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

Recommendations on the use of Medicago COVID-19 vaccine (Covifenz)

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PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH

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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 Medicago COVID-19 vaccine (Covifenz) is the first virus-like particle (VLP) COVID-19 vaccine authorized in Canada. Medicago Covifenz was authorized for use in adults 18-64 years of age by Health Canada on February 24, 2022.

The National Advisory Committee on Immunization's (NACI) 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 January 25, 2022 and February 1, 2022, NACI reviewed the available efficacy, immunogenicity and safety evidence on the use of Medicago Covifenz COVID-19 vaccine that included manufacturer's clinical data available in the regulatory submission to Health Canada and available published scientific literature. NACI also considered aspects of the ethics, equity, feasibility, and acceptability (EEFA) of the use of Medicago Covifenz in the current context of the pandemic. NACI approved their recommendations on the use of Medicago Covifenz in adults 18-64 years of age on March 6, 2022.

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

Further information on NACI's process and procedures is available elsewhere.

EPIDEMIOLOGY

COVID-19 BURDEN OF DISEASE

At the time of this Statement's release, Canada has been facing a wave of the COVID-19 pandemic driven mainly by the Omicron variant of concern (VOC) that emerged in November 2021. This Omicron variant of SARS-CoV-2 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 available on COVID-19 mRNA vaccines suggest that they offer reduced protection against symptomatic infection with Omicron, 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.

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

The Medicago COVID-19 vaccine is an adjuvanted vaccine consisting of recombinant SARS-CoV-2 spike glycoproteins stabilized in the prefusion conformation that are produced by transient expression in *Nicotiana benthamiana* plants and become membrane imbedded in self-assembled enveloped virus-like particles (VLP). The vaccine also contains Adjuvant System 03 (AS03), produced by GlaxoSmithKline, that was used as the adjuvant in three influenza vaccines: Prepandrix (H5N1), Pandemrix (H1N1pdm09) and Arepanrix (H1N1pdm09).

Characteristics of the Medicago Covifenz COVID-19 vaccine currently authorized for use in Canada are summarized in Table 1.

Table 1. Medicago Covifenz Vaccine Characteristics

Product characteristics	Medicago Covifenz
Manufacturer	Medicago Inc.
Date of authorization in Canada	February 24, 2022
Type of vaccine	Plant-based virus-like particle [VLP] (recombinant, adjuvanted)
Product specification	Adult formulation
Age	18 to 64 years of age
Presentation	Vials containing 2.5 mL of antigen suspension (10 doses of 0.25 mL) and vials containing 2.5 mL of AS03 adjuvant emulsion (10 doses of 0.25 mL)
Dose	0.5 mL (3.75 mcg SARS-CoV-2 recombinant spike protein)
Doses per vial following mixing	10
Potential allergens	Polysorbate 80 May contain trace amounts of polyethylene glycol [PEG], kanamycin and carbenicillin.
Adjuvant	AS03 oil-in-water emulsion with polysorbate 80, α-tocopherol and squalene
Storage requirements	2°C to 8°C for a maximum of 6 months protected from light and stored upright. Do not freeze.
Opened mixed vial storage	20°C to 30°C for up to 6 hours after mixing, and protected from light

For complete prescribing information for Medicago Covifenz, 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 MEDICAGO COVIFENZ COVID-19 VACCINE AS A PRIMARY SERIES

Medicago Covifenz COVID-19 vaccine was evaluated for efficacy, immunogenicity, safety and tolerability in a randomized, multinational, placebo-controlled, observer-blinded pivotal Phase 2/3 trial (CP-PRO-CoVLP-021) conducted across sites in Canada, the United States, the United Kingdom, Brazil, Argentina, and Mexico.

Eligible trial participants were adults 18 years of age and older, stratified into three population subgroups:

1. Healthy adults 18 to 64 years of age
2. Healthy adults 65 years of age and older
3. Adults 18 years of age and older with significant comorbidities that put them at higher risk for severe COVID-19 disease. Comorbidities include, but are not limited to, obesity (moderate or greater), hypertension, type 1 or type 2 diabetes, chronic obstructive pulmonary disease, cardiovascular diseases, chronic kidney diseases, or immunocompromise (e.g., treatment-controlled HIV infection, organ transplant recipients, or patients receiving cancer chemotherapy).

