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FOCUS ON

COVID-19 Vaccines: Protein Subunit Vaccines

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Introduction

The novel coronavirus disease (COVID-19) pandemic has stimulated unprecedented efforts globally to develop vaccines that provide protection against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1]

This Focus On is intended for health care providers and public health partners. It provides an overview of protein subunit vaccines, including products authorized for use in Canada. This document will be updated as new information becomes available.

The Basics: Protein Subunit Vaccines

Protein subunit vaccines are a well-established vaccine platform, and have been widely used for several decades, most recently for vaccines that provide protection against hepatitis B and pertussis.[2-5]

What is a Protein Subunit Vaccine?

A protein subunit vaccine is a type of subunit vaccine that contains a purified piece of the virus (a protein or fragment of protein, known as a peptide), that has been specifically selected for its ability to trigger an immune response without causing infection.[2-5] An example of a protein sub-unit vaccine is the Hepatitis B vaccine that is produced through recombinant deoxyribonucleic (DNA) technology. In this process, DNA is taken from the virus which we want to be protected against and inserted into cells grown in a laboratory (e.g., yeast cells), which then manufacture large quantities of the protein.[6]

Other types of subunit vaccines include:

- Polysaccharide vaccines which contain chains of polysaccharides (sugars) isolated from the outer cell wall of a bacteria.[3] An example of this type of vaccine is the pneumococcal polysaccharide (Pneu-P-23) vaccine.
- Conjugate vaccines which contain carrier protein that is chemically attached to a polysaccharide chain, providing improved immune response over polysaccharide vaccines.[3] Examples of this type of vaccine include pneumococcal conjugate 13 (Pneu-C-13) and meningococcal conjugate C (Men-C-C) vaccines.

Vaccines work by training our immune system to recognize and respond to infectious agents.[6] For many vaccines, this is accomplished by delivering a weakened or inactivated virus or component of the virus to the body which triggers an immune response.[6] Whereas, protein subunit vaccines use a specific component of the virus such as a particular, highly purified protein (i.e., purified whole protein, recombinant proteins and peptides) which is recognized as foreign to our body.[2-5] These proteins, known as antigens, use the body's normal processes to safely produce an immune response.[2-5]

Protein subunit vaccines containing viral protein antigen(s) primarily trigger the production of antibodies with relatively less induction of cellular mediated (T-cell) immunity.[5,6] Antibody levels generally wane after vaccination, whereas activation of cell-mediated immune responses are expected to play a central role in providing us with long-term protection.[7] To enhance the efficacy of these antigens and durability of immune responses, some protein subunit vaccines, including the COVID-19 protein subunit vaccine, are delivered with adjuvants which are agents that stimulate the immune system to enhance the response.[2,6-9]

What is an Adjuvant?

Adjuvants are substances that accelerate, enhance, and prolong the immune response to vaccine antigen.[6-9] Adjuvants have been used safely for decades in a number of vaccines and work to: [6-9]

- Enhance the ability of a vaccine to elicit a stronger and more durable immune response;
- Reduce the concentration of antigen and the number of immunizations that are required in a primary vaccine series to elicit a durable immune response; and
- Modulate the nature of immune response, both humoral and cell-mediated (T-lymphocytes) responses, with cell-mediated immunity providing longer duration of immune protection.[6-9]

Key Messages

1. You cannot get COVID-19 or other infections from a protein subunit vaccine.

Protein subunit COVID-19 vaccines are non-infectious (they do not contain whole or live virus), they cannot replicate and they only contain protein or peptide fragments of the virus. Therefore, they are not capable of causing disease and are considered very safe.[10]

2. Protein subunit vaccines are a well-established vaccine platform.

Protein subunit vaccine use is well-established and has been used safely and effectively for several decades for preventing diseases such as pertussis (i.e., whooping cough) and hepatitis B, respectively.[2,6] The manufacturing technology and process for recombinant protein subunit vaccines is well-established.[8]

Mechanism of Action and Immune Response

COVID-19 protein subunit vaccines consist of two primary components: the protein antigen and the adjuvant, which are responsible for eliciting both humoral and cell-mediated immune responses.[11]

- The protein antigen is produced from a recombinant piece of SARS-CoV-2 DNA encoding the spike (S) glycoprotein which normally acts to mediate receptor binding and membrane fusion of the SARS-CoV-2 virus with the human host cell.[11-13]

- Using recombinant DNA technology, a specific piece of the COVID-19 virus's genetic material (DNA) that contains instructions for creating the viral protein, the SARS-CoV-2 spike (S) glycoprotein, is synthesized and inserted into baculovirus (BV).[10] The BV is then used to infect *Spodoptera frugiperda* (sf9 cells). The genetically stable material inserted into the BV does not integrate or interact with our DNA since it is used in production to infect the insect cells. [10]

- Using the moth cell's cellular machinery, properly folded protein antigens that resemble the SARS-CoV-2 S glycoprotein's native structure, with presentation of key structures to the immune system, are produced and assembled (nanoparticles).[10,11] These highly immunogenic nanoparticles can then be used to stimulate an immune response in our bodies.

