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

Guidance on an additional COVID-19 booster dose in the spring of 2023 for individuals at high risk of severe illness due to COVID-19

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Directives sur une dose de rappel supplémentaire du vaccin contre la COVID-19 au printemps 2023 pour les personnes présentant un risque élevé de maladie sévère due à la COVID-19

To obtain additional information, please contact:

Public Health Agency of Canada
Address Locator 0900C2
Ottawa, ON K1A 0K9
Tel.: 613-957-2991
Toll free: 1-866-225-0709
Fax: 613-941-5366
TTY: 1-800-465-7735
E-mail: publications-publications@hc-sc.gc.ca

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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 January 20, 2023, NACI published Guidance on COVID-19 vaccine booster doses: Initial considerations for 2023. This guidance consolidated and reinforced previously established booster dose recommendations and extended the fall booster program for those who had not yet received a 2022 recommended booster dose into 2023.

Since that time:

- Omicron sub-lineages continue to be the dominant strains of COVID-19 circulating in Canada. Viral sequencing is currently showing clear dominance of variants BQ.1 and BQ.1.1, while an increase in the XBB.1.5 recombinant sub-lineage is also being observed. Based on neutralization studies, BQ* and XBB* sub-lineages are more immune evasive than earlier sub-lineages (such as BA.2 and BA.5), with XBB* described as the most immune evasive sub-lineage.
- While there are fluctuations in COVID-19 transmission indicators (i.e., cases reported, hospitalizations, and deaths) and variation across provinces and territories, COVID-19 activity has been relatively stable with hospitalizations remaining at a relatively high level since the widespread circulation of Omicron in early 2022.
- Additional evidence has emerged on the performance and safety of bivalent vaccines, and the duration of protection of vaccination and hybrid immunity which help to inform the need for and benefit of additional booster doses.

NACI continues to monitor the rapidly evolving scientific data 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 last 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

On February 6 and 7, 2023, NACI reviewed the available epidemiology and evidence on vaccine protection and hybrid immunity, including the performance of bivalent vaccines based on clinical trial data and real-world evidence from observational studies. Preliminary modelling data were also considered, as were ethics and acceptability considerations. NACI continues to apply the decision-making framework for booster doses in their deliberations. NACI approved these recommendations on February 19, 2023.

For further information on NACI's recommendations on the use of COVID-19 vaccines, please refer to National Advisory Committee on Immunization (NACI): 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 [1, 2].

Overview of Evidence

Available information as of February 5, 2023, is summarized below.

Evolving epidemiology

- The evolutionary trajectory of SARS-CoV-2, including the emergence of novel variants of concern (VOCs), remains uncertain.
- Omicron BQ.1 sub-lineages are currently the dominant strains circulating in Canada, while viral sequencing is also showing increases in the XBB.1.5 recombinant sub-lineage.
- Recently circulating sub-lineages of Omicron (e.g., BQ*, XBB*) are more immune evasive than previous sub-lineages (e.g., BA.2, BA.4/5), based on the ability of recent sub-lineages to more efficiently evade neutralizing antibodies elicited from vaccination and past infection [3-10].
- Rates of hospitalizations and deaths in Canada continue to be highest in unvaccinated individuals, particularly for adults 60 years of age and older, with risk increasing with age and highest among those ≥80 years, and lowest for those recently vaccinated [11].
- Seroepidemiologic studies demonstrate high levels of antibodies to vaccines and/or infection in the Canadian population [12].

Vaccine effectiveness and duration of vaccine protection of mRNA COVID-19 vaccine booster doses

Vaccine protection against infection and symptomatic disease with original monovalent COVID-19 vaccines has been shown to wane over time; however, protection against severe outcomes persists longer than protection against symptomatic disease [13-24]. Evidence suggests that a fourth dose of an original monovalent COVID-19 vaccine provides an increase in vaccine effectiveness (VE) against infection; however, waning of protection is observed over time, consistent with the waning of protection after two or three doses [25-30]. VE against severe disease from booster doses is generally higher and more sustained than against infection. Due to the short follow-up period to date, there are no estimates available regarding waning following bivalent booster doses against infection or severe disease.

