

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

Recommendations on the use of Novavax
Nuvaxovid COVID-19 vaccine

Published: February 17, 2022

PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH



Public Health
Agency of Canada

Agence de la santé
publique du Canada

Canada

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.

INTRODUCTION

The Novavax Nuvaxovid COVID-19 vaccine is the first COVID-19 recombinant protein subunit vaccine authorized in Canada. Novavax Nuvaxovid was authorized for use in adults ≥ 18 years of age by Health Canada on February 17, 2022.

NACI's recommendations are aligned with the following goals of the Canadian COVID-19 Immunization Program, updated in October 2021:

- To enable as many Canadians as possible to be immunized as quickly as possible against COVID-19, while ensuring that high risk populations be prioritized;
- To minimize serious illness and overall deaths while preserving health system capacity;
- To reduce transmission to protect high risk populations.

Refer to the chapter on [COVID-19 vaccine in the Canadian Immunization Guide](#) for further information on COVID-19 vaccines.

METHODS

On December 14, 2021, January 25, 2022, and February 1, 2022, NACI reviewed the available evidence on efficacy, immunogenicity and safety of the use of Novavax Nuvaxovid (including manufacturer's clinical data in the regulatory submission to Health Canada and published scientific literature). NACI also considered the ethics, efficacy, feasibility, and acceptability of the use of Novavax Nuvaxovid in the current context of the pandemic. NACI approved their recommendations on the use of Novavax Nuvaxovid in adults ≥ 18 years of age on February 12, 2022.

NACI recommendations on the use of COVID-19 vaccines are available in the chapter on COVID-19 vaccine in the Canadian Immunization Guide.

Refer to NACI's [process and procedures](#) further information on NACI's recommendation development process.

EPIDEMIOLOGY

COVID-19 BURDEN OF DISEASE

Canada has been facing a wave of the COVID-19 pandemic driven mainly by the Omicron variant of concern (VOC), which is partially evasive to previous immunity conferred by COVID-19 vaccine or a previous SARS-CoV-2 infection. Although evidence is suggesting that symptoms appear to be less severe overall, the transmissibility of this strain has resulted in disease activity that has exceeded those of previous waves. Current data suggests that COVID-19 vaccines offer reduced protection against symptomatic infection with Omicron compared to the protection offered against previous strains/VOC, with breakthrough cases in individuals of all age groups who have received 2 or 3 doses of mRNA and other COVID-19 vaccines. Vaccine protection against severe disease and hospitalization due to COVID-19 has been more durable than protection against symptomatic

infection, and is higher following a booster dose compared to those who have only completed a primary series.

For the most up to date information on the epidemiology of COVID-19 in Canada, please refer to the [COVID-19 daily epidemiology update](#).

VACCINE

PREPARATION AUTHORIZED FOR USE IN CANADA

Novavax Nuvaxovid consists of a purified full-length SARS-CoV-2 recombinant spike (S) protein nanoparticle administered as a co-formulation with the adjuvant Matrix-M. Matrix-M is a novel saponin-based adjuvant that facilitates activation of the cells of the innate immune system, which enhances the magnitude of the S protein-specific immune response. Matrix-M has been used in Novavax Nuvaxovid clinical trials and in pre-licensure studies targeting other pathogens, but has not previously been used in any licensed vaccine.

Characteristics of Novavax Nuvaxovid currently authorized for use in Canada is summarized in Table 1.

Table 1. Novavax Nuvaxovid characteristics

Manufacturer	Novavax
Date of authorization in Canada	February 17, 2022
Type of vaccine	Recombinant protein subunit (adjuvanted)
Product specification	Adult formulation
Age	18 years of age and older
Diluent	None
Dose	0.5 mL (5 mcg SARS-CoV-2 recombinant spike protein)
Doses per vial	10
Potential allergens	Polysorbate 80
Adjuvant	Matrix-M adjuvant (50 mcg)
Storage requirements	2°C to 8°C for a maximum of 6 months. Do not freeze. Keep the vials in the outer carton in order to protect from light.
Opened multi-dose vial storage	2°C to 25°C for up to 6 hours after first needle puncture

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

CLINICAL TRIAL DATA ON THE NOVAVAX NUVAXOVID COVID-19 VACCINE AS A PRIMARY SERIES

Novavax Nuvaxovid (NVX-CoV2373) was evaluated in two pivotal Phase 3 trials: 2019nCoV-301 conducted in the United States and Mexico ⁽¹⁾ and 2019nCoV-302 conducted in the United

Kingdom ⁽²⁾. Vaccine efficacy was also assessed in a Phase 2a/b clinical trial 2019nCoV-501 in South Africa ⁽³⁾. The safety of NVX-CoV2373 was evaluated from an interim analysis of pooled data from five ongoing clinical trials ⁽¹⁻⁵⁾ conducted in Australia, South Africa, the United Kingdom, the United States, and Mexico. At the time of the analysis, a total of 49,950 participants received at least one dose of NVX-CoV2373 (n=30,058) or placebo (n=19,892). The median follow-up duration was at least 2 months post dose 2, with 66% of subjects completing at least 2 months follow-up.

In all trials, eligible participants were adults 18 years of age and older who were healthy or were individuals with stable chronic medical conditions (including individuals with chronic pulmonary, renal or cardiovascular disease, diabetes mellitus type 2, or well-controlled human immunodeficiency virus [HIV] infection). Individuals with a known previous history of laboratory confirmed SARS-CoV-2 infection or COVID-19, or known immunosuppression were excluded.

Adult study participants were randomized to receive two doses (5 µg per 0.5 mL dose) of NVX-CoV2373 or placebo (0.5 mL normal saline) administered 21 days (+ 7-day window) apart.

These trials were conducted prior to the emergence of Delta and Omicron, and there is very limited immunogenicity data, and no efficacy/effectiveness data to demonstrate what level of protection NVX-CoV2373 offers against the Omicron variant.

VACCINE EFFICACY

The primary efficacy endpoint in all clinical trials was the efficacy of NVX-CoV2373 against the first episode of polymerase chain reaction (PCR)-confirmed, symptomatic (mild, moderate or severe) COVID-19 illness with onset at least 7 days after Dose 2 in participants seronegative for SARS-CoV-2 infection at baseline.