- To enhance the immunologic response to the protein antigen, the SARS-CoV-2 recombinant spike (rS) glycoprotein is mixed with the Matrix-M™ adjuvant.[11-14] Matrix-M is composed of nanometer-sized particles based on saponin extracted from the *Quillaja saponaria* Molina bark together with cholesterol and phospholipid.[11,15,16] The adjuvant induces the influx of antigen presenting cells (APCs) that help to process and present the protein antigen to the rest of the immune system. This enhances the humoral response, by increasing antibodies and inducing long-lasting memory B cells. The APC also increase the recruitment of T-cells, thereby enhancing cellular immune responses to the vaccine.[11,14]

Once vaccinated, our immune system recognizes these proteins as foreign in our body and begins making antibodies and T-lymphocytes. If infected in the future, these memory cells will recognize and fight the virus.[4] Antibody-mediated responses directed against the SARS-CoV-2 spike glycoprotein are believed to be important for blocking the virus from entering our cells, and the induction of T-lymphocytes is expected to provide long-lasting protection.[17]

Advantages and Limitations

An advantage of COVID-19 protein subunit vaccine is that it provides a new vaccine option for individuals who are unable to receive other COVID-19 vaccines due to an allergy or contraindication and for individuals who are not willing to receive other COVID-19 vaccine platforms despite their demonstrated safety and efficacy.

However, due to its recent deployment, the current Health Canada authorized COVID-19 protein subunit vaccine (Novavax Nuvaxovid) has limited post-marketing vaccine safety data compared to more established COVID-19 vaccine platforms but this data will accumulate over time.[18]

COVID-19 Protein Subunit Vaccines

In February 17, 2022, Health Canada under the *Food and Drug Regulations* granted full authorization to the COVID-19 protein subunit vaccine, Novavax Nuvaxovid.[15,16] Detailed characteristics of the vaccine are outlined in Table 1.

Table 1: Characteristics of protein subunit vaccines authorized for use in Canada

Trade Name	Novavax Nuvaxovid COVID-19 Vaccine[a]
Manufacturer	Novavax Inc.[10-13,16]
Generic Name	NVX-CoV2373[10-13,16]
Vaccine Platform	Adjuvanted, recombinant protein vaccine[10-13,16]
Antigenic Target	Pre-fusion, SARS-CoV-2 recombinant spike (rS) glycoprotein[10-13,16]
Authorized Ages for Use	18 years of age and older[16]
No. of Doses Administered	2 doses[11,16]
Dosage	5 µg recombinant protein per 0.5 mL dose[10-13,16]
Adjuvant	50 µg of Matrix-M™ adjuvant, which contains *Quillaja saponaria* saponin fraction-A (42.5 µg) and fraction-C (7.5 µg) per 0.5 ml dose[10,11,14]
Diluent	No[11]
Schedule[b] (Two-dose primary series)[c]	Authorized Interval: 21 days (3 weeks)[16] Optimal Interval: At least 8 weeks[18,d] Minimum Interval: 21 days (3 weeks)[11]

[a] The vaccine is also manufactured by the Serum Institute of India under the trade name Covovax.[12,13]

[b] The authorized interval is the dosing schedule approved by Health Canada, based on evidence from clinical trials. The recommended interval is determined by NACI and is included in their recommendations following review of available data and based on expert opinion. The minimum interval is the interval between doses in which an adequate immune response will be achieved.

