Interim recommendations for the use of the Janssen Ad26.COV2.S (COVID-19) vaccine

Interim guidance

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Updated 15 June 2021
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Updated 6 June 2022

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 extraordinary meeting on 15 March 2021 *(1)* and updated during its extraordinary meeting on 27 May 2021 *(2)* and 7 December 2021 *(3)*. The interim recommendations were further updated on 6 June 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 paper on the Phase 3 trial of the Janssen Ad26.COV2.S (COVID-19) vaccine *(4)* and the longer term follow-up of a small number of participants for the durability of humoral and cellular immune responses *(5)*.

Annexes which include GRADE and evidence-to-recommendations (ETR) tables have also been updated to reflect the updated recommendations *(6)*.

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.

These interim recommendations refer to the Ad26.COV2.S vaccine, manufactured by Janssen (Johnson and Johnson). The vaccine is also known as the Johnson & Johnson's/Janssen COVID-19 Vaccine. In the subsequent text the vaccine will be referred to as Ad26.COV2.S. On 12 March 2021, Ad26.COV2.S vaccine was granted WHO's Emergency Use Listing (EUL).

Methods

SAGE applies the principles of evidence-based medicine and has set in place a thorough methodological process for issuing and updating recommendations. A detailed description of the methodological processes as they apply to COVID-19 vaccines can be found in the SAGE evidence framework for COVID-19 vaccines *(7)*. This framework contains guidance on considering data emerging from clinical trials in relation to the issuance of vaccine-specific evidence-based recommendations.

General goal and strategy for the use of the Janssen Ad26.COV2.S (COVID-19) vaccine

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 *(8)* and the WHO Values

Framework *(9)* as guidance for their prioritization of target groups. The WHO Prioritization Roadmap recommends that priority of vaccine use be given to the highest priority-use groups (health workers, older persons, persons with moderate to severe immunocompromising conditions), and high priority-use groups (persons with comorbidities, teachers, pregnant women etc). Within the capacity of programmes and vaccine availability, additional priority-use groups should be vaccinated as outlined in the WHO Prioritization Roadmap, taking into account national epidemiological data and other relevant considerations.

Performance of the Janssen Ad26.COV2.S (COVID-19) vaccine

Ad26.COV2.S vaccine against COVID-19 is a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector encoding a full-length and stabilized SARS-CoV-2 spike protein. This vaccine does not contain adjuvants, preservatives, materials of animal origin, or fetal tissue.

Single dose trials and post-introduction studies:

The Phase 3 efficacy trial (ENSEMBLE 1; one dose) showed that a single dose of Ad26.COV2.S protected against moderate to severe-critical Covid-19 with onset at least 14 days after administration (116 cases in the vaccine group vs. 348 in the placebo group; efficacy, 67%; adjusted 95% confidence interval [CI], 59–73) and at least 28 days after administration (66 vs. 193 cases; efficacy, 66%; adjusted 95% CI: 55–75). Vaccine efficacy against severe-critical Covid-19 was 77% [adjusted 95% CI: 55–89] for onset at ≥14 days and 85% [adjusted 95% CI: 54–97] for onset at ≥28 days) *(10)*. Vaccine efficacies were similar in different gender, age and ethnic groups. At the time of this analysis, the median follow-up was 58 days, with 55% of participants having had 2 months and more of follow-up. In further follow-up of participants in the trial, after a median follow-up of about 4 months, the efficacy against symptomatic disease declined to about 50% two or more months after vaccination, whereas the efficacy against severe-critical Covid-19 was maintained.

Variants of concern: In the USA, where newly emerging variants of concern were not predominant at the time of the Phase 3 vaccine trial, vaccine efficacy, 14 or more days after vaccination, for moderate to severe COVID-19 was 74% (95% CI: 65–82), and efficacy for severe-critical COVID-19 was 78% (95% CI: 33–95). In South Africa, where the Beta variant (B.1.351 lineage) was the predominant strain, the efficacy against moderate to severe COVID-19 (52%, 95% CI: 30–67) was lower than in the USA but similar against severe COVID-19 (73%, 95% CI: 40–89). In Brazil, where a variant from the P.2 lineage was predominant, efficacy against moderate to severe-critical COVID-19 was 68% (95% CI: 49–81) and against severe/critical COVID-19 88% (95% CI: 8–100).

