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

Updated recommendations on the use of COVID-19 vaccine booster doses in children 5 to 11 years of age and concurrent vaccine administration

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Recommandations mises à jour sur l'utilisation des doses de rappel du vaccin contre la COVID-19 chez les enfants de 5 à 11 ans et l'administration concomitante de vaccins

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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 December 9, 2022, Health Canada authorized the use of the Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (10 mcg) COVID-19 vaccine as a single booster dose in individuals 5 to 11 years of age, following the authorization on October 7, 2022 of the Pfizer-BioNTech BA.4/5 Bivalent (30 mcg) as a booster dose in individuals ≥12 years of age. On August 19, 2022, NACI published Recommendations on the use of a first booster dose of Pfizer-BioNTech Comirnaty COVID-19 vaccine in children 5 to 11 years of age, which provided guidance on the first COVID-19 booster product (original formulation) authorized for use in children 5 to 11 years of age 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. COVID-19 epidemiological activity in Canada increased in the summer months, and again in the fall. Consistent with other respiratory viruses, it is possible that the incidence of COVID-19 may again increase in the colder months and that new variants of concern (VOCs) may emerge. However, seasonality of SARS-CoV-2 virus is yet to be established.
- The Omicron variant has demonstrated partial immune evasion conferred by the original COVID-19 vaccines or by a previous infection with a SARS-CoV-2 variant that emerged prior to Omicron. The immune evasion exhibited by more recent Omicron subvariants (e.g., BA.4 and BA.5, and BQ.1) may be greater than that exhibited by previous Omicron subvariants, although evidence is still emerging.
- The proportion of Canadian children 5 to 11 years of age vaccinated with a primary series is roughly 40%; however, only 5% of children in this age group have received at least one booster dose [(1)].

NACI continues to recommend a primary series with an original mRNA vaccine in all authorized age groups, and a booster dose with a recommended vaccine product for those who are eligible. 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. A booster dose is most important for authorized populations considered at increased risk of severe COVID-19 disease. 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).

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., population-level cumulative immunity and vaccine coverage) as outlined in the NACI 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 November 1, 2022, the NACI COVID-19 Working Group (COVID-19 WG) convened to discuss and review data on the optimal use of the Pfizer-BioNTech Comirnaty BA.4/5 Bivalent COVID-19 vaccine in children 5 to 11 years of age. Input was provided by the PHAC Vaccine Coverage, and PHAC Surveillance and Epidemiology Divisions. The COVID-19 WG reviewed available evidence including COVID-19 epidemiological trends among pediatric populations, evidence on vaccine effectiveness (VE) and duration of protection following a primary series with Pfizer-BioNTech vaccine (10 mcg), evidence on the post-market safety of booster doses of mRNA vaccines, available preclinical evidence on Pfizer-BioNTech Comirnaty BA.4/5 Bivalent COVID-19 vaccine, as well as available clinical trial data and real-world evidence on the immunogenicity of the Pfizer-BioNTech Comirnaty BA.4/5 Bivalent COVID-19 vaccine and the Moderna Spikevax BA.4/5 Bivalent COVID-19 vaccine in adults. The COVID-19 WG also reviewed the available evidence on the risks and benefits of concurrent administration of COVID-19 vaccines with non-COVID-19 vaccines in all ages including evidence on the post-market safety of the primary series of mRNA vaccines in pediatric populations, including children under 5 years of age.

On November 15, 2022, NACI reviewed the evidence presented to the COVID-19 WG in addition to post-market safety data on bivalent vaccines in individuals aged ≥12 years.

NACI approved the updated recommendations on the use of COVID-19 vaccine booster doses on November 28, 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 [2, 3].