[c] mRNA COVID-19 vaccines are preferred and are authorized for a 3-dose primary series in moderately to severely immunocompromised individuals, while Novavax Nuvaxovid is not currently authorized as a 3-dose primary series in these populations.[18] Based on clinical discretion, and with informed consent on the limited evidence on the use of Novavax Nuvaxovid in this population, a recombinant protein subunit vaccine may be offered as a 3-dose primary series for moderately to severely immunocompromised individuals in the authorized age group who are not able or willing to receive an mRNA COVID-19 vaccine.[18,21]

[d] An interval of 8 weeks between the first and second dose of Novavax is recommended, based on evidence with mRNA vaccines that longer intervals between the first and second doses of COVID-19 vaccines result in more robust and durable immune responses and higher vaccine effectiveness that is expected to be longer-lasting.[18]

Trade Name	Novavax Nuvaxovid COVID-19 Vaccine[a]
Route of Administration	Intramuscular (IM) [11,16]
Storage Conditions	Pre-puncture, 2 to 8 °C for up to 9 months or expiry date[11] Post-puncture, 2°C to 25°C for up to 6 hours[11] Do not freeze[11] Keep vials in original packaging to protect from light[11]

Vaccine Efficacy

Primary Series

Vaccine efficacy data for Novavax Nuvaxovid come from one phase 2a/b clinical trial in South Africa and two phase 3 clinical trials in Mexico/United States (US) and the United Kingdom (UK).[3,4,19] The primary outcome was the first episode of symptomatic COVID-19 infection (mild, moderate, or severe) confirmed by a real-time polymerase chain reaction (RT-PCR) as SARS-CoV-2 positive nasopharyngeal specimen in adults aged 18 and older who were healthy or had stable chronic medical conditions with no prior history of SARS-CoV-2 infection.[3,4,19]

Clinical trial data available to date show that the Novavax Nuvaxovid COVID-19 vaccine is efficacious in preventing confirmed symptomatic COVID-19 disease in the short-term. In the phase 2a/b study conducted in South Africa during a period in which the Beta variant of concern (VOC) was predominant, vaccine efficacy against symptomatic infection was 48.6% (95% confidence interval [CI], 28.4–63.1%) from 7 days after the second dose with a median follow-up of 105 days.[19] However, vaccine efficacy against moderate to severe disease was 37.6% (95%CI 7.8-57.8%).[19]

In a phase 3 study conducted in the United Kingdom (UK) during a period in which the Alpha VOC was predominant, vaccine efficacy against symptomatic COVID-19 infection was 89.7% (95% CI, 80.2–94.6%) from 7 days after the second vaccine dose, with a median follow-up of 56 days after the second dose.[20] Vaccine efficacy against COVID-19 infection in persons less than 65 years of age (90%; 95% CI, 80–95) was comparable to those 65 years of age and older (89%; 95% CI, 20–100).[20] Against moderate or severe COVID-19, vaccine efficacy across all age groups was 87% (95% CI: 74–94).[20] In a phase 3 study in Mexico and the USA when multiple variants but not Omicron were in circulation, vaccine efficacy against symptomatic infection was 90% (95% CI, 83–95), with a median follow-up of 64 days after the second dose.[22] Vaccine efficacy against moderate or severe COVID-19 across all age groups was 100% (95% CI: 87.0–100.0%).[22]

Vaccine Safety

Homologous Series

In clinical trials of adults 18 years and older, common local and systemic events were injection site tenderness and pain, and headache, muscle pain, malaise, and fatigue, respectively.[19,20,22] Adverse events occurred most commonly within 7 days of vaccination, and in young adults (18 to 64 years, compared to those ≥ 65 years), and were generally mild to moderate and transient, resolving in one to two days.[19,20, 22] Two cases of myocarditis with a mild clinical course were reported in adolescent males shortly after receiving a second dose of Novavax Nuvaxovid vaccine.[12,18]

Heterologous Series

A UK study examined community dwelling adults aged 50 years and older who received Novavax Nuvaxovid 8-12 weeks following a single dose of AstraZeneca Vaxzevria or Pfizer-BioNTech Comirnaty.[23] Local reactions, such as injection site pain, were generally less frequent for recipients who received Novavax Nuvaxovid as their second dose compared to those who received a homologous series of either AstraZeneca Vaxzevria or Pfizer-BioNTech Comirnaty.[23]

Recommendations

NACI preferentially recommends a complete series with an mRNA COVID-19 vaccine to individuals in authorized age groups without contraindication to the vaccine. However, a recombinant protein subunit vaccine (Novavax Nuvaxovid) may be used to start or complete a primary series or used as a booster dose by individuals in the authorized age group without contraindications who are not able or willing to receive an mRNA COVID-19 vaccine.[18] In Ontario, a booster dose of an authorized recombinant protein subunit COVID-19 vaccine (Novavax Nuvaxovid) may be offered ≥ 3 months (84 days) after completion of a primary COVID-19 vaccine series to adults (≥ 18 years old) without contraindications to the vaccine who are not able or willing to receive an mRNA vaccine.[21]

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