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

Initial guidance on a second booster dose of COVID-19 vaccines in Canada

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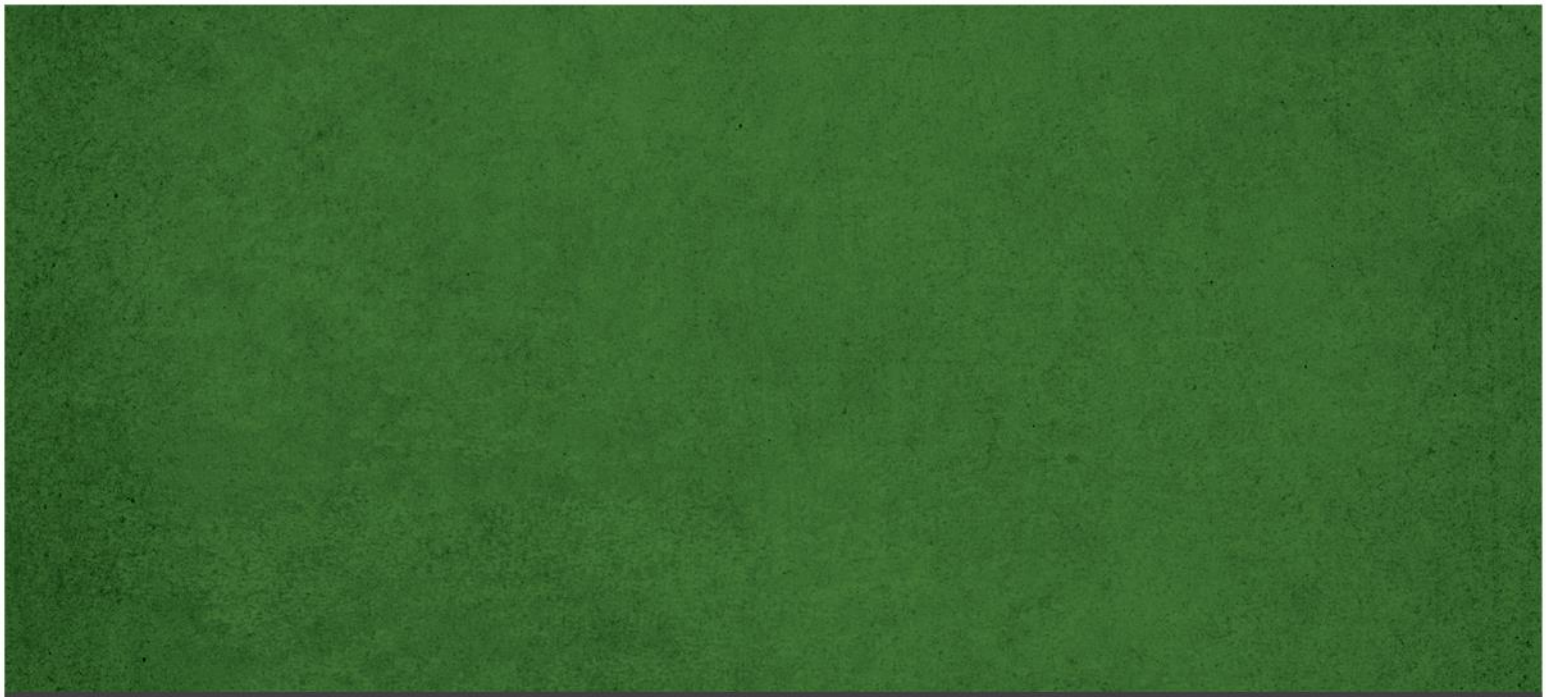

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PREAMBLE

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

How to optimally define primary series and "booster doses" for COVID-19 vaccines are still in evolution. While the term "booster dose" is used in this guidance, NACI continues to monitor the emerging scientific data and will adjust the terminology as required. In this guidance, the term "second booster dose" will refer to the dose given after the first booster dose which follows a complete primary series. For example, a second booster will correspond to a 4th dose among immunocompetent individuals as they have a recommended 2-dose primary series, while it will correspond to a 5th dose among moderately to severely immunocompromised individuals as they have a recommended 3-dose primary series.

