

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

Recommendations on the use of COVID-19
Vaccines

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January 12, 2021

PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH



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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 and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) 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 December 23, 2020.

Section	Update	Date
Dose, route of administration, and schedule	Section on “Delay in receipt of dose 2 in a COVID-19 vaccine series” has been updated to include calculated vaccine efficacy estimates of COVID-19 vaccines after the first dose.	January X, 2021
Recommendations	Options for the administration of a complete COVID-19 vaccines series to maximize population health benefits in the context of vaccine delivery, epidemiological, and healthcare system capacity considerations have been added.	January X, 2021
Recommendations	Recommendations for immunosuppressed persons, persons with an autoimmune condition, and pregnancy and breastfeeding have been revised for clarity.	January X, 2021
Management Options	A section of management options for COVID-19 immunization program roll-out in the context of limited vaccine supply has been added. This section summarizes available evidence and considerations with decision points to guide jurisdictions in the roll-out of an effective, efficient, and equitable COVID-19 immunization program.	January X, 2021
Appendix A	Calculated vaccine efficacy estimates of the Pfizer-BioNTech COVID-19 vaccine after the first dose have been added.	January X, 2021
Appendix B	Calculated vaccine efficacy estimates of the Moderna COVID-19 vaccine after the first dose have been added.	January X, 2021

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)

- These 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).
- In clinical trials, the vaccines are efficacious in the short-term against symptomatic, confirmed COVID-19 disease; trials are ongoing.
- Protection offered by the first dose is lower than the efficacy achieved after the second dose and there are very limited data on duration of protection from one dose. Peak humoral and specific cellular immune responses occur after the second dose.
- There is currently insufficient 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 both vaccines, some solicited adverse events are reported to be very common (defined as 10% or more) among vaccinees. 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 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 COVID-19 vaccine(s) should be prioritized for the key populations outlined in [NACI's Guidance on the Prioritization of Initial Doses of COVID-19 Vaccine\(s\)](#).

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 vaccine(s) in different key populations, as well as effective and efficient immunization of populations in remote and isolated communities.
- Efforts should be made to improve knowledge about the benefits of vaccines in general and of COVID-19 vaccine(s) 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 vaccine(s) 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 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. [Recommendations on the use of COVID-19 Vaccine](#), published on December 12, 2020 with evidence available to date, including information on the Pfizer-BioNTech COVID-19 vaccine authorized on December 9, 2020. The advisory committee statement was updated on December 23, 2020 with new evidence available and the authorization of the Moderna COVID-19 vaccine on December 23, 2020. This current statement, published on January X, 2021, has been updated to provide options for the administration of a complete COVID-19 vaccines series to maximize population health benefits and to clarify recommendations on those who are immunosuppressed, have an autoimmune condition, or are pregnant or breastfeeding.

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 and December 15, 2020 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.
- 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 vaccine(s).

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. VACCINE(S)

The following section summarizes information about COVID-19 vaccines authorized for use in Canada. More detailed vaccine-specific information is included in the appendices. 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.

IV.1 Preparation(s) of COVID-19 vaccines authorized for use in Canada

Table 1. COVID-19 vaccine(s) authorized for use in Canada

Product Brand Name (Manufacturer)	Pfizer-BioNTech COVID-19 Vaccine (Pfizer-BioNTech)	Moderna COVID-19 Vaccine (Moderna)
Type of vaccine	COVID-19 mRNA	COVID-19 mRNA
Date of authorization in Canada	December 9, 2020	December 23, 2020
Authorized ages for use	16 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)
Schedule ^b	2 Doses, 21 days apart (alternate schedule 28 days apart)	2 Doses, 28 days apart
Route of administration	IM	IM
Nature of the antigen	Prefusion spike protein	Prefusion spike protein
Adjuvant (if present)	None	None
Primary storage requirements pre-puncture	-80°C to -60°C ^c	-25°C to -15°C ^{c, d}
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
Diluent	Yes	No
Usage limit post-puncture	6 hours at +2°C to +25°C ^e	6 hours at +2°C to +25°C
Formats available	Multi-dose vial (5 doses) ^a , preservative-free	Multi-dose vial (10 doses), preservative-free