- Real-world effectiveness data from the US suggest that in adults, a booster dose of a BA.4/5 bivalent mRNA COVID-19 vaccine provides increased protection against both symptomatic disease and hospitalization, compared to those who did not receive a bivalent booster dose but received at least 2 previous doses of original monovalent vaccines in the past [31, 32]. The relative VE of the bivalent booster increased with increased time since the original vaccine group received their last dose, due to increased waning over time in this group. From these observational studies, it cannot be determined if the benefit is due to the recent receipt of a booster dose and/or specifically the receipt of a bivalent booster.
- Other clinical data comparing relative VE from a bivalent booster dose to an original monovalent booster dose are emerging. Although there are some limitations in these studies (often including earlier receipt of an original booster than a bivalent booster), the emerging evidence suggests that the bivalent vaccine performs at least as well as, and possibly better than, the original vaccine against circulating strains.

- Two recent studies by Lin et al. used linked administrative data from North Carolina to provide evidence regarding the VE of bivalent BA.4/5 booster doses compared to original monovalent booster doses.
    - The first study of individuals ≥12 years of age assessed relative VE against severe outcomes of a single booster dose (original or bivalent BA.4/5, manufacturer not specified) compared to a previous original vaccine dose (primary series, or a first or second booster dose) during a period of 15-99 days after the booster dose. A single BA.4/5 bivalent mRNA booster dose provided greater and somewhat more sustained relative protection against severe outcomes than the relative protection from a single original mRNA booster dose. However, the original booster was administered and assessed over a three-month period occurring earlier than that of the bivalent booster, and other factors such as circulating variants and the extent of previous infection may have been different between the groups [(33)].
    - The second study (preprint) of children 5 to 11 years of age found that the relative VE against infection of a booster dose compared to only receiving two previous original vaccine doses was higher for those who received the BA.4/5 bivalent vaccine (manufacturer not specified) as a booster than the original vaccine as a booster. However, like the previous study, the original vaccine was given during an earlier period than the bivalent vaccine. As well, in some instances, the third dose may have been part of a 3-dose primary series recommended for immunocompromised individuals instead of a booster dose, and the distribution of those who are immunocompromised may have differed between the groups [(34)].
- Preliminary data from Ontario that was presented to NACI demonstrates that short-term (<90 days) VE against severe outcomes in community dwelling adults aged ≥50 years was similar between those receiving original and bivalent mRNA vaccine booster doses and between the available vaccine products (Moderna Spikevax original or BA.1 bivalent and Pfizer-BioNTech Comirnaty original or BA.4/5 bivalent) during a period when BA.5 was the predominant Omicron sub-lineage and BQ.1 was emerging [(35)].
- Preliminary data (preprint) from four Scandinavian countries used linked administrative data to evaluate the VE of a fourth dose (either original, BA.1 bivalent or BA.4/5 bivalent) up to 60 days after receipt of the booster dose relative to a third original vaccine dose. Regardless of product received, a fourth dose was associated with significantly reduced risks of hospitalization and death, compared to receiving only three doses. There was a trend towards increased protection against severe outcomes associated with a fourth dose of bivalent vaccine compared to a fourth dose of original vaccine, however effect estimates were imprecise with wide confidence intervals (CI) [(36)]. When comparing the BA.1 bivalent and BA.4/5 bivalent vaccines (manufacturer not specified), the BA.4/5 bivalent vaccine was associated with a somewhat lower relative risk of hospitalization compared to the BA.1 bivalent vaccine. However, this observation was based primarily on the comparative VE from Denmark. The VE estimate was not significant for Norway, and not estimable in the other two countries.
- A randomized clinical trial conducted by Moderna in the United Kingdom (preprint) compared those ≥16 years of age randomized to receive a bivalent BA.1 booster to those randomized to receive an original monovalent booster. Although the primary endpoint was immunogenicity, exploratory analyses revealed that the

efficacy against symptomatic disease was somewhat higher for the bivalent booster than the original booster against sub-lineages BA.2 (relative VE of bivalent booster compared to original booster vaccine of 32.6%; 95% CI: -15.1 to 60.5%) and BA.4 (41.6%; 95% CI: -5.1 to 67.5%), but not against BA.5 (4.4%; 95% CI: -27.2 to 28.2%) [37].