Study participants were randomized 1:1 to receive two doses of Medicago Covifenz or placebo administered 21 days apart. The study randomized 24,141 participants 18 years of age and older (n=12,074 in the vaccine group, n=12,067 in the placebo group), constituting the intention-to-treat (ITT) population. Less than 1% of the participants were 65 years of age and older, and less than 10% had significant co-morbidities. Among randomized study participants, 24,076 (99.7%) received at least one dose of assigned intervention (vaccine or placebo). However, during the study there were substantial losses of participants from both the vaccine and placebo arms, with losses greater in the placebo arm (vaccine group: 1,508; 12.5%; placebo group: 4,567; 37.9%). The main reasons for the loss of participants was “due to receipt of a deployed vaccine” (vaccine group: n=600, 5.0%; placebo group: n=2,712, 22.5%) and “withdrawal of consent” (vaccine group: 500, 4.2%; placebo group: 1,345, 11.2%). As the Medicago clinical trials began, a number of COVID-19 vaccines had been approved and were being administered around the world. The per-protocol (PP) population consisted of 20,090 study participants (n=10,554 in the vaccine group, n=9,536 in the placebo group). Estimates of vaccine efficacy were analysed using both the ITT and PP populations, that included less than 15% who were seropositive at baseline. The data cut-off date for the efficacy analysis was August 20, 2021, when at least 160 symptomatic COVID-19 episodes had been identified, and the median duration of safety follow-up for at least 3,000 study participants in each of the vaccine and placebo groups was at least 2 months.

These trials were conducted prior to the emergence of Omicron, and there are very limited immunogenicity data, and no efficacy data to demonstrate what level of protection Medicago Covifenz offers against the Omicron variant.

VACCINE EFFICACY

Efficacy against laboratory confirmed symptomatic SARS-CoV-2 infection

The primary efficacy endpoint was the efficacy of Medicago Covifenz against the first episode of laboratory confirmed, symptomatic SARS-CoV-2 infection with onset at least 7 days after Dose 2. The analysis was conducted in both the ITT and PP populations, and included participants found to be seropositive at baseline. The estimate of efficacy against this outcome was 69.5% (95% CI: 56.7 to 78.8%) in the ITT population, based on the identification of 165 cases (40 cases in the vaccine group and 125 cases in the placebo group). The estimate of vaccine efficacy in the PP population was comparable at 71.0% (95% CI: 58.7 to 80.0%), based on the identification of 157 cases (39 cases in the vaccine group and 118 cases in the placebo group).

Estimates of vaccine efficacy against the primary outcome by subgroup (age, presence of medical comorbidities, sex, race/ethnicity, baseline serostatus, and disease severity) were generally comparable to the overall estimate of efficacy. However, there were an insufficient number of cases (n=2) identified in study participants 65 years of age and older (n=206) to generate a reliable estimate of vaccine efficacy.

Efficacy against moderate and severe COVID-19

The estimates of vaccine efficacy against severe COVID-19 (degree of severity – mild, moderate and severe – being defined as symptoms and signs of pneumonia with varying severity of clinical complications) from at least 7 days after Dose 2 for both the ITT and PP populations were imprecise due to the very wide confidence intervals around the point estimate of efficacy that included zero (ITT: 100.0%, 95% CI: -63.7 to not applicable; PP: 100.0%, 95% CI: -204.4 to not applicable), based on zero severe cases identified in the vaccine group and 2 severe cases identified in placebo group of the PP population and one additional severe case identified in the placebo group of the ITT population, for a total of 3 severe cases.

