

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

Recommendations on the use of bivalent Omicron-
containing mRNA COVID-19 vaccines

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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 June 29, 2022, NACI published [interim guidance on planning considerations for a fall 2022 COVID-19 vaccine booster program in Canada](#). The statement outlined recommendations for booster doses in specific populations ahead of the uncertain trajectory of the COVID-19 pandemic in the coming months. Since that time:

- On September 1 2022, Health Canada authorized the use of Moderna Spikevax Bivalent (50 mcg) COVID-19 vaccine as a booster dose in adults ≥ 18 years of age. The Moderna Spikevax Bivalent (50 mcg) COVID-19 vaccine is the first bivalent Omicron BA.1-containing mRNA COVID-19 vaccine authorized for use in Canada.
- The epidemiology of COVID-19 continues to change and there is still considerable uncertainty with regard to the likelihood, timing, and severity of any potential future COVID-19 waves. It is possible that, consistent with other respiratory viruses, the incidence of COVID-19 may increase in the later fall and winter seasons and that new variants of concern (VOCs) may emerge.
- The emergence of Omicron subvariants BA.4 and BA.5 have led to a resurgence in COVID-19 cases nationally, and these subvariants currently make up the majority of new COVID-19 cases in Canada (previous Omicron subvariants, including Omicron BA.1 make up <5% of new COVID-19 cases in Canada). Nationally, indicators of disease severity, including hospitalizations and deaths, have also increased during the summer wave ⁽¹⁾.
- Although Omicron and its subvariants have largely been associated with less severe illness compared to previous VOCs, the severity of Omicron subvariants BA.4 and BA.5 in comparison to other Omicron subvariants is currently unclear and data are still emerging at this time ⁽²⁻⁴⁾.
- The Omicron variant has demonstrated it is partially evasive of immunity conferred by 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 subvariants BA.4 and BA.5 may be greater than that exhibited by previous Omicron subvariants, although evidence is still emerging at this time.
- Available evidence to date suggests three doses of an authorized, original mRNA COVID-19 vaccine continues to provide strong and sustained protection against severe outcomes from COVID-19.
- 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, especially in younger age groups.

NACI continues to recommend a primary series with an authorized mRNA vaccine in all authorized age groups. NACI has also provided recommendations for a booster dose with an authorized COVID-19 vaccine for all adults, adolescents, and children 5 to 11 years of age. Immunization of those who are eligible for vaccination but have not yet received their recommended doses (primary or booster) remains a top priority in Canada. As with previous COVID-19 booster programs, a fall booster dose with any authorized COVID-19 vaccine will be most important for older adults and other populations at increased risk of severe COVID-19 disease, regardless of the number of booster doses previously received.

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 increased risk of decreased protection, and 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 August 18, 2022, NACI reviewed available evidence on the burden of illness in the Canadian population, as well as booster dose acceptability in the Canadian population. NACI also reviewed the available evidence on the use of the Moderna Spikevax Bivalent COVID-19 vaccine in adults ≥18 years of age (including manufacturer's clinical data in the regulatory submission to Health Canada and published scientific literature). Additionally, NACI reviewed evidence of post-market safety on 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 recommendations on the use of bivalent Omicron-containing mRNA COVID-19 vaccines on August 26, 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 ^(5, 6).

OVERVIEW OF EVIDENCE

Evolving epidemiology

- Canada has recently experienced a resurgence in confirmed SARS-CoV-2 infections, driven primarily by the Omicron BA.4 and BA.5 subvariants. Although signs of stabilization are being observed, significant regional variability remains, and test positivity remains elevated compared to historical trends. It is also possible that, consistent with other respiratory viruses, the incidence of COVID-19 will increase again in the later fall and winter seasons, 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 daily epidemiology update](#).
- Indicators of disease severity (i.e., hospitalizations and intensive care unit [ICU] admissions) increased during the summer wave; however, signs of stabilization are being observed. The incidence of severe outcomes remains significantly higher in adults ≥80 years of age compared to younger age groups, and hospitalization rates in this age group are higher than pandemic averages.
- Even though Omicron and its subvariants 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/BA.5 relative to previous Omicron subvariants. In addition, the surge in SARS-CoV-2 infections caused in part by the increased transmissibility of Omicron BA.4/BA.5, has had a substantial impact on health system infrastructure.
- NACI continues to monitor emerging data on additional Omicron subvariants of interest, such as BA.2.75. To date, there have been only a very small number of Omicron BA.2.75 sequences detected in Canada.

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 infection or vaccination alone. However, the duration of protection from hybrid immunity has yet to be fully characterized, and evidence is still emerging with regard to hybrid immunity and protection against Omicron subvariants BA.4 and BA.5, the current predominately circulating variants in Canada.
- In fully-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, although the durability of this protection has yet to be established (3, 4, 7-10). However, preliminary evidence also suggests that in fully-vaccinated individuals, protection against reinfection is lower against Omicron BA.5, compared to earlier Omicron subvariants (i.e., BA.2), highlighting the potential immune-escape capability of Omicron BA.5.
- 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 rates (both with a primary series and with additional doses) compared to younger adults (11), and according to recent seroprevalence data, are less likely to have been infected during the Omicron wave compared to younger adults and adolescents (12).