NACI recommended a first booster dose for long-term care home (LTC) residents and seniors living in other congregate settings on September 28, 2021. On October 29, 2021, NACI recommended booster doses for adults 80 years of age and over, with a discretionary recommendation for those 70 to 79 years of age and some other groups. On December 3, 2021, NACI published updated guidance on booster COVID-19 vaccine doses in Canada for adults 18 years of age and older. These recommendations on booster doses of COVID-19 vaccines were reviewed and reaffirmed in the context of the emergence of Omicron (B.1.1.529) variant of concern (VOC) on December 14, 2021. Since that time:

- NACI released advice on the use of booster COVID-19 vaccine doses in adolescents 12 to 17 years of age (January 28, 2022), on the timing of COVID-19 vaccination for individuals previously infected with SARS-CoV-2 (February 4, 2022), on the use of Novavax Nuvaxovid COVID-19 vaccine (February 17, 2022) and on the use of Medicago Covifenz COVID-19 vaccine (March 11, 2022).
- The Omicron variant, including the newly emerging Omicron sub-variant BA.2, is partially evasive to previous immunity conferred by COVID-19 vaccines or previous SARS-CoV-2 infection, thus impacting booster dose considerations. The epidemiology of COVID-19 is continuing to change as public health measures are modified and as VOCs emerge and circulate. The long term evolution of the COVID-19 pandemic remains unclear at this time.
- The Omicron COVID-19 wave had been declining nationally in Canada, including hospitalizations and deaths as of January 2022, but recent surveillance data indicate that there is regional variability in COVID-19 activity across Canada. There are signs of stabilization of disease activity at elevated levels in some jurisdictions or signs of viral resurgence in others.
- Some jurisdictions had implemented a second booster of COVID-19 vaccine among LTC residents or other high-risk groups. Some data on vaccine protection from a second booster dose against the Omicron variant has become available.
- Based on provincial and territorial roll out of first booster programs, individuals who were the first to receive a booster dose of COVID-19 vaccine in Canada (e.g., LTC residents) may have reached or are approaching 6 months since their first booster dose.

NACI continues to recommend a primary series with an authorized mRNA vaccine in all authorized age groups and a first booster dose among adults (for whom a first booster is authorized) and among high-risk adolescents (for whom a first booster is currently off-label). Immunization of those who are eligible for vaccination but have not yet received a primary vaccine series remains a top priority in Canada.

NACI's recommendations remain aligned with the goals of the Canadian COVID-19 Pandemic Response that have been 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 entitled Interim guidance on booster COVID-19 vaccine doses in Canada. Recommendations are based on evidence of the *need for* (e.g., evidence of decreased vaccine effectiveness (VE) against severe illness and/or infection depending on the population) and *benefit of* (e.g., safety and effectiveness) booster doses in the Canadian context.

On March 1, 2022, and March 22, 2022, NACI reviewed emerging evidence on the duration of protection of the first booster dose and the VE/safety of a second booster dose of COVID-19 vaccines. NACI also reviewed data on the current epidemiology of COVID-19, risk factors associated with severe outcomes from COVID-19 among older adults living in the community, and residents of long-term care homes or other congregate living settings for seniors.

NACI approved these updated recommendations on March 31, 2022.

For further information on NACI's recommendations on the use of COVID-19 vaccines, please refer to the COVID-19 vaccine chapter in the Canadian Immunization Guide (CIG).

Further information on NACI's process and procedures is available elsewhere [1, 2].

