Background document on the Novavax (NVX-CoV2373) vaccine against COVID-19

Background document to the WHO Interim recommendations for use of the Novavax (NVX-CoV2373) vaccine against COVID-19

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World Health Organization

Note. This background document was developed to inform the initial recommendation-making process. It will not be updated on a regular basis. The latest Grade and ETR tables can be obtained here: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-novavax-nvx-cov2373-annexes

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Background

This background document was prepared by the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on Novavax COVID-19 vaccines (NVX-CoV2373) to inform the discussions of SAGE at its meeting on 16 December 2021, which resulted in the issuance of the interim recommendations *(1)* and evidence to recommendation tables (annexes) *(2)*. These are available on the SAGE COVID-19 webpage: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials.

Declarations of interests were collected from all external contributors and assessed for any conflicts of interest. Summaries of the reported interests can be found on the SAGE meeting webpage and SAGE Covid-19 Working Group webpage.

This document refers to the COVID-19 vaccine developed by Novavax and the Serum Institute of India using the Novavax platform of recombinant protein nanoparticles formulated with Matrix M (NVX-CoV2373), and authorized under the emergency use listing (EUL) procedure by WHO. It is based on the Novavax core non-clinical and clinical data for regulatory evaluation. NVX-CoV2373 will be marketed as Nuvaxovid (Novavax) and COVOVAX (Serum Institute of India). These vaccines are considered fully equivalent, although they are produced at different manufacturing sites and assigned different product names. In the subsequent text, the vaccine will be referred to as NVX-CoV2373.

Context

NVX-CoV2373 is a recombinant spike protein nanoparticle-based vaccine. It contains the full-length SARS-CoV-2 spike protein and a saponin-based Matrix-M adjuvant. Protein-based vaccines cannot replicate and therefore cannot infect individuals.

Matrix-M is an adjuvant added to enhance the immune response to the vaccine. In studies of Matrix-M, the adjuvant was found to be antigen dose-sparing, and induced cluster of differentiation (CD)4+ T-cell responses that were biased towards a T helper 1 (Th1) response *(3)*. Matrix-M is a novel saponin-based adjuvant that has been administered in studies of NVX-CoV2373 (~30 000 recipients across phase 1 to phase 3 trials) and in prelicensure studies targeting other pathogens (~4200 recipients overall), but has not previously been used in any licensed vaccine. The adjuvant has been used in a total of 29 clinical trials (14 sponsored by Novavax and 15 sponsored by other collaborating entities) in the United States of America, United Kingdom, mainland Europe, Australia, and Africa. Of these, 19 have been completed (9 sponsored by Novavax) and 10 are ongoing, and may or may not have unblinded data available. The integrated safety analysis of Novavax-sponsored studies showed that, in all age groups, the rate of solicited adverse events (AEs) was higher in the Matrix-M adjuvanted groups than in the unadjuvanted vaccine or placebo groups after both the first and second vaccinations. These differences were largely due to injection site pain.

Characteristics of NVX-CoV2373 (COVID-19) vaccine

Composition

NVX-CoV2373 includes the following ingredients: SARS-CoV-2[1] recombinant spike protein (5 µg per dose) with Matrix-M adjuvant (50 µg per dose), constructed from the full-length, wild-type SARS-CoV-2 S glycoprotein based on the GenBank gene sequence MN908947 (Wuhan-Hu-1 isolate) nucleotides 21563–25384; inactive ingredients include disodium hydrogen phosphate dibasic heptahydrate, sodium dihydrogen phosphate monohydrate, sodium chloride and Polysorbate 80. The adjuvant Matrix-M contains 42.5 µg of fraction-A and 7.5 µg of fraction-C of *Quillaja saponaria* Molina extract per 0.5 ml dose.

Dosing regimen

NVX-CoV2373 is administered intramuscularly in 2 doses (0.5 ml per dose) given 3-4 weeks apart. It is standard practice for individuals who receive a first dose of NVX-CoV2373 to complete the vaccination course with NVX-CoV2373.

