Interim recommendations for use of the Novavax NVX-CoV2373 vaccine against COVID-19

Interim guidance

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World Health Organization

Background

This interim guidance has been developed on the basis of the advice issued by the Strategic Advisory Group of Experts (SAGE) on Immunization at its meeting on 16 December 2021 (1) and updated on 27 September 2022 based on new data that became available by August 2022.

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 website and SAGE Working Group website.

The guidance is based on the evidence summarized in the background document on the NVX-CoV2373 Nuvaxovid™ vaccine against COVID-19 developed by Novavax (2). Annexes (3) which include GRADE and Evidence to Recommendations tables have also been updated to reflect the updated recommendations. All referenced documents are available on the SAGE COVID-19 webpage: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials. This guidance should be considered along with the broader COVID-19 policy advice to WHO member states and in particular the advice on how to reach the COVID-19 vaccination targets.

These interim recommendations refer to the COVID-19 vaccine developed by Novavax and Serum Institute of India using the Novavax platform on recombinant protein nanoparticles formulated with Matrix M™ (NVX-CoV2373), based on the Novavax core clinical data for regulatory evaluation and authorized under the emergency use listing procedure by WHO in December 2021. NVX-CoV2373 is marketed as Nuvaxovid™ and COVOVAX™. These vaccines are considered fully equivalent, even if produced at different manufacturing sites or assigned different product names. In the subsequent text the vaccine will be referred to as NVX-CoV2373.

Methods

SAGE applies the principles of evidence-based medicine and has set in place a thorough methodological process for issuing and updating recommendations *(4)*. A detailed description of the methodological processes as they apply to COVID-19 vaccines may be found in the SAGE evidence framework for COVID-19 vaccines *(5)*. This framework contains guidance on considering data emerging from clinical trials and post-introduction effectiveness and safety monitoring.

General goal and strategy for the use of the NVX-CoV2373 vaccine against COVID-19

The COVID-19 pandemic has caused significant morbidity and mortality throughout the world, as well as major social, educational and economic disruptions. There remains an urgent global need to make COVID-19 vaccines available and deploy them at scale and equitably across all countries. Countries are recommended to use the WHO Prioritization Roadmap (6) and the WHO Values Framework (7) as guidance for their prioritization of target groups. The WHO Prioritization Roadmap recommends that vaccine use be prioritised to the highest priority-use groups (health workers, older persons, persons with moderate to severe immunocompromising conditions), and high priority-use groups (including persons with comorbidities, teachers, and pregnant persons). Within the capacity of programmes and vaccine availability, additional priority-use groups should be vaccinated as outlined in the WHO Prioritization Roadmap (6), taking into account national epidemiological data and other relevant considerations.

Vaccine performance

The NVX-CoV2373 vaccine is protein-based and consists of a recombinant SARS-CoV-2 spike protein nanoparticle administered as a co-formulation with the adjuvant Matrix-M™. Protein-based vaccines have been used for diseases such as pertussis, human papillomavirus, and hepatitis B. Matrix-M™ is a novel saponin-based adjuvant that has been used in clinical studies of NVX-CoV237 (~30,000 recipients across Phase 1 to Phase 3 trials) and in pre-licensure studies targeting other pathogens (~4,200 recipients overall) but has not been used in any previously licensed vaccine. The adjuvant is added to enhance the immunogenicity of the vaccine as Matrix-M™ promotes the activation of innate immune cells and antigen processing (8).

The efficacy of NVX-CoV2373 has been assessed in three Phase 2 and Phase 3 trials involving participants aged 18 years or older. In a Phase 3 study conducted in the UK during a period in which the SARS-CoV-2 Alpha variant was predominant, vaccine efficacy (VE) against symptomatic (mild, moderate, or severe) COVID-19 was 90% (95% CI: 80–95) from 7 days after the second vaccine dose, after a median follow-up of 56 days after the second dose and was 83% (95% CI: 73–89) with the analysis at 6 months of follow-up the protection against severe disease was 100% (95% CI: 18–100) (9). Of participants in the Phase 2 and Phase 3 efficacy studies, 16% were aged ≥65 years (with trial-specific percentages of 4%, 12%, and 28% for the studies in South Africa, the USA/Mexico, and the UK, respectively). VE against symptomatic disease in persons less than 65 years of age in the UK was 90% (95% CI: 80–95) and in those 65 years and older was 89% (95% CI: 20–100). VE against moderate or severe COVID-19 across all age groups was 87% (95% CI: 74–94). In a Phase 2a/b study conducted in South Africa during a period in which the Beta variant was predominant, VE against symptomatic COVID-19 was 49% (95% CI: 28–63), with a median follow-up of 45 days after the second dose. In a Phase 3 study conducted in the USA and Mexico during a period in which multiple variants were circulating, VE against symptomatic COVID-19 was 90% (95% CI: 83–95), with a median follow-up of 64 days after the second dose. VE against moderate or severe COVID-19 across all age groups was 100% (95% CI: 87–100). Across the three studies, with an overall sample size of 42,261 in the primary VE endpoint calculations (25,740 NVC-CoV2373 recipients and 16,521 placebo recipients), there were 14 cases of severe COVID-19 occurring at least 7 days after the second vaccine dose, all of which occurred in the placebo group. The Alpha variant (B.1.1.7) of SARS-CoV-2 was the predominant circulating variant during the period of case accrual for VE assessments (10).

