
    a. What factors affect acceptability of immunization with a COVID-19 vaccine in these groups?
    b. What factors affect acceptability of immunization in general?
    c. How will acceptability of prioritized key populations for early immunization with COVID-19 vaccines evolve in different epidemiological contexts across the country?
    d. What strategies can improve acceptability of a COVID-19 vaccine in these groups?
4. How can vaccine allocation decisions be communicated to individuals and communities in order to maintain trust in public health authorities?

5. What COVID-19 vaccination strategies or implementation strategies can reduce health inequities in populations directly targeted by vaccination and in populations not directly targeted by immunization?
6. Can a different COVID-19 vaccine be used to complete a primary series or as a booster dose? How are returning travellers managed if they have initiated but not completed a COVID-19 vaccine series abroad?

Health-Related Quality of Life and Well-being

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

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

VII. SURVEILLANCE ISSUES

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

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

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

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

TABLES

Table 7. 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*
AE	Adverse event
AEFI	Adverse event following immunization
CDC	Centres for Disease Control and Prevention (United States)
ChAd	Chimpanzee Adenovirus
CI	Confidence interval
CIC	Canadian Immunization Committee
CIG	Canadian Immunization Guide
COVID-19	Coronavirus disease 2019
EEFA	Ethics, Equity, Feasibility, and Acceptability
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HIV	Human immunodeficiency virus
IM	Intramuscular
Ig	Immunoglobulin
IGRA	Interferon gamma release assay
JCVI	Joint Committee on Vaccination and Immunisation (UK)
MenACWY	Quadrivalent meningococcal vaccine
mRNA	messenger ribonucleic acid
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
SOC	System organ class
TST	Tuberculin skin test
UK	United Kingdom
VPD	Vaccine Preventable Disease
WHO	World Health Organization

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APPENDIX A: EVIDENCE SUMMARY FOR PFIZER-BIONTECH COVID-19 VACCINE

Study C4591001 is the pivotal Phase 1/2/3 trial for the Pfizer-BioNTech COVID-19 vaccine. Evidence on immunogenicity is available for adults 18 to 55 and 65 to 85 years of age. Evidence on the safety and efficacy of the vaccine is available for adults 16 years of age and older. Studies did not include participants from long term care facilities. The Phase 2/3 portion of the trial involved approximately 44,000 study participants randomized (1:1) to receive either the vaccine or placebo. The data presented below are for an interim analysis, therefore the time of follow-up is not consistent but was less than four months after the second dose (maximum of 14 weeks) for all participants.

Evidence from the ongoing Phase 2/3 trial were published recently, after NACI's review of the evidence [21].

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 [22].

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

Symptomatic COVID-19 disease
The estimated vaccine efficacy at least 7 days after Dose 2 was 94.6% (95% CI: 89.9 to 97.3%), with 9 confirmed symptomatic COVID-19 cases, as defined in trial protocol [21] identified among vaccine recipients (N=19,965) compared to 169 cases among placebo recipients (N=20,172). The vaccine efficacy at least 14 days after Dose 2 in this population was comparable (94.4%, 95% CI: 89.1 to 97.3%). Results were similar when estimating the efficacy specifically in individuals without evidence of prior SARS-CoV-2 infection at 95.0% (95% CI: 90.3 to 97.6%) with 8 confirmed cases among vaccine recipients (N=18,198) compared to 162 cases among placebo recipients (N=18,325).

When study participants without evidence of prior SARS-CoV-2 infection were stratified by age, vaccine efficacy against COVID-19 from 7 days after Dose 2 was between 93.7% (>55 years) and 95.6% (16 to 55 years). In individuals ≥65 years of age, vaccine efficacy was 94.7% (95% CI: 66.7 to 99.9%), while in participants ≥75 years of age, the observed vaccine efficacy was 100% compared to placebo, but with a wide confidence interval including zero which resulted from an insufficient number of events reported (0 vs 5 cases, 95% CI: –13.1 to 100.0%). The estimated

vaccine efficacy against confirmed COVID-19 from 7 days after Dose 2 was greater than 91% (between 91.7% and 100.0%) in all subgroups stratified by “at risk” status (e.g., presence of a 1 or more comorbidities). The estimated vaccine efficacy against confirmed COVID-19 from 7 days after Dose 2 was greater than 89% for all races (89.3 to 100%) and 94% for all ethnicities included in the sub-analysis (94.4 to 95.4%).