An ad-hoc analysis further examined vaccine efficacy by moderate and by moderate or severe COVID-19. The estimates of efficacy against moderate COVID-19 with onset at least 7 days after Dose 2 are 76.9% (95% CI: 51.5 to 90.0%) in the ITT population and 76.6% (95% CI: 50.5 to 90.0%) in the PP population (based on 8 cases in the vaccine group and 30 cases in the placebo group). The corresponding estimates of efficacy against moderate or severe COVID-19 are 78.8% (95% CI: 55.8 to 90.8%) in the ITT population and 78.1% (95% CI: 53.9 to 90.5%) in the PP population.

Efficacy against laboratory confirmed symptomatic SARS-CoV-2 infection by variants of interest/concern

As of December 3, 2021, sequencing data were available for 122 of 165 (73.9%) of the laboratory confirmed SARS-CoV-2 infections identified in the ITT population and for 114 of 157 (72.6%) of the laboratory confirmed infections identified in the PP population. Genetic sequencing identified cases due to Alpha, Delta, Gamma variants of concern and Lambda and Mu variants of interest, with dominance varying by country and few of the VOI. There were no cases identified due to the ancestral strain or the Omicron variant.

In the PP population, estimates of vaccine efficacy against symptomatic SARS-CoV-2 infection with onset at least 7 days after Dose 2 were 100.0% for Alpha (95% CI: 28.0 to not applicable), 75.3% for Delta (95% CI: 52.8 to 87.9%), and 88.6% for Gamma (95% CI: 74.6 to 95.6%). The estimates of vaccine efficacy in the ITT population were comparable.

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 [(1)]. 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 VOCs on the association between neutralizing antibodies or other potential immunological correlates and vaccine efficacy has not been described. Immunological evidence in support of vaccine efficacy is indirect and cannot directly be used to estimate efficacy.

Humoral immune responses

Neutralizing antibody responses were induced after the first dose of vaccine and further increased after the second dose. In a Phase 2 study, antibody titres 21 days after the second dose were similar in healthy adults 18 to <65 years of age, healthy adults ≥65 years of age and adults ≥18 years of age with significant comorbidities. For the majority, antibodies were still detectable 180 days after dose 2, with an approximate 11-fold drop compared to titres measured 21 days after dose 2.

Cellular immune responses

In the same Phase 2 study, cellular immune responses were detected after the first dose of vaccine and further increased after the second dose. The characterization of these responses indicates a Th1-biased cellular immune response. Cellular immune responses were higher in healthy adults 18 to <65 years of age compared to responses in healthy adults ≥65 years of age and adults ≥18 years of age with significant comorbidities. Cellular immune responses were still detectable 180 days after dose 2, with approximately a 3-fold drop in Th1 responses compared to 21 days after dose 2.

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, authorized COVID-19 vaccines, March 11, 2022

Vaccine product	Immunization Schedule[a]	Age Indication	Minimum Interval	Authorized Interval	NACI-Recommended Interval[b]
Pfizer-BioNTech Comirnaty (30mcg)	2-dose schedule	12 years of age and over	19 days[c]	21 days	8 weeks
Pfizer-BioNTech Comirnaty (10mcg, pediatric formulation)	2-dose schedule	5 to 11 years of age	19 days	21 days	At least 8 weeks
Moderna Spikevax (100mcg)	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]	21 days[f]	8 weeks
Medicago Covifenz	2-dose schedule	18-64 years of age	21 days[g]	21 days	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 and Pfizer-BioNTech Comirnaty 10mcg pediatric formulation], is recommended.
[c] The basis for this minimum interval is that the per-protocol design for the Pfizer-BioNTech Comirnaty COVID-19 vaccine clinical trial was 19 to 23 days.
[d] The basis for this minimum interval is that the majority of participants in the Moderna Spikevax COVID-19 vaccine (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.
[f] The authorized interval was defined as three weeks in the product monograph
[g] The minimum interval follows from the clinical trial protocol.

