



## Important Notice

On November 3, 2022, Health Canada authorized the use of the Moderna Spikevax BA.4/5 bivalent mRNA COVID-19 vaccine in adults 18 years of age and older.

Information regarding the use of this vaccine is available in the [Summary of National Advisory Committee on Immunization \(NACI\) updates of November 3, 2022: Recommendations on the use of Moderna Spikevax BA.4/5 bivalent mRNA \(50 mcg\) COVID-19 booster vaccine in adults](#).

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

Updated guidance on COVID-19 vaccine booster doses  
in Canada

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Directives mises à jour sur les doses de rappel du vaccin contre la COVID-19 au Canada

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

## BACKGROUND

On September 1, 2022, NACI published [Recommendations on the use of bivalent Omicron-containing mRNA COVID-19 vaccines](#). This followed Health Canada's authorization of the Moderna Spikevax BA.1 Bivalent (50 mcg) Omicron-containing vaccine as a booster dose for adults  $\geq 18$  years of age. The statement outlined recommendations for the use of this bivalent Omicron-containing mRNA vaccine as a booster dose in specific populations, ahead of the uncertain trajectory of the COVID-19 pandemic in the coming months, and how this new vaccine fit into the current landscape of the Canadian COVID-19 vaccination program. Since that time:

- On October 7, 2022, Health Canada authorized the use of the Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg) COVID-19 vaccine as a booster dose in individuals  $\geq 12$  years of age. The Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg) COVID-19 vaccine is the second bivalent Omicron-containing mRNA COVID-19 vaccine authorized for use in Canada.
- The epidemiology of COVID-19 continues to change and there is still considerable uncertainty regarding the likelihood, timing, and severity of potential future COVID-19 waves. It is possible that, consistent with other respiratory viruses, the incidence of COVID-19 may increase in late fall and winter and/or that new variants of concern (VOCs) may emerge.
- Although Omicron and its sublineages have largely been associated with less severe illness compared to previous VOCs, the severity of Omicron sublineages BA.4 and BA.5 in comparison to other Omicron sublineages is currently unclear, and data are still emerging at this time <sup>(1-3)</sup>.
- The Omicron variant has demonstrated partial evasion of immunity conferred by the original COVID-19 vaccines or by a previous infection with a SARS-CoV-2 variant that emerged prior to Omicron. The immune evasion exhibited by Omicron sublineages BA.4 and BA.5 may be greater than that exhibited by previous Omicron sublineages, although evidence is still emerging at this time.
- While the proportion of Canadians vaccinated with a primary series is high, the proportion who have received at least one additional dose has plateaued at a much lower level.

NACI continues to strongly recommend a primary series with an original mRNA vaccine in all individuals 5 years of age and up, and that children 6 months to 4 years of age may receive a primary series with an original mRNA vaccine. NACI has also previously provided recommendations for a booster dose with an authorized COVID-19 vaccine for all adults, adolescents, and children 5-11 years of age. Immunization of those who are eligible for vaccination but have not yet received their recommended doses (primary series or booster) remains a top priority in Canada. As with previous COVID-19 booster programs, a fall booster dose will be most important for older adults (i.e.,  $\geq 65$  years of age) and other populations at increased risk of severe COVID-19 disease (e.g., individuals with immunocompromising conditions).



NACI continues to monitor the rapidly evolving scientific data while recognizing that the trajectory of the COVID-19 pandemic remains unclear. Updated recommendations will be made as needed.

NACI's recommendations remain aligned with the goals of the Canadian COVID-19 Pandemic Response that were updated on [February 14, 2022](#):

- To minimize serious illness and death while minimizing societal disruption as a result of the COVID-19 pandemic
- To transition away from the crisis phase towards a more sustainable approach to long term management of COVID-19

## METHODS

NACI's recommendations on booster doses are based on the decision-making framework outlined in the published statement [Interim guidance on booster COVID-19 vaccine doses in Canada](#). This framework has been updated with evolving evidence (e.g., including considerations of population level cumulative immunity and vaccine coverage) as outlined in the published statement [Interim guidance on planning considerations for a fall 2022 COVID-19 vaccine booster program in Canada](#). Recommendations are based on evidence of the need for (e.g., increased risk of severe illness from COVID-19 and/or waning protection due to increased time since last dose or infection) and benefit of (e.g., safety and effectiveness) booster doses in the Canadian context.

On September 13 and 27, 2022, NACI reviewed available evidence on the burden of illness and booster dose acceptability in the Canadian population and evidence of waning vaccine effectiveness of the original mRNA COVID-19 vaccines. NACI also reviewed available preclinical data on the use of the Pfizer-BioNTech Comirnaty BA.4/5 Bivalent Omicron-containing mRNA COVID-19 vaccine (including manufacturer's preclinical data in the regulatory submission to Health Canada and published scientific literature) and available clinical data on the use of the Pfizer-BioNTech Comirnaty BA.1 Bivalent Omicron-containing mRNA COVID-19 vaccine candidate. Additionally, NACI reviewed evidence of post-market safety of original mRNA vaccines pertaining to myocarditis and/or pericarditis.

Ethical considerations related to the use of, and recommendations for, bivalent Omicron-containing mRNA COVID-19 vaccines were discussed with the Public Health Ethics Consultative Group (PHECG) on July 12, 2022.

NACI approved the updated recommendations on the use of COVID-19 vaccine booster doses on September 30, 2022.

For further information on NACI's recommendations on the use of COVID-19 vaccines, please refer to [NACI's: Statements and publications](#) and the [COVID-19 vaccine chapter](#) in the [Canadian Immunization Guide \(CIG\)](#).

Further information on [NACI's process and procedures](#) is available elsewhere <sup>(4, 5)</sup>.