SARS-CoV-2 neutralizing and binding antibodies increase over time up to approximately 3 months post primary vaccination and remain stable up to at least 6 months after vaccination in participants 18–55 years of age. A decline in responses is observed between 6 and 8 months after vaccination. In participants ≥65 years of age antibody levels were lower and showed a more pronounced decline over time *(5)*. Based on several real world evidence studies of Covid-19 vaccines to date, the effectiveness of a single dose against Covid-19 symptomatic disease ranges from 51–79% *(11, 12)*, while the effectiveness against hospitalizations ranges from 60–96% *(13-16)*. In those studies, evaluating effectiveness over time, the effectiveness against hospitalization and severe disease remains high over the 5–6 months of the study duration including the months when the delta variant emerged and became dominant in the USA *(13-16)*.

In Sisonke's study in South Africa *(17)*, over a three-month period, 477 234 health care workers (HCWs) were vaccinated in 122 vaccination sites across South Africa. VE derived from datasets comprising 215 813 HCWs was 83% (95% CI: 75–89) to prevent Covid-19 deaths, 75% (95% CI: 69–82) to prevent hospital admissions requiring critical or intensive care and 67% (95% CI: 62–71) to prevent Covid-19 related hospitalizations. The VEs for all three outcomes were consistent across three datasets. The VE was maintained in older HCWs and those with comorbidities including HIV infection. VE remained similar throughout the Beta and Delta dominant phases of the study. A more recent study on VE of Ad26.COV2.S against Omicron in South Africa showed VE against hospitalization for Covid-19 was 55% (95% confidence interval [CI], 22 to 74) within 13 days after the second dose, 74% (95% CI, 57 to 84) at 14 to 27 days, and 72% (95% CI, 59 to 81) at 1 to 2 months *(18)*.

Two dose trials and immunogenicity studies[1]:

The primary analysis results (cut-off 25 June 2021) of the ongoing phase 3 trial (ENSEMBLE 2; two doses) *(19)* in which a second dose of Ad26.COV2.S was administered 2 months after the first vaccination with Ad26.COV2.S (median follow-up of 36 days after the second dose in the double-blind phase), shows that VE against moderate to severe/critical COVID-19 (primary endpoint) was 75% (adjusted

[1] Regulators and the manufacturer refer to the first dose as primary dose and the second dose as booster dose. To be consistent with other vaccine products and for the purpose of simplicity, this document uses the terminology of "first" and "second" dose.

95% CI: 55–87) and VE against severe/critical COVID-19 was 100% (0 versus 8 cases, adjusted 95% CI: 33– 100), when evaluated at least 14 days after the second vaccination. ENSEMBLE 2 was conducted in multiple regions (North and South America, Africa, Europe and Asia) at a time when new lineages of the virus were emerging. A second dose 2 months after the initial dose substantially increases efficacy, especially against symptomatic infections, including when caused by SARS-CoV-2 variants of concern. In the US, the vaccine efficacy of 2 doses, 2 months apart, was 94%. In comparison, the single dose vaccine efficacy in the USA was 72%. Furthermore, in the single dose trial the efficacy against symptomatic disease two months after vaccination had fallen to about 50%.

Consistent with the efficacy results, immunogenicity data indicate that a booster dose 2 months after the initial dose substantially increases humoral immune responses (ELISA titres) by about 4-fold as compared to pre-boost levels. Overall, Ad26.COV2.S has an acceptable reactogenicity profile after both the first dose and second dose, with the reactogenicity post-second dose being similar or milder than post-dose 1.

No Phase 3 trial was conducted to investigate the efficacy of two doses given 6 months apart. However, a small study of immunogenicity found that administration of Ad26.COV2.S 6 months after the initial dose increased geometric mean antibody titres by about 9–12-fold relative to the level 29 days after the first dose.