RECOMMENDATIONS

The NACI recommendations on a **first** booster dose in younger age groups, including adolescents 12-17 years of age, are under review and an update will be forthcoming. For details on the current recommendations, consult the following statements: updated guidance on booster COVID-19 vaccine doses in Canada for adults 18 years of age and older, guidance on the use of booster COVID-19 vaccine doses in adolescents 12 to 17 years of age and timing of COVID-19 vaccination for individuals previously infected with SARS-CoV-2.

In addition, regarding a **second** booster dose, NACI now makes the following recommendations based on the current evidence, the objectives of the Canadian COVID-19 pandemic response, and the evolving epidemiology of the COVID-19 pandemic.

In the context of protection against severe disease potentially decreasing over time following the first booster dose, and/or risk of immune evasion by highly transmissible VOC which can cause severe disease:

1. **NACI recommends that jurisdictions prepare for the rapid deployment of a second COVID-19 vaccine booster dose program over the coming weeks prioritizing the following populations, as close surveillance and assessment suggest concerning trends in the COVID-19 pandemic:**

    a. **Adults 80 years of age and over living in the community**
    (Strong NACI Recommendation)

    b. **Residents of long-term care or other congregate living settings for seniors**
    (Strong NACI Recommendation)

    c. **While the greatest benefit is expected in adults 80 years of age and older, jurisdictions may also consider offering a second COVID-19 booster dose to adults 70-79 years of age living in the community.**
    (Discretionary NACI Recommendation)

- **Timely, close, ongoing monitoring and assessment of provincial/territorial, national and international data are important to determine possible triggers for rapid implementation of local or provincial/territorial COVID-19 vaccination campaigns along with public health measures.**
- **In general, jurisdictions should aim to provide a second booster dose 6 months after receipt of the previous booster dose, but this 6 month interval may need to be balanced with local and current epidemiology. As a result, shorter intervals may be indicated for these older adult populations in these settings at this time. When applicable, timing of recent COVID-19 infection should also be considered.**
- **A second booster dose among adults younger than 70 years of age in or from First Nations, Métis, or Inuit communities may be considered*. Autonomous decisions should be made by Indigenous Peoples with the support of healthcare and public health partners in accordance with the United Nations Declaration on the Rights of Indigenous Peoples.**
- **Among adults 70 years of age and over living in the community and residents of long-term care homes or other congregate living settings for seniors, either**

Moderna Spikevax (50mcg) or Pfizer-BioNTech Comirnaty (30mcg) may be considered for second booster doses. The use of the Moderna Spikevax vaccine (100mcg) as the booster may also be considered based on clinical discretion. The Novavax Nuvaxovid COVID-19 vaccine may be offered as a booster dose to individuals who are unable or unwilling to receive an mRNA COVID-19 vaccine.

The planning and deployment of a second COVID-19 booster dose program** for other high-risk groups (such as key populations*** previously prioritized) AND/OR for the general population may also be relevant in the future if surveillance and assessment**** suggest concerning trends in the COVID-19 pandemic (e.g., emergence or re-emergence of VOC causing severe disease). Planning should take into account that vaccine deployment may be required for broader population groups in the fall of 2022 or earlier depending on the COVID-19 pandemic context.

NACI will continue to monitor the evidence and update its recommendations as needed.

**A second booster dose among adults younger than 70 years of age in or from First Nations, Métis, or Inuit communities may be considered as these communities have a younger age distribution but increased risk for severe disease due to a variety of intersecting factors including underlying medical conditions and potential decreased access to health care.*
***Details on options and considerations for vaccine types among certain adult populations are available in Table 4 of the recommendations on the use of Medicago COVID-19 vaccine*
****NACI is currently reviewing the **key populations** and will provide further details in future statements*
***** Factors to consider in the surveillance and assessment for future booster doses may vary by jurisdiction and are summarized in Table 1 below (updated from NACI's Interim guidance on booster COVID-19 vaccine doses in Canada)*