# OVERVIEW OF EVIDENCE

## Evolving epidemiology

- Canada experienced a resurgence in confirmed SARS-CoV-2 infections during the 2022 summer months, driven primarily by the Omicron BA.4 and BA.5 sublineages. Although the number of confirmed SARS-CoV-2 infections has decreased in recent weeks, test positivity remains elevated compared to historical trends and is considered high compared to other low points during the Omicron period. It is also possible that, consistent with other respiratory viruses, the incidence of COVID-19 will increase again in the late fall and winter, thus posing a risk for individuals/communities and increasing pressure on health systems. For the most up-to-date epidemiology of COVID-19 in Canada, please refer to the Government of Canada's [COVID-19 epidemiology update](#).
- Indicators of disease severity (i.e., hospitalizations and intensive care unit [ICU] admissions) also increased during the summer wave. Recent weeks have seen a decrease in hospitalization and ICU rates; however, it is possible that disease severity indicators increase again in the late fall and winter. The incidence of severe outcomes remains significantly higher in unvaccinated compared to vaccinated populations and in adults ≥65 years of age compared to younger age groups; current hospitalization rates in adults ≥80 years of age are higher than pandemic averages.
- Even though Omicron and its sublineages have largely been associated with a smaller proportion of severe disease compared to the previous variants, there is still uncertainty regarding the disease severity of Omicron BA.4 and BA.5 (which currently account for approximately 98% of circulating SARS-CoV-2 in Canada) relative to previous Omicron sublineages. In addition, the surge in SARS-CoV-2 infections caused in part by the increased transmissibility of Omicron BA.4 and BA.5, has had a substantial impact on health system capacity.
- NACI continues to monitor emerging data on additional Omicron sublineages of interest, such as BA.2.75 and BA.4.6. There remains considerable uncertainty regarding the evolutionary trajectory of SARS-CoV-2 and it remains a possibility that future waves of COVID-19 will be driven by either additional Omicron sublineages or novel VOCs.

## Hybrid immunity & seroprevalence

- Available evidence to date shows that hybrid immunity (i.e., protection conferred from both vaccination and infection) is more robust than immunity due to either infection or vaccination alone. However, the duration of protection from hybrid immunity has yet to be fully characterized, and evidence is still emerging regarding hybrid immunity and protection against Omicron sublineages BA.4 and BA.5, the current predominately circulating variants in Canada.
- In vaccinated individuals, a previous SARS-CoV-2 infection with an Omicron VOC confers significant protection from reinfection with Omicron BA.4 and/or BA.5, although the durability of this protection has yet to be established <sup>(2, 3, 6-8)</sup>. However, preliminary evidence also suggests that in vaccinated individuals, protection against reinfection is lower against Omicron BA.5, compared to earlier Omicron sublineages (i.e., BA.2), highlighting the potential immune-escape capability of Omicron BA.5 <sup>(3, 6, 9)</sup>.

- Emerging Canadian evidence suggests that a large proportion of older adults are protected by vaccination but may not have acquired hybrid immunity. In Canada, older adults have higher vaccination coverage (both with a primary series and with additional doses) compared to younger adults <sup>(10)</sup>, and according to recent seroprevalence data, are less likely to have been infected during the Omicron wave compared to younger adults and adolescents <sup>(11)</sup>.
- It is expected that individuals who have been infected with SARS-CoV-2 may optimize their benefit from future vaccine doses by timing them according to the interval since infection, using similar immunological principles to those informing intervals between vaccine doses. Emerging evidence indicates that a longer interval between SARS-CoV-2 infection and vaccination is associated with improved immune responses to COVID-19 vaccines <sup>(12, 13)</sup>. Individuals should carefully assess their individual risk (i.e., risk of SARS-CoV-2 infection and severe outcomes from COVID-19) if choosing to delay the interval between SARS-CoV-2 infection and vaccination beyond those suggested.

#### Vaccine effectiveness of original COVID-19 booster vaccines

- Evidence has shown a reduced vaccine effectiveness (VE) of original COVID-19 vaccines against Omicron compared to VE observed against previous VOCs. VE against Omicron infection after a first booster dose of an original mRNA COVID-19 vaccine is approximately 60% shortly after receipt of the booster dose, and decreases considerably over time in most studies <sup>(14-21)</sup>. However, current data suggests that original mRNA COVID-19 vaccines continue to provide significant protection against hospitalization and severe disease. Initial VE against severe disease is approximately 90% following a first booster dose, and while it remains above 75% up to 26 weeks from the first booster in most studies <sup>(22-26)</sup>, the duration of protection is not yet fully characterized. The majority of available studies were conducted while Omicron BA.1 and BA.2 were the predominately circulating sublineages, and data on VE waning against Omicron BA.4 and/or BA.5 are limited at this time <sup>(27, 28)</sup>.
- Evidence on VE of a second COVID-19 booster dose is currently limited. Recent data from the US have shown that during a period of Omicron BA.2 dominance, among adults at least 50 years of age, a second booster dose of an original mRNA COVID-19 vaccine provided additional protection against emergency department and/or urgent care visits due to COVID-19, as well as hospitalization, compared to those who received one booster dose of an original mRNA COVID-19 vaccine <sup>(22)</sup>. VE studies from Canada and Israel have also demonstrated additional protection compared to a first booster, including against severe disease <sup>(29-33)</sup>. However, the duration of protection from a second booster dose is currently unknown.

#### Summary of Moderna Spikevax BA.1 Bivalent (50 mcg)

- Moderna Spikevax BA.1 Bivalent (50 mcg) was authorized by Health Canada on September 1, 2022 as a booster dose in individuals ≥18 years of age. This 50-mcg formulation contains equal parts (25 mcg each) of mRNA encoding for the original SARS-CoV-2 virus and the Omicron BA.1 variant. When administered as a second booster dose, Moderna Spikevax BA.1 Bivalent (50 mcg) elicited higher neutralizing antibody responses



against the original strain, Omicron BA.1 and Omicron BA.4/BA.5 among individuals with and without prior infection when compared to a second booster dose of Moderna Spikevax original (50 mcg). This effect was consistent across age groups studied (assessed in individuals 18-65 years of age and individuals >65 years of age).