- 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 ^(13, 14).

Vaccine effectiveness of original COVID-19 booster vaccines

- Evidence has shown a reduced vaccine effectiveness (VE) of currently-available COVID-19 vaccines against Omicron compared to the effectiveness observed with 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 over time in most studies ⁽¹⁵⁻²²⁾. However, current data suggest 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 remains above 75% up to 26 weeks from the first booster in most studies ⁽²³⁻²⁷⁾; duration of protection against severe disease is not yet known.
- 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 ⁽²³⁾. VE studies from Canada and Israel have also demonstrated additional protection compared to a first booster, including against severe disease ⁽²⁸⁻³²⁾. However, the duration of this increased protection from a second booster dose is currently unknown.

Summary of Moderna Spikevax Bivalent (50 mcg)

- Moderna Spikevax 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 Bivalent (50 mcg) elicited higher neutralizing antibody responses against the original strain, Omicron BA.1 and Omicron BA.4 and 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, in individuals 18-65 years of age and individuals >65 years of age.
- Clinical trial data ⁽³³⁾ showed that Moderna Spikevax 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 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 Bivalent (50 mcg). However, given the number of participants enrolled in the bivalent clinical trial (trial details are summarized in [Appendix A](#)), 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 Bivalent (50 mcg) against the original strain were superior to those obtained in Phase 3 studies of Moderna Spikevax original, for which clinical efficacy was demonstrated. However, the clinical relevance (i.e., applicability to VE) of the changes in neutralizing antibody levels observed with Moderna Spikevax Bivalent (50 mcg) compared to Moderna Spikevax original (50 mcg) is unknown at this time. Evidence monitoring for VE of Moderna Spikevax Bivalent (50 mcg) is ongoing.
- More details regarding the Moderna Spikevax Bivalent clinical trial can be found in [Appendix A](#).

Potential benefits of bivalent vaccines

- Omicron and its subvariants are antigenically distinct from the original SARS-CoV-2 virus, as well as earlier SARS-CoV-2 VOCs, with BA.1 emerging as one of the most antigenically distinct subvariants ⁽³⁴⁾. Given the potential for substantial virus evolution and uncertainty about the emergence of future variants, modification of the strain composition of COVID-19 vaccines may broaden immune protection against divergent SARS-CoV-2 spike protein antigens. Available data, including clinical data on immune responses against BA.4 and BA.5 with a BA.1-targeted, bivalent mRNA vaccine, suggest that inclusion of Omicron in an updated booster vaccine composition may have immediate benefits in the form of increased protection against variants such as Omicron BA.4 and BA.5 ⁽³⁵⁾. The BA.1-targeted, bivalent mRNA vaccines may also 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 ⁽³⁴⁾.
- In individuals previously exposed to SARS-CoV-2 (either through infection or vaccination), infection with Omicron elicits a robust and broadly cross-reactive antibody response ⁽³⁶⁾. This includes an elevated antibody response against Omicron BA.4 and BA.5 ⁽³⁷⁾.
- In a clinical trial, individuals who received a second booster dose with Moderna Spikevax Bivalent (50 mcg), and who had no evidence of prior SARS-CoV-2 infection, had larger relative increases in neutralizing antibody titres from pre- to post-booster when compared to those who had evidence of prior SARS-CoV-2 infection. Individuals who received a second booster dose with Moderna Spikevax Bivalent (50 mcg) who had evidence of prior SARS-CoV-2 infection, had significantly higher levels of neutralizing antibody titres at both time points (pre- and post-booster) compared to individuals without evidence of prior infection, however with a smaller relative increase from pre-booster levels.
- 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 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 using manufacturer-authorized booster dosage appears to be lower than the risk following the second dose of the primary series ⁽³⁸⁻⁴⁴⁾.
 - 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 (50 mcg) original booster doses have been administered to individuals under the age of 30 given the vaccine recommendations/authorizations in each country for this age group.
 - Preliminary post-marketing surveillance data from the US ⁽³⁸⁾ and France ⁽⁴⁰⁾ have shown similar rates of myocarditis following administration of the Moderna Spikevax (50 mcg) original or Pfizer-BioNTech Comirnaty (30 mcg) booster doses. Of note, during the period of surveillance, in the US, Moderna Spikevax original (50 mcg) was authorized for use among individuals aged ≥ 18 years and, in France, Moderna Spikevax original (50 mcg) was recommended for use among individuals aged ≥ 30 years.
 - No product-specific differences between Pfizer-BioNTech Comirnaty (30 mcg) and Moderna Spikevax (50 mcg) original have been identified with respect to the risk of myocarditis after administration of a booster dose.
- In addition, preliminary safety data indicate that the risk of myocarditis and/or pericarditis associated with a second booster dose of an original mRNA COVID-19 vaccine is lower than the risk following the second dose of the primary series ^(44, 45).
- 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 focus 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 the 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 of COVID-19 vaccines.
- 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 as each becomes available, address misinformation, and communicate transparently about COVID-19 vaccine allocation decisions.
- 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 neutralizing antibody responses that have been reported from the Moderna Spikevax Bivalent clinical trial are related to the prevention of severe outcomes from COVID-19.
- No participants in the Moderna Spikevax 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, are currently limited. However, no specific safety concerns have been identified to date ⁽⁴⁶⁻⁵²⁾. Studies to assess the safety and immunogenicity of concurrent administration of COVID-19 vaccines with other vaccines are ongoing.
- Currently, there are no data available on the use of bivalent Omicron-containing mRNA COVID-19 vaccines as a primary series, first booster dose or in a mixed series with vaccines other than Moderna Spikevax original. All participants in the Moderna Spikevax Bivalent clinical trial were administered Moderna Spikevax Bivalent (50 mcg) as a second booster dose after a two-dose primary series (100 mcg doses) and a first booster dose of Moderna Spikevax original (50 mcg) ⁽³⁵⁾. 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 first booster. NACI will continue to monitor new evidence as it becomes available.
- Although the authorized 50 mcg dose of Moderna Spikevax Bivalent is half of the authorized 100 mcg dose of Moderna Spikevax original administered as part of a primary series, if Moderna Spikevax Bivalent (50 mcg) 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 individuals ≥ 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 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 – 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 the authorized dose of a bivalent Omicron-containing mRNA COVID-19 vaccine should be offered as a booster dose to the authorized age groups (≥ 18 years of age). If the bivalent Omicron-containing mRNA COVID-19 vaccine is not readily available, an original mRNA COVID-19 vaccine should be offered to ensure timely protection. *(Strong NACI recommendation)***
 - Individuals [eligible for a fall booster](#) dose, particularly those in groups at a higher risk of severe outcomes from COVID-19, should not delay their planned vaccination in anticipation of a bivalent Omicron-containing mRNA vaccine. Individuals choosing to delay a booster dose in anticipation of a new vaccine formulation should carefully assess their individual risks (i.e., risks of SARS-CoV-2 infection and severe outcomes from COVID-19) and benefits associated with deferring a booster dose.
 - NACI continues to recommend that COVID-19 booster doses may be offered at an interval of 6 months after a previous COVID-19 vaccine dose or SARS-CoV-2 infection, regardless of the product offered. However, a shorter interval of at least 3 months may be warranted in the context of heightened epidemiologic risk, as well as operational considerations for the efficient deployment of the vaccine program.
 - NACI continues to recommend that for all currently COVID-19 vaccine-eligible 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.