Abbreviations: IM: intramuscular; mRNA: messenger ribonucleic acid

^a After dilution. Refer to the product monograph available through [Health Canada's Drug Product Database](https://healthcanada.ca/drug-product-database) for choice of diluent and dilution instructions

^b Authorized or alternate schedule. Refer to Table 2 for details

^c Protected from light during storage

^d Do not store on dry ice or below -40°C

^e After dilution, vaccine must be used within 6 hours

IV.2 Efficacy and Effectiveness

Due to the availability of only short-term clinical trial data, the duration of 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) 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) and [Appendix B](#) (for the Moderna 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 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.

The clinical trial data demonstrates that the authorized 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 mRNA COVID-19 vaccines, however trials are ongoing and this Statement will be updated as evidence emerges.

Efficacy against severe disease

There are no data yet to be able to assess the efficacy of the authorized mRNA COVID-19 vaccines against hospitalizations or deaths specifically.

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.

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 and studies are ongoing.

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, medium (longer than 3 months) and 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) 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) and [Appendix B](#) (for the Moderna COVID-19 vaccine).

Humoral immune responses

The peak humoral immune response to both authorized mRNA COVID-19 vaccines occurred one to two weeks after administration of the second dose, based on a small number of participants. The antibody response decreased from peak levels but was detectable after the full series for the latest date of follow-up; four weeks (Pfizer-BioNTech COVID-19 vaccine) to 3 months (Moderna COVID-19 vaccine). Evidence beyond these time intervals after series completion for these vaccines, is not available at this time. The immune response (neutralizing antibodies) elicited by one dose accounted for a portion of the maximum response seen after the second dose, with evidence of boosting after the second dose. In general, immune responses in older adults were equivalent or lower than immune responses in younger adults.

Cellular immune responses

The authorized mRNA COVID-19 vaccines have been shown to produce a cellular immune response by one to two weeks after administration of the second dose. Increases in this response were seen in both younger and older adults. Refer to [Appendix A](#) and [Appendix B](#) 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.

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.

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	28 days

Moderna COVID-19 (Moderna)	2-dose schedule	21 days	28 days	None
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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.

Delay in receipt of dose 2 in a 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 7-14 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. The efficacy estimates are based on a short period of follow-up (median 28 days) and therefore cannot predict the duration of protection offered by one dose beyond this short period of time. 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 the [Management Options](#) section 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 C](#) 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.

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.

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. 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. Active surveillance of effectiveness and safety of this mixed schedule will

be important in these individuals. 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.

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

IV.5 Serological Testing

Serologic testing is not needed before or after immunization with COVID-19 vaccine.

IV.6 Storage Requirements

Pfizer-BioNTech COVID-19 vaccine

Frozen vials prior to use

The Pfizer-BioNTech COVID-19 vaccine must be stored at ultra-low temperatures of -80°C to -60°C and protected from light, in the original packaging, until ready to use.

Refer to the re-icing guidelines (available at [CVDVaccine.ca](https://www.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 +25°C) for no more than 2 hours. During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light. Thawed vials can be handled in room light conditions.

Do not refreeze thawed vials.

Thawed, punctured vials (after dilution)

The Pfizer-BioNTech COVID-19 vaccine must be stored between +2°C to +25°C and used within 6 hours from the time of dilution. During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light. After dilution, the vaccine vials can be handled in room light conditions.

Moderna COVID-19 vaccine

Frozen vials prior to use

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

Thawed, unpunctured vials

If not punctured, the Moderna COVID-19 vaccine can be thawed and stored at +2°C to +8°C for up to 30 days, or at +8°C to +25°C for up to 12 hours.

Do not refreeze thawed vials.

Thawed, punctured vials

The Moderna COVID-19 vaccine can be stored between +2°C to below +25°C but must be discarded after 6 hours from the time of first puncture.

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 the administration of the complete two-dose vaccine series of an mRNA 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 administering a COVID-19 vaccine to prevent erroneous attribution of an AEFI to a particular vaccine.