[1] SARS-CoV-2 recombinant spike protein is produced by DNA technology using a baculovirus expression system in an insect cell line derived from Sf9 cells of the *Spodoptera frugiperda.*

Stability and shelf-life

A shelf-life of 9 months is proposed. The vaccine is provided as a refrigerated suspension stored at 2–8 °C in a single-dose vial or a vial containing 10 doses (0.5 ml each). The vials should be protected from light. After the first dose has been withdrawn, the vial may be held at 2–8 °C for up to 6 hours. The vial should be discarded if the vaccine is not used within these times.

The expiry date of the vaccine is indicated on the label and packaging.

Drug product description

NVX-CoV2373 is a sterile suspension for intramuscular injection.

Container

The vaccine is provided in single-dose (0.5 ml) and multidose glass vials (10 doses).

Developmental and reproductive toxicity

Developmental and reproductive toxicity (DART) studies compliant with good laboratory practice (GLP) were performed in Sprague Dawley rats, with dosing prior to conception and during gestation. These studies investigated reproductive performance, embryonic and fetal development *in utero,* and effects in neonates from birth until weaning. There were no adverse findings for fertility, pregnancy, lactation, or development of the embryo, fetus and offspring through postnatal day 21.

Pharmacology

A comprehensive pharmacology programme evaluating the NVX-CoV2373 vaccine was undertaken, comprising multiple studies to evaluate both humoral and cell-mediated immune responses in rodents and nonhuman primates. Robust humoral immune responses, including anti-spike (anti-S) immunoglobin G (IgG), hACE2 binding inhibiting, and wild-type virus-neutralizing antibodies, were generated following vaccination, with the response dominated by the T helper 1 (Th1) phenotype.

Administration of NVX-CoV2373 to mice produced a Th1-dominant response, as demonstrated by induction of strong Th1-type CD4+ T-cell responses. These included multifunctional effector phenotypes (producing interferon gamma (IFNγ), tumour necrosis factor alpha (TNFα), and interleukin 2 (IL2)), which were generally induced at much higher levels than interleukin 4 (IL4)-producing Th2 cells. NVX-CoV2373 vaccine administered to baboons at human dose levels also induced strong Th1-dominant CD4+ T-cell responses, which included polyfunctional effector phenotypes. In rhesus macaques, immunization with NVX-CoV2373 elicited high levels of both S-specific and receptor-binding domain (RBD)-specific antibodies. Changes in circulating immune cell abundance postvaccination were consistent with typical responses to a potent adjuvant, as well as recruitment of lymphocytes to lymphoid organs. B-cell responses after the second dose were consistent with a rapid recall of memory B cells. T-cell responses again indicated a Th1-skewed response, and the presence of circulating T follicular helper (Tfh) cells after the boost suggested an ongoing germinal centre reaction.

Protective efficacy studies evaluating live virus challenge following vaccination, with necropsy and histopathological evaluations, have also been conducted across multiple species, including mice, hamsters, cynomolgus macaques, and rhesus macaques *(4)*. The vaccine was immunogenic in all species, inducing high titres of anti-S IgG antibodies, as well as functional hACE2 receptor-binding-inhibiting and virus-neutralizing antibodies. NVX-CoV2373 also elicits multifunctional CD4+ and CD8+ T cells, CD4+ follicular helper T cells (Tfh), and antigen-specific germinal center (GC) B cells in the spleen.

Animals vaccinated with NVX-CoV2373 were protected from viral replication in the upper and lower respiratory tract following challenge with live SARS-CoV-2. Importantly, there was no evidence of vaccine-enhanced disease following exposure to SARS-CoV-2 virus in any study *(5)*.

Single-dose toxicity

No single-dose toxicity studies have been conducted.

Repeat-dose toxicity

Toxicity testing of NVX-CoV2373 includes a completed GLP repeat-dose toxicology study conducted in New Zealand White (NZW) rabbits. Effects were consistent with immune stimulation, i.e. transiently increased C-reactive protein (CRP), globulin and fibrinogen, and reversible injection site inflammation. Microscopic findings at the injection sites consisted of minimal to moderate subacute inflammation characterized by mixed inflammatory infiltrates of heterophils, macrophages and lymphocytes. Inflammation was generally similar between vaccine groups with and without Matrix-M1 and similar in incidence and severity across all studies.

