Saskatchewan Health Authority

University of Saskatchewan

COVID-19 Evidence Support Team
RAPID REVIEW REPORT

What is the safety/efficacy of the Novavax COVID-19 vaccine?

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Full author statement available at the end of report.

Key Findings

- Novavax was authorized for use in Canada February 16, 2022 and has also been authorized for use in 35 other countries as a 2-dose primary series given as an intramuscular injection, 21 days apart
- Phase 3 trials of Novavax in US/Mexico and UK showed an overall vaccine effectiveness of 89.7-90.4% against all severity COVID infection and 100% against moderate/severe infection and death
- In the US/Mexico, vaccine effectiveness against the dominant Alpha variant was found to be 92.6%, while in the UK, it's effectiveness dropped to 86.3%
- The most frequently reported local and systemic adverse events in both trials were tenderness and pain at the injection site and headache, myalgia and fatigue, respectively. Adverse events were mild-to-moderate and transient in nature, and more frequently reported following the second dose
- A Phase 2 trial assessing safety and efficacy of Novavax in South Africa in adults 18-64 years during Beta dominance found a vaccine efficacy of only 49.4%, however, in subgroup analysis of only HIV negative individuals, efficacy rose to 60.1% overall, and 51% against the Beta variant. (). While efficacy against disease severity was not measured, the majority of infections reported in both the vaccine and placebo group were mild to moderate

Limitations

- Only clinical trial data is currently available, evidence of real-world effectiveness is not yet available
- Only short-term safety and efficacy data are available at this time

Strength of Evidence

☐ Mature evidence
☒ Emerging Supportive evidence
☐ Mixed evidence
☐ Weak evidence

Quality of Evidence Assessment

1. **Adequacy of primary studies**: Phase 2/3 clinical trials have been conducted in the US/Mexico and the UK, as well as South Africa. Long-term and real-world evidence is not yet available.

2. **Methodological limitations**: Long-term data is not yet available for Phase 3 studies. The Phase 2 study in South Africa was limited to individuals 18-64 years of age, thus the results may not be applicable to older populations. In addition, all trials were conducted during a time period of Alpha/Beta dominance and effectiveness against the currently dominant variant, Omicron, is not currently known.

3. **Relevance to review question**: Short-term safety data for the Novavax vaccine indicating general safety, resulting in large-scale approvals in 36 countries. Vaccine effectiveness in clinical trials indicated a high level of effectiveness, however it cannot be guaranteed to be extrapolated to vaccine effectiveness against currently circulating variants.

4. **Generalizability of findings**: The Novavax vaccine appears to be safe and well tolerated in the general population when used according to manufacturer's instructions. While effectiveness data from initial clinical trials is promising, it may not be accurate against currently circulating variants such as Omicron.

Background/Context

1. Clinical Context

Since the first approval by Health Canada of the Pfizer Comirnaty COVID-19 vaccine on December 9, 2020 several variants of concern have emerged, prompting the need for the evolution of vaccine development and leading to several other COVID-19 vaccine products being approved in Canada and around the world. One of the most recently approved vaccines in Canada is the Novavax Nuvaxoid vaccine, a protein subunit vaccine approved for use in adults 18 years and over as 2 doses via intramuscular injection, 21 days apart.

2. Purpose

To outline the safety and efficacy of the Novavax Nuvaxoid COVID-19 vaccine in the general population.

3. Review Question(s)

- What is the safety/efficacy of the Novavax COVID-19 vaccine?