In clinical trial 2019nCoV-301, estimates of vaccine efficacy were analysed using the per-protocol efficacy analysis set consisting of 25,452 participants (17,312 in the vaccine group and 8,140 in the placebo group). The estimate of efficacy against PCR-confirmed, symptomatic COVID-19 illness with onset at least 7 days after Dose 2 in participants seronegative for SARS-CoV-2 infection at baseline was 90.4% (95% CI: 82.9 to 94.6%), based on the identification of 77 cases: 14 cases in the vaccine group (64-day follow-up) and 63 cases in the placebo group (58-day follow-up). All cases identified in the vaccine group were mild. There were 49 mild, 10 moderate and 4 severe cases identified in the placebo group. The estimate of efficacy against the secondary endpoint of prevention of PCR-confirmed, symptomatic moderate or severe COVID-19 beginning at least 7 days after Dose 2 in participants not previously infected with SARS-CoV-2 was 100% (95% CI: 87.0 to 100.0%).

In clinical trial 2019nCoV-302, estimates of vaccine efficacy were analyzed using the per-protocol efficacy analysis set consisting of 14,039 participants (7,020 in the vaccine group and 7,019 in the placebo group). The estimate of vaccine efficacy against the primary endpoint after a median follow-up after Dose 2 of 54 and 56 days in the placebo and vaccine groups, respectively, was 89.7% (95% CI: 80.2 to 94.6%), based on 10 cases in the vaccine group (1 was mild and 9 were of moderate severity) and 96 cases in the placebo group (28 were mild, 63 were of moderate severity and 5 were severe). The estimate of vaccine efficacy against PCR-confirmed symptomatic moderate or severe COVID-19 with onset at least 7 days after Dose 2 in study

participants seronegative at baseline was 86.9% (95% CI: 73.7 to 93.5%). Vaccine efficacy against PCR-confirmed symptomatic COVID-19 with onset after post-Dose 1 was 57.1% (95% CI: -18.8 to 86.5%) for the period beginning 14 days after Dose 1 to before Dose 2, and 83.4% (95% CI: 73.6 to 89.5%) for the period following 14 days post-Dose 1. As the vast majority of participants received Dose 2 of the intervention during the surveillance follow-up period for case identification, the latter estimate of vaccine efficacy after Dose 1 is not solely due to Dose 1, and the interpretation is challenging.

The estimates of vaccine efficacy against confirmed symptomatic COVID-19 with onset at least 7 days after Dose 2, by various pre-specified subgroups (e.g., age, sex, race, ethnicity, presence of comorbidities, high-risk status for COVID-19), were comparable to the overall vaccine efficacy estimate.

Efficacy against variants of concern

The majority of confirmed cases in study participants were identified at a time when the original SARS-CoV-2 strain, Alpha variant or Beta variant were the predominant circulating strain in the local geographic region. No data are available on vaccine efficacy/effectiveness against the Delta or Omicron variant, although there is limited immunogenicity data for these variants from the clinical trial on booster doses.

In a post-hoc analysis restricted to the Alpha variant, the estimate of vaccine efficacy was 93.6% (95% CI: 81.7 to 97.8%) in clinical trial 2019nCoV-301, and 86.3% (95% CI: 71.3 to 93.5%) in clinical trial 2019nCoV-302. The estimate of efficacy against moderate or severe COVID-19 was 83.8% (95% CI: 64.0 to 92.7%) against the Alpha variant in clinical trial 2019nCoV-302.

In clinical trial 2019nCoV-501, conducted when Beta was the predominant circulating strain in South Africa, estimates of vaccine efficacy were analyzed using the per-protocol efficacy analysis set consisting of 2,770 participants (1,408 in the vaccine group and 1,362 in the placebo group). The estimate of vaccine efficacy against PCR-confirmed symptomatic COVID-19 beginning 7 days after Dose 2 in baseline seronegative participants was 48.6% (95% CI: 28.4 to 63.1%), based on 147 identified cases: 51 cases identified in the vaccine group and 96 cases in the placebo group. The estimate of vaccine efficacy against PCR-confirmed symptomatic moderate or severe COVID-19 beginning 7 days after Dose 2 in baseline seronegative participants was 37.6% (95% CI: 7.8 to 57.8%), based on 102 identified cases: 40 cases identified in the vaccine group and 62 cases in the placebo group.

VACCINE IMMUNOGENICITY

Recent evidence suggesting that neutralizing antibodies may serve as a correlate of protection for vaccines against SARS-CoV-2 in humans is evolving ⁽⁶⁾. However, since no correlate of protection has been established for COVID-19 at this time, it is unknown how reported immune responses are related to prevention of SARS-CoV-2 infection or disease or the ability to transmit infection to others. The effect of VOC and booster doses on the association between neutralizing antibodies or other potential immunological correlates and vaccine efficacy has not been described. All immunological evidence in support of vaccine efficacy is indirect and cannot directly be used to estimate efficacy.

Humoral immune responses

Both binding and neutralizing antibodies against the SARS-CoV-2 spike protein are induced by this vaccine ⁽⁵⁾. Binding and neutralizing antibody titres were slightly lower in older participants (≥65 years of age) compared to younger participants (18 to <65 years of age) after 2 doses, and were similar in clinical trials 2019nCoV-301 and 2019nCoV-302. Binding and neutralizing antibodies were both induced by one dose of vaccine and boosted by the second dose of vaccine. Maximal immune responses were seen on day 35, 14 days after the second dose, before declining. Antibodies were still detectable up to day 189, with neutralizing antibodies declining more sharply compared to binding antibodies, with an approximately 32-fold drop and a 12-fold drop, respectively, compared to titres measured on day 35 ⁽⁷⁾.

Cellular immune responses

Cellular immune responses specific to the SARS-CoV-2 spike protein were elicited 7 days after the first dose of vaccine and further increased 7 days after the second dose. The characterization of these responses indicates a Th-1 biased cellular immune response ⁽⁴⁾.

Immunogenicity of a Novavax Nuvaxovid booster dose

A booster dose of Novavax Nuvaxovid administered at least 6 months after the primary series was shown to be immunogenic. Cross-reactivity assays showed an increase in levels of IgG and hACE receptor binding inhibiting antibodies against VOC, including the Delta and Omicron variants, 7 days after receiving a booster dose compared to 7 days after receiving a second dose ⁽⁷⁾.

VACCINE ADMINISTRATION AND SCHEDULE

Refer to Table 2 for a summary of immunization schedules for authorized COVID-19 vaccines.