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

IV.8 Vaccine Safety and Adverse Events Following Immunization (AEFI)

Due to limitations in the number of participants and duration of follow-up from COVID-19 clinical trials, medium- and long-term evidence on vaccine safety is limited. However, studies are ongoing.

The following section highlights key safety and AEFI data for the authorized mRNA COVID-19 vaccines. For additional details regarding trial design, including study population and length of follow-up, and safety for the mRNA vaccines, refer to the evidence summaries in [Appendix A](#) (for the Pfizer-BioNTech COVID-19 vaccine) and [Appendix B](#) (for the Moderna 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 vaccinees; very common adverse events occur in 10% or more of vaccinees. Please see [Appendix D](#) for a summary of adverse events identified in clinical trials of authorized mRNA COVID-19 vaccines.

mRNA COVID-19 Vaccines

Local

Pain at the injection site is very common after administration of the currently authorized COVID-19 vaccines. More than 80% 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. Pain at the injection site was slightly more frequent in younger adults compared to older adults.

Systemic

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

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

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

mRNA COVID-19 Vaccines

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 but was uncommonly reported after administration of the Pfizer-BioNTech COVID-19 vaccine.

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

Contraindications

The authorized COVID-19 vaccines are contraindicated in individuals with a history of anaphylaxis after previous administration of the vaccine. Vaccine is also contraindicated in persons with proven immediate or anaphylactic hypersensitivity to any component of the vaccine or its

packaging. 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. Individuals with a history of severe allergic reaction to a component of the COVID-19 vaccine should not receive that COVID-19 vaccine.

For a comprehensive list of components in the vaccine and packaging, please consult the product leaflet or information contained within the product monograph available through [Health Canada's Drug Product Database](#).

Potential non-medicinal ingredients in the vaccines known to cause type 1 hypersensitivity reactions ranging from mild cutaneous reactions to anaphylaxis are summarized in Table 3.

Table 3. Potential allergens known to cause type 1 hypersensitivity reactions

Vaccine product (manufacturer)	Potential allergen included in the vaccine or its container*	Other products where the allergen may be found^a
Pfizer-BioNTech COVID-19 (Pfizer-BioNTech)	polyethylene glycol (PEG)	Bowel preparation products for colonoscopy, laxatives, cough syrup, cosmetics, contact lens care solutions, skin care products, and as an additive in some food and drinks
Moderna COVID-19 (Moderna)	polyethylene glycol (PEG)	Bowel preparation products for colonoscopy, laxatives, cough syrup, cosmetics, contact lens care solutions, skin care products, and as an additive in some food and drinks

^aN.B. This may not be a complete list.

In situations of suspected hypersensitivity or non-anaphylactic allergy to COVID-19 vaccine components, investigation is indicated which may lead to vaccination in a controlled setting. Consultation with an allergist is advised. Most instances of anaphylaxis to a vaccine begin within 30 minutes after administration of vaccine. Therefore, if there is a specific concern about a possible allergy to a component of the COVID-19 vaccine being administered, an extended period of observation post-vaccination of 30 minutes may be warranted. [Recommendations for the post-vaccination observation period for other vaccines during the pandemic, such as for influenza vaccine](#), should continue to be followed.

Refer to [Anaphylaxis and Other Acute Reactions Following Vaccination](#) in the CIG, Part 2 - Vaccine Safety for additional information on the management of anaphylaxis post-vaccination in a community setting.

Precautions

In individuals with bleeding disorders, the condition should be optimally 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 infection with SARS-CoV-2 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 symptoms of an acute illness that could be confused with symptoms of COVID-19 or a vaccine adverse event are resolved before vaccinating with an authorized COVID-19 vaccine.

Refer to [Contraindications, Precautions and Concerns](#) 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.