NACI RECOMMENDED DOSING INTERVAL FOR THE PRIMARY SERIES

The NACI-recommended dosing interval for Medicago Covifenz is described in Table 2 and it is consistent with current NACI recommendations for other vaccine products. Evidence [2] continues to emerge that longer intervals between the first and second doses of mRNA COVID-19 vaccines result in more robust and durable immune response and higher vaccine effectiveness. Evidence on COVID-19 mRNA 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 [3-5], and expected to also apply to recombinant VLP 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., Medicago Covifenz should be offered a minimum of 21 days after Pfizer-BioNTech Comirnaty [30 mcg]).

BOOSTER DOSES

Medicago Covifenz is not currently authorized for use as a booster dose in Canada. Clinical trials of a booster dose of this vaccine are planned for Spring 2022. At the time of publication, there are no data available on the use of Medicago Covifenz as a booster dose in either a homologous or heterologous schedule.

Informed consent when administering a Medicago primary series should therefore include mention that this vaccine is not currently authorized for use as a booster dose in Canada. NACI has recommended that a booster dose of an 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, regardless of which COVID-19 vaccine was previously used for the primary series. For more information on booster doses 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.

Mixed schedules using Medicago Covifenz with other COVID-19 vaccines have not been studied. Refer to the interchangeability section below for additional detail on mixed vaccine schedules.

INTERCHANGEABILITY

Medicago Covifenz has not yet been evaluated in a heterologous (mixed) primary series.

Mixed schedules using Medicago Covifenz specifically and other COVID-19 vaccines, have not been studied. Available evidence for other COVID-19 vaccine products indicates that mixed schedules have acceptable safety profiles.

Informed consent should include a discussion of the benefits and risks given the absence of data available on mixed schedules with Medicago Covifenz.

SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES

As post-market surveillance for this vaccine is in the early stages, administering Medicago Covifenz alone can assist with the assessment of any adverse event following immunization (AEFI) by preventing erroneous attribution. While no safety concerns have been identified to date with the simultaneous administration of other COVID-19 vaccines and concomitant administration of non-COVID-19 vaccines for routine immunizations, there are no data from clinical trials for the use of Medicago Covifenz with other vaccines.

Informed consent should include a discussion of the benefits and risks given the absence of data on administration of the Medicago Covifenz simultaneously with other vaccines.

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 FOLLOWING IMMUNIZATION

Vaccine safety for the Medicago Covifenz vaccine was evaluated in Phase 1 and Phase 2/3 studies. The Phase 1 study included 180 subjects, with 98.9% (178) receiving a second dose. The pivotal Phase 2/3 study of efficacy and safety was a multinational trial (CP-PRO-CoVLP-021) described above, in adults 18 years of age and older. The safety analysis set included 12,036 participants receiving CoVLP and 12,040 placebo recipients, including a population with significant comorbidities that put them at higher risk for severe COVID-19 disease. Of the total, 91.7% received both vaccine doses. A solicited adverse event (AE) subset included 4,136 (CoVLP) and 3,683 (placebo) recipients followed for 7 days after each dose.

SOLICITED ADVERSE EVENTS

Overall, Medicago Covifenz was well tolerated. Adverse events after vaccination were usually of mild or moderate intensity and resolved within 1 to 3 days. Grade 2 and higher solicited AEs (both local and systemic) were more frequent after the second dose compared to the first. The frequencies of reported solicited local and systemic events are provided in the Appendix. Overall, the proportion of subjects reporting solicited AEs was higher among those who received the CoVLP formulation (3,923 subjects, 94.9%) than those who received placebo (2,678, 72.7%). The incidence was similar between dose 1 and dose 2 following the vaccine formulation (89.6% vs 88.3%) while it appeared higher after the first dose compared to the second dose of placebo formulation (61.2% vs 51.2%).

UNSOLICITED ADVERSE EVENTS

Among participants aged 18 to 64 years old who received the first and/or second vaccination of Medicago Covifenz (11,933 participants) or placebo (11,924 participants) within the safety analysis set, 3,140 (26.3 %) who received Medicago Covifenz and 2,759 (23.1 %) who received placebo experienced an unsolicited AE (includes both non-serious and serious events). In general, the incidence of unsolicited AEs after the first and second vaccinations were similar. Most events were mild, with less than 0.5% classified as moderate and less than 0.1% as severe. A similar proportion of participants in the vaccine and placebo groups reported serious AEs. Forty-seven (47) participants (0.4 %) who received Medicago Covifenz, and 38 participants (0.3 %) who received placebo experienced a serious AE.