The Phase 2a/b study of NVX-CoV2373 in South Africa included 244 medically stable PLWH (122 vaccine and 122 placebo recipients). The study was unable to assess VE against COVID-19 in this population given the limited sample size. The safety profile of NVX-CoV2373 was similar in HIV-positive and HIV-negative, and the vaccine induced a robust immune response in both HIV-positive and HIV-negative participants. Among participants who were seronegative to SARS-CoV-2 at baseline, antibody concentrations (IgG targeting the SARS-CoV-2 spike protein) were approximately 2-fold higher for HIV-negative than HIV-positive individuals. Antibody concentrations were comparable between these groups among participants who were seropositive to SARS-CoV-2 at baseline (23)

NVX-CoV2373 has demonstrated an acceptable safety and reactogenicity profile in adults ≥18 years of age. These safety data encompass approximately 30,000 individuals who have received NVX-CoV2373 which includes Matrix-M™ adjuvant across the Phase 1 to Phase 3 clinical studies. Aside from its use in studies of NVX-CoV2373, the Matrix-M™ adjuvant has been administered to approximately 4,200 participants in clinical trials of other antigens, with no major safety concerns identified to date.

Myocarditis or pericarditis was reported in temporal association with NVX-CoV2373 vaccination, suggesting a possible causal relationship. Six cases of myocarditis or pericarditis of a total of 41,546 vaccine trial recipients aged ≥16 years, including within both pre-crossover and post-crossover vaccine arms, were detected; five occurred within 20 days of vaccination. Among these five, four did not have likely alternative aetiologies, suggesting a possible causal relationship with vaccine. Cases of myocarditis or pericarditis have also been detected in global post authorization surveillance; during a period in which 744,235 doses of NVX-CoV2373 were administered in Australia, Canada, the European Union, New Zealand, and South Korea, 35 people (20 male and 15 female vaccine recipients with a median age of 34 years (range 23–62 years) reported 36 adverse events: 29 reports of pericarditis, including five in persons with a history of pericarditis after mRNA COVID-19 vaccine; four myocarditis cases; two myopericarditis cases; and one case of carditis, not otherwise specified. At the same time a post marketing analysis from Australia identified three cases of myocarditis and 12 cases of pericarditis reported during a period in which 160,000 NVX-CoV2373 doses were administered (10). More recent data from Australia (until 21 August 2022) with now 209,000 NVX-CoV2373 doses administered, these numbers have risen to 7 cases as likely myocarditis and 26 cases as likely pericarditis.

Additionally, cases of paraesthesia and hypoesthesia have been reported spontaneously (189 paraesthesia and 67 hypoesthesia cases reported worldwide from more than 1.5 million vaccine doses distributed worldwide by 31 May 2022) as well as one case of angioedema and one case of Guillain-Barré syndrome (GBS), which both of the latter were also considered to be potentially related to vaccination (10).

Booster:

From the phase 2 study in healthy adults aged 18–84 years with a BMI of 17-35, a single booster shot of NVX-CoV2373 was given about 6 months (day 189) after the primary series. In the per protocol immunogenicity population at day 217 IgG GMT had increased by 4·7-fold and MN_{50} GMT by 4·1-fold for the ancestral SARS-CoV-2 strain compared with the day 35 titres [MN_{50} GMT at day 217 was 6023 (95% CI: 4542–7988; n=64), compared with 1470 (95% CI: 1008–2145; n=50) at day 35]. For the Beta variant at day 217 the MN_{50} GMT was 661 (95% CI: 493–886; n=65) compared with 13 (95% CI: 11–15; n=84) at day 189. Fold increases after boosting were higher in older adults (i.e, aged 60–84 years; 5·1-fold) than in younger adults (i.e, aged 18–59 years; 4·1-fold) (11, 12).

The likelihood of short-term adverse reactions increased with each subsequent dose of this vaccine. Local and systemic adverse events were reported more frequently after the booster (third) dose compared with following the second primary dose (local: 82.5% vs. 70.0%; systemic: 76.5% vs. 52.8%). Following the booster, local and systemic events were mainly mild to moderate in severity and short-lived, with a median duration of 2.0 days (95% CI: 1.0–3.0). Grade 4 local reactions were rare, with two events (i.e. pain and tenderness) reported by one participant after the booster compared with no participants following the primary vaccination series. Both local and systemic events were less frequent and severe in older adults (60 to 84 years) than in younger adults (18 to 59 years) (11, 12).