OVERVIEW OF EVIDENCE

Evolving epidemiology, vaccine coverage, and hybrid immunity in children 5 to 11 years of age

- Canada experienced a resurgence in confirmed SARS-CoV-2 infections during the summer months, driven primarily by the Omicron BA.4 and BA.5 subvariants, and again in the fall. Although the fall surge of COVID-19 cases seems to have plateaued, emerging Omicron variants including BQ.1.1 and BF.7 are on the rise [4]. Consistent with other respiratory viruses, it is possible that the incidence of COVID-19 may increase again in the colder months, 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.
- While some children do get severe COVID-19 disease, the risks of severe outcomes from COVID-19 remains low in children 5 to 11 years of age compared to older age groups [5]. Since the start of the pandemic in Canada, children 5 to 11 years of age represent the age group with the lowest average monthly rates of hospitalization from COVID-19, and this has remained true during the Omicron period. In the four-week period from August 29, 2022 to September 25, 2022, the hospitalization rate was 2.2/100,000 in unvaccinated children 5 to 11 years of age and 1.5/100,000 in children 5 to 11 years of age who have completed their primary series [6].
- Available Canadian pediatric seroprevalence data range in percent estimates, regions surveyed, and study period, however taken together suggest that seroprevalence in children 5 to 11 years of age has increased since Omicron variants began circulating in late December 2021 [7-9].
- Hybrid immunity (i.e., protection conferred from both vaccination and infection) is more robust than immunity due to either infection or vaccination alone [10]. However, evidence on the duration of this protection is limited. Omicron infection in a previously-vaccinated individual confers significant protection from reinfection with Omicron, including subvariants BA.4 and BA.5 [10-13]. Evidence on protection against BQ.1 (conferred by previous vaccination, infection, or hybrid immunity) is still emerging.
- As of November 6, 2022, approximately 40% of children 5 to 11 years of age have been vaccinated with a complete primary series, however only 5% have received at least one booster dose [1].
- It is expected that children 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. A longer interval between SARS-CoV-2 infection and vaccination is associated with improved immune responses to COVID-19 vaccines [14-16]. However, the benefits of a longer interval (e.g., better, more durable immune response) should be balanced with the risks of infection and associated sequelae as protection from the previous dose or infection decreases over time.

Vaccine effectiveness of COVID-19 vaccines in children 5 to 11 years of age

- VE of the original mRNA COVID-19 vaccines against Omicron infection in children and adolescents is lower than VE against infection with ancestral SARS-CoV-2 and previous VOCs [17-20]. VE against Omicron infection after completion of a primary series in children 5 to 11 years of age has shown evidence of waning, similar to that seen in older populations [17]. However, VE against severe disease in children aged 5 to 11 years is higher than VE against infection in the context of the Omicron variant [21, 22]. To date, there is no available data for VE following an mRNA booster dose in children 5 to 11 years of age.
- While VE of pediatric COVID-19 vaccines against post-COVID-19 condition (PCC) is also not known at this time, evidence from adult populations shows that COVID-19 vaccination reduces the risk of PCC. Those who are vaccinated with two or more doses are less likely to develop PCC if they do become infected compared to those who are unvaccinated [23].
- There are no data (preclinical or clinical) on the use of the Pfizer-BioNTech BA.4/5 Bivalent vaccine as a primary series in any age; however, trials are ongoing.

For further information on the efficacy/effectiveness of mRNA COVID-19 vaccines against severe outcomes of COVID-19 including hospitalization due to multisystem inflammatory syndrome in children (MIS-C), please refer to the NACI: Statements and publications and the COVID-19 vaccine chapter in the Canadian Immunization Guide.