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

Table 8. Pfizer-BioNTech vaccine efficacy against the first occurrence of symptomatic COVID-19 disease after dose 1[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 (https://www.inspq.qc.ca/sites/default/files/publications/3098_vaccination_covid19_2e_dose_contexte_penurie.pdf)

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

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

Immunogenicity

Humoral immune responses
Both SARS-CoV-2 binding and neutralizing antibodies induced by this vaccine had similar trends across both age groups studied (N=195). Maximal immune responses were seen on day 28, 7 days after the second dose. Binding and neutralizing antibodies were both induced by one dose of vaccine and boosted by the second dose of vaccine. The immune response elicited by one dose accounted for 10-20% of the maximal immune response. Up to day 35, older adults (65-85 years of age) had a lower immune response compared to younger adults (18-55 years of age). After the peak on day 28, immune responses decreased until the final evaluation point on day 52, 30 days after dose 2 in younger adults, while no decrease was observed in older adults. At all time points and age groups, immune responses were higher than placebo.

Cellular immune responses
Both CD4+ and CD8+ T-cells specific to SARS-CoV-2 were induced by the vaccine, as demonstrated by the increase in these cell population percentages from day 1 to day 28. Increases were seen in both younger adults (18-55 years of age) and older adults (65-85 years

of age). The characterization of these cells indicates a Th-1 biased cellular immune response. Intermediate time points were not reported.

Vaccine Safety and Adverse Events Following Immunization

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

Local Reactions
In vaccine recipients, frequency of local reactions was similar after Dose 1 and Dose 2. Pain at the injection site was very common (occurred in 66.1 to 83.1%, dependent on age and whether it was Dose 1 or Dose 2 administered). Most local reactions among vaccine recipients were mild or moderate in severity, with any severe reactions being reported by ≤0.6% of participants. No Grade 4 local reactions were reported. Across both age groups, local reactions after either dose had a median onset between zero and 2 days post-vaccination and a median duration of 1 to 2 days.

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

Across age groups, the median onset day for most systemic events after either dose of vaccine was 1 to 2 days post-vaccination, with a median duration of 1 day. The majority of systemic events were mild or moderate in severity.

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

Severe or Serious Adverse Events
In total, 1.1% and 0.1% of participants in the vaccine group experienced at least one severe AE and one life-threatening adverse events (AE), respectively, compared to 0.7% and 0.1% of participants in the placebo group. There were no clinically meaningful differences in AEs by category observed by age, sex, or race/ethnicity.

The proportions of participants who reported at least 1 serious adverse event (SAE) were similar in the vaccine group (0.5%) and in the placebo group (0.4%). Three of the SAEs in the vaccine group and none in the placebo group were assessed by the investigator as related to study

intervention: 1 SAE each of shoulder injury related to vaccine administration, ventricular arrhythmia, and lymphadenopathy. No clinically meaningful differences in SAEs were observed by age, sex, or race/ethnicity. After either vaccine dose, no participant reported an immediate allergic reaction to vaccine.

Other serious adverse events

Lymphadenopathy

Lymphadenopathy was not a solicited AE. Among participants (n=37,586) who were followed for <2 weeks to <14 weeks after Dose 2, AEs of lymphadenopathy were reported in 0.3% (n=64) participants (0.5% [n=54] in the younger age group and 0.1% [n=10] in the older age group) in the vaccine group and 6 participants (0.0%) in the placebo group. Among the AEs of lymphadenopathy in the vaccine group, the majority (47 of 64) were judged by the investigator as related to the vaccine. Most lymphadenopathy events were reported within 2 to 4 days after vaccination. The average duration of these events was approximately 10 days, with 11 events ongoing at the time of the data cut-off.