Adolescents:

The efficacy, immunogenicity and safety of NVX-CoV2373 in adolescents 12 to 17 years of age, was evaluated in an interim analysis of the paediatric expansion portion of the ongoing phase 3 study in United States. A total of 1,799 participants (NVX-CoV2373 n=1205; placebo n=594) who did not have a confirmed infection or prior infection due to SARS-CoV-2 at the time of randomisation, were included in the per protocol efficacy population and 2232 adolescents (NVX-CoV2373 n=1487; placebo n=745) were included in the safety population. Demographic characteristics were similar among participants in both groups. There were 20 cases of PCR-confirmed mild COVID-19 (NVX-CoV2373, n=6 [0.5%]; placebo, n=14 [2.4%]) resulting in a point estimate of VE of 80% (95% CI: 47%–92%). At the time of this analysis, the Delta (B.1.617.2 and AY lineages) variant of concern was the predominant variant circulating in the US and accounted for the cases from which sequence data are available (11/20, 55%) (13). VE specifically against the Delta variant was 82% (95% CI: 32–95) (14). The SARS-CoV-2 neutralizing antibody response (GMT) 14 days after the second dose was 3859.6 (95%CI 3422.8–4352.1) and was 1.46 (1.25–1.71) times higher in comparison with the adult 18 to <26-year-old population 2633.6 (95%CI 2388.6–2903.6), thus achieving non-inferiority (the lower bound of confidence interval was ≥0.67). The difference in seroconversion rates also met non-inferiority criteria [>-10%, SCR difference 1.1 (13).

Safety data were collected from 2,232 participants from the same study, with and without evidence of prior SARS CoV-2 infection, who received at least one dose of NVX-CoV2373 (n=1,487) or placebo (n=745). No reports of rare adverse events such as myocarditis or pericarditis were reported in the trial. The most frequent adverse reactions were injection site tenderness (71%), injection site pain (67%), headache (63%), myalgia (57%), fatigue (54%), malaise (43%), nausea or vomiting (23%), arthralgia (19%), injection site swelling (19%), pyrexia (17%), and injection site redness (17%). The serious adverse events were similar in both arms, and none were assessed to be related to the vaccine (0.5% (7) for NVX-CoV2373 and 0.3% (2) for placebo, form data on file). Fever was observed more frequently in adolescents aged 12 to 17 years when compared with adults and was more common after the second dose (1.0% versus 0.1% after the first dose and 16.9% versus 12% for after the second dose for adolescents and adults 18 to <26 respectively, from data on file). Adverse reactions were usually mild to moderate in severity with a median duration of less than or equal to 2 days for local events and less than or equal to 1 day for systemic events following vaccination (13).

Intended use

Persons aged 12 years and older.

WHO recommendation for use

For prioritization by age and other considerations, please see the WHO Prioritization Roadmap (6). Healthy adolescents belong to the lowest priority-use group, adolescents with comorbidities belong to the medium priority-use group, and adolescents with moderate to severe immunocompromising conditions belong to the highest priority-use group.

Administration

The recommended primary vaccine series is 2 doses (5 µg of recombinant spike protein with 50 µg of Matrix-M™ per dose; 0.5 ml) given intramuscularly into the deltoid muscle. According to the product label, the interval between the two doses is 3–4 weeks. Based on the evidence of reduced risk of myocarditis or pericarditis after vaccination with an extended interval between first and subsequent doses in persons receiving mRNA COVID-19 vaccines, an 8-week interval is recommended between primary series doses of NVX-CoV2373 as a precaution.

Additional doses to the primary series

Additional doses of a vaccine may be needed as part of an extended primary vaccination series for target populations where the immune response following the standard primary series is likely to be insufficient. In view of consistent evidence for other COVID-19 vaccines of immunocompromised individuals mounting a lower immune response after a standard primary series, WHO recommends an additional dose after the standard 2-dose primary series of NVX-CoV2373. see under "Immunocompromised persons".

Booster doses

In accordance with the WHO Prioritization Roadmap, the first booster dose is recommended for the highest priority-use groups (e.g. older adults, persons with moderate to severe immunocompromising conditions, and health workers), 4-6 months after the completion of the primary series. Once high booster dose coverage has been achieved in the highest priority-use group, countries should also consider a booster for lower priority-use groups[1]. If more than 6 months have elapsed since completion of the primary series, the booster dose should be given at the earliest opportunity.

To further reduce the risk of severe disease, deaths and disruptions of health services, WHO recommends countries should consider a second booster dose 4-6 months after the first booster dose for all older persons (age specific cut-off should be defined by countries based on local COVID-19 epidemiology), all persons with moderate and severe immunocompromising conditions, regardless of age, adults with comorbidities that put them at higher risk of severe disease, pregnant persons and health workers (https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-good-practice-statement-second-booster).

For adolescents 12-18 years of age, there is currently insufficient evidence for recommending a booster dose, except for those with immunocompromising conditions. If more data become available for the need of booster doses in this age group, this recommendation will be updated.

Interchangeability with other COVID-19 vaccines (heterologous schedules)

Two clinical trials have assessed heterologous schedules involving the administration of NVX-CoV2373 after other WHO EUL COVID-19 vaccines as either a second dose (in a heterologous primary series) or a booster dose (following a 2-dose homologous primary series) (15, 16). Compared with homologous schedules involving ChAdOx1-S alone, heterologous schedules involving ChAdOx1-S followed by NVX-CoV2373 induced higher neutralizing antibody titres (post-vaccination ratios of 2.0 and 3.8 for primary and booster schedules, respectively) and cellular responses. Compared with homologous schedules involving BNT162b2 alone, heterologous schedules involving BNT162b2 followed by NVX-CoV2373 induced lower neutralising antibody titres (post-vaccination ratios of 0.3 and 0.4 for primary and booster schedules, respectively) and cellular responses at day 28. Heterologous NVX-CoV2373 doses had a similar reactogenicity profile to homologous doses. These trends persisted at day 84 (17). No data are currently available for schedules involving administration of other WHO EUL COVID-19 vaccines after NVX-CoV2373.