- Clinical trial data <sup>(34)</sup> showed that Moderna Spikevax BA.1 Bivalent (50 mcg) administered as a second booster dose to individuals ≥18 years of age had a similar reactogenicity profile to that of Moderna Spikevax original (50 mcg) given as a second booster dose. Also, the frequency of adverse events following Moderna Spikevax BA.1 Bivalent (50 mcg) given as a second booster dose was similar or lower compared to that of a first booster dose of Moderna Spikevax original (50 mcg), and of the second dose of the Moderna Spikevax original primary series (100 mcg). There were no vaccine-related cases of myocarditis, pericarditis or deaths reported during the study period. No new safety signals were identified with Moderna Spikevax BA.1 Bivalent (50 mcg). However, given the number of participants enrolled in the bivalent clinical trial, it is unlikely that rare adverse events would be detected. NACI will monitor post-market safety surveillance data as it emerges and update its recommendations as needed.
- The levels of antibodies produced by Moderna Spikevax BA.1 Bivalent (50 mcg) as a booster dose against the original strain were superior to those obtained in Phase 3 studies of Moderna Spikevax original, for which clinical efficacy was demonstrated <sup>(35)</sup>. However, the clinical relevance (i.e., applicability to VE) of the changes in neutralizing antibody levels observed with Moderna Spikevax BA.1 Bivalent (50 mcg) compared to Moderna Spikevax original (50 mcg) is unknown at this time. Currently, there are no estimates of VE available for Moderna Spikevax BA.1 Bivalent (50 mcg). Evidence monitoring for VE of Moderna Spikevax BA.1 Bivalent (50 mcg) is ongoing.
- More details regarding the Moderna Spikevax BA.1 Bivalent clinical trial can be found in the appendix of NACI's previously published [Recommendations on the use of bivalent Omicron-containing mRNA COVID-19 vaccines](#).

### Summary of Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg)

- Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg) was authorized by Health Canada on October 7, 2022, as a booster dose in individuals ≥12 years of age. This updated formulation contains equal parts (15 mcg each) of mRNA encoding for the original SARS-CoV-2 virus and the Omicron BA.4/BA.5 variant. No clinical data is currently available for Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg), and thus the regulatory review process was centered around preclinical immunogenicity data from the Pfizer-BioNTech Comirnaty BA.4/5 Bivalent vaccine, as well as indirect clinical data from the use of the Pfizer-BioNTech Comirnaty BA.1 Bivalent (30 mcg) and Pfizer-BioNTech Comirnaty BA.1 Monovalent (30 mcg) vaccine candidates in clinical trials.
- Available preclinical evidence indicates that when given as a booster dose, Pfizer-BioNTech Comirnaty BA.4/5 Bivalent elicited higher neutralizing antibody responses against Omicron BA.2 and BA.4/BA.5, as well as an equivalent neutralizing antibody response against Omicron BA.1, when compared to Pfizer-BioNTech Comirnaty original.

- Immunogenicity and safety of a booster dose of Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg) is inferred from clinical data from the studies of a booster dose of Pfizer-BioNTech Comirnaty BA.1 Bivalent (30 mcg). Data from the Pfizer-BioNTech Comirnaty BA.1 Bivalent vaccine candidate clinical trial (15 mcg each of mRNA encoding for the original strain and Omicron BA.1 variant) [see [Appendix A](#)] <sup>(36)</sup> demonstrated that in adults >55 years of age without evidence of prior SARS-CoV-2 infection receiving a fourth dose, Pfizer-BioNTech Comirnaty BA.1 Bivalent (30 mcg) elicited higher neutralizing antibody responses against Omicron BA.1 and Omicron BA.4/BA.5, as well as an equivalent neutralizing antibody response against the original SARS-CoV-2 strain when compared to Pfizer-BioNTech Comirnaty original (30 mcg). As with other bivalent mRNA COVID-19 vaccines, there are no estimates of vaccine efficacy available for Pfizer-BioNTech Comirnaty BA.4/5 or BA.1 Bivalent vaccines, and the clinical relevance (i.e., applicability to VE) of the changes in neutralizing antibody levels is currently unknown. Evidence monitoring for VE of Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg) is ongoing.
- There are no clinical safety data currently available for Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg) specifically; however, indirect data (clinical and post-market safety data from Pfizer-BioNTech Comirnaty BA.1 Bivalent and Comirnaty original, respectively) suggest that Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg) will likely be well tolerated with a similar safety profile to Comirnaty original (30 mcg) and Comirnaty BA.1 Bivalent (30 mcg), when used as a booster dose. Data from the Pfizer-BioNTech Comirnaty BA.1 Bivalent vaccine candidate clinical trial (see [Appendix A](#)) demonstrated that Pfizer-BioNTech Comirnaty BA.1 Bivalent (30 mcg) had a similar reactogenicity profile as Comirnaty original (30 mcg), when administered as a fourth dose to individuals >55 years of age. There were no vaccine-related cases of myocarditis, pericarditis or deaths reported with the use of Pfizer-BioNTech Comirnaty BA.1 Bivalent (30 mcg), and no new safety signals were identified. However, given the number of participants enrolled in the Pfizer-BioNTech Comirnaty BA.1 Bivalent (30 mcg) clinical trial (see [Appendix A](#)), it is unlikely that rare adverse events would be detected. NACI will vigilantly monitor post-market safety surveillance data as it emerges and update its recommendations as needed.
- Further indirect data for adults 18 to 55 years of age using the Pfizer-BioNTech Comirnaty BA.1 Monovalent (30 mcg) vaccine candidate also demonstrated similar immunogenicity and safety trends in younger adults.
- More details regarding Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg) and BA.1 Bivalent (30 mcg) can be found in [Appendix A](#).