Following the results of the ENSEMBLE 2 study, which demonstrated improved vaccine efficacy of a two-dose regimen of Ad26.COV.2 vaccine given 2 months apart, the Sisonke study in South Africa was expanded amongst almost 500 000 health care workers (HCW) to include a second dose of the Ad26.COV, and included the period when Omicron emerged. VE for hospitalisation increased over time since second dose, from 63% (95%CI 31-81%); to 84% (95% CI 67-92%) and then 85% (95% CI: 54-95%), 0-13 days, 14-27 days, and 1-2 months post-boost *(18)*.

Intended use

Persons aged 18 years and above (refer to the WHO Prioritization Roadmap *(8)*).

Administration

The vaccine received Emergency Use Listing for a single dose at 0.5ml given intramuscularly into the deltoid muscle based on a Phase 3 trial using a single dose. A subsequent Phase 3 trial involving two doses, given 2 months apart, showed that 2 doses result in a higher efficacy for all clinical endpoints (symptomatic infection and severe disease) compared to a single dose.

WHO recommends two doses, 2-6 months apart. If administration of the second dose is delayed beyond 6 months, it should be given at the earliest opportunity.

Considerations for two versus one dose

Many countries may either face vaccine supply constraints or vaccine delivery challenges. Under such circumstances, countries may consider using a single dose only. A single dose may for example also be a preferred option for vaccinating hard-to-reach populations such as nomads, refugees and migrants or remote communities where delivering a second dose is programmatically challenging. Even in these populations, WHO recommends that all efforts should be taken to provide two doses, in particularly to the highest and high priority-use groups.

A longer inter-dose interval between the two doses with Ad26.COV2.S (6 months rather than 2 months) has been shown to result in a larger increase in humoral immune responses (ELISA titres). The two-month interval increased responses by 4–6-fold and the six-month interval by 12-fold *(20)*. Countries could therefore consider an inter-dose interval of up to 6 months.

Booster doses beyond the second dose

The need for, and timing of, additional doses beyond two doses remains to be determined.

Interchangeability with other COVID-19 vaccines (Heterologous schedules)

When a second dose is given, it is currently considered standard practice for the same product to be used for both doses. However, WHO supports a flexible approach to homologous versus heterologous vaccination schedules, taking into account current vaccine supply, vaccine supply projections, and other access considerations, alongside the potential benefits and risks of the specific products being used.

Evolving evidence suggests that heterologous COVID-19 vaccine schedules (using WHO EUL vaccine products from different platforms) may be more immunogenic and effective than homologous schedules, depending on the specific platforms and order of the products used. In particular, two trials have demonstrated that among individuals who have received a single dose of Ad26.COV.S, a second dose of mRNA vaccine (BNT162b2 or mRNA-1273) induces neutralising antibody concentrations 4–22-fold higher than a second dose of Ad26.COV2.S *(21, 22)*.

Ad26.COV.2 as heterologous booster following a completed primary vaccination series with another COVID-19 platform: Ad26.COV.2 has the capacity to boost antibody concentrations six months after a primary two-dose series of mRNA vaccine with increases in antibody responses at week four following the boost comparable to a homologous third dose of mRNA vaccine, but with higher T cell responses *(23)*.

Recommendations will be updated as further information becomes available on interchangeability between vaccine products and platforms.

Co-administration with other vaccines

For adults, based on several co-administration studies of COVID-19 vaccines and inferred from co-administration studies of other adult vaccines, COVID-19 vaccines may be given concomitantly, or any time before or after, other adult vaccines including live attenuated, inactivated, adjuvanted, or non-adjuvanted vaccines *(8)*. When administered concomitantly, the vaccines should be injected in separate sites, preferably different extremities. Continued pharmacovigilance monitoring is recommended.

Contraindications

A history of anaphylaxis to any component of the vaccine is a contraindication to vaccination. People who have an anaphylactic reaction following the first dose of Ad26.COV2.S should not receive any further doses of the same vaccine. People who have had TTS following the first dose of this vaccine should not receive a second dose of the same vaccine.