Using the same vaccine for all doses (homologous schedule) is considered standard practice based on the substantial safety, immunogenicity, and efficacy data available. WHO supports a flexible approach to homologous versus heterologous vaccination schedules and considers two heterologous doses of any EUL COVID-19 vaccine to be a complete primary series.[2] However, the available evidence on NVX-CoV2373 in the context of heterologous usage is currently limited. Heterologous vaccination should be implemented with careful consideration of current vaccine supply, vaccine supply projections, and other access considerations, alongside the potential benefits and risks of the specific products being used.

Co-administration with other vaccines

Based on several co-administration studies of COVID-19 vaccines and inferred from co-administration studies of other vaccines, COVID-19 vaccines may be given concomitantly, or any time before or after, other vaccines, including live attenuated, inactivated, adjuvanted, or non-adjuvanted vaccines (18). When administered concomitantly, the vaccines should be injected in separate sites, preferably different extremities. Continued pharmacovigilance monitoring is recommended.

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[1] In some circumstances, there may be a relatively close trade-off in optimizing the impact of vaccine use between offering booster doses to older adults to avert more hospitalizations and deaths versus offering primary series doses to the remaining adults, adolescents, and children, that depend on country conditions, including supply and roll-out timelines, past epidemic dynamics and infection-induced immunity, vaccine product, vaccine effectiveness, and waning of protection.

[2] In moderately and severely immunocompromised individuals, WHO recommends an extended primary series including an additional dose (see "Moderately and severely immunocompromised persons, including persons living with HIV with CD4 cell count of <200 cells/μl" below).

Contraindications

A history of anaphylaxis to any component of this vaccine is a contraindication to its use. People who have an anaphylactic reaction following the first dose of NVX-CoV2373 should not receive a second dose of the same vaccine.

Precautions

No serious allergic reactions or anaphylaxis caused by NVX-CoV2373 have been recorded in the context of clinical trials. As with all vaccine administration, NVX-CoV2373 should be given under health-care supervision, with the appropriate medical treatment available in case of allergic reactions, and an observation period of 15 minutes after vaccination.

A history of anaphylaxis to any other vaccine or injectable therapy (i.e. intramuscular, intravenous, or subcutaneous vaccines or therapies) is not a contraindication to vaccination. For such persons, a risk assessment should be conducted by a health professional. Such individuals should be observed for 30 minutes after vaccination in health-care settings where anaphylaxis can be immediately treated (19).

Myocarditis and pericarditis are very rare adverse events that have been reported after receipt of NVX-CoV2373. Additionally, a few cases of paraesthesia and hypoesthesia have also been reported after receipt of NVX-CoV2373. Continued monitoring and surveillance of these conditions with the use of NVX-CoV2373 vaccine is recommended.

Countries should consider the individual and population benefits of immunisation relevant to their epidemiological and social context when developing their COVID-19 immunisation policies and programmes (20).

Vaccinated individuals should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis, such as new onset and persisting chest pain, shortness of breath, or palpitations following vaccination. It is important to rule out other potential causes of myocarditis and pericarditis, including SARS-CoV-2 infection and other viral aetiologies.

Anyone with an acute febrile illness (body temperature over 38.5 °C) should postpone vaccination until they are afebrile.

Vaccination of specific populations

Older people

The risk of severe COVID-19 and death increases steeply with age. The trial data across studies indicate that the vaccine has an acceptable safety profile for this age group and induces a robust antibody response. Vaccination is recommended for older persons without an upper age limit.

Persons with comorbidities

The Phase 3 trials in the UK and the USA/Mexico have demonstrated that NVX-CoV2373 has similar efficacy in persons with various underlying medical conditions that place them at increased risk for severe COVID-19. The comorbidities studied in the clinical trials included cardiovascular, respiratory, renal, neurologic, hepatic, and immunocompromising conditions as well as obesity and diabetes.

Certain comorbidities have been identified as increasing the risk of severe COVID-19 and death. Vaccination is recommended for persons with comorbidities that have been identified as increasing the risk of severe COVID-19 in alignment with the WHO Prioritization Roadmap.

Adolescents 12 to 17 years of age

Adolescents aged 12 to 17 years with comorbidities that put them at higher risk of serious COVID-19-related disease should be offered vaccination.

For healthy adolescents COVID-19 is rarely lethal. MIS-C and post-acute COVID sequelae are rare but may occur even after mild or asymptomatic infection. Adolescents can experience significant morbidity, but most infections are self-limiting, with only a small proportion requiring hospitalization.

Countries contemplating vaccinating adolescents should consider the benefit-risk, affordability, epidemiological situation, programmatic trade-offs, national adolescent vaccination programmes and opportunity costs, seroprevalence rates, and community acceptance. It is of utmost importance for children to continue to receive the recommended childhood vaccines for other infectious diseases.