#### Potential benefits of bivalent Omicron-containing vaccines

- Omicron and its sublineages are antigenically distinct from the original SARS-CoV-2 virus, as well as earlier SARS-CoV-2 VOCs, with BA.1 and BA.4/BA.5 emerging as some of the most antigenically distinct sublineages observed to date <sup>(37)</sup>. Given the potential for substantial virus evolution and uncertainty about the emergence of future variants, modification of the strain composition of COVID-19 vaccines is expected to broaden immune protection against divergent SARS-CoV-2 spike protein antigens. Available data, including clinical data on immune responses against BA.1 and BA.4/BA.5 with bivalent Omicron-containing mRNA vaccines, suggest that inclusion of an Omicron component in

an updated booster vaccine composition may have benefits in the form of increased protection against Omicron sublineages <sup>(38)</sup>, although no effectiveness data is currently available. Booster doses with bivalent Omicron-containing mRNA vaccines are expected to elicit a greater breadth of immune response, potentially providing additional protection against future variants of concern, although given the unpredictable nature of the ongoing evolution of SARS-CoV-2, this is uncertain at this time <sup>(37)</sup>.

- Infection with Omicron elicits a robust and broadly cross-reactive antibody response <sup>(39)</sup>. This includes an elevated antibody response against Omicron BA.1 and BA.4/BA.5 <sup>(40)</sup>. Real-world evidence to date demonstrates that in vaccinated individuals, a previous SARS-CoV-2 infection with the Omicron VOC confers significant protection from reinfection with Omicron BA.4 and/or BA.5 <sup>(2, 3, 6-8)</sup>.
- In a clinical trial, individuals who received a second booster dose with Moderna Spikevax BA.1 Bivalent (50 mcg), and who had no evidence of prior SARS-CoV-2 infection, had larger relative increases in neutralizing antibody titres against Omicron BA.1 and BA.4/BA.5 from pre- to post-second booster when compared to those who had evidence of prior SARS-CoV-2 infection. Individuals who received a second booster dose with Moderna Spikevax BA.1 Bivalent (50 mcg) who had evidence of prior SARS-CoV-2 infection, had significantly higher levels of neutralizing antibody titres against Omicron BA.1 and BA.4/BA.5 at both time points (pre- and post-second booster) compared to individuals without evidence of prior infection, however with a smaller relative increase from pre-second booster levels. Similar data were not available for Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg) or BA.1 Bivalent (30 mcg).
- It is possible individuals who are less likely to have been infected during Omicron waves (particularly older adults) may realize additional benefits from a bivalent Omicron-containing mRNA COVID-19 vaccine over time, by priming the immune response to the Omicron variant. Additionally, individuals who were previously infected may experience a greater and more rapidly-induced immune response from a bivalent Omicron-containing mRNA COVID-19 vaccine.

#### Post-market safety of original mRNA booster doses

- Available surveillance data to date from Canada and international jurisdictions indicate that the risk of myocarditis and/or pericarditis following a first booster dose of an original mRNA COVID-19 vaccine appears to be lower than the risk following the second dose of the primary series <sup>(41-48)</sup>.
  - This trend is observed for both Pfizer-BioNTech Comirnaty (30 mcg) and Moderna Spikevax (50 mcg) original vaccine products and across all age groups (including individuals under 30 years of age, for whom the risks are highest). However, a limited number of Moderna Spikevax original (50 mcg) booster doses have been administered to individuals under the age of 30, with even more limited use in adolescents 12-17 years of age given that preferential vaccine recommendations for the Pfizer-BioNTech Comirnaty product for those under the age of 30 exist in many countries and the very limited authorization of adolescent booster doses using Moderna Spikevax original (50 mcg) to date.

- Preliminary post-marketing surveillance data from the US <sup>(41)</sup> and France <sup>(43)</sup> did not identify a statistically significant difference in the rates of myocarditis following administration of the Moderna Spikevax (50 mcg) original booster doses compared to Pfizer-BioNTech Comirnaty (30 mcg) booster doses. Of note, during the period of surveillance, in the US, Moderna Spikevax original (50 mcg) was authorized as a booster dose for use among individuals aged ≥18 years and, in France, Moderna Spikevax original (50 mcg) was recommended for use as a booster dose among individuals aged ≥30 years.
- NACI will also continue to monitor post-market safety and surveillance data and update its recommendations as needed.

#### Ethics, equity, feasibility, and acceptability

- Given the considerable uncertainty regarding the trajectory of the COVID-19 pandemic, NACI based its recommendations on an evidence-informed framework and recommends booster doses focused on those at greatest risk of severe illness from COVID-19.
- Intentions to accept a booster dose of a COVID-19 vaccine in Canada have decreased in 2022, especially amongst younger age groups (i.e., adolescents and young adults). Acceptability surveys indicate that new, bivalent Omicron-containing mRNA COVID-19 vaccines may help to increase acceptance and uptake of booster doses among individuals with positive attitudes regarding COVID-19 vaccines, but may have limited influence on those who are more hesitant.
- PHAC is anticipating sufficient vaccine supply this fall to be able to offer a bivalent Omicron-containing mRNA COVID-19 vaccine to all individuals in the currently authorized age groups.
- NACI continues to recommend the following elements to guide ethical decision-making, as outlined in [NACI's guidance on the Prioritization of Key Populations for COVID-19 Immunization](#):
  - Efforts should be made to increase access to immunization services to prevent and reduce health inequities without further stigmatization or discrimination, and to engage systemically marginalized populations and racialized populations in immunization program planning.
  - Jurisdictions should ensure close and rapid monitoring of safety, coverage and effectiveness of the vaccines in different key populations, as well as effective and efficient immunization of populations in hardly reached, remote and isolated communities.
  - Efforts should be made to improve knowledge about the benefits of vaccines in general and of COVID-19 vaccines in particular, as each becomes available, address misinformation, and communicate transparently about COVID-19 vaccine recommendations.
  - NACI continues to emphasize the importance of completing a primary series of COVID-19 vaccines, the benefit from which is further enhanced with subsequent booster doses.