Appendicitis

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

Death

There were 6 participants who died as of 14 November 2020, the data cut-off date for the interim analysis. This included 2 participants in the vaccine group and 4 participants in the placebo group. None of these deaths in the vaccinated group were assessed by the investigator as related to the vaccine.

APPENDIX B: EVIDENCE SUMMARY FOR MODERNA COVID-19 VACCINE

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

Efficacy

Severe outcomes due to COVID-19
There are no efficacy data for hospitalizations and deaths specifically, however data exists for efficacy against severe COVID-19 outcomes, as defined in the trial protocol [23].

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 [23] 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*

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%)

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

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

Immunogenicity

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

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

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

Cellular immune responses
Both CD4+ and CD8+ T-cells specific to SARS-CoV-2 were induced by the vaccine. Maximal induction of both CD4+ and CD8+ T cells was observed on day 43, 14 days after dose 2. The percentage of CD8+T cells was lower for all age groups compared to CD4+ T cells. By comparing the percentage of cells that express Th-1 (IFN gamma, IL-2, TNF) vs. Th-2 (IL-4 and IL-13), it was demonstrated that this vaccine induces a Th1-biased cellular immune response.

Vaccine Safety and Adverse Events Following Immunization

Safety evidence is based on interim analyses of 30,351 participants with a median follow-up time of 63 days after Dose 2 (92 days after Dose 1). 23,276 participants had at least one month of follow-up after Dose 2 (12,021 individuals received the vaccine) and 7,667 individuals had at least 2 months of follow-up after Dose 2 (3894 individuals received the vaccine) [24]. 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 [24]. 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.

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%) [24].

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

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

Unsolicited Severe or Serious Adverse Events

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

Three SAEs in vaccinated individuals were considered by the study sponsor to be related to the trial intervention: two cases of facial swelling and one case of nausea and vomiting with headaches and fever.

Four additional SAEs in vaccine recipients and five SAEs in placebo recipients were considered to be related to the trial intervention by trial investigators [24]. 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

Death

A total of 13 deaths were reported, 6 in the vaccine group and 7 in the placebo group. None of these deaths were assessed to be related to any study intervention or COVID-19.

APPENDIX C: EVIDENCE SUMMARY FOR ASTRAZENECA COVID-19 VACCINE

Results from four clinical trials (two Phase 1/2, one Phase 2/3, and one Phase 3) were available at time of authorization for the AstraZeneca COVID-19 vaccine. Results from an ongoing Phase 3 trial in the US are not available at time of writing. Evidence on efficacy, immunogenicity, and safety is available for adults ≥18 years of age. The Phase 2/3 trial (COV002) trial and Phase 3 trial (COV003) assessed efficacy safety and immunogenicity of the vaccine. The Phase 2/3 trial was based in the United Kingdom, (UK) while the Phase 3 trial was based in Brazil. These two studies underwent a series of protocol amendments and logistical challenges during the conduct of the trials that resulted in significant changes to the trials' methodology. There were changes from a single to a two-dose vaccine regimen, the use of both a low dose/standard dose (LD/SD) (in COV002 only, due to dosing error) and standard dose/standard dose (SD/SD) vaccine regimen, and the recruitment of progressively older study participants (56–69 and then ≥70 years of age) after the initial focus on adults 18–55 years of age. In the SD/SD vaccine regimen, study participants were randomized (1:1) to receive either the AstraZeneca COVID-19 vaccine, AZD1222 (5×10^{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 [25].

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% confidence interval)
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 the 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[11]

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 [26]. 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 the second dose. However, neutralization is not the only anti-vector immune response that could impact vaccine-induced immunity. It remains unclear if immune responses to the ChAd vector will impact the efficacy or effectiveness of this vaccine.