The most frequent non-serious reported unsolicited AEs included headache and respiratory symptoms such as nasal congestion, cough, sore throat and runny nose, along with diarrhea, nausea, and muscle aches. Notably, the reported incidence was similar in the vaccine and placebo groups.

SERIOUS ADVERSE EVENTS AND OTHER ADVERSE EVENTS OF INTEREST

There were no reported cases of severe allergic reactions or anaphylaxis, Guillain-Barré syndrome (GBS) or vaccine-associated enhanced disease in the trial. A total of 13 fatal cases were reported. Four of the cases were reported following vaccine in the follow up period after the second dose, and 9 following placebo. None were deemed related to Medicago Covifenz or COVID-19.

VACCINATION OF SPECIFIC POPULATIONS

The following populations (18 years of age and older) were either excluded from, or included in small numbers, in clinical trials of Medicago Covifenz. NACI will continue to monitor the evidence and update recommendations as needed:

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

The safety and efficacy of Medicago Covifenz has not been established in these populations. However, Medicago Covifenz may be used in these populations for individuals for whom mRNA COVID-19 vaccine is contraindicated, or who are not able or willing to receive an mRNA COVID-19 vaccine. Informed consent should include discussion that there is currently limited evidence on the use of the Medicago Covifenz in these populations, and there is accumulating evidence on the safety and effectiveness of mRNA COVID-19 vaccines in these populations.

CONTRAINDICATIONS AND PRECAUTIONS

Severe immediate allergic reactions (e.g., anaphylaxis) have not been reported following immunization with Medicago Covifenz in the clinical trials. However, the size of the clinical trial would not detect rare or very rare adverse events that may occur at a frequency less often than 1 in 1,000 people. Health Canada, the Public Health Agency of Canada (PHAC) and NACI will continue to monitor the safety of the vaccine.

In general, an allergy to a component of a specific vaccine or its container is considered a contraindication. Table 3 lists potential non-medicinal ingredients in Medicago Covifenz that have been associated with allergic reactions in other products. These reactions have occurred rarely and ranged from mild cutaneous reactions to anaphylaxis. It is important to note that other, less serious reactions may mimic allergic reactions (e.g., vasovagal syncope) and vaccination is not contraindicated in these cases.

Table 3: Ingredients of Medicago Covifenz COVID-19 vaccine 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*
Medicago Covifenz	Polysorbate 80[a]	• medical preparations (e.g., vitamin oils, tablets, and anticancer agents), cosmetics[b]
	Trace amounts of: Polyethylene glycol (PEG) Kanamycin Carbenicillin	• PEG: over the counter (e.g., cough syrup, laxatives), and prescription medications, medical bowel preparation products for colonoscopy, skin care products, dermal fillers, cosmetics, contact lens care solutions, products such as ultrasound gel [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 Case reports of anaphylaxis to polysorbate 80 have been described.

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

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 [(6)].

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 considered the available evidence on Medicago Covifenz and the accumulating real-world evidence on the effectiveness and safety of other Health Canada-authorized COVID-19 vaccines.

Medicago Covifenz offers an additional opportunity to protect individuals who have been unable or unwilling to get vaccinated or to complete a primary vaccine series. This might have been due to either contraindications or hesitancy with regard to mRNA and viral vector COVID-19 vaccines, or due to an adverse event following a previous dose.

