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

Updated guidance on the use of protein subunit COVID-19 vaccine (Novavax Nuvaxovid)

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Mise à jour des directives sur l'utilisation du vaccin à sous-unités protéiques contre la COVID-19 (Nuvaxovid de Novavax)

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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 5, 2023, Health Canada authorized the use of the protein subunit-based vaccine Novavax Nuvaxovid XBB.1.5 for individuals 12 years of age and older as a single dose for those who have previously been vaccinated against COVID-19, and as a 2-dose series 3 weeks apart for those who have never been vaccinated against COVID-19.
- Similar to the mRNA COVID-19 vaccines Pfizer-BioNTech Comirnaty Omicron XBB.1.5 and Moderna Spikevax XBB.1.5, Novavax Nuvaxovid XBB.1.5 is a monovalent vaccine that targets the spike protein of the Omicron XBB.1.5 variant.

Methods

On November 24, December 5, 2023 and January 19, 2024, the NACI COVID-19 Working Group (COVID-19 WG) reviewed the recent epidemiology and the available evidence on the immunogenicity and safety of the Novavax Nuvaxovid XBB.1.5 and original COVID-19 vaccines, rates of myocarditis and/or pericarditis following Novavax Nuvaxovid original, and cross-neutralization by XBB.1.5 vaccines against other emerging variants.

On February 7, 2024, NACI reviewed the evidence presented to the COVID-19 WG, reached consensus on proposed recommendations and approved the statement on February 28, 2024.

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

Overview of evidence

Information available as of February 7, 2024 is summarized below.

Epidemiology

- Omicron sublineages of SARS-CoV-2 continue to circulate in Canada and globally [3]. From sequencing data up to the week of January 21, 2024, BA.2.86 sublineages, particularly JN.1, are the most prevalent among all positive cases sampled across Canada.
- There is high infection-acquired seroprevalence in the Canadian population [4]. Among adults, infection-acquired seroprevalence decreases with increased age, with older individuals having higher levels of immunity derived from vaccination alone.

Summary of Novavax Nuvaxovid XBB.1.5

Clinical data:

- At the time of authorization, no clinical (human) data were available for Novavax Nuvaxovid XBB.1.5, and thus the regulatory review process was centered around preclinical immunogenicity data with Novavax Nuvaxovid XBB.1.5, as well as indirect clinical data from the use of Novavax Nuvaxovid original as a primary series and booster dose, and clinical data after booster doses of two investigational vaccines from Novavax

targeting the Omicron BA.1 or BA.5 variants [5]. Data on the efficacy, immunogenicity and safety of Novavax Nuvaxovid original has been described previously [6].

- Individuals vaccinated with the updated XBB.1.5-containing COVID-19 vaccines are expected to benefit from a better immune response against currently circulating strains compared to earlier formulations, based on clinical data suggesting cross-neutralization from the mRNA XBB.1.5-containing vaccines against newer circulating variants that are descendants of the XBB and BA.2.86 lineages.

Preclinical animal data for Novavax Nuvaxovid XBB.1.5:

- Pre-clinical data from mice and non-human primates (Rhesus macaques) who received primary vaccination with a protein subunit bivalent BA.5 vaccine (original + BA.5) and a subsequent booster dose with monovalent Novavax Nuvaxovid XBB.1.5 vaccine, demonstrated broadly neutralizing antibody responses against XBB* subvariants, including XBB.1.5, XBB.1.16, XBB.2.3 and EG.5.1 [7] .
- In these mice, antibody titres against BA.2.86 (a precursor of currently circulating JN.1) were also elevated after a booster dose with Novavax Nuvaxovid XBB.1.5 compared to pre-booster titres, but were lower compared to titres against XBB* subvariants [7].
- Novavax Nuvaxovid XBB.1.5 given as a 2-dose primary series to mice also induced robust neutralizing antibody responses against XBB* subvariants, significantly higher than those induced by Novavax Nuvaxovid original [7]. Immune responses against BA.2.86 were not reported.