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 6 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). 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 COVID-19 vaccine should be prioritized for the key populations outlined in [NACI's Guidance on the Prioritization of Initial Doses of COVID-19 Vaccine\(s\)](#). (Strong NACI Recommendation)**

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.
- 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 complete series 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. There is currently very limited data available on protection provided by an incomplete series (i.e., one dose) and data available have an extremely short follow up period. Efficacy of a two-dose series was consistent across age groups, and 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 vaccines are similarly safe and efficacious in those with one or more comorbidities (e.g., body mass index ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, cardiac disease).
- **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 vaccine by delaying the second dose, until further supplies of the 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](#) section 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°C is now possible.
 - Please refer to NACI's previous guidance on [key populations for early COVID-19 immunization](#) and [prioritization of initial doses of 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 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 mRNA 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. 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 vaccine in this population. (*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 mRNA 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 mRNA vaccines.
- People living with HIV that 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 vaccine 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 vaccine 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 vaccine 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 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 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 an mRNA COVID-19 vaccine. An mRNA 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 the mRNA 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 vaccine(s) should not be offered to individuals who are not in the authorized age group. (*Strong NACI Recommendation*).**

- 8a. 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) and 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 clinical trials 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 vaccine(s) in different key populations, as well as effective and efficient immunization of populations in remote and isolated communities.
- Efforts should be made to improve knowledge about the benefits of vaccines in general and of COVID-19 vaccine(s) specifically once available, address misinformation, and communicate transparently about COVID-19 vaccine allocation decisions.

MANAGEMENT OPTIONS FOR COVID-19 IMMUNIZATION PROGRAM ROLL-OUT IN THE CONTEXT OF LIMITED VACCINE 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 4.

Table 4. 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 ¹¹ (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 ¹² (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.” -“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 ¹³ (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 ¹⁴ (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 (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 5. Management Options Table for COVID-19 immunization program roll-out in the context of limited vaccine supply

Options to distribute initial doses of COVID-19 vaccine	Considerations <i>(Summary of available evidence and issues for consideration)</i>
<p>Distribute all of the initial doses of COVID-19 vaccine without assurance that initial vaccine recipients can receive both doses in accordance with the recommended interval.</p> <p>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.</p>	<p>Epidemiology</p> <ul style="list-style-type: none"> -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. <p>Efficacy/Effectiveness</p> <ul style="list-style-type: none"> -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. <p>Immunogenicity</p> <ul style="list-style-type: none"> -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. -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.

	<p>- 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.</p> <p>Ethics*</p> <p>-An individual's ability to make an informed choice may be limited in the face of uncertainty in protection and supply with this option.</p> <p>-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, sufficient evidence is not yet available and more research is encouraged.</p> <p>Equity</p> <p>-This option may provide greater access to vaccine for a greater number of individuals identified as high risk key populations,^(15,16) 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.</p> <p>Feasibility</p> <p>-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.</p> <p>-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.</p> <p>Acceptability</p> <p>-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.</p> <p>Given uncertainties around the impact of the extended interval, if the rationale for this option is not communicated clearly and transparently it may:</p> <ul style="list-style-type: none"> -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 -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 COVID-19 vaccine in a manner that ensures all initial	<p>Epidemiology</p> <p>-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.</p>

<p>vaccine recipients can receive both doses in accordance with the recommended interval (e.g. reserve or stagger doses).</p> <p>This may result in fewer individuals who will receive the first dose of vaccine early on in the roll out of the immunization program.</p>	<ul style="list-style-type: none"> -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. <p>Efficacy/Effectiveness</p> <ul style="list-style-type: none"> -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. <p>Immunogenicity</p> <ul style="list-style-type: none"> -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. <p>Ethics*</p> <ul style="list-style-type: none"> -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. <p>Equity</p> <ul style="list-style-type: none"> -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. <p>Feasibility</p> <ul style="list-style-type: none"> -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. <p>Acceptability</p>
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	<p>-Individuals who are expecting a complete two-dose vaccine series according to the recommended schedule will find this option more acceptable.</p> <p>-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.</p>
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* 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 5, 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^(15,16)
 - 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 vaccinees 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 and medium and long-term duration of protection of a complete series of COVID-19 vaccine?
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, 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. 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?
 - b. 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. Is SARS-CoV-2 natural infection (symptomatic or asymptomatic) associated with protection against re-infection or severe disease? How are immune responses induced by natural infection similar or different from those induced by vaccines against COVID-19?
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?
 - b. Which immune responses are most important for protection from infection (adaptive or innate immunity), severe disease or transmissibility?
 - c. Are immunoglobulin (Ig)A/IgG/IgM antibodies protective against SARS-CoV-2 and what is the correlate of protection?
 - d. Is there a cell-mediated immunity correlate of protection against SARS-CoV-2?
6. What level of COVID-19 vaccination coverage is required to achieve herd immunity and is herd immunity achievable given the available vaccine(s)' characteristics?
7. What is the efficacy, effectiveness, and immunogenicity of a single dose of COVID-19 vaccine(s) authorized as a two-dose series? How long is the duration of protection for an incomplete series?