Summary of evidence on Pfizer-BioNTech Comirnaty BA.4/5 Bivalent vaccines

- The Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (10 mcg) vaccine contains equal parts (5 mcg each) of mRNA encoding for the spike protein of the original SARS-CoV-2 virus and that of the Omicron BA.4/5 variant [24].
- There is currently no clinical evidence on the safety, immunogenicity, or efficacy of the Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (10 mcg) vaccine in children 5 to 11 years of age. The regulatory review process leveraged preliminary clinical trial data on the Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg) vaccine in adolescents and adults ≥12 years of age, clinical trial data on the use of the Pfizer-BioNTech Comirnaty BA.1 Bivalent (30 mcg) and Pfizer-BioNTech Comirnaty BA.1 Monovalent vaccines in adults, as well as immunogenicity and safety data of Pfizer-BioNTech Comirnaty original (10 mcg) vaccine in children 5 to 11 years of age.
- Preliminary reports of clinical trial data in adults over 55 years of age indicated that the geometric mean titres (GMTs) against Omicron BA.4/5 one month after receipt of a booster dose of Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg) vaccine was approximately 4-fold higher than the GMTs one month after receipt of a booster dose of Pfizer-BioNTech Comirnaty original (30 mcg) [25]. In adults who received Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg), GMTs against Omicron BA.4/5 rose by 13.2-fold (95% CI: 8.0 to 21.6%) compared to pre-boost levels. In adults who received Pfizer-BioNTech Comirnaty original (30 mcg), GMTs against Omicron BA.4/5 rose by 2.9-fold (95% CI: 2.1 to 3.9%) compared to pre-boost levels [25].
- Three preliminary real-world studies from the United States (US) evaluating neutralizing antibody responses against the original SARS-CoV-2 strain and various Omicron

sublineages (including BA.4, BA.5, and BQ.1) in adults approximately 2 to 6 weeks after a Pfizer-BioNTech or Moderna BA.4/5 bivalent booster dose, showed variable (e.g., similar or higher) immune responses compared to the original vaccine booster [26].

- A preliminary study from the US on BA.4/5 bivalent mRNA booster formulations reported improved VE against symptomatic SARS-CoV-2 infection following bivalent boosters among individuals who had previously received at least 2 original formulation vaccine doses. Of note, this study was limited to older (≥18 years) age groups and products assessed differed in dosage from the Pfizer-BioNTech Comirnaty BA.4/5 (10 mcg) vaccine authorized for children 5 to 11 years of age. Additionally, the analysis pooled data on VE from both the Moderna Spikevax (50 mcg) and the Pfizer-BioNTech Comirnaty BA.4/5 Bivalent vaccines [27]. Note this study was released following NACI deliberations and therefore was not considered in their decision.
- Preliminary post-market safety surveillance data in individuals ≥12 years of age from Canada and the US suggest the BA.4/5 bivalent vaccines are well tolerated with a similar safety profile to the original mRNA COVID-19 vaccines when administered as booster doses [28-30].
- No participants in the Pfizer-BioNTech Comirnaty BA.1 or BA.4/5 bivalent clinical trials 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, and there is no evidence specifically in pediatric populations. However, no specific safety concerns have been identified to date [31-37]. Studies to assess the safety and immunogenicity of concurrent administration of COVID-19 vaccines (including bivalent Omicron-containing mRNA vaccines) with other vaccines are ongoing.

Potential benefits of bivalent Omicron-containing vaccines

- Omicron and its subvariants are currently the most antigenically distinct VOCs from the original SARS-CoV-2 virus [38]. Given the potential for substantial virus evolution and uncertainty about the emergence of future variants, modification of the strain composition of COVID-19 vaccines is expected to broaden immune protection against divergent SARS-CoV-2 spike protein antigens [38]. Bivalent Omicron-containing mRNA vaccines are expected to elicit a greater breadth of immune responses compared to original mRNA vaccines, 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 [38].
- It is possible that children who have yet to be infected with the Omicron variant may realize additional benefits from a bivalent Omicron-containing mRNA COVID-19 vaccine over time, by priming their immune response to the Omicron variant. Additionally, children 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 data on pediatric mRNA COVID-19 vaccines and on concurrent administration of COVID-19 vaccines with other vaccines