4. NACI recommends that the authorized dose of a bivalent Omicron-containing mRNA COVID-19 vaccine may be offered to adolescents 12 to 17 years of age with [moderately to severely immunocompromising conditions](#) and/or who [have biological or social risk factors that place them at high risk](#) of severe outcomes from COVID-19. (*Discretionary NACI recommendation*)

- Pfizer-BioNTech Comirnaty (30 mcg) is preferred to Moderna Spikevax original (50 mcg) for a booster dose in adolescents 12 to 17 years of age, as there are currently limited data on the use of Moderna Spikevax original (50 mcg). The use of either product as a booster dose is off-label in this age group, with the exception of adolescents 16 to 17 years of age for whom the use of Pfizer-BioNTech Comirnaty (30 mcg) as a booster dose is authorized.
- There are currently no data available on the efficacy, immunogenicity or safety of bivalent Omicron-containing mRNA COVID-19 vaccines in this age group. The use of bivalent Omicron-containing mRNA COVID-19 vaccines are not currently authorized by Health Canada in adolescents 12 to 17 years of age, and therefore this recommendation is based on expert opinion and constitutes off-label use in this population.
- The relative risks and benefits of a bivalent Omicron-containing mRNA COVID-19 vaccine in individuals under the age of 18 remains unclear. However, NACI acknowledges that some populations are at an increased risk of severe outcomes from COVID-19 due to various biological (i.e., immunocompromising or other pre-existing medical conditions) and social factors. Factors that contribute to severe outcomes from COVID-19 may also overlap, further increasing risk. Any combination of risk factors, as well as varying access to healthcare services, has the potential for disproportionate consequences for specific populations, characterized by increased rates of severe illness, hospitalizations, and deaths.

Note: No recommendations on the use of bivalent Omicron-containing mRNA COVID-19 vaccines for use in the general adolescent population 12 to 17 years of age are being made at this time, however [NACI's previous recommendations for a fall booster dose in this population](#) remain in place with respect to the use of original mRNA COVID-19 vaccines.

Considerations for the use of a bivalent Omicron-containing mRNA COVID-19 vaccine

- 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 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.
- 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.

Please refer to Table 1 for options and considerations regarding which booster (vaccine type and dose) may be preferred in certain populations.