Table 2. Immunization schedule for primary series, by COVID-19 vaccine

Vaccine Product	Immunization Schedule ^a	Age Indication	Minimum Interval	Authorized Interval	NACI-Recommended Interval ^b
Pfizer-BioNTech Comirnaty (30 mcg)	2-dose schedule	12 years and over (Orange cap formulation for 5 to 12 years of age)	19 days ^c	21 days	8 weeks
Moderna Spikevax (100 mcg)	2-dose schedule	12 years of age and over	21 days ^d	28 days	8 weeks
AstraZeneca Vaxzevria	2-dose schedule	18 years of age and over	28 days	4 to 12 weeks	At least 8 weeks
Janssen COVID-19 vaccine	1-dose schedule	18 years of age and over	N/A	N/A	N/A
Novavax Nuvaxovid	2-dose schedule	18 years of age and over	21 days ^e	3 weeks	8 weeks

^a Moderately to severely immunocompromised individuals should be immunized with a primary series of 3 doses with an mRNA COVID-19 vaccine.

^b There is emerging evidence that longer intervals between the first and second doses of COVID-19 vaccines result in more robust and durable immune response and higher vaccine effectiveness. Balancing this enhanced protection from a longer interval with simultaneously minimizing the time at risk of infection due to having protection from only 1 dose, an 8-week interval (or at least 8 weeks in the case of AstraZeneca Vaxzevria) is recommended.

^c The basis for this minimum interval is that the per-protocol design for the Pfizer-BioNTech Comirnaty (30 mcg) clinical trial was 19 to 23 days.

^d The basis for this minimum interval is that the majority of participants in the Moderna Spikevax (100 mcg) clinical trial received the second dose 21 to 42 days after the first, as per the pre-defined window.

^e The basis for this minimum interval is that the majority of participants in the Novavax Nuvaxovid clinical trial received the second dose 21+7 days after the first, as per the pre-defined window.

NACI RECOMMENDED DOSING INTERVAL FOR THE PRIMARY SERIES OF COVID-19 VACCINES

There is evidence that longer intervals between the first and second doses of COVID-19 vaccines result in more robust and durable immune response and higher vaccine effectiveness. Evidence on mRNA COVID-19 vaccines in adult populations indicates that a longer dose interval such as 8 weeks, compared with the authorized 21-day interval, improves the immune response and is associated with greater vaccine effectiveness that may last longer. A similar observation was also seen with longer intervals for the AstraZeneca COVID-19 vaccine. This is consistent with general principles of vaccinology⁽⁸⁻¹⁰⁾, and expected to also apply to recombinant protein subunit COVID-19 vaccines.

The NACI-recommended intervals between doses also apply to mixed vaccine schedules ([Table 2](#)). For mixed COVID-19 vaccine schedules, the minimum interval between doses should be based on the minimum interval of the product used for the first dose (e.g., Novavax Nuvaxovid should be offered a minimum of 19 days after Pfizer-BioNTech Comirnaty [30 mcg]).

BOOSTER DOSES AND RE-IMMUNIZATION

NACI has recommended that a booster dose of an authorized mRNA COVID-19 vaccine be offered ≥ 6 months after completion of a primary COVID-19 vaccine series in adults 18 years of age and older. There are some populations for whom a booster dose should be offered. For more information on booster doses for adults ≥ 18 years of age please see the [NACI updated guidance on booster COVID-19 vaccine doses in Canada](#) and the chapter on [COVID-19 vaccine in the Canadian Immunization Guide](#).

While the term “booster dose” is used, NACI continues to monitor the emerging scientific data on whether this dose is indeed a booster dose (to stimulate the memory response once protection has truly waned), or should be considered part of the primary series (to establish strong immune response and memory). NACI will adjust the terminology as required.

There is evidence that Novavax Nuvaxovid administered as a booster dose in adults 18 years of age and older, approximately 6 months following the completion of a 2-dose Novavax Nuvaxovid primary series, is safe and immunogenic⁽⁷⁾. While an incremental increase in the frequency of solicited local and systematic reactogenicity events was observed with each additional dose, the booster dose was well tolerated overall, with most events being mild to moderate in nature and resolving quickly. An increase in reactogenicity with third doses has not been observed with mRNA vaccines. Similar to booster studies for other COVID-19 vaccines, the immune response two weeks after receipt of the booster dose was greater than that observed two weeks following receipt of the second dose.

INTERCHANGEABILITY

Novavax Nuvaxovid may be used in a heterologous (mixed) primary series or as a booster dose in a heterologous prime-boost series, for individuals for whom mRNA COVID-19 vaccine is contraindicated, inaccessible, or has been refused.

A heterologous primary series is a primary series where more than one COVID-19 vaccine product is used (e.g., Pfizer-BioNTech [30 mcg] and Moderna Spikevax [100 mcg] or AstraZeneca Vaxzevria and Pfizer-BioNTech [30 mcg] for a 2-dose primary series). A heterologous prime-boost series is one where the booster dose differs from the COVID-19 vaccine product(s) used in the primary series (e.g., AstraZeneca Vaxzevria primary series and Pfizer-BioNTech [30 mcg] booster).

Informed consent should include a discussion of the benefits and risks given the limited data available on mixed schedules with Novavax Nuvaxovid, and that this vaccine is not currently authorized for use as a booster dose in Canada. There is currently no data on the use of Novavax Nuvaxovid in a mixed series with Moderna Spikevax (100 mcg) or Janssen COVID-19 vaccines.

Heterologous primary series with Novavax Nuvaxovid

There is evidence from a Phase 2 randomized controlled trial (Com-COV2) that Novavax Nuvaxovid is safe and immunogenic when used as a second dose administered 8-12 weeks following a first dose of either Pfizer-BioNTech Comirnaty (30 mcg) or AstraZeneca Vaxzevria. The immune response for an AstraZeneca Vaxzevria /Novavax Nuvaxovid series was statistically superior than that of a homologous AstraZeneca Vaxzevria series. However, the immune response for a Pfizer-BioNTech Comirnaty/Novavax Nuvaxovid series did not meet non-inferiority criteria compared to a homologous Pfizer-BioNTech Comirnaty (30 mcg) series⁽¹¹⁾. Solicited local and systemic reactions were similar or less frequent in Novavax Nuvaxovid recipients compared to those who received homologous series of Pfizer-BioNTech Comirnaty or AstraZeneca Vaxzevria.

Heterologous prime-boost series with Novavax Nuvaxovid

There is evidence from a Phase 2 randomized controlled trial (COV-BOOST), that Novavax Nuvaxovid administered as a booster dose approximately 10-12 weeks following a homologous primary series of AstraZeneca COVID-19 or Pfizer-BioNTech Comirnaty (30 mcg) vaccines is safe and immunogenic⁽¹²⁾. Compared to responses after a homologous booster dose, Novavax Nuvaxovid generated better humoral and cellular immune responses following a primary series of AstraZeneca Vaxzevria and lower relative increases in humoral and cellular immune responses compared to after a primary series of Pfizer-BioNTech Comirnaty (30 mcg). Compared to other booster vaccines, Novavax Nuvaxovid produced higher relative increases in immune responses than a booster dose of AstraZeneca Vaxzevria but lower immune responses overall compared to a booster dose with an mRNA COVID-19 vaccine (Moderna Spikevax [100 mcg] or Pfizer-BioNTech Comirnaty [30 mcg]).

SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES

There are limited data on Novavax Nuvaxovid COVID-19 vaccine administered on the same day as an influenza vaccine. A sub-set of participants (N = 431) in clinical trial 2019nCoV-302 received an influenza vaccine the same day they received the first dose of Novavax Nuvaxovid, and administered in the opposite deltoid muscle⁽¹³⁾. Efficacy against confirmed symptomatic COVID-

19 illness for participants aged 18 to <65 years (n = 402/431) in the sub-study was comparable to the main study [87.5% (95% CI -0.2 to 98.4) vs. 89.8% (95% CI 79.7–95.5), respectively], with too few cases in older adults (age ≥65 years) to report an efficacy estimate (n=29/431). Same-day administration resulted in no change to influenza vaccine immune response although a reduction in antibody responses to Novavax Nuvaxovid was noted. After the first day of vaccination, the frequency of solicited local and systemic adverse events (AE) were higher in those 18-64 years of age in recipients who received both Novavax Nuvaxovid and influenza vaccines, compared to those who received Novavax Nuvaxovid or influenza vaccine alone. In older adults, at least 65 years of age, the frequency of solicited local and systemic AE were lower age in recipients who received Novavax Nuvaxovid and influenza vaccines compared to those who received influenza vaccine only, but comparable to those who received Novavax Nuvaxovid only. AE were also lower in older adults compared to those 18-64 years of age. The frequencies of solicited local and systemic AE were similar between the sub-study and main study after the second dose of Novavax Nuvaxovid.

NACI currently recommends that mRNA and viral vector COVID-19 vaccines may be given simultaneously with (i.e., same day), or at any time before or after, non-COVID-19 vaccines (including live and non-live vaccines) for individuals 12 years of age and older. It is currently not known if the reactogenicity of COVID-19 vaccines is increased with simultaneous administration of other vaccines. However, no specific safety concerns have been identified to date based on real world use.

There is extensive data and experience on the simultaneous administration of non-COVID-19 vaccines for routine immunizations, which includes recombinant subunit vaccines (e.g., Hepatitis B and herpes zoster vaccines). Although a precautionary minimum waiting period is not being recommended, the post-market surveillance for Novavax Nuvaxovid is in the early stages. Administering Novavax Nuvaxovid alone could assist with the assessment of any adverse event following immunization (AEFI) by preventing erroneous attribution. If vaccines are being provided simultaneously, then informed consent should include a discussion of the benefits and risks of simultaneous vaccine administration given the limited data available on administration of the Novavax Nuvaxovid simultaneously with other vaccines.

Studies to assess the safety and immunogenicity of concomitant administration of COVID-19 vaccines with other vaccines are ongoing.

Refer to [Timing of Vaccine Administration](#) in the CIG, Part 1 - Key Immunization Information for additional general information on simultaneous administration of other vaccines in general.

VACCINE SAFETY AND ADVERSE EVENTS^a FOLLOWING IMMUNIZATION

Overall, Novavax Nuvaxovid was well tolerated. The frequencies of reported solicited local and systemic AE are provided in the [Appendix](#). In clinical trial 2019nCOV-301, solicited local and systemic AE were higher among younger adults (18-64 years) compared to older adults (≥65 years). For participants ≥65 years of age, the frequency of systemic reactions was similar between

^a Common AE occur in 1% to less than 10% of vaccine recipients. Very common AE occur in 10% or more of vaccine recipients. Uncommon AE occur in 0.1% to less than 1% of vaccine recipients. Rare and very rare AE occur, respectively, in 0.01% to less than 0.1% and less than 0.01% of vaccine recipients.

Novavax Nuvaxovid and placebo groups (32.61% vs 31.42% respectively), both of which were lower than among participants 18-64 years of age (49.77% and 41.21% respectively).

Across the assessments, the safety profile of Novavax Nuvaxovid in HIV-positive participants was similar to that seen in HIV-negative participants.

SOLICITED LOCAL REACTIONS

Local reactions were very common, mostly mild to moderate in severity, and occurred more frequently after the second dose. The median onset of solicited local reactions was 1-2 days after any dose and reactions resolved after a median of 1-2 days.

SOLICITED SYSTEMIC REACTIONS

Systemic AE were predominantly fatigue, headache and muscle pain; they were very common and occurred more frequently after the second dose. Grade 3^b solicited local and systemic events were common (about 1% for local and < 2.5% for systemic, and local reactions following dose 2 at 6.58%), with grade 4 events being uncommon (<0.2%). Overall, older vaccine recipients experienced lower frequencies of grade 3 and 4 events than the younger cohort.

SERIOUS ADVERSE EVENTS AND OTHER ADVERSE EVENTS OF INTEREST

Fatal events were rare, with 21 deaths reported (13 in the vaccine group and 8 in the placebo groups). The incidence was similar in the younger age cohort between the vaccine and placebo group, but slightly higher in the vaccine group in the older age cohort. Events were mostly consistent with the morbidity associated with age and underlying medical conditions in the study population and none were assessed as related to the vaccine.

No specific adverse events led to study discontinuation. Severe adverse events (about 1%) were infrequently reported and similar between the vaccine and placebo groups. Also similar between groups were serious adverse events, medically attended adverse events, and adverse events of special interest. There were no serious allergic reactions reported in the study.

Serious events of Hepatobiliary Disorders were reported only in the vaccine group in participants 18 to 64 years of age, but these events (n=12) were assessed as not related to the vaccine. These were mostly reports of cholecystitis and cholelithiasis, but the majority of vaccine recipients who experienced these events had one or more risk factors for these types of outcomes.

Myocarditis and/or pericarditis following vaccination with Novavax Nuvaxovid

Cases of myocarditis and/or pericarditis had been reported following the administration of Novavax Nuvaxovid including two teenage males who had myocarditis shortly after receiving a second dose of vaccine. In both individuals, clinical course was mild with complete resolution and no sequelae⁽¹⁴⁾. The biological mechanisms of action that could explain the association of myocarditis and/or pericarditis occurring after receipt of a COVID-19 vaccine are still under investigation and the information currently available is insufficient to determine a causal relationship with the vaccine. It is unclear whether these cases are indicative of a safety signal. Post-market safety surveillance is required to determine whether this is an adverse event of interest associated with Novavax Nuvaxovid.