Vaccine Safety and Adverse Events Following Immunization

Safety evidence is based on interim analyses of 23,745 participants of which 12021 received at least one dose of the AZ COVID-19 vaccine and 11724 received a control. The safety analyses were conducted in different analysis sets. Solicited adverse events occurring within 7 days after any dose were assessed among 2648 vaccine recipients who received at least one dose (SD) and 2497 control recipients. Approximately one third of study participants received their second vaccine dose within 6 weeks of receiving Dose 1. The majority (~90%) of study participants in the safety cohort were less than 65 years of age. The median duration of follow-up was 105 days post-Dose 1 and 62 days post-Dose 2.

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

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

APPENDIX D: FREQUENCY OF SOLICITED ADVERSE EVENTS FOLLOWING IMMUNIZATION FOR COVID-19 VACCINES

Table 15. Frequency of solicited local adverse events in authorized populations[a]

AEFI	Pfizer-BioNTech COVID-19 Vaccine				Moderna COVID-19 Vaccine				AstraZeneca COVID-19 Vaccine			
	Vaccine		Placebo control		Vaccine		Placebo control		Vaccine		MenACWY 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	Very Common	Very Common	Very Common	Very Common
Redness	Common	Common	Common	Rare	Common	Common	Uncommon	Uncommon	Common	Common	Common	Uncommon
Swelling	Common	Common	Rare	Rare	Common	Very Common	Uncommon	Uncommon	Common	Common	Common	Common
Lymphadenopathy[b]/ Axillary swelling and tenderness	NS	NS	NS	NS	Very Common	Very Common	Common	Common	NS	NS	NS	NS
Warmth	NS	NS	NS	NS	NS	NS	NS	NS	Very Common	Very Common	Very Common	Very Common
Pruritis	NS	NS	NS	NS	NS	NS	NS	NS	Common	Common	Common	Common
Induration	NS	NS	NS	NS	NS	NS	NS	NS	Common	Uncommon	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] Lymphadenopathy was not a solicited adverse event for the Pfizer BioNTech COVID-19 vaccine or AstraZeneca COVID-19 vaccine and was reported as an unsolicited adverse event. Please see Appendix A and C for more details.

Table 16. Frequency of solicited systemic adverse events in authorized populations[a]

AEFI	Pfizer-BioNTech COVID-19 Vaccine				Moderna COVID-19 Vaccine				AstraZeneca COVID-19 Vaccine			
	Vaccine		Placebo control		Vaccine		Placebo control		Vaccine		MenACWY 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	Very Common	Very Common	Very Common	Very Common	Very Common
Chills	Very Common	Very Common	Common	Common	Common	Very Common	Common	Common	Very Common	Common	Common	Common
Joint Pain	Common	Very Common	Common	Common	Very Common	Very Common	Very Common	Very Common	Very Common	Very Common	Common	Common
Fever[b]	Common	Very Common	Uncommon	Uncommon	Uncommon	Very Common	Uncommon	Uncommon	Very Common	Uncommon	Uncommon	Uncommon
Feverishness[b]	NS	NS	NS	NS	NS	NS	NS	NS	Very Common	Very Common	Common	Common
Diarrhea	Common	Common	Common	Common	NS	NS	NS	NS	NS	NS	NS	NS
Nausea and/or Vomiting[c]Vomiting	Uncommon	Common	Uncommon	Uncommon	Common	Very Common	Common	Common	Very Common/ Common	Common/ Uncommon	Very Common/ Uncommon	Very Common/ Uncommon

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

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

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

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

APPENDIX E: APPLICATION OF THE EEFA FRAMEWORK – ETHICAL ANALYSIS OF OPTIONS FOR THE DELIVERY OF A SECOND DOSE OF MRNA COVID-19 VACCINES IN THE CONTEXT OF A LIMITED VACCINE SUPPLY