- VE and duration of protection are still emerging for more recent variants (i.e., XBB.1.5 and BQ.1).
    - A recent US study compared relative VE against symptomatic disease in immunocompetent adults who had and had not received a bivalent BA.4/5 booster among those who had previously received 2 to 4 original monovalent vaccine doses. Relative VE for the bivalent vaccine booster compared to past monovalent doses for at least 3 months after bivalent vaccination ranged from 37% to 52% (with somewhat lower VE with increasing age) against Omicron subvariants which were determined likely XBB/XBB.1.5-related and ranged from 40 to 49% against likely BA.5-related strains based on S-gene target status. The relative VE estimates for the bivalent BA.4/5 vaccine against XBB/XBB.1.5-related and BA.5-related strains were similar [38].
    - There are currently no available data regarding bivalent vaccine protection against severe disease caused by XBB/XBB.1.5.

Safety of Omicron-containing bivalent mRNA COVID-19 vaccines

- Available evidence from Canada and internationally show that overall, the safety profile of the bivalent mRNA COVID-19 vaccine boosters is comparable to that of original mRNA COVID-19 vaccine boosters among individuals aged ≥5 years [39-45].
- The safety profile appears to be similar in those with or without previous SARS-CoV-2 infections.
- A possible association between Pfizer-BioNTech Comirnaty bivalent BA.4/5 booster and ischemic stroke in persons ≥65 years of age has been identified by the US Vaccine Safety Datalink (VSD) [46, 47]. This possible association has not been replicated in other surveillance systems used to monitor vaccine safety in the US or in other countries. As well, this potential safety signal has not been identified with the Moderna Spikevax bivalent BA.4/5 mRNA COVID-19 vaccine. To date, the totality of the US data suggests that it is very unlikely that the potential signal in VSD represents a true clinical risk [46-48]. This is supported by international data including from Canada, Israel, Europe, and Singapore where a similar signal has not been identified. Monitoring of the potential safety signal is ongoing. NACI updates its recommendations as needed.

Hybrid immunity

- Hybrid immunity results from ≥1 exposure(s) from vaccination and ≥1 exposure(s) from SARS-CoV-2 infection (before or after vaccination). Previous infection and vaccination may provide superior protection (as measured by neutralization capacity) against VOCs, including Omicron, compared with primary vaccination only, or previous SARS-CoV-2 infection without vaccination.
- In Canada, hybrid immunity population profiles differ by age group. A greater proportion of older adults are protected by vaccination only and have not been infected, as compared to younger ages. Adolescents and young adults have the highest proportion of hybrid immunity, and a large proportion of children have been infected but not vaccinated [12].