Table 1. Options and considerations for vaccine types and doses offered for COVID-19 booster dose for certain populations, as of September 1, 2022

Population	Vaccine type (and dose) for which booster doses may be preferred	Rationale
<ul style="list-style-type: none"> • Adults ≥65 years of age • Adults living in LTC homes for seniors or other congregate living settings that provide care for seniors • Moderately to severely immunocompromised adults ≥18 years of age 	<ul style="list-style-type: none"> • Moderna Spikevax <i>Bivalent</i> (50 mcg), Moderna Spikevax original (50 mcg), or Pfizer-BioNTech Comirnaty (30 mcg) should be offered^a 	<ul style="list-style-type: none"> • Moderna Spikevax <i>Bivalent</i> (50 mcg), Moderna Spikevax original (50 mcg), and Pfizer-BioNTech Comirnaty (30 mcg) are all authorized by Health Canada as booster doses in individuals ≥18 years of age. • Moderna Spikevax <i>Bivalent</i> (50 mcg) elicited higher neutralizing antibody responses against the original SARS-CoV-2 strain, Omicron BA.1 and Omicron BA.4 and BA.5 compared to Moderna Spikevax original (50 mcg), when given as a second booster dose. However, the clinical relevance of these differences in antibody responses is unclear at this time. • Moderna Spikevax <i>Bivalent</i> (50 mcg) demonstrated a similar safety profile to Moderna Spikevax original (50 mcg), when given as a second booster dose. • Groups at high-risk for severe outcomes from COVID-19 are likely to realize the greatest benefits from a fall COVID-19 booster dose. • Maximizing the benefit of protection of a booster dose may be affected by the interval between doses. A longer time between doses may result in a better response after any subsequent dose, as this allows time for the immune response to mature in breadth and strength. A longer interval may, however, also increase the chance of a period with waning (lower) protection while awaiting a next dose.
<ul style="list-style-type: none"> • Adults 18 to 29 years of age 	<ul style="list-style-type: none"> • Moderna Spikevax <i>Bivalent</i> (50 mcg), Moderna Spikevax original (50 mcg), or Pfizer-BioNTech Comirnaty (30 mcg) should be offered. ^a 	<ul style="list-style-type: none"> • In addition to the considerations and rationale listed above, NACI previously recommended that Pfizer-BioNTech (30 mcg) may be preferred to Moderna Spikevax original (50 mcg) as a booster dose in this age group. This recommendation was issued based on precautionary principles, in the absence of direct evidence, informed by the observed product-specific difference in risks of myocarditis and/or pericarditis after the primary series. Evidence of the risks of myocarditis and/or pericarditis following a booster dose was limited at the time and not available in all populations.

		<ul style="list-style-type: none"> Post-market safety surveillance data to date indicate that the risk of myocarditis following a booster dose is lower compared to that following the second dose in the primary series, and current data do not show a product-specific difference in the risks of myocarditis and/or pericarditis after a booster dose of an mRNA COVID-19 vaccine. Adults 18 to 29 years of age can receive a booster dose with any available mRNA COVID-19 vaccine for which they are currently eligible.
<ul style="list-style-type: none"> Adolescents 12 to 17 years of age with moderately to severely immunocompromising conditions, or with biological or social risk factors placing them at high risk of severe outcomes 	<ul style="list-style-type: none"> Pfizer-BioNTech Comirnaty (30 mcg) should be offered and is the preferred product. Moderna Spikevax original (50 mcg) and Moderna Spikevax <i>Bivalent</i> (50 mcg) may also be offered. 	<ul style="list-style-type: none"> The use of Pfizer-BioNTech Comirnaty (30 mcg) is preferred to Moderna Spikevax original (50 mcg), as there are currently limited data available on the use of Moderna Spikevax original (50 mcg) in this age group. The use of either product as a booster dose is off-label in this age group, with the exception of adolescents 16 to 17 years of age for whom the use of Pfizer-BioNTech Comirnaty (30 mcg) as a booster dose is authorized. Moderna Spikevax <i>Bivalent</i> (50 mcg) is not currently authorized by Health Canada as a booster dose in individuals <18 years of age. There are currently no data on the efficacy, immunogenicity or safety of Moderna Spikevax <i>Bivalent</i> (50 mcg) in individuals <18 years of age. The use of Moderna Spikevax <i>Bivalent</i> (50 mcg) in this age group represents an off-label recommendation and is informed by expert opinion. The inclusion of an Omicron component in Moderna Spikevax <i>Bivalent</i> may provide additional immunological benefits to adolescents at high risk of severe outcomes from COVID-19, which may outweigh the unknowns around potential risks associated with a lack of data with the use of Moderna Spikevax <i>Bivalent</i> in this age group.
<ul style="list-style-type: none"> All other adolescents 12 to 17 years of age 	<ul style="list-style-type: none"> Pfizer-BioNTech Comirnaty (30 mcg) may be offered and is the preferred product. Moderna Spikevax original (50 mcg) may also be offered. 	<ul style="list-style-type: none"> The use of Pfizer-BioNTech Comirnaty (30 mcg) is preferred to Moderna Spikevax original (50 mcg), as there are currently limited data available on the use of Moderna Spikevax original (50 mcg) in this age group. The use of either product as a booster dose is off-label in this age group, with the exception of adolescents 16 to 17 years of age for whom the use of Pfizer-BioNTech Comirnaty (30 mcg) as a booster dose is authorized. Considering the burden of COVID-19 illness in the general adolescent population, the goals of the Canadian COVID-19 Immunization Program, and rare risks of myocarditis and/or pericarditis following mRNA vaccination, the overall benefit of a bivalent Omicron-containing mRNA booster dose in this population remains unclear.
<ul style="list-style-type: none"> Children 5 to 11 years of age 	<ul style="list-style-type: none"> Pfizer-BioNTech Comirnaty (10 mcg) 	<ul style="list-style-type: none"> Pfizer-BioNTech Comirnaty (10 mcg) is authorized by Health Canada as a booster dose in individuals 5 to 11 years of age.