Clinical studies

The pivotal safety, efficacy, and immunogenicity data informing registration of the vaccine are derived from the following studies.

- **2019nCoV-101 (part 1).** A 2-part, phase 1/2, randomized, observer-blinded study to evaluate the safety and immunogenicity of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with or without Matrix-M adjuvant in healthy subjects *(6)*.
    - This is part 1 (phase 1 first-in-human) of 2019nCoV-101. It included participants aged 18–59 years, and evaluated the vaccine with and without adjuvant, as a bedside-mixed antigen and adjuvant.
- **2019nCoV-101 (part 2).** A 2-part, phase 1/2, randomized, observer-blinded study to evaluate the safety and immunogenicity of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with or without Matrix-M adjuvant in healthy subjects.
    - This is part 2 (phase 2) of 2019nCoV-101. It included participants aged 18–84 years, and evaluated the vaccine with adjuvant as a co-formulated drug product (as in the remaining phase 2 and phase 3 studies) *(7)*.
- **2019nCoV-501.** A phase 2a/b, randomized, observer-blinded, placebo-controlled study to evaluate the efficacy, immunogenicity, and safety of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix-M adjuvant in South African adult subjects living without HIV; and safety and immunogenicity in adults living with HIV.
- **2019nCoV-302.** A phase 3, randomized, observer-blinded, placebo-controlled trial to evaluate the efficacy and safety of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix-M adjuvant in adult participants 18–84 years of age in the United Kingdom *(8)*.
- **2019nCoV-301.** A phase 3, randomized, observer-blinded, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix-M adjuvant in adult participants ≥18 years with a paediatric expansion in adolescents (12 to <18 years) *(9)*.

Studies in other populations (e.g. children with and without comorbidities) are also planned.

Immunogenicity studies in humans

Clinical study 2019nCoV-101 (part 1) compared two-dose regimens of 5 µg or 25 µg NVX-CoV2373 with 50 µg Matrix-M adjuvant administered 21 days (+ 7 days) apart, a one-dose 25 µg adjuvanted regimen, a two-dose 25 µg unadjuvanted regimen, and placebo in healthy adults aged 18–59 years. Both adjuvanted 2-dose regimens induced robust immune responses (anti-S protein IgG, wild-type neutralizing antibodies, and hACE2 receptor-binding inhibition), which peaked 2 weeks after the second vaccination (day 35). Matrix-M adjuvant was antigen-sparing and induced high levels of functional antibodies and a Th1-biased immune response. No dose response was seen between the 5-µg and 25-µg doses. A strong correlation was observed between anti-S protein IgG levels or hACE2 receptor-binding inhibition and neutralizing antibodies from day 35 through day 189 *(6)*.

Two-dose regimens of 5 µg or 25 µg NVX-CoV2373 with 50 µg Matrix-M adjuvant, administered 21 days (+ 7 days) apart as a co-formulated product in part 2 of clinical study 2019nCoV-101, showed similar results to part 1 at day 35, in healthy adults aged 18–84 years, regardless of baseline SARS-CoV-2 serostatus. There was an approximate 2-fold attenuation of immune response in participants aged 60–84 years. Collectively, the data from part 1 and part 2 supported selection and further development of the two-dose 5 µg adjuvanted vaccine regimen *(7)*.

A two-dose regimen of NVX-CoV2373, administered 21 days (+ 7 days) apart, similarly induced robust immune responses (anti-S protein IgG and neutralizing antibody) relative to placebo in adults aged 18–84 years in clinical studies 2019nCoV-302 (7) and 2019nCoV-301 *(9)* with higher levels in the younger adult cohort (18–64 years) than in those aged 65–84 years, but with similarly high seroconversion rates (see Table 1).