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The purpose of the EEFA (Ethics, Equity Feasibility, Acceptability) Framework[2] is to provide evidence-informed tools for the systematic consideration of programmatic factors in order to develop clear, comprehensive recommendations for timely, transparent decision-making. The application of the Core Ethical Dimensions Filter, an evidence-informed tool that is part of the EEFA Framework, ensures that guidance upholds and integrates core ethical dimensions for public health (respect for persons and communities, beneficence and non-maleficence, justice, and trust). This Filter incorporates the other evidence-informed tools of the EEFA Framework to assess equity, feasibility and acceptability considerations. As part of the Core Ethical Dimensions Filter, if a major risk is identified, an in-depth scenario-based ethics analysis is conducted using the following steps:

1. Identify issue and context
2. Identify ethical considerations
3. Identify and assess options
4. Select best course of action and implement
5. Evaluate

In the context of a limited initial supply of COVID-19 vaccines, the National Advisory Committee on Immunization (NACI) has identified a risk to adherence of the recommendation to offer a complete two-dose series with an authorized mRNA COVID-19 vaccine product according to the schedule summarized in Table 2 of this advisory committee statement. As such, the NACI Secretariat conducted the first three steps of the ethics analysis described above, incorporating the results of a consultation with the Public Health Ethics Consultative Group (PHECG) on December 15, 2020. If, due to logistical constraints, jurisdictions cannot vaccinate individuals with two doses of an authorized COVID-19 vaccine product as close as possible to the authorized or alternate schedules outlined in Table 2, they may refer to this ethics analysis to assess their options, select the best course of action to implement, and evaluate.

SCENARIO-BASED ETHICS ANALYSIS

Step 1: Identify issue and context

The NACI recommends that a complete vaccine series with an authorized COVID-19 vaccine should be offered to individuals in the authorized age group without contraindications to the vaccine. (Strong NACI Recommendation). NACI further recommends that the vaccine series should be completed with the same COVID-19 vaccine product. The two vaccine doses should be administered according to the authorized or alternate intervals, as outlined in Table 2 of the NACI Advisory Committee Statement. The rationale and evidence for these recommendations are summarized in the guidance document. Though the evidence continues to evolve, the balance of evidence at this time supports NACI's recommendations. NACI will continue to monitor the evidence and update recommendations as needed.

Issue: In the context of limited initial vaccine supply and uncertain subsequent vaccine supply, should provinces and territories immediately distribute all doses of COVID-19 vaccines without reserving half of the initial doses (to ensure completion of the two-dose vaccine series in accordance with the recommended interval in initial vaccine recipients) in order to vaccinate a greater number of people in a shorter timeframe with the first dose?

Step 2: Identify the ethical considerations (using the Core Ethical Dimensions Filter of the EEFA Framework[2])

Core Ethical Dimension for Public Health (and Description)	Considerations

Respect for persons and communities
 	
(Right to exercise informed choice based on all available evidence)
	• Individual autonomy, choice and perspectives of unique and diverse populations need to be respected. Keeping doses in reserve to ensure completion of a vaccine series enhances autonomy and respect for persons and communities.
	• The public also expects that public health authorities will fulfill their responsibility to determine which course of action is in the best interest of the public when making recommendations. There is an obligation to be truthful and honest with those impacted.
	• If schedule deviations are intentionally anticipated, there should be a clear and strong rationale available to the affected population.
	• NACI's guidance is transparent about what is known and unknown regarding COVID-19 vaccines. This is included in the rationale for its recommendations to offer a complete two-dose vaccine series.
	• Informed consent of those receiving vaccine will be vital.
	  ○ ***If half the initial doses are kept on reserve*** so that all initial vaccine recipients can receive both doses in accordance with the recommended interval, individuals can make a comparatively better informed choice than would be the case if no doses were kept in reserve.
	  ▪ Evidence on the safety and efficacy available from clinical trials could be provided with assurance if a second dose would be provided on schedule.