^b AE can be graded by the following levels of severity: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (potentially life threatening)

The probability of detection of very rare adverse events in clinical trials is low given clinical trial population sizes; therefore, ongoing pharmacovigilance is essential and underway.

NACI continues to review information as it becomes available and will take appropriate action as needed.

Refer to [Reporting Adverse Events Following Immunization \(AEFI\) in Canada](#) and to the [Brighton Collaboration case definition](#) of myocarditis/pericarditis for additional information on the completion and submission of AEFI reports.

VACCINATION OF SPECIFIC POPULATIONS

The safety and efficacy of Novavax Nuvaxovid have not been established in the following populations:

- Individuals previously infected with SARS-CoV-2;
- Individuals who are immunocompromised due to disease or treatment;
- Individuals who are pregnant or breastfeeding;
- Individuals who have an autoimmune condition.

Informed consent should include discussion that there is currently limited evidence on the use of the Novavax Nuvaxovid in these populations, while there is evidence on the safety profile and effectiveness of mRNA COVID-19 vaccines in these populations based on real world use with large numbers of individuals. NACI will continue to monitor the evidence and update recommendations as needed.

For individuals with serious polyethylene glycol (PEG) allergy or previous serious allergic reaction to an mRNA vaccine precluding vaccination with mRNA vaccines, Novavax Nuvaxovid may be the preferred product for vaccination, based on consultation with an allergist or other appropriate physician.

CONTRAINDICATIONS AND PRECAUTIONS

Severe immediate allergic reactions (e.g., anaphylaxis) have not been reported following immunization with Novavax Nuvaxovid in the clinical trials. However, given the size of the clinical trials, rare and very rare side effects of the Novavax Nuvaxovid are not likely to have been identified at this time.

In general, an allergy to a component of a specific vaccine or its container is considered a contraindication. For more details on the administration of Novavax Nuvaxovid to individuals with allergies to components of the vaccine or its container, please see Table 3 which lists potential non-medicinal ingredients in Novavax Nuvaxovid that have been associated with allergic reactions in other products. These reactions have occurred rarely and ranged from mild cutaneous reactions to anaphylaxis.

Table 3: Ingredients of authorized COVID-19 vaccines that have been associated with allergic reactions in other products

Vaccine product	Potential allergen included in the vaccine or its container	Other products where the potential allergen may be found*
Novavax Nuvaxovid	Polysorbate 80 ^a	<ul style="list-style-type: none"> Medical preparations (e.g., vitamin oils, tablets, and anticancer agents), cosmetics^{b,c}

* N.B.: This is not a complete list of products.

^a There is a potential of cross-reactive hypersensitivity between PEG and polysorbates.

^b PEG is an additive in some food and drinks but allergic reactions to PEG in food or drinks have not been documented.

^c Case reports of anaphylaxis to polysorbate 80 have been described ^(15, 16).

Refer to [Table 4](#) and the section titled **myocarditis and/or pericarditis following vaccination with Novavax Nuvaxovid for more information and considerations applicable to individuals with a past history of myocarditis and/or pericarditis following immunization.**

ETHICS, EQUITY, FEASIBILITY AND ACCEPTABILITY CONSIDERATIONS

NACI uses a published, peer-reviewed framework and evidence-informed tools to ensure that issues related to ethics, equity, feasibility, and acceptability (EEFA) are systematically assessed and integrated into its guidance ⁽¹⁷⁾.

NACI evaluated the following ethical considerations when making its recommendations: promoting well-being and minimizing risk of harm, maintaining trust, respect for persons and fostering autonomy, and promoting justice and equity. NACI took into account the available evidence on Novavax Nuvaxovid and the accumulating real-world evidence on the effectiveness and safety of the mRNA COVID-19 vaccines.

Novavax Nuvaxovid offers an opportunity to protect individuals who have been unable to get vaccinated due to contraindications to other COVID-19 vaccine products, and to complete the vaccination schedule in individuals who were unable or hesitant to get an additional dose of COVID-19 vaccine due to an adverse event following a previous vaccine dose.

In addition, data collected over the course of the pandemic has consistently found that Canadians cite "ensuring the safety of the vaccine" as the main reason for delaying or not getting COVID-19 vaccination. For some individuals, their safety concern or vaccine hesitancy has focused on the viral vector or mRNA vaccine platforms. There is currently more experience with mRNA COVID-19 vaccines, but Novavax Nuvaxovid, now provides another option for use.

RECOMMENDATIONS

NACI recommendations for the use of available COVID-19 vaccines in Canada are presented below, with inclusion of the recombinant protein subunit COVID-19 vaccine Novavax Nuvaxovid. Please see [Table 5](#) for an explanation of strong versus discretionary NACI recommendations.

For individuals for whom a primary series of COVID-19 vaccine is recommended:

1. **NACI preferentially recommends that a complete series with an mRNA COVID-19 vaccine *should be offered* to individuals in the authorized age group without contraindications to the vaccine*.**
(Strong NACI Recommendation)
2. **NACI recommends that an authorized recombinant protein subunit COVID-19 vaccine (Novavax Nuvaxovid) *may be offered* to individuals in the authorized age group without contraindications to the vaccine who are not able or willing to receive an mRNA COVID-19 vaccine*.**
(Discretionary NACI Recommendation)
3. **NACI recommends that a viral vector COVID-19 vaccine *may be offered* to individuals in the authorized age group without contraindications to the vaccine only when all other authorized COVID-19 vaccines are contraindicated*. Informed consent should include discussion about the risks and symptoms of vaccine-induced immune thrombotic thrombocytopenia (VITT) as well as the need to seek immediate medical care should symptoms develop.**
(Discretionary NACI Recommendation)

*Please refer to [Table 4](#) for options and considerations for vaccine types in certain populations.

For individuals for whom a booster dose is recommended:

1. **NACI preferentially recommends that a booster dose of an mRNA COVID-19 vaccine be offered ≥ 6 months after completion of a primary COVID-19 vaccine series to those without contraindications to the vaccine*.**
(Discretionary NACI Recommendation)
 - There are some populations for whom a booster dose should be offered. Please refer to the section on booster doses in the chapter on [COVID-19 vaccine in the Canadian Immunization Guide](#) for information on individuals for whom a booster dose is recommended.
2. **NACI recommends that a booster dose of a recombinant protein subunit COVID-19 vaccine (Novavax Nuvaxovid) *may be offered** ≥ 6 months after completion of a primary COVID-19 vaccine series to adults without contraindications to the vaccine who are not able or willing to receive an mRNA COVID-19 vaccine*.**
(Discretionary NACI Recommendation)

For simultaneous administration with other vaccines:

1. NACI recommends that mRNA, viral vector and recombinant protein subunit (Novavax Nuvaxovid) COVID-19 vaccines may be given simultaneously with (i.e., same day), or at any time before or after, non-COVID-19 vaccines (including live and non-live vaccines). (Discretionary NACI recommendation)

*Please refer to Table 4 for options and considerations for vaccine types in certain populations.