Table 1. Neutralizing antibody titres by day and age group for the two-dose schedule

Days since first dose	Metric	18–64 years (*n*=554)		≥65 years (*n*=207)	
		Vaccination (*n*=270)	Placebo (*n*=284)	Vaccination (*n*=111)	Placebo (*n*=96)
A. United Kingdom (study 302)[a, b]					
Day 0 (baseline)	GMT	10	10	10	10
	95% CI	10–10	10–10	10–11	10–10
	Median	10	10	10	10
	Min, Max	10, 20	10, 40	10, 160	10, 10
Day 35 (14 days post-dose 2)	GMT	1241	11	908	10
	95% CI	1069–1441	10–11	720–1145	10–10
	Median	1280	10	1280	10
	Min, Max	10, 20 480	10, 5120	10, 10 240	10, 10
B. Mexico and USA (study 301) [b, c]					
Day 0 (baseline)	GMT	11	10	10	10
	95% CI	10–11	10–10	10.0–11	10–10
	Median	10	10	10	10
	Min, Max	10, 10 240	10, 10	10, 2560	10, 20
Day 35 (14 days post-dose 2)	GMT	1293	11	902	11
	95% CI	1128–1482	10–11	764–1063	10–12
	Median	1280	10	1280	10
	Min, Max	10, 40 960	10, 640	10, 20 480	10, 640

[a] Immunogenicity data are based on the neutralization assay subset of the per-protocol immunology analysis set. Data lock date 15 March 2021.

[b] Neutralizing antibodies specific for SARS-CoV-2 wild-type virus were measured using a validated virus neutralizing assay (VNA) with wild-type virus (SARS-CoV-2 hCoV-19/Australia/VIC01/2020 [GenBank MT007544.1]; 360biolabs, Melbourne, Australia). The lower limit of quantification (LLOQ) for this assay was a titre of 20, with titres below this level documented as 10.

[c] Data lock date 9 August 2021.

Immunogenicity for variants of concern

During a phase 2 study in Australia and the USA, in blood samples collected 14 days after the second dose of NVX-CoV2373, antibody responses were 4-fold, 4.8-fold, and 3-fold lower for alpha, beta, and delta variants, respectively, than for the ancesteral virus.

Efficacy studies

The following discussion relates to the phase 2a/b trial in South Africa (study 501) and two phase 3 trials (studies 301 and 302) in Mexico/USA and the United Kingdom.

Case definitions

Case definitions for mild, moderate, and severe COVID-19 are given in Box 1. Study endpoints are described in Box 2 *(9)*.

Box 1. Case definitions for mild, moderate and severe COVID-19 in the phase 2a/b and phase 3 studies

The case definition for symptomatic COVID-19 was a SARS-CoV-2-positive nasopharyngeal swab, determined by real-time polymerase chain reaction (RT-PCR), plus symptoms as described below.

The disease was considered mild if, at any time during the course of observation, there was one or more of the following:

- fever (defined subjectively or objectively, regardless of use of antipyretic medications);
- new onset cough;
- two or more additional COVID-19 symptoms:
    - new onset or worsening of shortness of breath or difficulty breathing compared with baseline;
    - new onset fatigue;
    - new onset generalized muscle or body aches;
    - new onset headache;
    - new loss of taste or smell;
    - acute onset of sore throat, congestion, or runny nose;
    - new onset nausea, vomiting, or diarrhoea.

The case was considered moderate if there was one or more of the following:

- high fever (≥38.4 °C) for ≥3 days (not necessarily contiguous, and regardless of use of antipyretic medications);
- evidence of significant lower respiratory tract infection (LRTI):
    - shortness of breath (or breathlessness or difficulty breathing), with or without exertion (greater than baseline);
    - tachypnoea: 24–29 (20-29 for the 302 and 501 studies) breaths per minute at rest;
    - oxygen saturation (SpO_2): 94– 95% on room air;
    - abnormal chest X-ray or computerized tomography (CT) scan consistent with pneumonia or LRTI;
- adventitious sounds on lung auscultation (e.g. crackles/rales, wheeze, rhonchi, pleural rub, stridor).