  * Includes all descendant lineages, unless otherwise specified.

Summary of evidence with one dose of Novavax Nuvaxovid original

- Geometric mean antibody titres (GMTs) against original SARS-COV-2 spike protein were compared between previously uninfected (seronegative) participants 12 years of age and older who received 2 doses of Novavax Nuvaxovid original and participants 12 years of age and older with a previous SARS-CoV-2 infection (seropositive) who received 1 dose of Novavax Nuvaxovid original. GMTs and seroconversion rates (SCRs) after 1 dose in seropositive participants did not meet non-inferiority criteria when compared to GMTs and SCRs after 2 doses in seronegative participants as titres were higher in seronegative 2 dose recipients than in seropositive 1 dose recipients. However, in both groups, vaccination with Novavax Nuvaxovid original resulted in large increases in antibody titres compared to pre-vaccination levels.

Post-market safety

- Cases of myocarditis and/or pericarditis have been rarely reported following the administration of Novavax Nuvaxovid original. With mRNA COVID-19 vaccines, myocarditis and/or pericarditis has been reported more frequently after the second dose of the primary series, particularly in adolescent and young adult males. It cannot be determined if there is a similar trend with Novavax Nuvaxovid, due to the relatively lower number of doses given and low numbers of reported cases of myocarditis and/or pericarditis.

- There is a wide variation in reported rates of myocarditis and/or pericarditis associated with Novavax Nuvaxovid original from various countries.
    - In Australia, approximately 261,000 doses of Novavax Nuvaxovid original have been administered as of June 25, 2023 [8]. Australia's Therapeutic Goods Administration has estimated reporting rates of approximately 3 to 4 cases of myocarditis per 100,000 doses administered and approximately 13 cases of pericarditis per 100,000 doses administered in Australia. A further breakdown of rates according to age group, sex and dose number is not available due to the relatively low number of doses given overall and low number of reported cases.
    - In South Korea, 974,021 doses of Novavax Nuvaxovid original were administered as of September 24, 2023. An analysis by the Korea Disease Control and Prevention Agency demonstrated similar myocarditis reporting rates for Pfizer-BioNTech Comirnaty, Moderna Spikevax and Novavax Nuvaxovid of 0.5, 0.7 and 0.4 cases per 100,000 doses administered, respectively [9].
    - In the US, 69,277 doses of Novavax Nuvaxovid original have been administered as of March 13, 2023. A cumulative review of safety data from the Vaccine Adverse Event Reporting System (VAERS) by the CDC identified no cases of myocarditis and 1 case of pericarditis.
    - In Canada as of January 5, 2024, approximately 35,000 doses of Novavax Nuvaxovid original have been administered and 1 case of myocarditis and/or pericarditis has been reported [10].

Ethics, equity, feasibility, and acceptability

- While there is a much greater experience with mRNA COVID-19 vaccines (measured by number of doses administered), the existing base of clinical evidence on Novavax Nuvaxovid original has demonstrated that the vaccine has a good safety profile and was immunogenic and efficacious against original SARS-CoV-2. With the updating of Novavax Nuvaxovid to target XBB.1.5, both mRNA and protein subunit COVID-19 vaccine platforms now target the same strain and therefore the need for a product preference for mRNA COVID-19 vaccines has been significantly diminished.
- Throughout the pandemic, regulatory agencies around the world have made similar decisions on the authorized use of COVID-19 vaccines. However, some variation is beginning to emerge, as observed with the authorization of the 1-dose schedule for unvaccinated individuals receiving Novavax Nuvaxovid XBB.1.5 by the European Medicines Agency compared to the 2-dose schedule by Health Canada and the US Food and Drug Administration. The divergent regulatory positions around the world may increase provider acceptability for off-label use of a 1-dose Novavax Nuvaxovid XBB.1.5 schedule for previously unvaccinated individuals in Canada, as this aligns with practices in some other countries. As well, a 1-dose schedule for unvaccinated individuals (for those who are not immunocompromised) facilitates alignment with the mRNA COVID-19 vaccine schedules for unvaccinated individuals (which is 1 dose for non-immunocompromised individuals 5 years of age and over), and would contribute to more streamlined COVID-19 vaccination recommendations in Canada.
- For mRNA COVID-19 vaccines, the 1-dose schedule for unvaccinated individuals 5 years of age and older takes into account high levels of seroprevalence due to SARS-CoV-2 infection in the population. The risk of myocarditis and/or pericarditis is also expected to

be lower with the use of a 1-dose schedule, compared to a 2-dose schedule. These considerations also apply to Novavax Nuvaxovid XBB.1.5.