In accordance with the WHO Prioritization Roadmap, the priority remains to prevent hospitalization and deaths by achieving high vaccine coverage (primary series and boosters) in the highest and high priority-use groups.

Pregnant persons

Pregnant persons with COVID-19 are at higher risk of developing severe disease, with increased risk of intensive care unit admission and invasive ventilation, compared to non-pregnant persons of reproductive age. COVID-19 in pregnancy is also associated with an increased risk of preterm birth and of neonates requiring neonatal intensive care. It may also be associated with an increased risk of maternal mortality (10, 11). Pregnant persons who are older (aged ≥35 years), or have high body mass index, or an existing comorbidity, such as diabetes or hypertension, are at particular risk of serious outcomes from COVID-19.

Developmental and reproductive toxicology (DART) studies have not shown harmful effects of NVX-CoV2373 in pregnant animals and their offspring. Available data on vaccination of pregnant persons with NVX-CoV2373 vaccine are insufficient to assess vaccine safety or efficacy in pregnancy. Post marketing surveillance data are being collected via pregnancy registries. The Matrix-M™ adjuvant has not been used in any other licensed vaccine. Available safety data specific to this adjuvant come from the clinical trials of NVX-CoV2373 vaccine and vaccine trials for other pathogens, which do not include a sufficient number of pregnant persons to draw conclusions regarding adjuvant safety. Post-introduction pharmacovigilance data relevant to the use of NVX-CoV2373 in pregnant persons is emerging - the limited data available to date has not identified a pregnancy-related safety concern. On the basis of previous experience with use of other protein-based vaccines during pregnancy, the effectiveness of NVX-CoV2373 vaccine in pregnant persons is expected to be comparable to that observed in non-pregnant persons of similar age. Continued monitoring and surveillance of pregnancy outcomes with the use of NVX-CoV2373 vaccine is recommended.

WHO has identified pregnant persons as a high priority-use group for COVID-19 vaccination, given their increased risk of severe outcomes. WHO recommends the use of NVX-CoV2373 in pregnant persons when the benefits of vaccination to the pregnant persons outweigh the potential risks. To help pregnant persons make this assessment, they should be provided with information about the risks of COVID-19 in pregnancy, the likely benefits of vaccination in the local epidemiological context, and the current limitations of the safety data in pregnant persons. WHO does not recommend pregnancy testing prior to vaccination. WHO does not recommend delaying pregnancy or terminating pregnancy because of vaccination.

Breastfeeding persons

Breastfeeding offers substantial health benefits to breastfeeding persons and their breastfed children. Vaccine effectiveness is expected to be similar in breastfeeding persons as in other adults. As NVX-CoV2373 vaccine is not a live virus vaccine, it is biologically and clinically unlikely to pose a risk to the breastfeeding child. On the basis of these considerations, WHO recommends the use of NVX-CoV2373 in breastfeeding persons as for other adults. WHO does not recommend discontinuing breastfeeding because of vaccination**.**

Persons living with HIV who are well-controlled on antiretroviral therapy

All persons living with HIV should be offered vaccination as soon as possible. Those who are well-controlled on antiretroviral therapy should be offered the standard primary series, for others please refer to the section below. It is not necessary to test for HIV infection prior to vaccine administration. Information and, where possible, counselling about vaccine safety and efficacy profiles should be provided to inform individuals on the potential benefit and risks. It is not necessary to test for HIV infection prior to vaccine administration.

Moderately and severely immunocompromised persons, including persons living with HIV with CD4 cell count of <200 cells/µl

Moderately and severely immunocompromised persons (ICPs) are at higher risk of severe COVID-19, regardless of age, although risk increases with age. Moderately and severely immunocompromised persons include those with active cancer, transplant recipients, immunodeficiency, and active treatment with immunosuppressives. It also includes persons living with HIV with a current CD4 cell count of <200 cells/µl, evidence of an opportunistic infection, not on HIV treatment, and/or with a detectable viral load.[3] For more details, see (21).

[3] **Active cancer:** Active immunosuppressive treatment for solid tumor or hematologic malignancy (including leukemia, lymphoma, and myeloma), or within 12 months of ending such treatment. **Transplant recipients**: Receipt of solid organ transplant and taking immunosuppressive therapy; receipt of stem cell transplant (within 2 years of transplantation, or taking immunosuppressive therapy). **Immunodeficiency:** Severe primary immunodeficiency; chronic dialysis. **HIV** with a current CD4 count of <200 cells/µl and/or lacking viral suppression. **Immunosuppressives:** Active treatment causing significant immunosuppression (including high-dose corticosteroids), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents, tumor-necrosis factor (TNF) blockers, and other drugs that are significantly immunosuppressive or have received in the previous 6 months immunosuppressive chemotherapy or radiotherapy

Available data for WHO EUL COVID-19 vaccine products suggest that vaccine effectiveness and immunogenicity are lower in ICPs compared to persons without immunocompromising conditions (8). Evidence suggests that an additional vaccine dose included in an extended primary series enhances immune responses in ICPs (22). Reactogenicity data on an additional (third) dose given to ICPs, where reported, have generally been similar to those observed for the standard primary series of the vaccine being administered. Given the significant risk of severe COVID-19 for ICPs, if infected, WHO considers that, based on available data, the benefits of an additional (third) dose in an extended primary series outweigh the risks, although additional safety monitoring is required.