Method

For each Rapid Review, the initial question is posed by a decision-maker in the health care system seeking the evidence base for a specific policy decision. According to the subject of the question, the COVID Evidence Support Team (CEST) Intake Committee allocates the question to the appropriate Working Group. Each Working Group may be comprised of a librarian, researcher, 1-2 clinicians, 1-2 subject matter experts, and a group leader. A reference interview is conducted to establish the parameters of the question to ensure it is articulated in a clear, searchable manner. The librarians assigned to the team then conduct a thorough search of the indexed literature, grey literature, news sources, or other sources as agreed upon. Some reference lists for especially pertinent articles are also reviewed. An Evidence Search Report is thereby created. See Appendix for more details on the search strategy. A Rapid Review of the identified literature is then performed by the researcher using the approach of a systematic review, but without a double review, formal assessment of quality of reported study, or meta-analysis. Importantly, the review is completed in a time-sensitive manner. Relevant evidence is summarized in both tabular and narrative form, key findings and limitations articulated, and the quality of the body of evidence evaluated using a four-point grading system that assesses the methodologies, adequacy of the included studies, the direct relevance to the question and the generalizability of the findings related to the question. The draft Rapid Review Report is reviewed and edited by the Working Group clinicians, experts, and leader. Once revisions are complete, the Rapid Review is submitted to the requesting decision-maker and placed in the COVID-19 repository and database. For certain topics with rapidly changing evidence, after a period of time an updated evidence search is performed, the review process repeated, and an updated Rapid Review released.

Summary of Evidence

Following the first Health Canada approval of a COVID-19 vaccine on December 9, 2020 for the Pfizer Comirnaty vaccine[1], a number of other vaccines using various technologies have been approved for Canadian use. The most recently approved vaccine in Canada is the Novaxovid COVID-19 vaccine, produced by Novavax[2] in the USA, a protein subunit vaccine containing a recombinant spike (rS) protein of the wild-type SARS-CoV-2 virus. The Novavax vaccine is indicated as a two dose primary series in adults over 18 years, given as an intramuscular injection, 21 days apart. Currently, the Novavax COVID-19 vaccine is approved for use in 36 countries, including Canada, the UK, Australia, New Zealand, Republic of Korea, Singapore and the countries of the European Union[3]. The same vaccine product is also being produced by the Serum Institute of India under the name Covovax, which is currently only approved in India, Indonesia and the Philippines[3]. Phase 3 trials assessing the safety and efficacy of the Novavax vaccine have been conducted in the United States, Mexico, the United Kingdom and a Phase 2 trial has been conducted in South Africa in adult populations.

Phase 3 trial results in the US/Mexico[4] and the UK[5] produced similar results with an overall VE of 90.4% in the US/Mexico trial and 89.7% in the UK trial against PCR-confirmed symptomatic disease. Post-hoc analysis of VE against the dominant strain at the time of the trials (Alpha in both trials) found a VE of 92.6% against any VOC and 86.4%, in each trial respectively. Both phase 3 trials reported a VE of 100% against moderate/severe disease and death. Reactogenicity in both trials was reported to be increased in vaccine groups, but mild to moderate in severity and transient in nature. The most frequently

reported local adverse effects in both trials were tenderness and injection-site pain with a median duration of less than 3 days, and the most commonly reported systemic events headache, muscle pain and fatigue, with a mean duration of less than two days. All reported adverse events tended to be higher in frequency and longer in duration following the second dose.

A Phase 2 trial in South Africa[6] assessed the safety and efficacy of the Novavax COVID-19 vaccine among adults aged 18-64 years that were either HIV negative or HIV positive but medically stable. The predominant circulating SARS-CoV-2 at the time of this trial was the Beta variant, and approximately 30% of participants were seropositive for SARS-CoV-2 at baseline. Overall, VE (in both HIV negative and medically stable HIV positive groups) was reported to be 49.4%, with cases in both vaccine and placebo groups being predominantly of mild to moderate severity. In HIV negative participants, overall VE was reported to be 60.1%, and further subgroup analysis demonstrated a VE of 51% against Beta variant in HIV negative participants. Similar to the phase 3 trials in US/Mexico and UK, the most commonly reported adverse event reported in the vaccine group was injection site pain generally lasting less than 3 days, with a higher frequency and longer duration reported following the second dose.