In addition, data collected over the course of the pandemic have consistently shown that Canadians cite "ensuring the safety of the vaccine" as the main reason for delaying or not getting COVID-19 vaccination. For some individuals, this safety concern has focussed on vaccine-related adverse events, or a desire for additional long-term, population-level experience with mRNA and/or viral vector vaccine platforms in particular. There is currently more experience with mRNA COVID-19 vaccines, but individuals who have been delaying vaccination due to product specific concerns may be more willing to accept vaccination with Medicago Covifenz. Medicago Covifenz is a new plant-based platform expressing a recombinant protein, but VLP technology has also been used in vaccines for human papillomavirus (HPV) and hepatitis B, and the AS03 adjuvant has been used in the influenza vaccine during the influenza H1N1 pandemic in 2009-2010.

RECOMMENDATIONS

NACI recommendations for the use of available COVID-19 vaccines in Canada are presented below with inclusion of the recombinant VLP COVID-19 vaccine Medicago Covifenz. Please see Table 5 for an explanation of strong versus discretionary NACI recommendations.

For those 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) or recombinant VLP COVID-19 vaccine (Medicago Covifenz) *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 simultaneous administration of a COVID-19 vaccine dose with other vaccines:

1. **NACI recommends that mRNA, viral vector, recombinant protein subunit (Novavax Nuvaxovid) or recombinant VLP (Medicago Covifenz) 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)**

- Informed consent should include a discussion of the benefits and risks given the current absence of data on Medicago Covifenz given simultaneously with other vaccines.

- Administering Medicago Covifenz alone, however, could assist with the assessment of any adverse event following immunization (AEFI) by preventing erroneous attribution.

Summary of evidence, rationale and considerations

- Clinical trial data available to date have shown that Medicago Covifenz is efficacious (~71%) in preventing confirmed symptomatic COVID-19 disease in the short-term starting at one to two weeks after receiving the full two-dose series, in populations where the Delta and Gamma variants of concern were predominantly in circulation.

- No efficacy or effectiveness data are available for Medicago Covifenz against the ancestral SARS-CoV-2 strain or the Omicron variant.
- Local and systemic adverse events after any dose were typically mild and transient, and no safety signals were detected in the clinical trials.
- The Medicago Covifenz COVID-19 vaccine may be used in a homologous primary series for individuals who are not able or willing to receive an mRNA COVID-19; or it may be used in a heterologous (mixed) primary series in select circumstances, determined based on clinical discretion. Individuals should be informed of the absence of data on the vaccine's use in a mixed schedule.
- Informed consent when administering a Medicago Covifenz primary series should include a discussion that Medicago Covifenz is not currently authorized for use as a booster dose. There are currently no data on Medicago Covifenz as a booster dose, as part of a homologous or heterologous schedule.
- NACI will assess evidence on the use of this vaccine as a booster dose as information becomes available and provide additional guidance as needed.

Table 4. Options and considerations for vaccine types* and doses offered for COVID-19 vaccine for certain adult populations as of March 11, 2022

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 (50 mcg or 100 mcg as per recommendations for primary series or booster dose) should be offered	• 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 are available for these products as compared to other vaccines as part of informed consent before offering an authorized alternative, including a recombinant VLP COVID-19 vaccine (Medicago Covifenz) or protein subunit (Novavax Nuvaxovid) COVID-19 vaccine. • Medicago Covifenz is only authorized for use in adults 18 to 64 years. • Unvaccinated individuals who are unwilling to receive mRNA vaccines should be made aware of the smaller clinical trials and absence of evidence currently available for the Medicago Covifenz vaccine with respect to booster doses as part of informed consent before offering the latter.
18-29 year olds	Pfizer-BioNTech Comirnaty (30 mcg)	• Lower reported rates of myocarditis/pericarditis following vaccination with Pfizer-BioNTech Comirnaty (30 mcg) compared to Moderna Spikevax (100 mcg).
Those with medically confirmed myocarditis (with or without pericarditis) following a dose of an mRNA vaccine	Defer subsequent COVID-19 vaccination until more information is available. For those who choose to continue with vaccination,	• 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.