Precautions

In the study COV3001, no cases were observed that met the Brighton Collaboration criteria for anaphylaxis. However, in an open-label trial in South Africa, one case of anaphylaxis occurred which met the Brighton Collaboration criteria. As for all COVID-19 vaccines, Ad26.COV2.S should be given under health care supervision, with the appropriate medical treatment available in case of allergic reactions. As a precautionary measure, an observation period of 15 min after vaccination should be ensured.

As of 27 April 2022, more than 50 million doses of Ad26.COV2.S (5×10^{10} vp) have been administered worldwide (the majority of doses in the USA, Europe, South Africa and Brazil).

Based on post-marketing safety surveillance, the following safety concerns were identified: thrombosis with thrombocytopenia syndrome and Guillain-Barre Syndrome.

Thrombosis with thrombocytopenia syndrome (TTS):

The following data were presented to SAGE: as of 27 April 2022, Janssen`s global safety data base reports on 109 cases of TTS following vaccination with Ad26.COV.S , approximately 2 cases per million doses administered globally. Of those, 70 cases (3.7 cases per million doses administered) are from the US. In Europe, 35 cases of TTS were reported (1.7 per million doses administered), 2 cases were reported from Brazil (0.4 cases per million doses administered) and 2 more from South Africa (0.23 per million doses administered). There is considerable geographic variation with regards to the reported incidence, with very few cases reported from low to middle income countries, despite extensive use of the vaccine in these countries. The majority of the cases (69%) were reported from the USA and in age groups below 65 years (83%), 45% in males and 55% in females. 108 of the 109 cases occurred after primary vaccination with Ad26.COV.S in individuals without or undocumented history of COVID-19 infection and one of the 109 cases occurred after a heterologous booster using Ad26.COV.S following an mRNA vaccine primary series. To date, there are no reports of TTS following homologous boosting regimens with Ad26.COV.S.

No TTS cases have been recorded after a second or subsequent dose. As data from additional studies become available, enabling better understanding of the pathophysiology of TTS and its relationship to the vaccine, recommendations on vaccination will be updated, as appropriate.

Guillain-Barre Syndrome (GBS):

As of 27 April 2022, cumulatively 535 cases of GBS have been reported, corresponding to 1.5 cases per million doses distributed worldwide. The annual background incidence of GBS is estimated at 4.15 per 100 000 persons. Based on a 42-day risk window for GBS after vaccination, this approximates to a background risk of 4–5 cases per million. Health workers should be alert to possible signs and symptoms of GBS to ensure timely and accurate diagnosis (or to rule out other causes) and management of potential cases.

In conclusion, in countries with ongoing SARS-CoV-2 transmission, the benefit of vaccination in protecting against COVID-19 far outweighs the risks of TTS and GBS. However, benefit–risk assessments may differ from country to country, and countries should consider their epidemiological situation, individual and population-level risks, availability of other vaccines, and alternate options for risk mitigation. The benefit–risk ratio is greatest in older age groups as the risk of severe COVID-19 disease outcomes including COVID-19 related thromboembolic events increases with age.

Anyone with an acute febrile illness (body temperature over 38.5 ºC) 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. Data from the phase 3 trial indicate that the efficacy and safety of the vaccine are comparable across all age groups (above the age of 18). Vaccination is recommended for older persons.

Persons with comorbidities

Certain comorbidities have been identified as increasing the risk of severe COVID-19 disease and death. The phase 3 clinical trial demonstrated that the vaccine has similar safety and efficacy profiles in persons with various underlying medical conditions, including those that place them at increased risk for severe COVID-19. Vaccination is recommended for persons with such comorbidities that have been identified as increasing the risk of severe COVID-19.

Children and adolescents below the age of 18 years

For most children and adolescents the disease profile is less severe. There are currently no efficacy or safety data on use of Ad26.COV.S in children or adolescents below the age of 18 years. Until such data are available, vaccination of individuals below 18 years of age is not routinely recommended.