- Real-world data from the US in children aged 5 to 11 years (n=3,249) indicated that local and systemic reactions in children 5 to 11 years of age were reported with similar frequency after a booster dose, compared to after the second dose of a primary series. The majority of reported symptoms following a booster dose were mild in severity. However, some reactions (i.e., pain and fatigue) were reported to be moderate or severe at a higher frequency after a booster dose than after the second dose. There were no reports of myocarditis after administration of a booster dose in children 5 to 11 years of age in this study [39].
- Evidence of surveillance data from Canada and international jurisdictions indicate that the risk of myocarditis and/or pericarditis following a first booster dose of an original mRNA COVID-19 vaccine appears to be lower than the risk following the second dose of the primary series, in particular among age groups at highest risk (i.e., adolescents and young adults) [40-46].
- With regard to mRNA COVID-19 vaccines for the youngest age groups (i.e., 6 months to 5 years), no safety signals (including no identified cases of myocarditis) have been identified for either Pfizer-BioNTech Comirnaty (3 mcg) or Moderna Spikevax (25 mcg), from clinical trials or post-market safety surveillance data in Canada (n=193,855 vaccine doses) [47] and the US (n=1,553,336 vaccine doses) [48, 49].
- There are currently limited data available on whether the reactogenicity of mRNA COVID-19 vaccines is increased with concurrent administration of other vaccines in children and adolescents. Post-market safety surveillance data mostly from adult populations [50-58] has not identified any specific safety concerns to date arising from concurrent administration of original mRNA COVID-19 vaccines (different dosage) with non-COVID-19 vaccines (primarily influenza vaccines) [50, 55, 58].
- For more information on the safety and tolerability of mRNA COVID-19 vaccines in children under 5 years of age, please see NACI's Recommendations on the use of Pfizer-BioNTech Comirnaty (3 mcg) COVID-19 vaccine in children 6 months to 4 years of age and Recommendations on the use of Moderna Spikevax COVID-19 vaccine in children 6 months to 5 years of age.

Ethics, equity, feasibility, and acceptability on pediatric COVID-19 vaccines

- Many children in Canada and internationally have fallen behind in routine vaccinations [59-62]. It is important for children to receive all recommended pediatric vaccinations as per jurisdictional guidance. Concurrent administration of mRNA COVID-19 vaccines with non-COVID-19 vaccines in individuals 6 months of age and older may increase the feasibility of administering all recommended childhood vaccines, at both the individual level and the immunization program level.
- National vaccine coverage data indicates limited uptake of COVID-19 booster doses in children in Canada aged 5 to 11 years [1]. The epidemiological context (e.g., severity of circulating variants) and/or availability of variant-specific vaccine formulations may increase acceptance and uptake of pediatric COVID-19 vaccines [63].

- Informed consent should include transparency about the known and unknown factors when describing the benefits and risks of the Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (10 mcg) vaccine.
- 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.

RECOMMENDATIONS ON THE USE OF A COVID-19 VACCINE BOOSTER DOSE IN CHILDREN 5 TO 11 YEARS OF AGE

Consistent with previous NACI guidance on the use of a Pfizer-BioNTech Comirnaty (10 mcg) booster dose in children 5 to 11 years of age:

For children 5 to 11 years of age with an underlying medical condition that places them at high risk of severe illness:

1. **NACI recommends that a booster dose of a Pfizer-BioNTech Comirnaty (10 mcg) COVID-19 vaccine should be offered ≥6 months after completion of a primary COVID-19 vaccine series or previous SARS-CoV-2 infection to children 5 to 11 years of age with an underlying medical condition that places them at high risk of severe illness due to COVID-19 (including those who are immunocompromised and who received a 3-dose primary series).** ***(Strong NACI recommendation)***

For all other children 5 to 11 years of age:

2. **NACI recommends that a booster dose of a Pfizer-BioNTech Comirnaty (10 mcg) COVID-19 vaccine may be offered ≥6 months after completion of a primary series or previous SARS-CoV-2 infection to all children 5 to 11 years of age who do not have underlying medical conditions that could place them at higher risk of severe illness due to COVID-19. *(Discretionary NACI recommendation)***

Additional considerations and rationale:

- For children 5 to 11 years of age, the Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (10 mcg) vaccine is currently the only bivalent Omicron-containing mRNA COVID-19 vaccine authorized by Health Canada for use as a booster dose.
- Consistent with current NACI guidance on the product offered for a COVID-19 booster dose in older age groups (i.e., 12 years of age and older), a bivalent booster (Pfizer-BioNTech Comirnaty BA.4/5 Bivalent [10 mcg]) is the preferred product for children aged 5 to 11 years who are recommended for a booster dose.
- Clinical trial data in older adults suggest that the Pfizer-BioNTech Comirnaty BA.4/5 (30 mcg) bivalent booster elicited higher neutralizing antibody titres against Omicron BA.4/5 compared to the original booster dose and has a similar safety profile. Recent preliminary real-world data in adult populations suggests the bivalent Omicron-containing mRNA COVID-19 vaccines have a similar safety profile to the original mRNA vaccines as a booster dose, and induces a similar or slightly higher neutralizing antibody response to BA.4/5 subvariants. However, while studies are underway, the relative VE of bivalent Omicron-containing mRNA vaccines remains unknown. Omicron-containing mRNA COVID-19 vaccines are expected to broaden the immune response and can potentially provide improved protection against the Omicron variant and subvariants compared to original mRNA COVID-19 vaccines.
- NACI is currently only recommending one booster dose after the primary series for children 5 to 11 years of age. However, at the provider's discretion, a bivalent booster dose (as per recommended interval) could be offered to children considered at high risk of severe COVID-19 who have previously received a booster dose with the original Pfizer-BioNTech Comirnaty mRNA vaccine.
- A shorter interval of at least 3 months may be considered particularly in the context of heightened epidemiologic risk, evolving SARS-CoV-2 epidemiology, as well as operational considerations for the efficient deployment of vaccine programs.
- 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. If a bivalent Omicron-containing mRNA COVID-19 vaccine is administered in error as part of a primary series, this dose should be considered valid as part of the primary series. NACI will continue to monitor evidence as it emerges, and update recommendations as needed.
- There is limited evidence on clinical risk factors for severe COVID-19 disease in children 5 to 11 years of age. Children at increased risk for severe outcomes may include children: with obesity, who are medically fragile/have medical complexities, who have more than

one comorbidity or neurological disorders, or who have Down syndrome or immunocompromising conditions, but this list is limited by scarcity of data. There is more evidence for chronic conditions associated with higher risk of severe COVID-19 in adolescents 12 to 17 years of age. For further information, please refer to the COVID-19 vaccine chapter in the Canadian Immunization Guide.

RECOMMENDATIONS ON THE CONCURRENT ADMINISTRATION OF COVID-19 VACCINES WITH OTHER RECOMMENDED VACCINES

1. **NACI recommends that for individuals 6 months of age and older, COVID-19 vaccines may be given concurrently (i.e., same day), or at any time before or after, non-COVID-19 vaccines (including live and non-live vaccines).** ***(Discretionary NACI recommendation)***
   - NACI recommends that COVID-19 vaccines (may be concurrently administered with other vaccines among all vaccine eligible populations (i.e., individuals 6 months of age and older) based on the following observations: 1) no safety signal has emerged from ongoing post-market safety surveillance for mRNA COVID-19 vaccine products in children 6 months to 5 years of age; and 2) there is no evidence of safety concerns for concurrent administration based on data from adult populations. In addition, concurrent administration will reduce barriers to the provision of routine childhood immunizations and seasonal influenza immunization.
   - This recommendation expands previous guidance from NACI supporting concurrent administration of COVID-19 vaccines with other vaccines to now include the youngest authorized (i.e., 6 months to 5 years) age group.