	subsequent dose should be at least 90 days after resolution of symptoms and based on clinical discretion with Pfizer-BioNTech Comirnaty (30 mcg)	• mRNA COVID-19 vaccines have been used for a year and therefore have longer term effectiveness and safety data as compared with newer authorized products. • Clinical trial data of Novavax Nuvaxovid have identified cases of myocarditis and/or pericarditis following vaccination, although the risk of these adverse events based on large-scale use is currently unknown.
Those with serious PEG allergy or previous serious allergic reaction to an mRNA vaccine precluding vaccination with mRNA vaccines based on consultation with an allergist or other appropriate physician	Novavax Nuvaxovid or Medicago Covifenz may be considered, based on consultation with an allergist or other appropriate physician	• Consultation with an appropriate health care provider and reference to NACI guidance is recommended for those with a history of severe, immediate allergic reactions to components in both mRNA vaccines or a previous mRNA vaccine. • Medicago Covifenz is only authorized for use in adults 18 to 64 years. • Although Medicago Covifenz may be offered as part of a heterologous primary series in some instances, it has not been evaluated as part of a mixed schedule. Individuals should be made aware of the lack of evidence on interchangeability for the Medicago Covifenz vaccine at this time as part of informed consent before offering this vaccine. • There is a potential of cross-reactive hypersensitivity between PEG and polysorbates. Novavax Nuvaxovid and Medicago Covifenz contain polysorbate 80. Medicago Covifenz may contain trace amounts of PEG.
• ≥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	Either Moderna Spikevax or Pfizer-BioNTech Comirnaty (30 mcg) may be considered for the primary series or booster dose. If Moderna Spikevax is being used as the booster product, a 100 mcg dose may be preferred for older adults. For moderately to severely immunocompromised adults, this is based on clinical discretion.	• 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 immunocompromised individuals). It is possible that Moderna Spikevax (100 mcg) may induce a better immune response than Moderna Spikevax (50 mcg), although there is currently no direct comparison of these two dosages as boosters. • 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 authorized by Health Canada as a booster dose. • Medicago Covifenz is only authorized for a primary series in adults 18 to 64 years. There are no data on the use of this vaccine 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 vaccine protection against infection and symptomatic disease decreases more quickly with viral vector vaccines compared to mRNA vaccines 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.

NACI is continuing to monitor the evidence and will update guidance as required. The Committee also 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 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 hardly 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 *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 offered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

RESEARCH PRIORITIES

- What is the efficacy, effectiveness, immunogenicity, and safety of Medicago Covifenz when used for individuals 65 years of age and older?
- What is the population effectiveness (against infection/transmission, hospitalization and death) and medium and long-term durability of protection of a single dose and a complete primary series, of Medicago Covifenz against SARS-CoV-2 VOCs, including Omicron?
- Are there adverse events associated with Medicago Covifenz that were not detected in clinical trials?
- What is the efficacy, effectiveness, immunogenicity and safety of Medicago Covifenz when used in a mixed dose schedule, as a booster dose, 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

Abbreviation	***Term***
COVID-19	Coronavirus disease 2019
EEFA	Ethics, equity, feasibility, and acceptability
ITT	Intention to treat
LTC	Long-term care
mRNA	messenger ribonucleic acid
mcg	microgram
NACI	National Advisory Committee on Immunization
PEG	Polyethylene glycol
PHAC	Public Health Agency of Canada
PP	Per protocol
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
VITT	Vaccine-induced immune thrombotic thrombocytopenia
VLP	Virus-like particle
VOC	Variant of concern

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

Table 1. Frequency of solicited local AEFI in adults 18 years of age and older for the Medicago Covifenz COVID-19 vaccine [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	Very common	Uncommon	Uncommon
Injection site swelling	Very 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] AEFI were solicited within 7 days after each dose in a Phase 3 clinical trial.

Table 2. Frequency of solicited systemic AEFI in adults 18 years of age and older for the Medicago Covifenz COVID-19 vaccine [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	Very common	Very common	Very common	Common
Fever[c]	Common	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] AEFI were solicited within 7 days after each dose in a Phase 3 clinical trial.
[c] Fever was objectively reported as having a temperature ≥38°C/100.4°F.