- There are Canadian data suggesting that vaccine protection may reach a plateau for adults with hybrid immunity, with limited benefit demonstrated in receiving booster doses of the original mRNA COVID-19 vaccines against Omicron subvariants BA.2 infection/symptomatic disease in healthcare workers with hybrid immunity and against BA.1, BA.2 and BA.4/5 hospitalization in non-institutionalized elderly populations with hybrid immunity [15, 49, 50]. Additionally, VE is lower in adults without previous infection and has more pronounced waning over time compared to those with previous infection.
- A systematic review and meta-regression study also found that protection against severe disease from hybrid immunity with primary series vaccination remained >95% until the end of available follow-up at 11 months after vaccination and up to 4 months based on available data from hybrid immunity with first booster vaccination. Based on statistical modelling projections, protection from hybrid immunity would be sustained at elevated levels to at least 12 months after primary series and at least 6 months after booster vaccination [51]. However, the analysis was based on studies on protection conferred by pre-Omicron SARS-CoV-2 strains and there was no consideration of the impact on protection due to circulation of more immune evasive Omicron subvariants.
- These data suggest that future booster program efforts may achieve the greatest impact among those who have not yet been infected by the SARS-CoV-2 virus. Further study will be needed to determine whether the findings regarding the protection from hybrid immunity would apply broadly to Omicron-containing bivalent COVID-19 vaccines (although based on available evidence regarding the performance of bivalent vaccines, this is expected to be the case) and against new subvariants and VOCs.

Ethics, equity, feasibility, and acceptability (EEFA)

- 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 at this time.
- COVID-19 vaccine uptake increases with age in Canada, but uptake with each subsequent dose has decreased suggesting acceptability has decreased over time.
- There may be variability in how each province, territory and community assesses risk and responds to the needs of their respective jurisdictions.
- Supply of bivalent vaccines (BA.1 or BA.4/5) in Canada is expected to be sufficient to accommodate NACI's recommendations for booster doses.

Other considerations

- Using assumptions based on recent VE studies, where waning protection against hospitalisations occurs most in older adults without hybrid immunity, modelling suggests that an additional booster dose in adults 65 years and older starting this spring could be expected to prevent hundreds or thousands of hospitalizations across the country this year if a booster dose restores protection to levels achieved shortly after the previous dose. Modelled estimates are dependent on various assumptions on aspects such as the durability of protection from bivalent booster doses, the rate of infection of future subvariants, and the ability of future subvariants to escape protection offered by the vaccines.

Recommendations

Please see Table 1 for an explanation of strong versus discretionary NACI recommendations.

NACI continues to recommend a COVID-19 vaccine primary series as follows:

1. Individuals 5 years of age and older should be immunized with a primary series of an authorized mRNA vaccine. *(Strong NACI recommendation)*
2. Children 6 months to under 5 years of age may be immunized with a primary series of an authorized mRNA vaccine. *(Discretionary NACI recommendation)*

Additional details including those pertaining to alternative vaccine products are available in the COVID-19 vaccine chapter in the Canadian Immunization Guide and NACI statements and publications.

3. For individuals who have not received previously recommended doses (primary series or booster doses, including the fall 2022 booster dose), NACI recommendations are available in Guidance on COVID-19 vaccine booster doses: Initial considerations for 2023.

4. **Starting in the spring of 2023, NACI recommends that an additional booster dose may be offered as per the recommended interval* to the following individuals who are at increased risk of severe illness from COVID-19:**

    - Adults 80 years of age and older
    - Adult residents of long-term care homes and other congregate living settings for seniors or those with complex medical care needs
    - Adults 18 years of age and older who are moderately to severely immunocompromised (due to an underlying condition or treatment)
    - Adults 65 to 79 years of age, particularly if they do not have a known prior history of SARS-CoV-2 infection**

    (*Discretionary NACI recommendation*)

    * The recommended interval is 6 or more months from the last COVID-19 vaccine dose or SARS-CoV-2 infection if applicable (whichever is longer). It should be noted that vaccination with shorter intervals between previous vaccination or infection has not been shown to pose a safety risk, though evidence shows that the antibody response is higher with longer intervals between infection and vaccination and with longer intervals between vaccination doses.

    **Previous infection can be defined in different ways based on jurisdictional policies and access to testing. The following suggestion can be considered to define previous infection with SARS-CoV-2:

        - Confirmed by a molecular (e.g., PCR) or Health Canada-approved antigen detection-based test; or
        - Symptomatic disease compatible with COVID-19 AND household exposure to a confirmed COVID-19 case.