Additional Considerations

- Preparation for implementation and deployment of a second booster dose program for groups outlined above is recommended given the increasing circulation of the BA.2 VOC and the possibility of waning protection against severe disease in those at highest risk.
- There remains considerable uncertainty regarding the long-term evolution of the COVID-19 pandemic. In addition to the current wave and other potential waves due to emerging VOCs, it is possible that, consistent with other respiratory viruses, incidence of COVID-19 will increase in the fall and winter seasons.
- There will be variability in how each province, territory and community assesses risk and responds to the needs of their respective jurisdictions. With the changing epidemiology, it is important to protect those at highest risk first. This includes prioritization of adults 80 years of age and over living in the community and residents of long-term care homes or other congregate living settings for older adults who are at high risk of severe illness from COVID-19.
- In general, if second booster doses of COVID-19 vaccines are being offered, jurisdictions should aim to provide this dose 6 months after receipt of the previous dose. However, an interval shorter than 6 months may be warranted in some individuals in the context of the rapidly evolving pandemic, as well as operational considerations for the expedient deployment of second booster doses in long-term care and congregate living settings. For individuals previously infected with SARS-CoV-2, timing of recent SARS-CoV-2 infection should also be considered. NACI has suggested a 3-month interval between infection and COVID-19 booster dose (i.e., 3 months after symptom onset or positive test if asymptomatic) or 6 months from the most recent vaccine dose, whichever is longer.

- Second COVID-19 booster doses are currently not authorized by Health Canada and therefore constitute off-label use.
- NACI continues to monitor and assess the evidence as it emerges and will update its recommendations as needed.

Table 1. Underlying factors for consideration to determine the need for and benefit of subsequent COVID-19 vaccine booster dose programs in various populations

Underlying factors for consideration	Evidence to review to determine the need for and benefit of a second booster dose of COVID-19 vaccine
Risk benefit analysis	• Risk of severe illness and death *(e.g., older age, underlying medical conditions, populations who have been disproportionately affected by the pandemic due to a number of intersecting equity factors)* • Risk of exposure *(e.g., inability to physically distance and lack/poor access to infection prevention and control measures, frontline healthcare providers, congregate living facilities)* • Risk of transmission to vulnerable populations *(e.g., caregivers of those at increased risk of severe illness and death)* • Risk of societal disruption *(e.g., frontline essential workers)* • Prevention of multisystem inflammatory syndrome in children (MIS-C) and post-COVID-19 syndromes
COVID-19 epidemic conditions	• Circulation of SARS-CoV-2 strain (re-emergence of a previous strain or emergence of new strain) in Canada or internationally • Breakthrough cases, outbreaks • Case rates, virulence and implications for health system capacity • Duration of protection for COVID-19 vaccines against infection and against severe outcomes of COVID-19
Population level cumulative immunity and vaccine coverage	• Initial vaccination series (time since last dose, coverage, type, interval between doses) • Previous SARS-CoV-2 infection
Vaccine characteristics in different groups against strain circulating or expected to circulate	• Duration of protection • Immunogenicity • Efficacy/effectiveness in preventing transmission, infection and severe disease • Safety
Vaccine types available and forecasted	• Number and type of available vaccines (including availability of vaccines expected to be effective against circulating strains) • Possible future vaccines (e.g., new formulations effective against variants, new vaccine technologies, or new delivery routes) • Global equity and supply

SUMMARY OF EVIDENCE

Evolving epidemiology

- There continues to be a high burden of disease as public health measures are lifted and Omicron BA.2 sub-variant spreads. For the most up to date information on the epidemiology of COVID-19 in Canada, please refer to the COVID-19 daily epidemiology update.
- Even though the Omicron wave had a smaller proportion of severe cases compared to the previous waves, incidence of severe outcomes was highest among older adults ≥80 years of age, followed by older adults 70 to 79 years of age in Canada.
- Beyond the current wave, there remains uncertainty with regards to the likelihood, timing and severity of any future wave of COVID-19 in Canadian jurisdictions due to the potential emergence of new or previously circulating variants and considering existing population protection from COVID-19 immunization programs and previous SARS-CoV-2 infections.