		<ul style="list-style-type: none"> No other COVID-19 vaccines are currently authorized or recommended for use as booster doses in this age group.
<ul style="list-style-type: none"> For all other populations in whom booster doses are recommended that have not been specified above 	<ul style="list-style-type: none"> Moderna Spikevax <i>Bivalent</i> (50 mcg), Moderna Spikevax original (50 mcg), or Pfizer-BioNTech Comirnaty (30 mcg) should be offered.^a 	<ul style="list-style-type: none"> Individuals in this cohort can receive any available, authorized, mRNA COVID-19 vaccine as a booster dose, as any option is expected to provide strong protection against severe outcomes from COVID-19. Maximizing the benefit of protection of a booster dose may be affected by the interval between doses. A longer time between doses may result in a better response after any subsequent dose, as this allows time for the immune response to mature in breadth and strength. A longer interval may, however, also increase the chance of a period with waning (lower) protection while awaiting a next dose.

^a For a first or second booster dose for adults 18 years of age and older who are not able or willing to receive an mRNA COVID-19 vaccine, a protein subunit COVID-19 vaccine (Novavax Nuvaxovid) may be offered to adults without contraindications to the vaccine. Novavax Nuvaxovid is not currently authorized for use as a booster dose in Canada. Medicago Covifenz is not currently authorized for use as a booster dose in Canada. Janssen Jcovden COVID-19 vaccine may be offered as a first booster to individuals 18 years of age and older without contraindications to the vaccine only when all other COVID-19 vaccines are contraindicated.

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 the degree and duration of protection conferred by each booster dose against circulating variants. The 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 or pericarditis in older and younger adult, adolescent, and pediatric populations.
2. Continuous monitoring of vaccine uptake and acceptance in the Canadian population, specifically following the authorization of new bivalent Omicron (BA.1)-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, in order to accurately inform potential risks associated with booster doses, for all COVID-19 vaccines, including bivalent Omicron (BA.1)-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) 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 A: MODERNA SPIKEVAX BIVALENT CLINICAL TRIAL DATA

Vaccine characteristics

For complete prescribing information for Moderna Spikevax Bivalent, consult the product leaflet or information contained within Health Canada’s authorized product monographs available through the [Drug Product Database](#).

Table 2. Moderna Spikevax Bivalent vaccine characteristics

Product characteristics	Moderna Spikevax Bivalent
Date of authorization	September 1, 2022
Age Indication	18 years of age and older
Dose	50 mcg (25 mcg original SARS-CoV-2 + 25 mcg Omicron BA.1)
Diluent	None required
Presentation	<ul style="list-style-type: none"> • 0.10 mg/mL • 5 doses per vial • Royal blue cap vial • Green label border
Potential Allergens	<ul style="list-style-type: none"> • Polyethylene glycol (PEG) • Tromethamine (Tris, Trometamol)
Storage ^a	<ul style="list-style-type: none"> • Frozen until expiry date printed on the label • Refrigerated for up to 30 days • Unpunctured vials may be stored between 8° to 25°C (46° to 77°F) for up to 24 hours • Once needle-punctured, vials can be stored at room temperature or refrigerated up to 24 hours but cannot be refrozen.
Transport	If transport at -50° to -15°C is not feasible, thawed vials in a liquid state may be transported at +2°C to +8°C for up to 12 hours.

^a Frozen is -25°C to -15°C; Refrigerated is +2°C to +8°C; Room temperature is +15°C to +25°C

Trial design

The Moderna Spikevax Bivalent COVID-19 vaccine was evaluated in an ongoing, Phase 2/3 open-label clinical trial in participants ≥18 years of age in the United States (Study P205) ⁽³⁵⁾. The study evaluated the safety, reactogenicity and immunogenicity of Moderna Spikevax Bivalent (50 mcg) when administered as a second booster dose to adults 18 years of age and older, who had previously received 2 doses of Moderna Spikevax original (100 mcg) as a primary series and a booster dose of Moderna Spikevax original (50 mcg) at least 3 months prior to enrollment. Individuals with a confirmed SARS-CoV-2 infection within 3 months from screening were not eligible for inclusion. Participants were enrolled between March 8, 2022, and March 23, 2022. A within-study, non-contemporaneous comparator group was used, in which participants received Moderna Spikevax original (50 mcg) as a second booster. Participants for the comparator group were enrolled between February 18, 2022, and March 8, 2022.