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

Recommendations

Please see Table 2 for an explanation of strong versus discretionary NACI recommendations.

NACI recommends the following for the use of COVID-19 vaccines:

1. **Individuals in the authorized age group being vaccinated against COVID-19 should receive the most recently updated COVID-19 vaccine.**

   (*Strong NACI Recommendation*)

   - Either an mRNA or protein subunit COVID-19 vaccine can be used in unvaccinated or previously vaccinated individuals who do not have contraindications to the vaccine. mRNA COVID-19 XBB.1.5 vaccines are authorized for age 6 months of age and over, and Novavax Nuvaxovid XBB.1.5 is authorized for 12 years of age and over. See Table 1 for a comparison between the two vaccine platforms.

For unvaccinated individuals 12 years of age and over receiving Novavax Nuvaxovid XBB.1.5, NACI provides the following schedule advice:

2. **While the authorized schedule is 2 doses, NACI recommends that unvaccinated individuals who are not immunocompromised and receiving Novavax Nuvaxovid XBB.1.5 may follow a 1-dose schedule.**

   (*Discretionary NACI Recommendation*)

3. **NACI recommends that unvaccinated individuals who are moderately to severely immunocompromised and receiving Novavax Nuvaxovid XBB.1.5 should receive a minimum of 2 doses.**

   - Refer to the Immunization of immunocompromised persons chapter of the Canadian Immunization Guide for additional details regarding vaccine schedules for moderately to severely immunocompromised individuals, including new recipients of hematopoietic stem cell transplantation (HSCT) and chimeric antigen receptor (CAR) T cell therapy, who should receive 3 doses.
   - Description of moderately to severely immunocompromising conditions and relevant considerations for COVID-19 immunization are available in the COVID-19 chapter of the Canadian Immunization Guide.

   (*Strong NACI recommendation*)

See Table 1 for a summary of the vaccine schedule.

Considerations on the use of Novavax Nuvaxovid XBB.1.5:

- The recommendation that an mRNA or protein subunit COVID-19 vaccine can be used is a change from the previous recommendation for Novavax Nuvaxovid only for those who were not willing or able to receive an mRNA vaccine.
- Due to lower overall usage to date, there is less data available about the protein subunit platform compared to the mRNA platform for COVID-19 vaccines, particularly for people who are pregnant or who are immunocompromised. Additional evidence on the use of protein subunit COVID-19 vaccines is expected to accumulate over time.
- If receiving 2 doses of Novavax Nuvaxovid XBB.1.5 in a primary series, NACI recommends an interval of 8 weeks for those who are not immunocompromised. For those who are moderately to severely immunocompromised, NACI recommends an interval of 4 to 8 weeks between doses in any primary series.

Table 1. Covid-19 vaccine platform comparison

	Protein subunit COVID-19 vaccine	**mRNA COVID-19 vaccines**
XBB.1.5 vaccine product	Novavax Nuvaxovid XBB.1.5	• Moderna Spikevax XBB.1.5 • Pfizer-BioNTech Comirnaty Omicron XBB.1.5
Authorized age group	Authorized for those 12 years of age and over.	Authorized for those 6 months of age and over.
XBB.1.5 vaccine schedule for unvaccinated individuals	1 dose schedule[a] may be used for those who are not immunocompromised as per NACI recommendation. At least 2 doses are recommended for those who are moderately to severely immunocompromised[b].	1 dose schedule for those 5 years of age and over who are not immunocompromised[c]. At least 2 doses are recommended for those who are moderately to severely immunocompromised[b].
XBB.1.5 vaccine schedule for previously vaccinated individuals	1 dose[b]	1 dose[b,c]
Immunogenicity[d]	XBB.1.5 product induces a good immune booster response against XBB-related strains in mice and	XBB.1.5 products induce a good immune booster response in humans against XBB-related strains, with a