## Other considerations

- As an immunological correlate of protection has not been determined for COVID-19 at this time, it is unknown how the increased neutralizing antibody responses observed with bivalent Omicron-containing mRNA COVID-19 vaccines are related to protection against severe outcomes from COVID-19.
- There are no clinical data currently available for the use of Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg). All data available to date are either preclinical, or indirect clinical data using a similar vaccine candidate (i.e., Comirnaty BA.1 Bivalent or Comirnaty BA.1 Monovalent). NACI will continue to monitor and assess clinical data for Comirnaty BA.4/5 Bivalent as it becomes available.
- The limited evidence available to date indicates that bivalent Omicron-containing mRNA COVID-19 vaccines induce stronger and more robust immune responses to the Omicron VOC and sublineages, compared to original mRNA vaccines. Currently, there are no clinical data comparing the immune response induced by BA.1 bivalent vaccines to that induced by BA.4/BA.5 bivalent vaccines.
- Real-world evidence from adult populations ( $\geq 18$  years of age) suggest that after a two-dose primary series, Moderna Spikevax original (100 mcg) may result in higher VE compared to Pfizer-BioNTech Comirnaty original (30 mcg) <sup>(49)</sup> and is also associated with a higher seroconversion rate among adult immunocompromised patients <sup>(50)</sup>. Booster vaccination with Moderna Spikevax original (50 mcg) was also found to be more effective than Pfizer-BioNTech Comirnaty original (30 mcg) within the first 12 weeks following vaccination, during a period of Delta followed by Omicron variant dominance <sup>(51)</sup>. However, the relative effectiveness of a booster dose of Moderna Spikevax BA.1 Bivalent (50mcg) compared to Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg) is yet to be determined.
- Although the number of confirmed SARS-CoV-2 infections has decreased in recent weeks, the future trajectory of the COVID-19 pandemic remains unclear and there remains considerable uncertainty regarding the evolutionary trajectory of SARS-CoV-2. Therefore, it remains a possibility that future waves of COVID-19 are driven by novel and distinct VOCs. At this time, it is unknown if an Omicron BA.1 or an Omicron BA.4/BA.5 bivalent vaccine will be more protective against future waves of COVID-19 or future SARS-CoV-2 VOCs. However, since all authorized bivalent vaccines to date contain an Omicron-specific component, any authorized bivalent mRNA COVID-19 vaccine is likely to provide a broad immune response against Omicron sublineages, other VOCs, as well as potential future variants. As the evidence base evolves and the epidemiology of circulating variants changes, if there is an advantage of one bivalent Omicron-containing vaccine over the other, NACI will revisit its recommendations accordingly, including issuing advice on a recommended interval between vaccine doses.
- No participants in the Moderna Spikevax BA.1 Bivalent or Pfizer-BioNTech Comirnaty BA.1 Bivalent clinical trial were concurrently administered other vaccines. Data with regard to the safety and immunogenicity of other authorized COVID-19 vaccines (including original mRNA COVID-19 vaccines) when given concurrently with other vaccines (e.g., influenza vaccination), are currently limited. However, no specific safety concerns have been identified to date <sup>(52-58)</sup>. Studies to assess the safety and immunogenicity of concurrent administration of COVID-19 vaccines with other vaccines are ongoing.



- Currently, there are no clinical data available on the use of bivalent Omicron-containing mRNA COVID-19 vaccines as a primary series, as a first booster dose or as part of a heterologous vaccine series. All participants in the Moderna Spikevax BA.1 Bivalent and Pfizer-BioNTech Comirnaty BA.1 Bivalent clinical trials were administered the vaccine as a second booster dose after a homologous primary series and first booster dose <sup>(38)</sup>. It is likely that the immunological benefits and safety profile will be similar in individuals receiving a bivalent Omicron-containing mRNA COVID-19 vaccine as a booster dose, regardless of number or type of doses previously received. NACI will continue to monitor new evidence as it becomes available.
- Although not authorized or recommended for use as part of a primary series, if a bivalent Omicron-containing mRNA COVID-19 vaccine is administered in error as part of a primary series, this dose should be considered valid as part of the primary series.

## RECOMMENDATIONS

Consistent with NACI's [Interim guidance on planning considerations for a fall 2022 COVID-19 vaccine booster program in Canada](#):

1. **NACI strongly recommends that all individuals  $\geq 65$  years of age and also individuals  $\geq 12$  years of age\* [who are at increased risk of severe illness from COVID-19](#)\*\* should be offered a fall COVID-19 vaccine booster dose regardless of the number of booster doses previously received. (*Strong NACI recommendation*)**
2. **NACI recommends that all other individuals 12 to 64 years of age may be offered a fall COVID-19 vaccine booster dose regardless of the number of booster doses previously received. (*Discretionary NACI recommendation*)**

\*On August 19, 2022, NACI released booster dose recommendations for individuals 5 to 11 years of age which will also be a component of fall booster programs. Please refer to NACI's [Recommendations on the use of a first booster dose of Pfizer-BioNTech Comirnaty COVID-19 vaccine in children 5 to 11 years of age](#).