The Novavax vaccine is not currently approved for use as a booster dose in Canada and approval guidelines from the UK[7] and European Union[8] indicate its use only as a 2-dose primary series. In Australia[9], the Novavax vaccine is authorized for use as a 3-dose primary series in immune compromised individuals, including as a part of a heterologous vaccine schedule but is not recommended to be used as a booster dose for the general population. A Phase 2 trial in the US[10] assessing the safety and efficacy of the use of the Novavax vaccine as a homologous booster dose approximately 6 months following the completion of the primary series found increased reactogenicity to the booster dose vs. the primary series both in frequency and severity. Antibody titers measured in vitro against VOCs found an increase of 61.2-fold against wild-type, 85.9-fold against Alpha, 65-fold against Beta, 92.5-fold against Delta and 73.5-fold against Omicron for sera 28-days following the booster compared to sera 14-days following the completion of the initial series.

While there are no contraindications for the coadministration of the Novavax COVID-19 vaccine with other vaccines, a sub-study in the UK phase 3 trial[11] of the coadministration of a single dose of the Novavax vaccine with the yearly influenza vaccine found an increased reactogenicity (both local and systemic) with coadministration and while the VE of the influenza vaccine was not affected, the VE observed in the sub-study was 87.5% versus 89.9% in the main study.

Conclusions

Preliminary clinical trial results assessing the safety and effectiveness of the Novavax COVID-19 vaccine, Nuvaxovid, indicate that the vaccine is well tolerated with mild-to moderate, transient adverse events (mainly tenderness and injection site pain, and headache, myalgia and fatigue) and demonstrates high levels of effectiveness against symptomatic COVID-19 infection in healthy adults. It is important to note that the vaccine was designed using the wild-type virus and that clinical trials were conducted during Alpha/Beta dominance and may not be accurate for vaccine effectiveness against the currently dominant Omicron variant.

Table 1: Summary of Evidence

Consult the Summary of Evidence table using the following link:

- https://covid19evidencereviews.saskhealthauthority.ca/en/permalink/coviddoc457

This link provides access to the database where it is possible to view the spreadsheet for review.

Reference List

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2. **Health Canada**. Details for: NUVAXOVID – COVID-19. Modified February 17, 2022. https://covid-vaccine.canada.ca/info/nuvaxovid-en.html
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7. **UK Government/Health Security Agency**. Novavax COVID-19 vaccine Nuvaxovid approved by MHRA. https://www.gov.uk/government/news/novavax-covid-19-vaccine-nuvaxovid-approved-by-mhra
8. **European Medicines Agency**. Nuvaxovid. https://www.ema.europa.eu/en/medicines/human/EPAR/nuvaxovid
9. **Government of Australia**. ATAGI statement on the use of Novavax COVID-19 vaccine (Nuvaxovid) 24 January 2022. https://www.health.gov.au/news/atagi-statement-on-the-use-of-novavax-covid-19-vaccine-nuvaxovid
10. **Mallory R, Formica N, Pfeiffer S, 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. DOI: 10.1101/2021.12.23.21267374. https://www.medrxiv.org/content/10.1101/2021.12.23.21267374v1
11. **Toback S, Galiza E, Cosgrove C, 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;10(2):167-79. DOI: 10.1016/S2213-2600(21)00409-4. https://www.ncbi.nlm.nih.gov/pubmed/34800364

Appendix 1: Evidence Search Details

Note: To view full search strategy details, please consult the associated Evidence Search Report.

Filters, Limits & Exclusions:	2021 – Current English
Sources Searched:	• MEDLINE • Embase • Trip • Clinicaltrials.gov • LitCOVID • Google Scholar • Google (Web) • European Clinical Trials Registry
Librarian(s):	Lukas Miller, Clinical Librarian, Saskatchewan Health Authority

Appendix 2: Evidence Search Strategies

Embase, Ovid MEDLINE(R)		
#	Searches	Results
1	(novavax or NVX-CoV2373 or nuvaxovid or covovax).tw,kf,rn,nm.	323
2	remove duplicates from 1	269
3	limit 2 to english language	262
4	limit 3 to yr="2021 -Current"	143
5	from 4 keep 1, 16, 49, 54, 71, 80...	36

Keywords Used in Other Resources

- Novavax, Nuvaxovid, NVX-CoV2373, NVX-CoV-2373, covovax

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The authors declare they have no conflicts of interest to report.