Pregnant persons

Pregnant women 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 women of reproductive age. COVID-19 in pregnancy is also associated with an increased risk of preterm birth, and of neonates requiring neonatal intensive care. COVID-19 in pregnancy may also be associated with an increased risk of maternal mortality *(24-26)*. Pregnant women who are older (age 35 years and above), or have high body mass index, or have an existing comorbidity such as diabetes or hypertension, are at particular risk of severe outcomes from COVID-19 *(26)*.

Ad26.COV2.S is a non-replicating vaccine. No safety issues have been identified following vaccination of more than 1 600 pregnant women using the Ad26 vaccine platform for vaccines against other pathogens, such as the Ebola virus. Animal developmental and reproductive toxicity studies show no harm to the development of the foetus. A pregnancy sub-study and a pregnancy exposure registry are underway *(27)*.

Compared with non-pregnant women, pregnancy is associated with higher rates of thrombosis, thrombocytopenia, and haemorrhage. However, current evidence does not suggest that pregnant women are at any greater risk of TTS than nonpregnant women. As data become available, recommendations on vaccination will be updated accordingly.

WHO has identified pregnant women as a priority-use group for COVID-19 vaccination, given their increased risk of severe outcomes. WHO recommends the use of Ad26.COV2.S vaccine in pregnant women when the benefits of vaccination to the pregnant woman outweigh the potential risks. To help pregnant women 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 epidemiologic context, and the current limitations of the safety data in pregnant women. 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 women and their breastfed children. Vaccine effectiveness is expected to be similar in breastfeeding women as in other adults. Data are not available on the potential benefits or risks of the vaccine to breastfed children. However, as Ad26.COV2.S 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 this vaccine in breastfeeding women as in non-breastfeeding individuals. WHO does not recommend discontinuing breastfeeding because of vaccination.

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 increasing age remains an important co-factor. For purposes of this interim recommendation, moderately and severely immunocompromised persons include those with active cancer, transplant recipients, immunodeficiency, and active treatment with immunosuppressives. It also includes people 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 (i.e., advanced HIV disease).[2] For more details, see *(28)*.

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 *(28)*. The emerging evidence suggests that an additional dose included in an extended primary series enhances immune responses in some ICPs *(29)*.

WHO recommends a second dose for all ICPs aged 18 years and older. Available evidence *(28)* suggests that this dose should be given 1–3 months after the first dose in order to increase protection as quickly as possible in ICPs. The most appropriate timing for a third 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. There are no data available to determine the need and timing of a additional doses. As data become available, these recommendations will be updated.

Given that protection may remain inadequate in a portion of immunocompromised persons even after the administration of an additional dose, WHO further recommends that close contacts (in particular 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 immunocompromised persons are also warranted depending on the local epidemic circumstances.

Persons living with HIV who are stable on antiretroviral therapy

Persons living with HIV (PLWH) may be at higher risk of severe COVID-19. Among the phase 3 clinical trial participants with well controlled HIV, there were no reported differences in safety signals. HIV-positive persons who are well controlled on highly active antiretroviral therapy and are part of a group recommended for vaccination can be vaccinated. The Sisonke study in South Africa showed high VE in PLWH *(17)*. Information and, where possible, counselling about vaccine safety and efficacy profiles in immunocompromised persons should be provided to inform individual benefit–risk assessment. It is not necessary to test for HIV infection prior to vaccine administration.

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 pooled analyses indicate that the vaccine is safe in people with evidence of prior SARS-CoV-2 infection. With the emergence of Omicron, reinfections after natural infection are common. Hybrid immunity induced by exposure to a vaccine and to natural infection is superior to immunity induced by vaccine or infection alone *(13)*. The optimal time interval between a natural infection and vaccination is not yet known. Persons with PCR-confirmed SARS-CoV-2 before the administration of the primary series may choose to delay vaccination for 3 months following the infection. 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.

[2] **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.