\*\*For the list of individuals considered to be at an increased risk of severe illness from COVID-19, please refer to NACI's [Interim guidance on planning considerations for a fall 2022 COVID-19 vaccine booster program in Canada](#).

With regard to the product offered;

3. **NACI recommends that bivalent Omicron-containing mRNA COVID-19 vaccines are the preferred booster products for the authorized age groups. (*Strong NACI recommendation*)**
  - Moderna Spikevax BA.1 Bivalent (50 mcg) is authorized by Health Canada as a booster dose in individuals  $\geq 18$  years of age. Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg) is authorized by Health Canada as a booster dose in individuals  $\geq 12$  years of age.
  - For individuals in authorized age groups who are not able or willing to receive a bivalent Omicron-containing mRNA COVID-19 vaccine, an original mRNA COVID-19 vaccine may be offered.

- Individuals who have received an mRNA COVID-19 vaccine as part of a fall COVID-19 vaccine booster program do not require an additional dose of a COVID-19 vaccine at this time. This includes individuals who were vaccinated using any authorized original or bivalent mRNA COVID-19 vaccine. Both original and bivalent mRNA COVID-19 vaccines will boost immune responses and are likely to provide significant protection against hospitalization and severe disease. This recommendation will be reassessed throughout the winter season, as new evidence becomes available.
- NACI continues to recommend that COVID-19 booster doses given as part of the fall program may be offered at an interval of 6 months after a previous COVID-19 vaccine dose or SARS-CoV-2 infection. However, a shorter interval of at least 3 months may be considered particularly in the context of heightened epidemiologic risk, evolving SARS-CoV-2 epidemiology, as well as operational considerations for the efficient deployment of the fall vaccine program. Based on what is known at this time about the virus and vaccines, it is not expected that a booster dose will be routinely provided every 3 months.
- NACI continues to recommend that for all individuals aged 5 years and older, concurrent administration of other vaccines (e.g., seasonal inactivated influenza vaccine) and any dose of a COVID-19 vaccine, regardless of product offered, is acceptable and may increase program efficiency.

#### **Additional considerations and rationale:**

- Currently, there are no clinical data comparing the immune response induced by BA.1 bivalent vaccines to that induced by BA.4/BA.5 bivalent vaccines. Bivalent Omicron-containing COVID-19 vaccines have all been shown to induce stronger and more robust immune responses to the Omicron VOC and sublineages, when compared to original mRNA vaccines, and any authorized bivalent Omicron-containing mRNA COVID-19 vaccine is expected to provide protection against severe outcomes from COVID-19. At this time, there is no evidence to suggest any meaningful difference in protection between the BA.1 and BA.4/BA.5 bivalent vaccines. Moving forward, bivalent vaccines are the preferred vaccine products for the 2022 fall booster program among individuals 12 years of age and older, as they contain Omicron, which is the most antigenically-distinct variant from the original SARS-CoV2 strain.
- There are currently no data available on the efficacy, immunogenicity or safety of bivalent Omicron-containing mRNA COVID-19 vaccines in adolescents 12-17 years of age. There is, however, extensive experience and post-market safety data on the use of Pfizer-BioNTech Comirnaty original (30 mcg) as a booster dose in the adolescent population and both Pfizer-BioNTech Comirnaty products (original and BA.4/5 Bivalent) contain the same total quantity of mRNA (30 mcg). In addition, available data to date suggest that the reactogenicity profile of the bivalent Omicron-containing mRNA COVID-19 vaccines appears similar to that of the original mRNA vaccines.

- In moderately to severely immunocompromised adolescents 12-17 years of age, Moderna Spikevax BA.1 Bivalent (50 mcg) may be considered for off-label use based on clinical discretion, as Moderna Spikevax BA.1 Bivalent (50 mcg) may induce a greater immune response compared to Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg), although there are no direct comparisons available. A Moderna Spikevax original (100 mcg) primary series has been associated with a higher seroconversion rate among adult immunocompromised patients compared to Pfizer-BioNTech Comirnaty original (30 mcg). In a general population of adults, booster vaccination with Moderna Spikevax original (50 mcg) was also found to be more effective than Pfizer-BioNTech Comirnaty original (30 mcg) during a period of Delta followed by Omicron variant dominance. However, these studies were conducted prior to the emergence of the Omicron BA.4/BA.5 VOC, and their applicability to all Omicron sublineages is uncertain.
- Individuals who are less likely to have been infected during Omicron waves (particularly older adults) may realize additional benefits from a bivalent Omicron-containing mRNA COVID-19 vaccine over time, by priming the immune response to the Omicron variant.
- There are currently no data on the use of bivalent Omicron-containing mRNA COVID-19 vaccines as part of a primary series. NACI continues to recommend a primary series with an original mRNA vaccine in all authorized age groups. NACI will continue to monitor evidence as it emerges, and update recommendations as needed.
- At this time, there is a high degree of uncertainty with regards to future booster dose recommendations. To date, SARS-CoV-2 does not have a seasonally established pattern of spread, and the beneficial effects of cumulative population immunity are not yet fully realized. As such, these recommendations apply specifically to [NACI's guidance for fall 2022 booster dose programs](#).
- There may be variability in how each province, territory and community assesses risk and responds to the needs of their respective jurisdictions, with a focus on protecting those at highest risk for serious outcomes from COVID-19.