8. What is the background level of Canadian vaccine-vector-specific responses? Are these responses higher in some groups? Will these responses interfere with vaccine efficacy of these highly seropositive groups?
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?

Vaccine Administration

13. Are COVID-19 vaccines of similar or different platforms interchangeable?
14. 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?
15. Are any other vaccines (e.g., Bacillus Calmette-Guérin) protective against COVID-19 through off-target effects?
16. 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?
17. 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 vaccine(s) 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 vaccine(s) evolve in different epidemiological contexts across the country?
 - d. What strategies can improve acceptability of a COVID-19 vaccine in these groups?
- 4. How can vaccine allocation decisions be communicated to individuals and communities in order to maintain trust in public health authorities?
- 5. What COVID-19 vaccination strategies or implementation strategies can reduce health inequities in populations directly targeted by vaccination and in populations not directly targeted by immunization?
- 6. Can a different COVID-19 vaccine be used to complete a primary series or as a booster dose? How are returning travellers managed if they have initiated but not completed a COVID-19 vaccine series abroad?

Health-Related Quality of Life and Well-being

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

VII. SURVEILLANCE ISSUES

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

1. Epidemiology
 - Enhance social and socioeconomic data collected and made available to understand and address health inequities related to COVID-19
 - Systematic examination of the Canadian burden and epidemiology of COVID-19 outbreaks by setting and severity, identifying high-risk activities, settings and populations
 - Evaluation of the success of public health interventions to minimize or prevent COVID-19 outbreak events, especially in vulnerable or high-risk communities
2. Laboratory (e.g., strain characterization)
 - Enhance laboratory surveillance in order to provide early warning of increasing or decreasing activity by age, sex, and presence of symptoms, and help interpret case data based on changes to testing algorithms
 - Conduct genomic surveillance to identify international and inter-provincial transmission and new strains/variants with differing severity, transmissibility, or vaccine comparability
 - Explore other SARS-CoV-2 detection kits at point of care with immediate results.
3. Vaccine (coverage, effectiveness, safety)
 - Reliably monitor coverage rates for each authorized COVID-19 vaccine in different key populations, ensuring data on series completion
 - Ensure existing mechanisms for the evaluation of adverse events are positioned to generate data for each authorized COVID-19 vaccine

TABLES

Table 6. Strength of NACI Recommendations

Strength of NACI Recommendation <i>based on factors not isolated to strength of evidence</i> (e.g., public health need)	STRONG	DISCRETIONARY
Wording	<i>"should/should not be offered"</i>	<i>"may/may not be offered"</i>
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

<i>Abbreviation</i>	<i>Term</i>
AE	Adverse event
AEFI	Adverse event following immunization
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
mRNA	messenger ribonucleic acid
NACI	National Advisory Committee on Immunization
PCR	Polymerase chain reaction
PHAC	Public Health Agency of Canada
SAE	Serious adverse events
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
VPD	Vaccine Preventable Disease
WHO	World Health Organization

ACKNOWLEDGMENTS

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

NACI gratefully acknowledges the contribution of: Ms. S. Pierre, Ms. C. Jensen, Ms. E Tice, Ms. K Farrah, Ms. A Sinilaite, Ms. MW Yeung, Ms. L Whitmore, Mr. J Shurgold, Ms. J Vachon, Ms. J Macri, Ms. J Mielczarek, Ms. M Matthieu-Higgins, Ms. V Ferrante, Ms. R Goddard, Mr. B Sader, Dr B Warshawsky, Mr. M Patel, Ms. A House, Ms. E Wong, and Dr. AA Nam, and the PHAC Public Health Ethics Consultative Group.