Study Population

Overall, demographic and baseline characteristics were similar between the Moderna Spikevax Bivalent (50 mcg) and Moderna Spikevax original (50 mcg) groups.

A total of 437 individuals (median of 60 years of age; range 20-88) received Moderna Spikevax Bivalent (50 mcg) as a second booster dose, at a median of 136 days (range 88-408) following their first booster dose. At baseline, 96 of 437 participants (22%) had evidence of previous SARS-CoV-2 infection. Median follow-up from injection was 43 days (range 22-51). Of the 437 participants, 2 discontinued from the study (withdrawal of consent to participate).

A total of 377 individuals (median of 60 years of age; range 20-96) received Moderna Spikevax original (50 mcg) as a second booster dose, at a median of 134 days (range 90-310) following their first booster dose. At baseline, 101 of 377 participants (27%) had evidence of previous SARS-CoV-2 infection. Median follow-up from injection was 57 days (range 51-66). All participants remained in the study as of the current data cut-off date.

Efficacy

Currently, there are no estimates of vaccine efficacy available for Moderna Spikevax Bivalent (50 mcg), as study P205 was not designed to evaluate vaccine efficacy. In the Moderna Spikevax Bivalent (50 mcg) group, with a median follow-up of 43 days, 11 participants (3.2%) had a confirmed SARS-CoV-2 infection starting at least 14 days after the administration of the booster dose. Of the 11 infections, 6 were asymptomatic. In the Moderna Spikevax original (50 mcg) group, with a median follow-up of 57 days, 5 participants (1.9%) had a confirmed SARS-CoV-2 infection starting at least 14 days after the administration of the booster dose. Of the 5 infections, 4 were asymptomatic. None of the participants with a confirmed SARS-CoV-2 infection in either group had an emergency room visit or hospitalization due to COVID-19.

Immunogenicity

In this study, the primary immunogenicity analysis was based on the primary immunogenicity set which includes participants with no evidence of SARS-CoV-2 infection at baseline (pre-booster). For the pre-specified primary objectives, there were four corresponding endpoints:

- Non-inferiority of the antibody response of the second booster dose of Moderna Spikevax Bivalent (50 mcg) compared with the second booster dose of Moderna Spikevax original (50 mcg) based on geometric mean ratios (GMR) against Omicron.
- Non-inferiority of the antibody response of the second dose of Moderna Spikevax Bivalent (50 mcg) compared to the second booster dose of Moderna Spikevax original (50 mcg) against Omicron based on the difference in seroresponse rate (SRR).
- Non-inferiority of the antibody response of the second booster dose of Moderna Spikevax Bivalent (50 mcg) compared to the second booster dose of Moderna Spikevax original (50 mcg) based on GMR against the original SARS-CoV-2.

- Superiority of the antibody response of the second booster dose of Moderna Spikevax Bivalent (50 mcg) compared to the second booster dose of Moderna Spikevax original (50 mcg) based on the GMR against Omicron.

Non-inferiority was considered met when the lower bound of the 97.5% confidence interval (CI) of GMR is ≥ 0.67 and of SRR difference is $> -10\%$. Superiority was considered met when the lower bound of the 97.5% CI of GMR is > 1 and for the difference in SRR > 0 .

Non-inferiority of Moderna Spikevax Bivalent based on GMR against Omicron

- In the primary analysis set, the observed geometric mean titres (GMTs) against Omicron pre-booster were 298.1 (95% CI; 258.8-343.5) and 332.0 (95% CI; 282.0-390.9) in the Moderna Spikevax Bivalent and Moderna Spikevax original groups, respectively. At Day 29, the GMTs against Omicron increased to 2372.4 (95% CI; 2070.6-2718.2) and 1473.5 (95% CI; 1270.8-1708.4) in the Moderna Spikevax Bivalent and Moderna Spikevax original groups respectively. This corresponded to geometric mean fold rises (GMFR) of 8.0 (95% CI; 7.2-8.8) and 4.4 (95% CI; 4.0-5.0) in the Moderna Spikevax Bivalent and Moderna Spikevax original groups, respectively.
- The pre-specified non-inferiority criteria for this primary immunogenicity endpoint was met, with a GMR of 1.75 (97.5% CI; 1.49-2.04). Consistent results were obtained in a supplementary analysis including all enrolled participants, regardless of evidence of prior SARS-CoV-2 infection (see [Table 3](#)).