NACI RESEARCH PRIORITIES

1. Continuous monitoring of data on the safety, immunogenicity, efficacy and effectiveness against a broad range of variants/sublineages and outcomes (including severe disease) of both the original and the various bivalent mRNA COVID-19 vaccines through clinical trials and real-world studies including comparisons between products, degree and duration of protection conferred by each booster dose against circulating variants. The research should be conducted in all age groups, to support the assessment of the need for booster doses in those 6 months to 4 years of age, and the need for and frequency of, repeat booster doses in older children, adolescents, and adults. Vaccine research should also consider the clinical implications of previous SARS-CoV-2 infection; repeated immunization with various product combinations; and outcomes after any infection such as MIS-C, PCC, or infection induced myocarditis and/or pericarditis in all populations.
2. Continuous monitoring of vaccine uptake and acceptance in the Canadian population, specifically following the authorization of new bivalent Omicron-containing mRNA COVID-19 vaccines.
3. Further evaluations of the optimal interval between booster dose and primary series, and between any subsequent booster doses as well as further evaluations of the optimal interval between previous SARS-CoV-2 infection and booster dose administration.
4. Vigilant monitoring and reporting of adverse events (AEs) 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-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. Evaluations of the potential impact of COVID-19 vaccines on the immune responses and effectiveness of other vaccines in the routine childhood schedule when administered concurrently.
7. 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.
8. Continuous monitoring of post-market safety and surveillance data in children.
9. Continued research to determine immunologic correlates of protection against infection, symptomatic COVID-19, and severe disease from COVID-19.
10. Continued research to assess novel vaccine technologies such as mucosal vaccines and pan-sarbecovirus vaccines.

ABBREVIATIONS

CI	Confidence Interval
CIG	Canadian Immunization Guide
COVID-19	Coronavirus disease 2019
GMFR	Geometric mean fold rise
GMT	Geometric mean titre
mcg	Micrograms
mRNA	Messenger Ribonucleic Acid
NACI	National Advisory Committee on Immunization
PHAC	Public Health Agency of Canada
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SR	Seroresponse
US	United States
VE	Vaccine effectiveness
VOC	Variant of Concern

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APPENDIX A: VACCINE

COVID-19 vaccine preparations authorized by Health Canada for use as a booster dose in children 5 to 11 years of age

Table 1. Use of COVID-19 vaccines authorized as a booster dose in children 5 to 11 years of age

Product Characteristics	Pfizer-BioNTech Comirnaty original	Pfizer-BioNTech Comirnaty BA.4/5 Bivalent
Age	5 to 11 years	5 to 11 years
Dose	10 mcg (0.2 mL); original SARS-CoV-2	10 mcg (0.2 mL) [(5 mcg original SARS-CoV-2 + 5 mcg Omicron BA.4/BA.5]
Presentation	Multidose vial of 10 doses after dilution Orange vial cap Orange label border	Multidose vial of 10 doses after dilution Orange vial cap; the label on the vial states “Bivalent Original & Omicron BA.4/BA.5” Orange label border
Diluent	Sterile 0.9% Sodium Chloride Injection, USP	Sterile 0.9% Sodium Chloride Injection, USP
Potential allergens	Polyethylene glycol (PEG), Tromethamine (trometamol or Tris)[a]	Polyethylene glycol (PEG), Tromethamine (trometamol or Tris)[a]
Storage[b,c]	• Store at temperatures -90°C to -60°C for up to 12 months from the date of manufacture • Do not store vials at -25°C to -15°C • Vials can be thawed and stored at +2°C to +8°C for up to 10 weeks, or at +8°C to +25°C for up to 12 hours if unpunctured • Post-dilution (i.e., first puncture), vials may be stored at +2°C to +25°C and discarded after 12 hours post-dilution (first puncture) • Do not refreeze once thawed	• Store at temperatures -90°C to -60°C for up to 12 months from the date of manufacture • Do not store vials at -25°C to -15°C • Vials can be thawed and stored at +2°C to +8°C for up to 10 weeks, or at +8°C to +25°C for up to 12 hours if unpunctured • Post-dilution (i.e., first puncture), vials may be stored at +2°C to +25°C and discarded after 12 hours post-dilution (first puncture) • Do not refreeze once thawed
Transport	If local transport of full cartons containing undiluted vials at -90°C to -60°C is not feasible, full	If local transport of full cartons containing undiluted vials at -90°C to -60°C is not feasible, full cartons or

	cartons or individual undiluted vials may be transported at +2°C to +8°C	individual undiluted vials may be transported at +2°C to +8°C