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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⁽¹⁷⁾.

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⁽¹⁸⁾.

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⁽¹⁸⁾ 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%).

Pfizer-BioNTech vaccine efficacy against the first occurrence of symptomatic COVID-19 disease after dose 1*			
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†	2	27	92.3% (69 to 98%)

*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)

†Comité sur l'immunisation du Québec. Stratégie de vaccination contre la COVID-19 : report de la 2^e 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 (SAEs)

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 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⁽¹⁹⁾.

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⁽¹⁹⁾ 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.

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. Peak S-2P binding for 100ug dose GMFR (vs day 1) on day 43 were 348444.2 and on day 119 were 120772.9 for the 18-55y age group; 52374.3 on day 43 and 11733.9 on day 119 for 56-70y; and 86577.5 on day 43 and 3275.3 on day 119 for 70y+.

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)⁽²⁰⁾. 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⁽²⁰⁾. 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%)⁽²⁰⁾.

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⁽²⁰⁾. 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 ($>38.9^{\circ}\text{C}$ 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 ($>40.0^{\circ}\text{C}$) 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⁽²⁰⁾. 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.

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

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 COVID-19 vaccine product according to the schedule summarized in Table 2 of this advisory committee statement. As such, the NACI Secretariat has 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
<p>Respect for persons and communities</p> <p>(Right to exercise informed choice based on all available evidence)</p>	<ul style="list-style-type: none"> • 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. <ul style="list-style-type: none"> ○ 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. <ul style="list-style-type: none"> ▪ Evidence on the safety and efficacy available from clinical trials could be provided with assurance if a second dose would be provided on schedule. ▪ 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. ○ 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: <ul style="list-style-type: none"> ▪ the timing of a second shipment of the authorized vaccine; and ▪ safety and efficacy.

Core Ethical Dimension for Public Health (and Description)	Considerations
	<ul style="list-style-type: none"> 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 <p>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.</p>
<p>Beneficence and non-maleficence</p> <p>(Promotion of well-being, minimize risk of harm vs benefits)</p>	<ul style="list-style-type: none"> • <i>If half the initial doses are kept on reserve</i> 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^(15,16) that have been identified to receive initial doses of COVID-19 vaccine by NACI. • <i>If all doses are immediately distributed</i> 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^(15,16) 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. However, there is a possible risk of harm in the longer term if subsequent vaccine supply does not arrive as planned with limited evidence on the efficacy of one dose compared to two doses, no evidence on interchangeability, and the potential for a wasted precious resource if one dose is found not to offer sufficient protection. Other risks of harm include: <ul style="list-style-type: none"> ○ Risk of increased vaccine hesitancy for COVID-19 vaccines and vaccines in general <ul style="list-style-type: none"> ▪ 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 ○ Risk of behaviours associated with a false sense of security in individuals vaccinated with an incomplete series ○ Potential consequences of distributing the vaccine in a manner that is not consistent with the recommendations from the manufacturer ○ Risk of anxiety in the vaccinated individual related to uncertainties in degree of protection and vaccine availability for a second dose
<p>Proportionality</p> <p>(Measures should be proportionate to the level of risk and benefits gained)</p>	<ul style="list-style-type: none"> • <i>If half the initial doses are kept on reserve</i> 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^(15,16). • <i>If all doses are immediately distributed</i> 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.