WHO recommends an extended primary series including an additional (third) dose for ICPs aged 12 years and older.

Available evidence (21) suggests that an additional (third) dose should be given 1-3 months after the second dose in the standard primary series in order to increase protection as quickly as possible in ICPs. If more than 3 months have elapsed since dose 2 in the primary series, the additional (third) dose should be given at the earliest opportunity. The most appropriate timing for the additional dose may vary depending on the epidemiological setting and the extent and timing of immune suppressive therapy, and should be discussed with the treating physician.

Information and, where possible, counselling about the limitations surrounding data on administration of an additional dose to ICPs should be provided to inform individual benefit–risk assessment.

Given that protection may remain inadequate in a portion of ICPs, even after administration of an additional dose, WHO further recommends that close contacts (particularly caregivers) of such individuals should be vaccinated if eligible (according to the product-specific vaccines that have received EUL). Additional public health and social measures at household level to protect ICPs are also warranted, depending on local epidemic circumstances.

Persons who have previously had SARS-CoV-2 infection

Vaccination should be offered regardless of a person's history of symptomatic or asymptomatic SARS-CoV-2 infection. Viral or serological testing for prior infection is not recommended for the purpose of decision-making about vaccination. Data from the UK Phase 3 study indicate that the vaccine is safe in people with evidence of prior SARS-CoV-2 infection. The optimal time interval between a natural infection and vaccination is not yet known. Persons with laboratory-confirmed SARS-CoV-2 infection before primary series vaccination may choose to delay vaccination for 3 months. Persons with breakthrough infections following any dose could also consider delaying the next dose by 3 months. When more data on duration of immunity after natural infection become available, the length of this time period may be revised as well as the number of doses needed.

Persons with current acute COVID-19

Persons with acute PCR-confirmed COVID-19, including occurrence between doses, should not be vaccinated until after they have recovered from acute illness, and the criteria for discontinuation of isolation have been met. The optimal minimum interval between a natural infection and vaccination is not yet known. Given that the additional benefit is likely to be limited if vaccination is given too soon after natural infection, an interval of at least 3 months is recommended.

Persons who previously received passive antibody therapy for COVID-19

In people who have previously received monoclonal antibodies or convalescent plasma as part of COVID-19 treatment as part, vaccination does not need to be delayed. Although some reduction in vaccine-induced antibody titers was observed in people who previously received antibody products, the clinical significance of this reduction is unknown, and the balance of benefits vs. risks favours proceeding with vaccination even considering the possibility of diminished vaccine effectiveness in this situation.

Special settings

Persons in settings such as refugee and detention camps, prisons, slums, and other settings with high population densities where physical distancing cannot be implemented, should be prioritized for vaccination, as outlined in the WHO Prioritization Roadmap (6), taking into account national epidemiological data, vaccine supply and other relevant considerations.

As noted in the WHO Prioritization Roadmap (6), national programmes should give special consideration to groups that are disproportionately affected by COVID-19, or that face health inequities as a result of social or structural inequities. Such groups should be identified, barriers to vaccination should be addressed, and programmes should be developed to enable equitable access to vaccines.

Other considerations

SARS-CoV-2 variants

SARS-CoV-2 undergoes evolution. Variants of concern may be associated with higher transmissibility, disease severity, risk of reinfection, or a change in antigenic composition resulting in lower vaccine effectiveness.

Data from the Phase 2a/b and Phase 3 clinical trials included individuals infected with VOCs including the Alpha and Beta variants. In the UK, VE against the Alpha variant was 86% (95% CI: 71–94), with similar VE against this variant observed in the USA and Mexico (VE 94% [95% CI: 82–98]). In South Africa, VE against mild, moderate, or severe COVID-19 during a period in which the Beta variant was predominant was 49% (95% CI: 28–63). Based on samples collected 14 days after the second dose of NVX-CoV2373 during a Phase 2 study in the USA and Australia, antibody responses relative to wild-type were reduced by 4-fold, 4.8-fold, and 3-fold for Alpha, Beta, and Delta variants, respectively. These findings must be interpreted with caution given that the relationship between fold reductions in antibody responses and vaccine performance against clinical disease has not yet been established. From the booster study, 40–50-fold increases in IgG and neutralisation antibody titres were seen following the booster dose from baseline. IgG titres were approximately 4·0-fold against the Beta variant compared to the titres seen for the ancestral Wuhan strain. Unlike IgG, MN_{50} GMTs for the Beta variant were lower following the booster than those for the ancestral strain following the primary vaccination series (11).

These findings highlight the urgent need for a coordinated approach for surveillance and evaluation of variants and their potential impact on vaccine effectiveness. WHO will continue to monitor this situation; as new data become available, recommendations will be updated accordingly.