Non-inferiority of Moderna Spikevax Bivalent based on SRR against Omicron

- In the primary analysis set, the Omicron SRRs were 100% (95% CI; 98.9-100) and 99.2% (95% CI; 97.2-99.9), at Day 29 in the Moderna Spikevax Bivalent and Moderna Spikevax original groups, respectively. The SRR difference was 1.5% (97.5% CI; -1.1, 4.0), meeting the non-inferiority criterion (lower bound of CI $> -10\%$) for this primary immunogenicity endpoint. Consistent results were obtained in a supplementary analysis including all enrolled participants, regardless of evidence of prior SARS-CoV-2 infection.

Non-inferiority of Moderna Spikevax Bivalent based on GMR against original SARS-CoV-2

- In the primary analysis set, the observed GMTs against original SARS-CoV-2 pre-booster were 1266.7 (95% CI; 1120.2-1432.5) and 1521.0 (95% CI; 1352.8-1710.2) in the Moderna Spikevax Bivalent and Moderna Spikevax original groups, respectively. At Day 29, the observed GMTs against original SARS-CoV-2 increased to 5977.3 (95% CI; 5321.9-6713.3) and 5649.3 (95% CI; 5056.8-6311.2) in the Moderna Spikevax Bivalent and Moderna Spikevax original groups respectively. This corresponded to a (GMFR) of 4.7 (95% CI; 4.4-5.1) and 3.7 (95% CI; 3.4-4.0) in the Moderna Spikevax Bivalent and Moderna Spikevax original groups, respectively.
- The pre-specified non-inferiority criteria for this primary immunogenicity endpoint was met, with a GMR of 1.22 (97.5% CI; 1.08-1.37). Consistent results were obtained in a supplementary analysis including all enrolled participants, regardless of evidence of prior SARS-CoV-2 infection (see [Table 3](#)).

- As a secondary immunogenicity endpoint, the SRR against original SARS-CoV-2 was also assessed. The SRR against the original SARS-CoV-2 was 100% in both the Moderna Spikevax Bivalent and the Moderna Spikevax original groups, with an SRR difference of 0. Therefore, the key secondary immunogenicity objective was also met. Consistent results were obtained in a supplementary analysis including all enrolled participants, regardless of evidence of prior SARS-CoV-2 infection.

Superiority of Moderna Spikevax Bivalent based on GMR against Omicron

- The observed Day 29 neutralising antibody GMTs against Omicron were 2372.4 (95% CI; 2070.6-2718.2) and 1473.5 (95% CI; 1270.8-1708.4) in the Moderna Spikevax Bivalent and Moderna Spikevax original booster groups, respectively, and the GMR was 1.75 (97.5% CI; 1.49-2.04), which met the pre-specified superiority criterion (lower bound of CI >1) for this primary immunogenicity endpoint.
- Neutralizing titres against Omicron subvariants BA.4 and BA.5 were also characterized. In the primary analysis set, the observed GMTs in the Moderna Spikevax Bivalent group against Omicron BA.4/BA5 pre-booster were 115.6 (95% CI; 98.5-135.6) and increased to 727.4 (95% CI; 632.8-836.1) at Day 29 with a GMFR of 6.3 (95% CI; 5.7-6.9). In the Moderna Spikevax original group, the GMTs were 139.7 (95% CI; 119.5-163.3) pre-booster and 492.1 (95% CI; 431.1-561.9) at Day 29 with a GMFR of 3.5 (95% CI; 3.2-3.9). The GMR for the comparison of Moderna Spikevax Bivalent with Moderna Spikevax original was 1.69 (95% CI; 1.51-1.90) with the lower bound of the CI > 1.

Individuals with prior SARS-CoV-2 infection

- In addition to the primary analysis, a pre-planned subgroup analysis was also performed to assess the consistency of results in participants with evidence of prior SARS-CoV-2 infection. Based on this analysis, results in individuals with evidence of prior SARS-CoV-2 infection were consistent with results in those without evidence of prior SARS-CoV-2 infection, with regards to meeting the primary and secondary immunogenicity endpoints.
- Individuals with evidence of prior SARS-CoV-2 infection had considerably higher GMTs pre-booster against both Omicron and the original SARS-CoV-2, compared to those without evidence of prior SARS-CoV-2 infection. Consequently, at Day 29 post-booster GMTs were considerably higher in those with evidence of prior SARS-CoV-2 infection, compared to those without (against both Omicron and original SARS-CoV-2). However, the GMFR from pre-booster levels was larger in those without evidence of prior SARS-CoV-2 infection compared to those with previous infection, by roughly 1.7-fold against Omicron and 1.8-fold against original SARS-CoV-2 in the Moderna Spikevax Bivalent group and 1.8-fold against Omicron and 1.9 fold in the Moderna Spikevax original group. A consistent result was observed for neutralizing antibody activity against Omicron BA.4 and BA.5 specifically.
- Of note, participants with a confirmed SARS-CoV-2 infection within 3 months of enrollment were not eligible for inclusion in the trial. With an enrollment period of Feb 18 – Mar 8 2022, the majority of individuals with evidence of prior SARS-CoV-2 infection enrolled in the trial were likely not infected with the Omicron VOC.