[a]Tromethamine (Tris or trometamol) is used as a buffer in vaccines and medications, including those for use in children, to improve stability and prevent pH fluctuations in the solution. No safety concerns have been identified with tromethamine. While tromethamine has been identified as a potential allergen, a review of existing evidence did not identify any cases of allergic reactions to tromethamine in children [27]

[b]Regardless of storage condition, vaccines should not be used after date of expiry.

[c]Frozen is -50°C to -15°C; Refrigerated is +2°C to +8°C; Room temperature is +15°C to +25°C.

For complete prescribing information for the pediatric formulations of the Pfizer-BioNTech Comirnaty COVID-19 vaccines authorized as a booster dose in children 5 to 11 years of age, please refer to the product leaflets or information contained within Health Canada's authorized product monographs available through the Drug Product Database.

APPENDIX B: SUPPLEMENTAL CLINICAL DATA ON THE SAFETY OF PFIZER-BIONTECH COMIRNATY BA.4/5 BIVALENT (30 MCG) IN INDIVIDUALS ≥12 YEARS OF AGE

Trial Design

The Pfizer-BioNTech Comirnaty BA.4/5 Bivalent vaccine (30 mcg) was evaluated in an ongoing, Phase 2/3, observer-blinded randomized controlled trial [64]. This study is evaluating the safety, reactogenicity and immunogenicity of Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg) administered as a fourth dose to individuals ≥12 years of age who previously received three doses of Pfizer-BioNTech Comirnaty original (30 mcg). Results were compared to those obtained from a similar clinical trial [65], in individuals >55 years of age who received Pfizer-BioNTech Comirnaty original (30 mcg) as a fourth dose.

Safety cohort

The safety cohort consisted of 316 individuals ≥12 years of age who received the Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg) vaccine as a fourth dose (107 individuals 12 to 17 years of age, 103 individuals 18 to 55 years of age and 106 individuals >55 years of age) [66]. Overall, 67% of individuals in the safety cohort had evidence of prior SARS-CoV-2 at baseline. Median time since last dose was 8.4 months for individuals 12 to 17 years of age and 11.0 months for individuals 18 to 55 and >55 years of age.

Safety

Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg) was generally well tolerated across all age groups (12 to 17, 18 to 55 and >55 years of age), with mostly mild or moderate reactogenicity events [66]. Pain at injection site was very commonly reported within 7 days of receiving the vaccine. Swelling and redness at the injection site were commonly reported. No other local adverse reactions were actively monitored. Most reactions were mild or moderate in severity, with one individual 12 to 17 years of age reported severe pain at the injection site. The most common systemic reactions within 7 days of receiving Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg) were fatigue, headache, and muscle pain. Most systemic events were mild or moderate in severity with a total of 5 severe systemic events being reported (1 report of fever, 3 reports of fatigue and 1 report of diarrhea). The pattern of local and systemic reactions reported within 7 days after receipt of the Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg) was similar to that observed with a booster of Pfizer-BioNTech Comirnaty original (30 mcg).

In total, 8 individuals reported an AE determined to be related to the study vaccination, all in the 12 to 17 year old age group [66]. Reported AEs were largely consistent with reactogenicity events (e.g., fatigue and injection site pain). None of the reported AEs were severe or life-threatening. No serious AEs, withdrawals due to AEs, or deaths were reported. No new AEs were identified with Pfizer-BioNTech Comirnaty BA.4/5 Bivalent (30 mcg); however, given the limited sample size, it is unlikely that any rare AEs would be detected.

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