SARS-CoV-2 tests

Prior receipt of the vaccine will not affect the results of SARS-CoV-2 nucleic acid amplification or antigen tests for diagnosis of acute/current SARS-CoV-2 infection. However, it is important to note that antibody tests currently available for SARS-CoV-2 assess levels of IgM and/or IgG to the spike or the nucleocapsid protein. The vaccine contains a recombinant SARS-CoV-2 spike protein; thus, a positive result in a test for spike protein IgM or IgG could indicate either prior infection or prior vaccination. To evaluate for evidence of prior infection in an individual who has received NVX-CoV2373, a test that specifically evaluates IgM or IgG to the nucleocapsid protein should be used. A positive nucleocapsid protein-based assay indicates prior infection. Antibody testing at an individual level is not currently recommended to assess immunity to COVID-19 following vaccination with NVX-CoV2373.

Role of vaccines among other preventive measures

As there is not yet sufficient evidence to date of an effect of the vaccine on transmission, public health and social measures must continue, including use of face masks, physical distancing, handwashing, appropriate ventilation, and other measures as appropriate in particular settings, depending on the COVID-19 epidemiology and potential risks of emerging variants. Government advice on public health and social measures should continue to be followed by both vaccinated and unvaccinated individuals. This advice will be updated as information on the impact of vaccination on virus transmission and indirect protection in the community is assessed.

Country strategies related to COVID-19 control should be designed to minimize disruption to children's participation in education and other aspects of social life (23).

Other programmatic considerations

Countries should consider broader integration of COVID-19 vaccination into primary health care through national immunization programmes.

WHO recommends that countries consider co-administration of COVID-19 vaccines with seasonal influenza vaccines, whenever feasible, dependent on seasonality. The known risk of serious illness for older adults and many other priority-use groups infected either with influenza virus or SARS-CoV-2 is substantial. Other adult vaccines may also be co-administered with COVID-19 vaccines as WHO aims for a life course approach for the implementation of COVID-19 vaccines. Such a programmatic approach will help to reach higher uptake of vaccines, increase efficiency and protect stretched health care systems.

Community engagement, effective communication, and legitimacy

Community engagement and effective communication (including risk communication) are essential to the success of COVID-19 vaccination programmes. The decisions and processes for vaccination prioritization should be transparent, and based on shared values, the best available scientific evidence, and appropriate representation and input by affected parties. Furthermore,

communication about the mechanism of action of vector-based vaccines needs to be strengthened, along with efficacy and safety data derived from clinical trials and post-marketing studies, background mortality, maternal and neonatal outcomes, and rates of adverse events of special interest (AESIs) in groups prioritized for vaccination. Strategies should include: (i) culturally-acceptable and linguistically-accessible communications regarding COVID-19 vaccination, made freely available; (ii) active community engagement and the involvement of community opinion leaders and trusted voices to improve awareness and understanding of such communications; and (iii) inclusion of diverse and affected stakeholder opinions in decision-making. Such efforts are especially important in subpopulations who may be unfamiliar with or distrustful of health-care systems and immunization.

Vaccination logistics

The NVX-CoV2373 vaccine is provided as a refrigerated liquid formulation stored at 2–8 °C in a multidose vial containing 10 doses (0.5 ml each). Unopened vials can be stored for 6 months at 2–8 °C, protected from light, and are stable for up to 12 hours at 25 °C. Vials should not be frozen. Chemical and physical in-use stability has been demonstrated for 6 hours at 2°C to 25°C from the time of first needle puncture to administration.

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded in patient records.

Appropriate medical treatment to manage anaphylaxis must be immediately available. Hence, this vaccine should only be administered in settings with the necessary resources and trained health workers, and in settings that allow for at least 15 minutes of post-vaccination observation.

Recommendations on addressing current knowledge gaps through further research

WHO recommends the following post-authorization monitoring activities and research.

- As recommended for all vaccines, post-introduction safety surveillance and monitoring (though passive surveillance systems in all countries, and active surveillance systems wherever possible) should be conducted to evaluate for new or rare adverse events, including:
  - all serious adverse events (e.g. death; life-threatening event requiring in-patient hospitalization; a persistent or significant disability/incapacity; a congenital anomaly/birth defect; or a medical event considered important by the health-care provider), including anaphylaxis and other serious allergic reactions;
  - cases of multisystem inflammatory syndrome following vaccination; or cases of COVID-19 following vaccination that result in hospitalization or death;
  - rates of myocarditis after booster doses
  - rates of myocarditis by age and sex
  - background rates of AESIs (including myocarditis, pericarditis, paraesthesia, hypoesthesia, angioedema, GBS), maternal and neonatal outcomes, and mortality in groups prioritized for vaccination;
  - vaccine-associated enhanced disease and vaccine-associated enhanced respiratory disease following vaccination;
  - vaccine safety assessment in the context of phase 4 studies, particularly in older persons and persons with comorbidities.
- Vaccine effectiveness:
  - in persons aged ≥60 years;
  - in persons with comorbidities;
  - in adolescents;
  - against severe COVID-19;
  - against post-COVID-19 conditions;
  - in pregnancy;
  - immunogenicity and vaccine effectiveness in relation to current (including BA.2.75, BA.4 and BA.5 Omicron variants) and future variants of concern;
  - vaccine effectiveness over time and whether protection can be prolonged by booster doses;
  - studies to investigate whether NVX-CoV2373 reduces SARS-CoV-2 transmission and viral shedding;
  - assessment and reporting of breakthrough infections and virus sequence information;
  - head-to-head studies with other vaccines on extent and duration of immunity using standardized neutralization, T-cell and mucosal immunity assays;
  - booster studies with homologous and heterologous vaccines.