Table 4. Options and considerations for vaccine types* and doses offered for COVID-19 vaccine for certain populations

Population	Vaccine type* which may be preferred	Rationale or additional considerations
For all populations not identified below	Pfizer-BioNTech Comirnaty (30 mcg) or Moderna Spikevax (100 mcg as per recommendations for primary series or 50 mcg for the booster dose) should be offered.	<ul style="list-style-type: none"> • Demonstrated high efficacy and effectiveness with longer-term safety data • Unvaccinated individuals who refuse mRNA vaccines should be made aware of the longer-term effectiveness and safety data that is available for these vaccine products as compared to other COVID-19 vaccines as part of informed consent before offering an authorized alternative, including a recombinant protein subunit (Novavax Nuvaxovid) COVID-19 vaccine.
18-29 year olds	Pfizer-BioNTech Comirnaty (30 mcg)	<ul style="list-style-type: none"> • Lower reported rates of myocarditis/pericarditis following vaccination with Pfizer (30 mcg) compared to Moderna (100 mcg)
Those with medically confirmed myocarditis (with or without pericarditis) following a dose of an mRNA vaccine	<p>Defer subsequent COVID-19 vaccination until more information is available.</p> <p>For those who choose to continue with vaccination, subsequent dose should be at least 90 days after resolution of symptoms and based on clinical discretion with Pfizer-BioNTech Comirnaty (30 mcg)</p>	<ul style="list-style-type: none"> • Lower reported rates of myocarditis/pericarditis following vaccination with Pfizer-BioNTech Comirnaty (30 mcg) compared to Moderna Spikevax (100 mcg) • Longer intervals between doses of mRNA vaccines appear to reduce the risk of myocarditis/pericarditis. • mRNA COVID-19 vaccines have been used for a year with longer term effectiveness and safety data. • Clinical trial data of Novavax Nuvaxovid has identified cases of myocarditis and/or pericarditis following vaccination but the information currently available is insufficient to determine a causal relationship with the vaccine. It is unclear whether these cases are indicative of a safety signal. Post-market safety surveillance is required to determine whether this is an adverse event of interest associated with Novavax Nuvaxovid, and the suitability for use in this population. • Viral vector vaccines have a risk of VITT and other adverse effects that are not concerns with mRNA vaccines.

<p>Those with serious PEG allergy or previous serious adverse reaction to an mRNA vaccine precluding vaccination with mRNA vaccines based on consultation with an allergist or other appropriate physician</p>	<p>Novavax Nuvaxovid</p>	<ul style="list-style-type: none"> • Consultation with an appropriate health care provider and reference to NACI guidance are recommended for those with a history of severe, immediate allergic reactions to components in both mRNA vaccines or a previous mRNA vaccine. • Although Novavax is not currently authorized for use as a booster dose, clinical trials have been conducted.
<ul style="list-style-type: none"> • ≥70 year olds • Adults living in LTC homes for seniors or other congregate living settings that provide care for seniors • Moderately to severely immunocompromised adults 	<p>Either Moderna Spikevax (100 mcg [primary series], 50 mcg [booster]) or Pfizer-BioNTech Comirnaty (30 mcg) are options to consider for the primary series or booster dose.</p> <p>If Moderna Spikevax is being used as the booster product, a 100 mcg dose may be preferred for older adults or adults living in long term care homes for seniors or other congregate living settings that provide care for seniors. For moderately to severely immunocompromised adults, this is based on clinical discretion.</p>	<ul style="list-style-type: none"> • Moderna Spikevax (100 mcg) induces somewhat higher antibody levels compared to Pfizer-BioNTech Comirnaty (30 mcg). • Protection (against infection and severe disease) from a primary series with Moderna Spikevax (100 mcg) may be more durable than Pfizer-BioNTech Comirnaty (30 mcg). • These populations may have less robust immune function (older adults) or a diminished immune response to the vaccine (some individuals who have immunocompromising conditions). It is possible that Moderna Spikevax (100 mcg) may induce a better immune response than Moderna Spikevax (50 mcg), although there is currently very limited data on the direct comparison of these two dosages as boosters ⁽¹⁸⁾. • Currently there are no data comparing the immune responses after a booster vaccination with Moderna Spikevax (100 mcg) and Pfizer-BioNTech Comirnaty (30 mcg) in these populations. • There is heterogeneity among those who are moderately to severely immunocompromised, and risks from COVID-19, as well as the likelihood of a reduced response to vaccines, will vary depending on age and the immunocompromising condition. • It should be noted that Moderna Spikevax (100 mcg) is not currently authorized by Health Canada as a booster dose.

* A viral vector COVID-19 vaccine should only be considered when all other authorized COVID-19 vaccines are contraindicated. Vaccine effectiveness against symptomatic infection and severe COVID-19 outcomes has consistently been somewhat lower, and lower vaccine protection against infection and symptomatic disease continues to be observed with viral vector vaccines compared to mRNA vaccines as protection decreases over time with both vaccine platforms when used in a primary series. Viral vector vaccines also have a risk of VITT and other adverse effects that are not concerns with mRNA vaccines.