## NACI RESEARCH PRIORITIES

1. Continuous monitoring of data on the safety, immunogenicity, efficacy, and effectiveness of both the original, and bivalent mRNA COVID-19 vaccines, through clinical trials and studies in real-world settings, including relative VE between COVID-19 vaccine products, degree and duration of protection conferred by each booster dose against circulating variants. Research should also consider the clinical implications of previous SARS-CoV-2 infection; repeated immunization; and outcomes after any infection such as Multisystem Inflammatory Syndrome in Children (MIS-C), post-COVID-19 condition (long COVID), or infection-induced myocarditis and/or pericarditis in older and younger adult, adolescent, and pediatric populations.
2. Continuous monitoring of vaccine coverage and acceptance in the Canadian population, specifically following the authorization of new bivalent Omicron-containing mRNA COVID-19 vaccines.
3. Further evaluations of the optimal interval between booster dose and primary series, and between any subsequent booster doses as well as further evaluations of the optimal interval between previous SARS-CoV-2 infection and booster dose administration.
4. Vigilant monitoring and reporting of adverse events of special interest, including myocarditis and/or pericarditis, to accurately inform potential risks associated with booster doses, for all COVID-19 vaccines, including bivalent Omicron-containing mRNA vaccines. Global collaboration should be prioritized to enable data sharing so decision makers around the world can weigh benefits and risks of multiple booster doses of COVID-19 vaccines.
5. Evaluations of whether bivalent Omicron-containing mRNA COVID-19 vaccines can be used as part of a primary series.
6. Continuous monitoring of COVID-19 epidemiology and VE in special populations (e.g., those with high-risk medical conditions, or social risk factors placing them at high-risk for severe outcomes) and the long-term consequences of COVID-19 in these populations.

## ABBREVIATIONS

CI	Confidence Interval
CIG	Canadian Immunization Guide
COVID-19	Coronavirus disease 2019
GMR	Geometric mean ratio
ICU	Intensive Care Unit
mcg	Micrograms
mRNA	Messenger Ribonucleic Acid
NACI	National Advisory Committee on Immunization
PHAC	Public Health Agency of Canada
PHECG	Public Health Ethics Consultative Group
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
US	United States
VE	Vaccine effectiveness
VOC	Variant of Concern



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## APPENDIX

For information on the Moderna Spikevax BA.1 Bivalent clinical trial data, please see [NACI Statement: Recommendations on the use of bivalent Omicron-containing mRNA COVID-19 vaccines](#) (September 1, 2022).

### Appendix A: Pfizer-BioNTech Comirnaty BA.4/5 Bivalent Data

For complete prescribing information for Pfizer-BioNTech Comirnaty BA.4/5 Bivalent, consult the product leaflet or information contained within Health Canada's authorized product monographs available through the [Drug Product Database](#).

#### Vaccine Characteristics

**Table 1. Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg) vaccine characteristics**

Product characteristics	Pfizer-BioNTech Comirnaty BA.4/5 Bivalent
Date of authorization	October 7, 2022
Age indication	12 years of age and older
Dose	30 mcg (0.3 mL) (15 mcg [0.15 mL] original SARS-CoV-2 + 15 mcg [0.15 mL] Omicron BA.4/BA.5)
Diluent	None required
Presentation	<ul style="list-style-type: none"> <li>• 6 doses per vial</li> <li>• Gray cap vial</li> <li>• Gray label border</li> </ul>
Potential allergens	<ul style="list-style-type: none"> <li>• Polyethylene glycol</li> <li>• Tromethamine (Tris, Trometamol)</li> </ul>
Storage <sup>a</sup>	<ul style="list-style-type: none"> <li>• Frozen until 12 months from the date of manufacture printed on the label</li> <li>• Refrigerated for up to 10 weeks</li> <li>• Unpunctured vials may be stored between 8° to 25°C (46° to 77°F) for up to 12 hours</li> <li>• Once needle-punctured, vials can be stored at room temperature or refrigerated up to 12 hours but cannot be refrozen.</li> </ul>
Transport	Full cartons containing unpunctured vials may be transported at -90°C to -60°C; full cartons or individual unpunctured vials may also be transported at 2°C to 8°C

<sup>a</sup> Frozen vials may be stored at an ultra-low temperature of -90°C to -60°C; Do not store vials at -25°C to -15°C; Refrigerated is +2°C to +8°C; Room temperature is +15°C to +25°C

#### Indirect clinical data using Pfizer-BioNTech Comirnaty BA.1 Bivalent (30 mcg)

Efficacy, immunogenicity and safety of a booster dose of Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg) is inferred from clinical data from the studies of a booster dose of the Pfizer-BioNTech Comirnaty BA.1 Bivalent (30 mcg) vaccine candidate.

### Trial design

The Pfizer-BioNTech Comirnaty BA.1 Bivalent COVID-19 vaccine candidate was evaluated in an ongoing Phase 3, observer-blinded, randomized clinical trial in participants >55 years of age ([Study C4591031, Substudy E](#)). The study evaluated the safety, reactogenicity and immunogenicity of Pfizer-BioNTech Comirnaty BA.1 Bivalent (30 mcg) administered as a fourth dose to adults >55 years of age in the US, who had previously received 3 doses of Pfizer-BioNTech Comirnaty original (30 mcg). Individuals with a previous confirmed SARS-CoV-2 infection were not eligible for inclusion <sup>(59, 60)</sup>. In an interim analysis of 610 individuals, GMRs and seroresponse rates were evaluated at 1 month after booster dose administration, up to a data cut-off date of May 16 2022, which represents a median of at least 1.7 months post-booster follow-up. The Pfizer-BioNTech Comirnaty BA.1 Bivalent (30 mcg) booster dose was administered 4.7 to 11.5 months (median 6.3 months) after the third dose.

### Study Population

Overall, demographic and baseline characteristics were similar between the Pfizer-BioNTech Comirnaty BA.1 Bivalent (30 mcg) and Pfizer-BioNTech Comirnaty original (30 mcg) groups.

### Efficacy

Currently, there are no estimates of vaccine efficacy available for Pfizer-BioNTech Comirnaty BA.1 Bivalent (30 mcg).