- Subpopulations:
  - prospective studies on the safety of the vaccine in pregnant and breastfeeding persons, which are particularly relevant given the novelty of the Matrix-M™ adjuvant;
  - immunogenicity and safety studies in persons aged <18 years;
  - safety data on vaccination in ICPs, including persons living with HIV and persons with autoimmune disease;
  - studies to assess the need for and timing of additional doses in persons where vaccine may result in lower immunogenicity, such as ICPs, persons living with HIV, and older persons.
- Correlates of protection and of duration of immunity.
- Vaccination logistics:
  - immunogenicity and safety studies of coadministration with other vaccines, including influenza and pneumococcal vaccines, to adults and older persons;
  - safety, immunogenicity, and impact of a delayed second dose;
  - interchangeability and "mix and match" studies within and across COVID-19 vaccine platforms.
- Variants of concern:
  - global surveillance of virus evolution and the impact of virus variants on vaccine effectiveness to support update of vaccines;
  - modelling to determine the trade-offs in the use of vaccines with reduced effectiveness against emergent variants;
  - effectiveness studies against virus variants.

Table of updates

Update 27 September 2022

Section	Rationale for update
Background	This section was updated to harmonize with the most recent Interim recommendations for other COVID-19 vaccines where SAGE had decided to update the wording as well as updates for NVX-CoV2373 since December 2021.
General goal and strategy for the use of the NVX-CoV2373 vaccine against COVID-19	This section was updated to harmonize with the most recent Interim recommendations for other COVID-19 vaccines where SAGE had decided to update the wording.
Vaccine performance	This section was updated to the include the post authorization surveillance data for safety including myocarditis and pericarditis, angioedema, GBS and paraesthesia and hypoesthesia, data for adolescents and booster administration.
Intended use	This section was updated to reflect the change in authorization of the age indication from age 12 years upwards.
WHO recommendation for use	This section now includes a new sub-section for the inclusion of the adolescent age group.
Administration	This section was updated text to include potential 8-week gap between primary doses.
Additional doses to the primary series	This section was updated to harmonize with the most recent Interim recommendations for other COVID-19 vaccines where SAGE had decided to update the wording.
Booster doses	This section was updated to harmonize with the most recent Interim recommendations for other COVID-19 vaccines where SAGE had decided to update the wording. This section was also updated with new booster data and for the clarification that no data for booster doses for adolescents is currently available.
Interchangeability with other COVID-19 vaccines in (heterologous schedules)	This section was updated to harmonize with the most recent Interim recommendations for other COVID-19 vaccines where SAGE had decided to update the wording.

Section	Rationale for update
Co-administration with other vaccines	This section was updated to harmonize with the most recent Interim recommendations for other COVID-19 vaccines where SAGE had decided to update the wording. This section was also updated to update the age indication from 12 years and above.
Precautions	This section was updated to the include the precautions for myocarditis and pericarditis, angioedema, GBS and paraesthesia and hypoesthesia, data for adolescents and booster administration.
Older people	This section was updated to harmonize with the most recent Interim recommendations for other COVID-19 vaccines where SAGE had decided to update the wording.
Persons with comorbidities	This section was updated to harmonize with the most recent Interim recommendations for other COVID-19 vaccines where SAGE had decided to update the wording.
Adolescents less than 18 years of age	This section was updated to harmonize with the most recent Interim recommendations for other COVID-19 vaccines where SAGE had decided to update the wording. This section was also updated to include recommendation for 12-17 years.
Pregnant persons	This section was updated to reflect the limited post-surveillance data now available.
Moderately and severely immunocompromised persons, including persons living with HIV with CD4 cell count of <200 cells/µl	This section was updated to harmonize with the most recent Interim recommendations for other COVID-19 vaccines where SAGE had decided to update the wording. This section was also updated to update the age indication from 12 years and above.
Persons living with HIV who are stable on antiretroviral therapy	This section was updated to harmonize with the most recent Interim recommendations for other COVID-19 vaccines where SAGE had decided to update the wording.
Persons with current acute COVID-19	This section was updated to harmonize with the most recent Interim recommendations for other COVID-19 vaccines where SAGE had decided to update the wording.
Special settings	This section was updated to harmonize with the most recent Interim recommendations for other COVID-19 vaccines where SAGE had decided to update the wording.
SARS-CoV-2 variants	This section was updated to harmonize with the most recent Interim recommendations for other COVID-19 vaccines where SAGE had decided to update the wording.
Other programmatic considerations	New section was added to harmonize with the most recent Interim recommendations for other COVID-19 vaccines where SAGE had decided to update the wording.
Vaccination logistics	This section was updated to harmonize with the most recent Interim recommendations for other COVID-19 vaccines where SAGE had decided to update the wording.

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