Summary of evidence and rationale

- Novavax Nuvaxovid may be used in a homologous primary series, heterologous (mixed) primary series or as a booster dose in a homologous or heterologous prime-boost series for individuals without contraindications for whom mRNA COVID-19 vaccine is contraindicated, inaccessible, or has been refused.
- Clinical trial data available to date have shown that Novavax Nuvaxovid is highly efficacious (~90%) in preventing confirmed symptomatic COVID-19 disease in the short-term starting at one to two weeks after receiving the full two-dose series.
- Estimates of vaccine efficacy against the original SARS-CoV-2 strain were comparable to estimates in countries where the predominant circulating strain was the Alpha variant. However, vaccine efficacy was lower against the Beta variant. No efficacy or effectiveness data is available for Novavax Nuvaxovid against the Delta or Omicron variants.
- Local and systemic adverse events after any dose were typically mild and transient.
- There are preliminary data on cases of myocarditis and/or pericarditis following the administration of Novavax Nuvaxovid from the clinical trial data. Post-market safety surveillance data will be closely monitored to determine whether this is an adverse event of interest associated with Novavax Nuvaxovid, similar to myocarditis and/or pericarditis associated with mRNA COVID-19 vaccines, and to identify risk factors associated with the adverse event, and the rate at which this adverse event occurs.
- Novavax Nuvaxovid had demonstrated safety and appeared immunogenic when studied in a heterologous primary series with either Pfizer-BioNTech Comirnaty (30mcg) or AstraZeneca Vaxzevria COVID-19 vaccine as a first dose. When used as the second dose in a heterologous primary series, Novavax Nuvaxovid is more immunogenic than two doses of AstraZeneca Vaxzevria COVID-19 vaccine, but not two doses of Pfizer-BioNTech Comirnaty (30mcg).
- There was demonstrated safety and Novavax Nuvaxovid appeared immunogenic when studied as a booster dose in a homologous or heterologous prime-boost series. However, it may not be as immunogenic as a booster dose with an mRNA COVID-19 vaccine when used as a heterologous booster.
- Novavax Nuvaxovid may be given simultaneously with (i.e., same day), or at any time before or after, non-COVID-19 vaccines (including live and non-live vaccines). Informed consent should include a discussion of the benefits and risks given the limited data available on administration of the Novavax Nuvaxovid simultaneously with other vaccines.
- Novavax Nuvaxovid can offer protection against SARS-CoV-2 to individuals who have been unable or hesitant to initiate or complete their primary series with the mRNA and viral vector COVID-19 vaccines.

NACI is continuing to monitor the evidence and will update guidance as required.

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](#):

1. 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.
2. 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 hardy reached, remote and isolated communities.

3. 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.

Refer to the chapter on [COVID-19 vaccine in the Canadian Immunization Guide](#) for further information on COVID-19 vaccines.

Table 5. Strength of NACI Recommendations

Strength of NACI Recommendation <i>based on factors not isolated to strength of evidence</i> (e.g., public health need)	STRONG	DISCRETIONARY
Wording	<i>“should/should not be offered”</i>	<i>“may/may not be offered”</i>
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 offered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

RESEARCH PRIORITIES

- What is the population effectiveness (against infection, symptomatic disease, hospitalization and death) and medium and long-term durability of protection of a single dose, complete primary series, and booster dose of Novavax Nuvaxovid against SARS-CoV-2 VOC?
- Are there special adverse events associated with Novavax Nuvaxovid, including myocarditis and/or pericarditis following vaccination? What is the rate at which these events occur, and what are the risk factors?
- What is the efficacy, effectiveness, immunogenicity and safety of Novavax Nuvaxovid when used in a mixed dose schedule or a mixed dose booster series? Does this change across diverse population groups (e.g., adults of advanced age, those with high-risk medical conditions including autoimmune conditions and transplant recipients, individuals with social or occupational vulnerabilities, individuals who are pregnant or breastfeeding, frailty)?

ABBREVIATIONS

ACS	Advisory Committee Statement
AE	Adverse event
AEFI	Adverse event following immunization
EEFA	Ethics, equity, feasibility, and acceptability
HIV	Human immunodeficiency virus
NACI	National Advisory Committee on Immunization
PCR	Polymerase chain reaction
PEG	Polyethylene glycol
PHAC	Public Health Agency of Canada
S	Spike
VITT	Vaccine-induced immune thrombotic thrombocytopenia
VOC	Variant of concern

ACKNOWLEDGMENTS

This statement was prepared by: E Wong, SJ Ismail, R Pless, R Krishnan, J Zafack, R Stirling, K Young, MC Tunis, B Sander, and R Harrison on behalf of NACI.

NACI gratefully acknowledges the contribution of: SH Lim, E Tarrataca, K Ramotar, L Coward, C Jensen, C Mauviel, N St-Pierre, B Warshawsky.

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, J Papenburg, A Pham-Huy, B Sander, S Smith, and S Wilson.

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

Ex-officio representatives: V Beswick-Escanlar (National Defence and the Canadian Armed Forces), E Henry (Centre for Immunization and Respiratory Infectious Diseases (CIRID), PHAC), M Lacroix (Public Health Ethics Consultative Group, PHAC), C Lourenco (Biologic and Radiopharmaceutical Drugs Directorate, Health Canada), D MacDonald (COVID-19 Epidemiology and Surveillance, PHAC), S Ogunnaike-Cooke (CIRID, PHAC), K Robinson (Marketed Health Products Directorate, HC), G Poliquin (National Microbiology Laboratory, PHAC), and T Wong (First Nations and Inuit Health Branch, Indigenous Services Canada).

NACI High Consequence Infectious Disease Working Group

Members: R Harrison (Chair), N Brousseau, Y-G Bui, S Deeks, K Dooling, K Hildebrand, M Miller, M Murti, J Papenburg, D Smith, and S Vaughan.

PHAC participants: NK Abraham, N Alluqmani, L Coward, N Forbes, C Jensen, CY Jeong, A Jirovec, A Killikelly, R Krishnan, SH Lim, N Mohamed, J Montroy, A Nam, S Pierre, R Pless, M Salvadori, A Sinilaite, A Stevens, R Stirling, E Tice, A Tuite, MC Tunis, B Warshawsky, E Wong, R Ximenes, MW Yeung, J Zafack.

APPENDIX A: FREQUENCY OF SOLICITED ADVERSE EVENTS FOLLOWING IMMUNIZATION FOR COVID-19 IN CLINICAL TRIALS

Table 1. Frequency of solicited local AEs in adults 18 years of age and older for Novavax Nuvaxovid^{a, b}

AEFI	Vaccine		Placebo Control	
	Dose 1	Dose 2	Dose 1	Dose 2
Tenderness at injection site	Very common	Very common	Very common	Very common
Pain at injection site	Very common	Very common	Very common	Very common
Redness/erythema	Common	Common	Uncommon	Uncommon
Swelling	Uncommon	Common	Uncommon	Uncommon

^a Very common = occur in 10% or more of vaccine recipients, common = occur in 1 to less than 10% of vaccine recipients, uncommon= occur in 0.1% to less than 1% of vaccine recipients

^b AEFIs were solicited within 7 days after each dose in a Phase 2/3 clinical trial. The information in this table is up to date as of February 11, 2022. For updated information, please consult the Novavax Nuvaxovid product monograph.