Core Ethical Dimension for Public Health (and Description)	Considerations
	▪ It is likely that the preference of individuals wishing to be vaccinated would be to complete the vaccine series within the recommended interval for optimal protection. o ***If all doses are immediately distributed*** without reserving doses to complete the vaccine series in accordance with the recommended interval, then the ability to make an informed choice will be limited to deciding whether to accept one dose of the vaccine in the face of considerable uncertainty about: ▪ the timing of a second shipment of the authorized vaccine; and ▪ safety and efficacy: a. the duration and comparative protection offered by one vs two doses of the authorized vaccine, b. the effectiveness of two doses that are given at a longer interval than the recommended interval, c. the safety and effectiveness of a mixed schedule with different vaccine products In such circumstances, it is uncertain whether individuals offered the vaccine with no guarantee of on time second dose will have the ability to make a meaningfully informed choice.
Beneficence and non-maleficence (Promotion of well-being, minimize risk of harm vs benefits)	• ***If half the initial doses are kept on reserve*** so that all initial vaccine recipients can receive both doses in accordance with the recommended interval, this will maximize benefit and minimize risks for those vaccinated in high-risk key populations [19, 20] that have been identified to receive initial doses of COVID-19 vaccine by NACI. • ***If all doses are immediately distributed*** without reserving doses to complete the vaccine series in accordance with the recommended interval, there may be at least a short-term benefit to a greater number of individuals identified as high risk key populations [19, 20] with a broader distribution of the vaccine. This will promote the health of the population and minimize the overall burden of disease as much as possible immediately, in the face of significant morbidity and mortality. The timing of administration of this first dose will likely be more impactful if administered at a time when transmission of SARS-CoV-2 is highest.. Other risks of harm include: o Risk of increased vaccine hesitancy for COVID-19 vaccines and vaccines in general ▪ Decreased acceptability for vaccine if vaccinated individuals get disease ▪ Decreased trust in public health officials making recommendations ▪ Decreased compliance to complete other vaccine series in accordance with recommended intervals o Risk of behaviours associated with a false sense of security in individuals vaccinated with an incomplete series o Potential consequences of distributing the vaccine in a manner that is not consistent with the recommendations from the manufacturer o Risk of anxiety in the vaccinated individual related to uncertainties in degree of protection and vaccine availability for a second dose
Proportionality (Measures should be proportionate to	• ***If half the initial doses are kept on reserve*** so that all initial vaccine recipients can receive both doses in accordance with the recommended interval, the level of risk is proportionate to the benefits gained particularly for those vaccinated in the high-risk key populations identified by NACI [19, 20].

Core Ethical Dimension for Public Health (and Description)	Considerations
the level of risk and benefits gained)	• ***If all doses are immediately distributed*** without reserving doses to complete the vaccine series in accordance with the recommended interval and subsequent supply is insufficient, the level of risk may not be proportionate to the anticipated benefits given the uncertainty of supply for a second dose, limited comparative evidence on the level and duration of protection offered by one vs two doses, and the absence of evidence on interchangeability of vaccine doses.

Effectiveness
 	
(Reasonable likelihood that the action will achieve goals and will be feasible)
	• ***If half the initial doses are kept on reserve*** so that all initial vaccine recipients can receive both doses in accordance with the recommended interval, this may be more likely to achieve Canada's pandemic response goal: "To minimize serious illness and overall deaths while minimizing societal disruption as a result of the COVID-19 pandemic." Though there is insufficient evidence for medium to long-term efficacy for a two-dose schedule, the evidence for duration of protection from a two-dose schedule is comparatively more than evidence of protection from a one-dose schedule. Higher efficacy and maximum immune response were observed after the second COVID-19 vaccine dose.
	• ***If all doses are immediately distributed*** without reserving doses to complete the vaccine series in accordance with the recommended interval, the likelihood that this action would achieve Canada's pandemic response goal may be diminished, due to the uncertainty in the efficacy of one dose beyond the time when the second dose should be given, as well as the uncertainty in arrival of subsequent vaccine supply. If successive shipments of vaccine are delayed, diminished, or do not arrive, this could lead to the following scenarios where the effectiveness is uncertain:
	  ○ Provision of a second dose at an extended interval
	  ○ Provision of a second dose with another mRNA vaccine (presuming availability)
	  ○ Inability to provide a second dose because of a lack of vaccine supply or because the individual who received the initial dose is lost to follow up (which may be more likely in this scenario)
	• However, if evidence evolves to suggest comparative protection with a single dose, delayed dose, or interchangeability of vaccines, then this option would more quickly achieve Canada's pandemic response goal with vaccination of double the number of vaccine recipients initially.