Table 3. Original SARS-CoV-2 and Omicron neutralizing antibody titers for Moderna Spikevax Bivalent (50 mcg) and Moderna Spikevax original (50 mcg) administered as second booster doses

Antibody: PsVNA nAb ID ₅₀ titres	Omicron Variant		Original SARS-CoV-2		Omicron BA.4 and BA.5	
	Moderna Spikevax Bivalent (50 mcg)	Moderna Spikevax original (50 mcg)	Moderna Spikevax Bivalent (50 mcg)	Moderna Spikevax original (50 mcg)	Moderna Spikevax Bivalent (50 mcg)	Moderna Spikevax original (50 mcg)
All individuals						
Sample size (n)	428	367	428	367	428	367
Pre-booster GMT (95% CI)	432.051 (372.466, 501.168)	511.984 (433.386, 604.836)	1603.353 (1420.264, 1810.045)	1944.781 (1725.353, 2192.116)	172.72 (147.45, 202.31)	209.31 (179.48, 244.10)
Day 29 GMT (95% CI)	3070.379 (2685.375, 3510.581)	1932.785 (1681.186, 2222.037)	6619.010 (5941.728, 7373.494)	6047.489 (5465.873, 6690.994)	940.57 (826.32, 1070.61)	645.37 (570.11, 730.55)
GMFR (95% CI)	7.107 (6.484, 7.789)	3.775 (3.422, 4.165)	4.128 (3.840, 4.438)	3.110 (2.877, 3.361)	5.44 (5.01, 5.92)	3.08 (2.84, 3.35)
GMR (95% CI)	1.781 (1.557, 2.037)		1.237 (1.117, 1.369)		1.68 (1.52, 1.84)	
No evidence of prior SARS-CoV-2 infection						
Sample size (n)	334	260	334	260	334	260
Pre-booster GMT (95% CI)	298.127 (258.753, 343.492)	1473.462 (1270.849, 1708.379)	1266.743 (1120.190, 1432.469)	1520.998 (1352.766, 1710.151)	115.59 (98.51, 135.64)	139.68 (119.51, 163.26)
Day 29 GMT (95% CI)	2372.424 (2070.634, 2718.200)	1473.462 (1270.849, 1708.379)	5977.257 (5321.897, 6713.320)	5649.331 (5056.848, 6311.231)	727.43 (632.85, 836.14)	492.13 (431.05, 561.85)
GMFR (95% CI)	7.958 (7.181, 8.819)	4.438 (3.971, 4.960)	4.719 (4.358, 5.109)	3.714 (3.420, 4.034)	6.30 (5.74, 6.91)	3.52 (3.21, 3.86)
GMR (95% CI)	1.745 (1.493, 2.040)		1.215 (1.078, 1.370)		1.69 (1.51, 1.90)	
Prior SARS-CoV-2 infection						
Sample size (n)	94	98	94	98	94	98
Pre-booster GMT (95% CI)	1614.640 (1149.671, 2267.658)	1558.360 (1088.941, 2230.136)	3703.953 (2793.198, 4911.670)	3637.972 (2742.046, 4826.629)	719.54 (531.64, 973.86)	609.12 (448.08, 828.05)
Day 29 GMT (95% CI)	7676.226 (5618.245, 10488.050)	3885.596 (2877.774, 5246.367)	9509.727 (7345.948, 12310.856)	7003.503 (5592.574, 8770.390)	2337.44 (1825.51, 2992.92)	1270.82 (987.28, 1635.80)
GMFR (95% CI)	4.754 (3.954, 5.716)	2.493 (2.058, 3.021)	2.567 (2.245, 2.936)	1.925 (1.649, 2.247)	3.25 (2.78, 3.80)	2.09 (1.80, 2.43)
GMR (95% CI)	1.898 (1.499, 2.403)		1.272 (1.070, 1.512)		1.60 (1.34, 1.91)	

Safety

The safety and reactogenicity of Moderna Spikevax Bivalent (50 mcg) administered as a second booster dose was similar to that of Moderna Spikevax original (50 mcg), given as a second booster dose^(33, 53). Also, the frequency of adverse events following immunization with Moderna Spikevax Bivalent^(33, 35, 53) was similar or lower relative to that of a first booster dose of Moderna Spikevax original (50 mcg)⁽⁵⁴⁾, and of the second dose of the Moderna Spikevax original primary series (100 mcg)⁽⁵⁵⁾. No new safety signals were identified. There were no vaccine related cases of death, myocarditis and/or pericarditis reported during the study period^(33, 53). Given the trial was limited to 814 participants receiving the Moderna Spikevax Bivalent (n=437) and Moderna Spikevax original (n=377) vaccines^(33, 53), it is unlikely that any rare adverse event would be detected. NACI will monitor post-market safety surveillance data as it emerges and update the recommendations as needed.