	macaques, with a lower but still boosted response against BA.2.86 in mice (no data were available for JN.1[e]) [7]. No data were available in humans for the XBB.1.5 product[e].	lower but still boosted response against JN.1 [11, 12].
Efficacy/effectiveness[d]	Good vaccine efficacy for original product. No efficacy or effectiveness data yet available for XBB.1.5 product.	Short-term vaccine effectiveness (VE) of XBB.1.5 vaccine approximately 50 to 60% against symptomatic disease and 60 to 70% against hospitalization [13-16].
Safety[d]	Novavax Nuvaxovid original has been shown to have a good safety profile, with over 1 million doses administered to date, globally [8-10]. Novavax Nuvaxovid original has been associated with rare cases of myocarditis and/or pericarditis based on the original vaccine. No data are currently available regarding the XBB.1.5 product.	mRNA COVID-19 vaccines have been shown to have a good safety profile, with over 100 million doses administered to date in Canada alone [17]. mRNA COVID-19 vaccines have been associated with rare cases of myocarditis and/or pericarditis, particularly in adolescents and young adult males, especially after the second dose in the primary series using the original vaccine and less so after a booster using the original vaccine or bivalent vaccine. No data are currently available regarding the XBB.1.5 product.
Use in specific populations (e.g., immunocompromised, pregnant people)	Less data available regarding use in these populations than with mRNA vaccines.	More data available regarding use in these populations than with protein subunit vaccines.

a. Two (2) doses of Novavax Nuvaxovid XBB.1.5 vaccine is the authorized schedule in Canada for those not previously vaccinated, but NACI has indicated that a 1-dose schedule may be used for those who are not moderately to severely immunocompromised. If 2 doses are used, they should be given 8 weeks apart for those who are not immunocompromised.
b. For those who are moderately to severely immunocompromised, an interval of 4 to 8 weeks is recommended between any dose. New recipients of hematopoietic stem cell transplantation (HSCT) and chimeric antigen receptor (CAR) T cell therapy should receive 3 doses. Refer to the

immunization of immunocompromised persons chapter of the Canadian Immunization Guide for more details.
c. Please refer to NACI's Updated guidance on the use of COVID-19 vaccines in individuals who have not previously been vaccinated against COVID-19 for the recommended schedule for children 6 months to less than 5 years of age.
d. Prospective head-to-head comparisons between Novavax Nuvaxovid and mRNA COVID-19 vaccines are limited. Interpreting differences in clinical data should be performed with caution.
e. Valid at the time of writing.

Research priorities

- Continuous monitoring of data on the safety, immunogenicity, efficacy, and effectiveness of COVID-19 vaccines, including with new formulations, through clinical trials and studies in real-world settings, including the degree and duration of protection conferred against circulating variants. The research should also consider the clinical implications of previous SARS-CoV-2 infection; repeated immunization; and outcomes after infection such as post-COVID-19 condition.
- Continuous monitoring of COVID-19 epidemiology and VE in special populations at high risk of severe outcomes and on the long-term consequences of infection with SARS-CoV-2.
- Further evaluations on the safety, immunogenicity, and effectiveness when there is concurrent administration of COVID-19 vaccines with other vaccines across different age groups, including concurrent administration with high-dose or adjuvanted influenza vaccines.
- Continuous monitoring of vaccine acceptance and coverage in Canada, for COVID-19 vaccines and other routine vaccines, including consideration of measures that may reduce the risk of disparities in vaccine confidence and uptake across different sub-populations.
- Continuous monitoring of the epidemiology of COVID-19, including SARS-CoV-2 variants and seasonal trends, to inform future programs.

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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