Precaution (Take prudent action in the face of scientific uncertainty)	• Given the higher degree of scientific uncertainty surrounding a one-dose vs two-dose schedule or a mixed schedule with different vaccine products at this time, the most prudent action would be to reserve half the initial doses so that initial vaccine recipients can receive both doses in accordance with the recommended interval, until more evidence becomes available. • Additional evidence on the efficacy of one dose, the duration of protection of one dose, interchangeability of vaccine products, maximum intervals between doses, and security of anticipated supply could mitigate risks of distributing all doses immediately without reserving doses to complete the vaccination schedule in accordance with the recommended interval.
Reciprocity (Minimize the disproportionate	• Healthcare providers and staff of congregate living settings that provide care for seniors are among the key populations identified to receive initial doses [20] of COVID-19 vaccine. • ***If half the initial doses are kept on reserve*** so that all initial vaccine recipients can receive both doses in accordance with the recommended interval, this would minimize the risks to these individuals who take on an additional burden and

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burden faced by those taking on additional risk to protect the public)	increased risk to provide care to protect the public and those who are most vulnerable to severe COVID-19 disease. Vaccinating with both doses on schedule enables those who receive the vaccine to receive the greatest possible protection, based on the best scientific evidence available. • ***If all doses are immediately distributed*** without reserving doses to complete the vaccine series in accordance with the recommended interval, double the number of healthcare providers and staff of congregate living settings that provide care for seniors could be vaccinated in the initial stages of vaccine roll out. However, there is a risk that these individuals will not be protected to the same degree and for the same length of time as if they had been vaccinated with two doses in accordance with the recommended interval.
Justice (Treat people and groups with equal concern and respect) • **Distributive justice** (Fair and feasible distribution of resource)	• ***If half the initial doses are kept on reserve*** so that all initial vaccine recipients can receive both doses in accordance with the recommended interval: o Those vaccinated in the high-risk groups identified as key populations for early immunization by NACI [19] with the guiding principle of equity will achieve maximum protection given the current state of evidence, which supports the principle of equity. o If initial vaccine supply is not sufficient to vaccinate all individuals in high risk groups identified as key populations for early immunization by NACI, then health equity principles may be undermined especially when local disease burden is high and there is some evidence of short-term protection with one dose of vaccine. o Reserving doses may be less logistically feasible initially due to storage requirements of reserved doses and security of these doses in the context of high demand for vaccine. o Fair and feasible distribution of resources will require consideration of when, where, and how follow up with individuals will be done to complete the vaccine series. • ***If all doses are immediately distributed*** without reserving doses to complete the vaccine series in accordance with the recommended interval: o This may provide greater access to a greater number of individuals providing at least some short-term protection, which could increase equity when local disease burden is high. However, health equity principles may be undermined if protection is not adequate and subsequent supply is insufficient, putting key populations at high risk of infection and disease. o High-risk groups prioritized for early immunization [19] could perceive that they are not worthy of receiving the complete vaccine schedule, leading to further stigmatization and disadvantage. o This may be more logistically feasible initially for vaccine rollout, however tracking of individuals for follow up dosing may be challenging and resource-intense. Logistical considerations would include: ▪ Fair and feasible distribution of resources will require consideration of when, where and how follow up with individuals will be done, as well as the capacity of immunizers to deliver vaccine quickly and concurrently to manage individuals on delayed schedules.