The case was considered severe if there was one or more of the following:

- tachypnoea: ≥30 breaths per minute at rest;
- resting heart rate ≥125 beats per minute;
- SpO2: ≤93% on room air or PaO_2/FiO_2 <300 mmHg;
- high-flow O_2 therapy or non-invasive ventilation (NIV)/non-invasive positive pressure ventilation (NIPPV) (e.g. continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]);
- mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
- dysfunction or failure of one or more major organ systems, defined by diagnostic testing, clinical syndrome or intervention, and including any of the following:
    - acute respiratory failure, including acute respiratory distress syndrome (ARDS);
    - acute renal failure;
    - acute hepatic failure;
    - acute right or left heart failure;
    - septic or cardiogenic shock (defined as systolic blood pressure <90 mm Hg or diastolic blood pressure <60 mm Hg);
    - acute stroke (ischaemic or haemorrhagic);
    - acute thrombotic event (myocardial infarction, deep vein thrombosis, pulmonary embolism);
    - requirement for: vasopressors, systemic corticosteroids, or haemodialysis;
- admission to an intensive care unit (ICU);
- death.

Box 2a. Primary and secondary efficacy and immunogenicity endpoints in the phase 2a/b and phase 3 studies : Study 2019nCoV-301

Primary efficacy endpoint

- First episode of RT-PCR-positive mild, moderate, or severe COVID-19.

Key efficacy secondary endpoint

- First episode of RT-PCR-positive COVID-19, as defined under the primary endpoint, shown by gene sequencing to represent a variant not considered as a "variant of concern / interest" according to the CDC Variants Classification.

Secondary efficacy endpoints

- First episode of PCR-positive moderate or severe COVID-19, as defined under the primary endpoint.
- ANY symptomatic SARS-CoV-2 infection, defined as: RT-PCR-positive nasal swab and ≥ 1 of any of the following symptoms:
  - Fever.
  - New onset cough.
  - New onset or worsening of shortness of breath or difficulty breathing compared to baseline.
  - New onset fatigue.
  - New onset generalized muscle or body aches.
  - New onset headache.
  - New loss of taste or smell.
  - Acute onset of sore throat, congestion or runny nose.
  - New onset nausea, vomiting or diarrhea.
- Description of course, treatment and severity of COVID-19 reported after an RT-PCR-confirmed case via the Endpoint Form.

Secondary immunogenicity endpoints

- Neutralizing antibody titers from Immunogenicity Population at Days 0, 35 and immediately prior to administration of the crossover set of vaccinations.[a]
- Serum immunoglobulin G (IgG) levels to SARS-CoV-2 S protein, human angiotensin converting enzyme 2 (hACE2) inhibition titers from Immunogenicity Population at Days 0, 35 and immediately prior to administration of the crossover set of vaccinations.[a]
- Serum IgG levels to SARS-CoV-2 spike protein, microneutralization (MN) and hACE2 inhibition titers from Immunogenicity Population at Months 12, 18 and 24.[a]
- Antibodies to SARS-CoV-2 NP at Days 0 and 35, immediately prior to administration of the crossover set of vaccinations, and at Months 12, 18 and 24 will be used to determine natural infection and to determine the incidence of asymptomatic infection acquired during study follow-up.[a]
- Antibodies to SARS-CoV-2 NP, regardless of whether the infection was symptomatic.[a]
- IgG antibodies to SARS-CoV-2 rS at approximately 35 days after the first crossover vaccination in approximately 300 active vaccine recipients 18 to ≤ 64 years of age enrolled at selected study sites.[a]
- Neutralizing antibody response at Day 35 for all adolescent participants seronegative to antiSARSCoV2 NP antibodies at baseline, compared with that observed in seronegative adult participants 18 to < 26 years of age from the Adult Main Study (Immunogenicity Population participants before crossover).
- Antibodies to SARS-CoV-2 NP, regardless of whether the infection was symptomatic.[a]