Core Ethical Dimension for Public Health (and Description)	Considerations
Effectiveness (Reasonable likelihood that the action will achieve goals and will be feasible)	<ul style="list-style-type: none"> • <i>If half the initial doses are kept on reserve</i> 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. • <i>If all doses are immediately distributed</i> 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: <ul style="list-style-type: none"> ○ 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)	<ul style="list-style-type: none"> • 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 burden faced by those taking on additional risk to protect the public)	<ul style="list-style-type: none"> • Healthcare providers and staff of congregate living settings that provide care for seniors are among the key populations identified to receive initial doses⁽¹⁶⁾ of COVID-19 vaccine. • <i>If half the initial doses are kept on reserve</i> 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 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. • <i>If all doses are immediately distributed</i> 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

Core Ethical Dimension for Public Health (and Description)	Considerations
	<p>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.</p>
<p>Justice</p> <p>(Treat people and groups with equal concern and respect)</p> <ul style="list-style-type: none"> • Distributive justice <p>(Fair and feasible distribution of resource)</p>	<ul style="list-style-type: none"> • <i>If half the initial doses are kept on reserve</i> so that all initial vaccine recipients can receive both doses in accordance with the recommended interval: <ul style="list-style-type: none"> ○ Those vaccinated in the high-risk groups identified as key populations for early immunization by NACI⁽¹⁵⁾ with the guiding principle of equity will achieve maximum protection given the current state of evidence, which supports the principle of equity. ○ 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. ○ 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. ○ 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. • <i>If all doses are immediately distributed</i> without reserving doses to complete the vaccine series in accordance with the recommended interval: <ul style="list-style-type: none"> ○ 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. ○ High-risk groups prioritized for early immunization⁽¹⁵⁾ could perceive that they are not worthy of receiving the complete vaccine schedule, leading to further stigmatization and disadvantage. ○ This may be more logistically feasible initially for vaccine rollout, however tracking of individuals for follow up dosing may be challenging and resource-intensive. Logistical considerations would include: <ul style="list-style-type: none"> ▪ 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. ▪ 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)
<p>Trust</p>	<ul style="list-style-type: none"> • Transparency is a key element for fostering public trust. Decision-makers should document, and must be prepared to justify, the decisions that they make.

Core Ethical Dimension for Public Health (and Description)	Considerations
(Long term reliability, integrity, sustainable and mutually fair relationship with individuals and communities)	<ul style="list-style-type: none"> • 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. • <i>If half the initial doses are kept on reserve</i> so that all initial vaccine recipients can receive both doses in accordance with the recommended interval: <ul style="list-style-type: none"> ○ 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. • <i>If all doses are immediately distributed</i> without reserving doses to complete the vaccine series in accordance with the recommended interval: <ul style="list-style-type: none"> ○ This may have a negative impact on public trust in the COVID-19 immunization program, the COVID-19 response, and vaccines in general. ○ 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^(15,16) experience social inequities and stigmatization and have been subject to inappropriate research historically. ○ 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⁽¹⁶⁾ 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.

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

AEFI	Pfizer-BioNTech COVID-19 Vaccine				Moderna COVID-19 Vaccine			
	Vaccine		Placebo control		Vaccine		Placebo control	
	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
Redness	Common	Common	Common	Rare	Common	Common	Uncommon	Uncommon
Swelling	Common	Common	Rare	Rare	Common	Very Common	Uncommon	Uncommon
Lymphadenopathy / Axillary swelling and tenderness	NS ^b	NS ^b	NS ^b	NS ^b	Very Common	Very Common	Common	Common
Fatigue	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
Muscle Pain	Very Common	Very Common	Common	Common	Very Common	Very Common	Very Common	Very Common
Chills	Very Common	Very Common	Common	Common	Common	Very Common	Common	Common
Joint Pain	Common	Very Common	Common	Common	Very Common	Very Common	Very Common	Very Common
Fever	Common	Very Common	Uncommon	Uncommon	Uncommon	Very Common	Uncommon	Uncommon
Diarrhea	Common	Common	Common	Common	NS	NS	NS	NS
Nausea and/or Vomiting	Uncommon	Common	Uncommon	Uncommon	Common	Very Common	Common	Common

Abbreviations: NS: not solicited

^a Very common = occur in 10% or more of vaccinees, common = occur in 1 to less than 10% of vaccinees, uncommon = occur in 0.1% to less than 1% of vaccinees

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