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	▪ Whether an alternate vaccine product would be available in the setting for the second dose (e.g., Moderna COVID-19 vaccine may be destined for remote and isolated communities due to different storage and handling conditions).
Trust (Long term reliability, integrity, sustainable and mutually fair relationship with individuals and communities)	• Transparency is a key element for fostering public trust. Decision-makers should document, and must be prepared to justify, the decisions that they make. • All plans and decisions must, as much as possible, be made with an appeal to reasons that are mutually agreed upon and work toward collaboratively derived goals. • Trust may be impacted by taking a programming risk management decision without supporting scientific evidence. • Conformity and consistency of COVID-19 immunization programs across jurisdictions in Canada is important, especially in the context of ongoing changes to and differences in recommendations in the pandemic context. • Providing an incomplete schedule early on could erode trust in the necessity of the complete series overall. This is of particular concern given the current state of trust in COVID-19 vaccines and vaccines generally. • Decisions and care should be taken to create opportunities that minimize moral distress, and maximize integrity and well-being. • ***If half the initial doses are kept on reserve*** so that all initial vaccine recipients can receive both doses in accordance with the recommended interval: o This may have a negative impact on public trust due to a perception that only a small number of individuals are getting preferential access despite availability of additional doses. This risk can be mitigated with open communication about the rationale. • ***If all doses are immediately distributed*** without reserving doses to complete the vaccine series in accordance with the recommended interval: o This may have a negative impact on public trust in the COVID-19 immunization program, the COVID-19 response, and vaccines in general. o Perceptions that certain populations are exposed to an experimental approach may be perpetuated. This is of particular concern as many of the key populations prioritized for early immunization [19, 20] experience social inequities and stigmatization and have been subject to inappropriate research historically. o The lack of consistency in approaches between jurisdictions in the initial phases of roll-out of the COVID-19 immunization program could erode public trust in the recommendations and process.

Step 3: Identify and assess options

- Option 1: Distribute half of the initial doses of COVID-19 vaccine and reserve the other half to ensure that all initial vaccine recipients can receive both doses in accordance with the recommended interval.

- Option 2: Distribute all of the initial doses of COVID-19 vaccine without reserving doses to ensure completion of the vaccine series in accordance with the recommended interval. If there is uncertainty in successive vaccine supply, possible subsequent scenarios for this option include:
    a. Subsequent vaccine supplies arrive on schedule with expected quantities of the same vaccine product
    b. Subsequent shipments are delayed or contain less than expected vaccine quantities. If this happens, jurisdictions may be faced with the following options:
        i. Provide second dose at extended interval with the same vaccine product
        ii. Provide the second dose with another mRNA vaccine (presuming availability)

In assessing the different options in the initial phase of vaccine roll out, provinces and territories should consider the ethical considerations outlined above in Step 2, as well as the following elements in their local contexts:

- Ability to vaccinate high risk key populations identified by NACI to receive initial doses of COVID-19 vaccine [20] with current vaccine supply
- COVID-19 epidemic conditions when initial vaccine supply becomes available
- The ability of the manufacturer to provide additional doses of vaccine
- The ability of other parties involved in vaccine delivery to fulfill their obligations to ensure timely delivery
- The availability of sufficient doses to plan for contingencies in the event of spoilage, unexpected logistical issues, etc.
- The ability to evaluate the chosen option
- The need for transparency in decision-making and communication of rationale for all stakeholders, including the individual considering vaccination.

Conclusion:
Provinces and territories will have to determine the best course of action based on their own analysis and logistical contexts, including risks and unintended consequences that may occur as a result of delaying the second dose of vaccine, and in consideration of the in-depth ethical analysis provided here, recognizing that decisions made by provincial/territorial jurisdictions have impact throughout the country. Transparency in decision-making will be vital to foster continued trust. This ethics analysis may evolve as more evidence (e.g., effectiveness and duration of protection from the first dose of COVID-19 vaccine) emerges and as the certainty of vaccine supply increases. Research and evaluation in this area is encouraged.