- Bivalent Omicron-containing mRNA COVID-19 vaccines are the preferred booster products.
- No other recommendations for additional booster doses are being made at this time.

- NACI will continue to monitor the SARS-CoV-2 epidemiology and emerging evidence, including duration of vaccine protection from bivalent booster doses in the coming months to provide recommendations on the timing of subsequent booster doses if warranted.
- Planning should consider that vaccine deployment may be recommended for broader population groups in the fall of 2023 depending on the COVID-19 pandemic context.

For further information on these recommendations, please refer to the COVID-19 vaccine chapter in the Canadian Immunization Guide (CIG).

NACI continues to monitor and assess the evidence as it emerges and will update its recommendations as needed.

RESEARCH PRIORITIES

1. Continuous monitoring of data on the safety, immunogenicity, efficacy, and effectiveness of COVID-19 vaccines, including bivalent mRNA booster doses, 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/post-acute COVID syndrome (long COVID), or infection-induced myocarditis and/or pericarditis in older adult, adult, adolescent, and pediatric populations.
2. Further evaluations of the optimal interval between dose administration, as well as further evaluations of the optimal interval between previous SARS-CoV-2 infection and vaccine dose administration.
3. Vigilant monitoring and reporting of adverse events of special interest to support the rapid identification of potential vaccine safety signals and accurately inform potential risks associated with any future booster doses. Global collaboration should be prioritized to enable data sharing so decision makers around the world can weigh benefits and risks of additional booster doses of COVID-19 vaccines.
4. Continuous monitoring of COVID-19 epidemiology and VE in special populations at high risk of severe outcomes or long-term consequences of infection with COVID-19, including but not limited to those with co-morbidities, immunocompromising conditions, and pregnant populations.
5. Further evaluation on the optimal timing and trigger for the initiation of potential future booster dose recommendations, as well as evaluation of potential risks associated with providing booster doses earlier than necessary.
6. Continuous monitoring of vaccine coverage in Canada, for COVID-19 vaccines and other routine vaccines, particularly in the context of COVID-19 vaccine booster doses and including consideration of measures that may reduce the risk of disparities in vaccine confidence and uptake across different sub-populations.

Table 1. Strength of NACI Recommendations

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

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NACI members: S Deeks (Chair), R Harrison (Vice-Chair), M Andrew, J Bettinger, N Brousseau, H Decaluwe, P De Wals, E Dubé, V Dubey, K Hildebrand, K Klein, M O'Driscoll, J Papenburg, A Pham-Huy, B Sander, and S Wilson.

Liaison representatives: L Bill / M Nowgesic (Canadian Indigenous Nurses Association), LM Bucci (Canadian Public Health Association), S Buchan (Canadian Association for Immunization Research and Evaluation), E Castillo (Society of Obstetricians and Gynaecologists of Canada), J Comeau (Association of Medical Microbiology and Infectious Disease Canada), M Lavoie (Council of Chief Medical Officers of Health), J MacNeil (Centers for Disease Control and Prevention, United States), D Moore (Canadian Paediatric Society), M Naus (Canadian Immunization Committee), M Osmack (Indigenous Physicians Association of Canada), J Potter (College of Family Physicians of Canada), and A Ung (Canadian Pharmacists Association).

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NACI COVID-19 Vaccine Working Group

Members: S Wilson (Chair), M Adurogbangba, M Andrew, Y-G Bui, H Decaluwe, P De Wals, V Dubey, S Hosseini-Moghaddam, M Miller, D Moore, S Oliver, and E Twentyman.

PHAC Participants: NK Abraham, O Baclic, L Coward, P Doyon-Plourde, N Forbes, M Hersi, N Islam, SJ Ismail, C Jensen, F Khan, A Killikelly, R Krishnan, SH Lim, N Mohamed, J Montroy, S Pierre, R Pless, M Salvadori, A Stevens, E Tice, A Tuite, MC Tunis, E Wong, R Ximenes, MW Yeung, and J Zafack.

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