Coverage and protection from recent infection

- Older adults currently have the highest vaccine coverage for the first booster dose, with 83.1% of adults 70 to 79 years of age and 84.6% of adults ≥80 years of age having received an additional dose after their primary series as of March 20, 2022 [3]. As the first booster vaccination programs were implemented starting in August or September 2021 in some Canadian provinces and territories, individuals who first received a booster have reached or are approaching six months since that last dose.
- Given high rates of Omicron infection in community and institutional settings between December 2021 and February 2022, a proportion of the population may have boosted their immune response following exposure to the Omicron variant. This will need to be taken into account when planning booster doses for those individuals with previous SARS CoV-2 infection.

VE over time following a first booster

- Current data suggest that COVID-19 vaccines offer reduced protection against Omicron infection and symptomatic disease and somewhat lower protection against hospitalization/ severe disease compared to the protection offered against the ancestral strain and previous VOCs. This lower protection is also occurring in the context of decreasing protection over time since the previous dose.
- VE against infection/symptomatic disease for the Omicron variant from a first booster of mRNA vaccine is approximately 60% and decreases over time since vaccination in most studies.
- Vaccine protection against severe disease and hospitalization due to COVID-19 has been more durable than protection against symptomatic disease or infection and is approximately 10 to 20% higher following a first booster compared to those who have only completed a primary series, reaching ~90% or more shortly following vaccination [4-9]. Evidence regarding the duration of protection of a first booster against severe disease is limited, with a few studies suggesting some decrease over time [4, 6]. As an example, VE against hospitalization was 78% (95% CI: 67 to 85%) at ≥4 months in one US study [4].

VE following a second booster

- Evidence on second booster VE is limited and has mainly been assessed as a relative benefit compared to the first booster [10-12]. Preliminary data indicates that a second booster dose provides additional protection compared to a first booster, including against severe disease. However, the duration of protection is currently unknown, and the absolute benefit will depend on the residual protection from the first booster dose and on the level of circulating disease in the community.
- In a study of a second booster among older adults ≥60 years of age who were vaccinated at least 4 months from their first booster [11], the rates of SARS-CoV-2 infection and COVID-19 severe illness were lower in those 12 or more days after the fourth dose (2.0-fold and 1.8-fold for infection and 4.3-fold and 4.0-fold for severe disease) compared to the two control groups, respectively (those eligible for the second booster dose but who did not receive it, and those who received the second booster dose but were within 3 to 7 days after receiving the second booster dose, which is before it is expected to take effect [11]).
- In a separate study of healthcare workers who received a second booster dose given at least 4 months after the first booster dose, there was a relative adjusted VE after a second booster compared to a first booster against symptomatic disease of 43% (95% CI: 7 to 65%) in the Pfizer-BioNTech group and 31% (95% CI: -18 to 60%) in the Moderna group [10].

  Since the NACI review, studies on second booster VE continue to become available [13, 14].

Immunogenicity of first or second booster doses in older adults and long-term care (LTC) residents

- Evidence on immune responses in older adults and LTC residents suggests that after a first booster of mRNA COVID-19 vaccine, humoral immune responses, including neutralizing antibody responses against the Omicron variant, increase to levels that are similar to or greater than those observed shortly after the second dose of the primary series [15-20]. After a second booster in LTC residents in Ontario [20] and in a separate study in healthcare workers ≥18 years of age in Israel [10, 21], a similar trend was observed where the second booster resulted in similar titres to that achieved after the first booster dose.
- Emerging evidence suggests that humoral immune responses after a first booster in older adults and LTC residents wane over a period of approximately 15 weeks [15-19]; longitudinal data on immune responses after a second booster are not available. It is currently unclear if the rate at which post first or second booster dose immune responses wane is different than the rate at which immune responses waned after previous doses, and it is not known if and for how long immune responses will remain above a threshold correlated with protection from infection or other clinical outcomes (e.g., severe disease). Immunological correlates of protection have not yet been defined for COVID-19. The impact of repeated vaccine doses is also yet to be determined.
- Longer intervals between doses have been shown to result in a better immune response [22, 23] and somewhat better VE [22, 24] than shorter intervals. Longer time between doses allows more time for waning protection, but may also result in a better response after the next dose, as this allows time for this response to mature in breadth and strength, and for circulating antibodies to decrease, thus avoiding immune interference when the next dose of vaccine is administered. NACI recommends jurisdictions aim for a 6 month interval from