Table 2. Frequency of solicited systemic AEs in adults 18 years of age and older for Novavax Nuvaxovid^{a, b}

AEFI	Vaccine		Placebo Control	
	Dose 1	Dose 2	Dose 1	Dose 2
Fatigue	Very common	Very common	Very common	Very common
Headache	Very common	Very common	Very common	Very common
Muscle pain	Very common	Very common	Very common	Very common
Joint pain	Common	Very common	Common	Common
Fever ^b	Uncommon	Common	Uncommon	Uncommon
Vomiting	Common	Very common	Common	Common

^a Very common = occur in 10% or more of vaccine recipients, common = occur in 1 to less than 10% of vaccine recipients, uncommon= occur in 0.1% to less than 1% of vaccine recipients

^b Fever was objectively reported as having a temperature $\geq 38^{\circ}\text{C}/100.4^{\circ}\text{F}$.

^c AEFIs were solicited within 7 days after each dose in a Phase 2/3 clinical trial. The information in this table is up to date as of February 11, 2022. For updated information, please consult the Novavax Nuvaxovid product monograph.

REFERENCES

1. Dunkle LM, Kotloff KL, Gay CL, Áñez G, Adelglass JM, Barrat Hernández AQ, et al. Efficacy and Safety of NVX-CoV2373 in Adults in the United States and Mexico. *N Engl J Med*. 2022 Feb 10;386(6):531,543. doi: 10.1056/NEJMoa2116185.
2. Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, et al. Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine. *N Engl J Med*. 2021 Sep 23;385(13):1172,1183. doi: 10.1056/NEJMoa2107659.
3. Shinde V, Bhikha S, Hoosain Z, Archary M, Bhorat Q, Fairlie L, et al. Efficacy of NVX-CoV2373 Covid-19 Vaccine against the B.1.351 Variant. *N Engl J Med*. 2021 May 20;384(20):1899,1909. doi: 10.1056/NEJMoa2103055.
4. Keech C, Albert G, Cho I, Robertson A, Reed P, Neal S, et al. Phase 1-2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine. *N Engl J Med*. 2020 Dec 10;383(24):2320,2332. doi: 10.1056/NEJMoa2026920.
5. Formica N, Mallory R, Albert G, Robinson M, Plested JS, Cho I, et al. Different dose regimens of a SARS-CoV-2 recombinant spike protein vaccine (NVX-CoV2373) in younger and older adults: A phase 2 randomized placebo-controlled trial. *PLoS Med*. 2021 Oct 1;18(10). doi: 10.1371/journal.pmed.1003769.
6. Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med*. 2021 Jul;27(7):1205,1211. doi: 10.1038/s41591-021-01377-8.
7. Mallory R, Formica N, Pfeiffer S, Wilkinson B, Marcheschi A, Albert G, et al. Immunogenicity and Safety Following a Homologous Booster Dose of a SARS-CoV-2 recombinant spike protein vaccine (NVX-CoV2373): A Phase 2 Randomized Placebo-Controlled Trial. *medRxiv*. 2021 Dec 25. <https://doi.org/10.1101/2021.12.23.21267374>.
8. Payne RP, Longet S, Austin JA, Skelly DT, Dejnirattisai W, Adele S, et al. Immunogenicity of standard and extended dosing intervals of BNT162b2 mRNA vaccine. *Cell*. 2021 Nov 11;184(23):5699,5714. doi: 10.1016/j.cell.2021.10.011.
9. Tauzin A, Gong SY, Beaudoin-Bussièrès G, Vézina D, Gasser R, Nault L, et al. Strong humoral immune responses against SARS-CoV-2 Spike after BNT162b2 mRNA vaccination with a 16-week interval between doses. *Cell Host Microbe*. 2022 Jan 12;30(1):97,109. doi: 10.1016/j.chom.2021.12.004.
10. Skowronski DM, Setayeshgar S, Febriani Y, Ouakki M, Zou M, Talbot D, et al. Two-dose SARS-CoV-2 vaccine effectiveness with mixed schedules and extended dosing intervals: test-negative design studies from British Columbia and Quebec, Canada. *medRxiv*. 2021 Oct 26. <https://doi.org/10.1101/2021.10.26.21265397>.
11. Stuart ASV, Shaw RH, Liu X, Greenland M, Aley PK, Andrews NJ, et al. Immunogenicity, safety, and reactogenicity of heterologous COVID-19 primary vaccination incorporating mRNA, viral-vector, and protein-adjuvant vaccines in the UK (Com-COV2): a single-blind, randomised,

phase 2, non-inferiority trial. *Lancet*. 2021 Dec 6;399(10319):36,49. doi: 10.1016/S0140-6736(21)02718-5.

12. Munro APS, Janani L, Cornelius V, Aley PK, Babbage G, Baxter D, et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. *Lancet*. 2021 Dec 2;398(10318):2258,2276. doi: 10.1016/S0140-6736(21)02717-3.

13. Toback S, Galiza E, Cosgrove C, Galloway J, Goodman AL, Swift PA, et al. Safety, immunogenicity, and efficacy of a COVID-19 vaccine (NVX-CoV2373) co-administered with seasonal influenza vaccines: an exploratory substudy of a randomised, observer-blinded, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2022 Feb;10(2):167,179. doi: 10.1016/S2213-2600(21)00409-4.

14. Committee for Medical Products for Human Use (CHMP). CHMP assessment report: Nuvaxovid [Internet]. Amsterdam (Netherlands): European Medicines Agency; 2022 Jan 4 [cited 2022 Feb 14]. Available from: https://www.ema.europa.eu/en/documents/assessment-report/nuvaxovid-epar-public-assessment-report_en.pdf.

15. Badiu I, Geuna M, Heffler E, Rolla G. Hypersensitivity reaction to human papillomavirus vaccine due to polysorbate 80. *BMJ Case Rep*. 2012 May 8. doi: 10.1136/bcr.02.2012.5797.

16. Palacios Castaño MI, Venturini Díaz M, Lobera Labairu T, González Mahave I, Del Pozo Gil MD, Blasco Sarramián A. Anaphylaxis Due to the Excipient Polysorbate 80. *J Investig Allergol Clin Immunol*. 2016;26(6):394,396. doi: 10.18176/jiaci.0109.

17. Ismail SJ, Hardy K, Tunis MC, Young K, Sicard N, Quach C. A framework for the systematic consideration of ethics, equity, feasibility, and acceptability in vaccine program recommendations. *Vaccine*. 2020 Aug 10;38(36):5861,5876. doi: 10.1016/j.vaccine.2020.05.051.

18. Lyke KE, Atmar RL, Islas CD, Posavad CM, Szydlo D, PaulChourdury R, et al. SARS-CoV-2 Omicron Neutralization After Heterologous Vaccine Boosting. *medRxiv*. 2022 Jan 14. <https://doi.org/10.1101/2022.01.13.22268861>.