### Immunogenicity

The primary objective of the interim analysis was to assess the superiority of Pfizer-BioNTech Comirnaty BA.1 Bivalent (30 mcg) with respect to level of neutralizing antibody titres against Omicron BA.1 and to assess the non-inferiority of Pfizer-BioNTech Comirnaty BA.1 Bivalent (30 mcg) with respect to SRR against Omicron BA.1, compared to Pfizer-BioNTech Comirnaty original (30 mcg) given as a fourth dose in individuals >55 years of age. Superiority was considered met when the lower bound of the 95% CI of GMR is >1 and non-inferiority was considered met when the lower bound of the 95% CI for the percentage difference in SRR is greater than -5. Seroresponse was defined as achieving ≥4-fold increase in GMTs from baseline (i.e., pre-booster). A descriptive analysis of GMTs against the original SARS-CoV-2 strain and Omicron BA.4/BA.5 was also performed for both groups.

#### Superiority of Pfizer-BioNTech Comirnaty BA.1 Bivalent based on GMR against Omicron BA.1

- In the interim analysis, the observed GMTs against Omicron BA.1 at 1 month post-booster were 711.0 (95% CI: 588.3-859.2) and 455.8 (95% CI: 365.9-567.6) in the Pfizer-BioNTech Comirnaty BA.1 Bivalent and Pfizer-BioNTech Comirnaty original groups respectively. The superiority criteria was met, with a GMR of 1.56 (95% CI: 1.17-2.08) <sup>(59, 61)</sup>.

#### Non-inferiority of Pfizer-BioNTech Comirnaty BA.1 Bivalent based on SRR against Omicron BA.1

- In the interim analysis, the Omicron BA.1 SRRs were 71.6% (95% CI: 64.2-78.3) and 57.0% (95% CI: 48.7-65.1), at one month post-booster in the Pfizer-BioNTech Comirnaty BA.1 Bivalent and Pfizer-BioNTech Comirnaty original groups, respectively. The SRR



difference was 14.6% (95% CI: 4.0-24.9), meeting the non-inferiority criterion (lower bound of CI >-5%) <sup>(59)</sup>.

#### Descriptive analysis of antibody response against the original SARS-CoV-2 strain

- In a descriptive analysis, the observed GMTs against original SARS-CoV-2 at 1 month post-booster were 5933.2 (95% CI: 5188.2-6785.2) and 5988.1 (95% CI: 5223.6-6887.4) in the Pfizer-BioNTech Comirnaty BA.1 Bivalent and Pfizer-BioNTech Comirnaty original groups, respectively. This corresponded to a GMR of 0.99 (95% CI: 0.82-1.20) <sup>(61)</sup>.

#### Descriptive analysis of antibody response against Omicron BA.4/BA.5

- In a descriptive analysis, the observed GMTs against Omicron BA.4/BA.5 at 1 month post-booster were 226.3 (95% CI: not provided) and 110.9 (95% CI: not provided) in the Pfizer-BioNTech Comirnaty BA.1 Bivalent and Pfizer-BioNTech Comirnaty original groups, respectively <sup>(61)</sup>.

**Table 2. Original SARS-CoV-2 and Omicron neutralizing antibody titers for Pfizer-BioNTech Comirnaty BA.1 Bivalent (30 mcg) and Pfizer-BioNTech Comirnaty original (30 mcg) administered as fourth doses**

Antibody: PsVNA nAb ID <sub>50</sub> titres	Omicron BA.1		Original SARS-CoV-2		Omicron BA.4 and BA.5	
	Pfizer-BioNTech Comirnaty BA.1 Bivalent (30 mcg)	Pfizer-BioNTech Comirnaty original (30 mcg)	Pfizer-BioNTech Comirnaty BA.1 Bivalent (30 mcg)	Pfizer-BioNTech Comirnaty original (30 mcg)	Pfizer-BioNTech Comirnaty BA.1 Bivalent (30 mcg)	Pfizer-BioNTech Comirnaty original (30 mcg)
<b>Sample size (n)</b>	178	163	186	182	13	17
<b>Pre-booster GMT (95% CI)</b>	77.2 (NP)	74.3 (NP)	NP	NP	NP	NP
<b>One month GMT (95% CI)</b>	711.0 (588.3-859.2)	455.8 (365.9-567.6)	5933.2 (5188.2-6785.2)	5998.1 (5223.6-6887.4)	226.3 (NP)	110.9 (NP)
<b>GMFR (95% CI)</b>	9.1 (NP)	5.8 (NP)	NP	NP	NP	NP
<b>GMR (95% CI)</b>	1.56 (1.17-2.08)		0.99 (0.82-1.20)		NP	

NP = not provided

#### Safety

When either vaccine was administered as a fourth dose to individuals >55 years of age who had previously received 3 doses of Pfizer-BioNTech Comirnaty original (30 mcg), both Pfizer-BioNTech Comirnaty BA.1 Bivalent (30 mcg) and Pfizer-BioNTech Comirnaty original (30 mcg) had similar local and systemic reactogenicity <sup>(61)</sup>. The most frequent adverse reactions reported by Pfizer-BioNTech Comirnaty BA.1 Bivalent (30 mcg) recipients were injection site pain (58%), fatigue (49%), headache (34%), myalgia (22%), chills (13%) and arthralgia (11%), which were reported at similar frequencies by Pfizer-BioNTech original (30 mcg) recipients <sup>(61)</sup>. There were no serious adverse events in the study deemed to be related to the vaccine, and no life-threatening (Grade 4) adverse events, in either group. No cases of myocarditis, pericarditis or deaths were reported during the study period <sup>(61)</sup>. However, as the trial was limited to 305 individuals receiving the Pfizer-BioNTech Comirnaty BA.1 Bivalent (30 mcg) COVID-19 vaccine, it is unlikely that any rare adverse event would be detected <sup>(36)</sup>.