the first to second booster dose. This interval needs to be weighed against the potential for increased susceptibility due to waning immunity in the context of widespread circulation of the BA.2 sub-variant.

Safety

- Preliminary data indicate that the safety of a second booster of an mRNA COVID-19 vaccine is comparable to previous doses. Overall, from both Canadian and International safety surveillance data, a second booster of mRNA COVID-19 vaccine was well tolerated and no new safety signal was identified [10, 25-27]. However, this second booster was generally administered in specific populations (e.g., LTC residents, older adults) or in small groups. Evidence monitoring is ongoing.

Ethics, equity, feasibility, and acceptability (EEFA)

- Residents of LTC homes and older adults living in other congregate settings were one of the first populations to be immunized against COVID-19 with a primary series and a first booster dose as they have been distinctly more vulnerable to COVID-19 than other populations, and have faced disproportionate harms from the COVID-19 pandemic.
- "Pandemic fatigue" may reduce acceptance of a second booster dose, but vaccine uptake increases with age and rising rates of the Omicron sub-variant BA.2 may encourage vaccine uptake.
- Public health and health care providers have considerable experience with efficient, rapid, large scale vaccination campaigns which can be used as the foundation for rapid implementation of subsequent booster doses for populations such as adults 80 years of age and older in the community and residents of long-term care homes and other congregate living settings for seniors.
- NACI continues to acknowledge the importance of global vaccine equity to address the pandemic impact even as global vaccine supply increases, recognizing that challenges in access and distribution may persist. The World Health Organization calls on individual countries to make vaccine booster dose policy decisions that balance the public health benefits to their population with support for global equity in vaccine access.
- 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 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, whose benefit is further enhanced with subsequent booster doses.

Other considerations

- While there is considerable understanding of the VE against the Omicron variant (both BA.1 and BA.2), there is uncertainty regarding the effectiveness of the current vaccines against potential new VOCs. Manufacturers are working on new COVID-19 vaccines, including multivalent vaccines and vaccines specifically targeting VOCs, although their exact composition and timing of availability are not yet known.
- As protection against infection is highest soon after vaccine administration, vaccination at a time of low disease incidence may have limited benefit particularly if there is an extended period of time before the next wave of SARS-CoV-2.

RESEARCH PRIORITIES

1. Continuous monitoring of data on the safety, immunogenicity, efficacy, and effectiveness of the COVID-19 vaccines, including booster doses, through clinical trials and studies in real-world settings, including with regard to the duration of protection from first booster doses and the impact and duration of protection from second booster doses.
2. Further evaluations of the optimal interval between booster dose administration, as well as further evaluations of the optimal interval between previous SARS-CoV-2 infection and booster dose administration.
3. Vigilant monitoring and reporting of adverse events of special interest, including myocarditis and/or pericarditis, in order to accurately inform potential risks associated with a future booster. Global collaboration should be prioritized to enable data sharing so decision makers around the world can weigh benefits and risks of second booster doses of COVID-19 vaccines.
4. Continuous monitoring of COVID-19 epidemiology and VE in special populations (e.g., residents of long-term care facilities, adults of advanced age, individuals with high-risk medical conditions, pregnancy, and communities disproportionately affected by COVID-19) and across a range of clinical outcomes (i.e., post-COVID-19 syndromes/long-term consequences of COVID-19 infection; MIS-C; severe disease).
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 uptake in the Canadian population, particularly in the context of subsequent booster doses.

Table 2. 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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