Persons with current acute COVID-19

Persons with acute PCR-confirmed COVID-19, including persons who are in-between doses, should not be vaccinated until after they have recovered from acute illness and the criteria for discontinuation of isolation have been met as per government advice. The optimal minimum interval between a natural infection and vaccination is not yet known. An interval of 3 months could be considered.

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 is not implementable, should be prioritized for vaccination as outlined in the WHO Prioritization Roadmap *(8)*, taking into account national epidemiological data, vaccine supply and other relevant considerations.

As noted in the WHO Prioritization Roadmap, 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 allow equitable access to vaccines.

Other considerations

SARS-CoV-2 variants

SARS-CoV-2 viruses undergo evolution. Some new virus variants may be associated with higher transmissibility, disease severity, risk of reinfection, or a change in antigenic composition resulting in lower vaccine effectiveness.

WHO currently recommends the use of Ad26.COV2.S according to the Prioritization Roadmap even if variants are present in a country. Countries should conduct a benefit-risk assessment according to the local epidemiological situation including the extent of circulating virus variants. There is an urgent need for a coordinated approach for surveillance and evaluation of variants and their potential impact on vaccine effectiveness. WHO will continue to monitor the 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 currently available antibody tests for SARS-CoV-2 assess levels of IgM and/or IgG to the spike or the nucleocapsid protein. The vaccine contains the spike protein; thus, a positive 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 the Ad26.COV2.S, a test that specifically evaluates IgM or IgG to the nucleocapsid protein should be used. A positive nucleocapsid protein-based assay indicates prior infection, while a negative nucleocapsid protein-based assay is expected after vaccination (unless a natural infection has occurred). Antibody testing is not currently recommended to assess immunity to COVID-19 following Ad26.COV2.S.

Role of vaccines among other preventive measures

As recent data suggest limited effect of the vaccine on transmission, in particular in the context of Omicron, public health and social measures to reduce SARS-CoV-2 transmission 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 vaccinated individuals, as well as those who have not yet been vaccinated.

Countries' strategies related to COVID-19 control should be designed to facilitate the participation of children in education and other aspects of social life, regardless of vaccination *(30)*.

Community engagement, and effective communication

Community engagement and effective communication (including risk communication) are essential to the success of COVID-19 vaccination programmes. Prioritization decisions should be made through transparent processes that are 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, and efficacy and safety data derived from clinical trials and post-marketing studies, as well as background mortality, maternal and neonatal outcomes and rates of adverse events of special interest (AESI) in groups prioritized for vaccination, needs to be strengthened. Strategies should include: (i) culturally acceptable and linguistically accessible communications regarding COVID-19 vaccination made freely available; (ii) active community engagement and 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 vaccine is provided to countries at -20 °C with a shelf life of 24 months in a multi-dose vial containing 5 doses (0.5ml each). The vaccine can be stored at 2 °C to 8 °C for 11 months. Once thawed the vaccine should not be re-frozen. The vials should be protected from light. After the first dose has been withdrawn, the vial should be held between at 2 °C to 8 °C for not longer than 6 hours in compliance with the WHO Multidose open vial policy. Any remaining doses in an opened vial must be discarded after 6 hours or at the end of the immunization session, whichever comes first.

When scheduling vaccination for occupational groups, e.g., health workers, consideration should be given to the reactogenicity profile of Ad26.COV2.S observed in clinical trials, which may occasionally necessitate time off work in the 24–48 hours following vaccination.

In considering the programme implications of implementing these recommendations, particular attention should be given to equity, including the feasibility, acceptability, and effectiveness of the programme in resource-constrained settings.

Recommendations on addressing current knowledge gaps through further research

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

- Safety surveillance and monitoring:
  - serious adverse events such as myocarditis, thrombosis with thrombocytopenia syndrome (TTS), anaphylaxis and other serious allergic reactions;
  - cases of multisystem inflammatory syndrome following vaccination, cases of COVID-19 following vaccination that result in hospitalization or death;
  - background rates of AESIs (including thromboembolic events, cerebral venous sinus thrombosis, and thrombosis with thrombocytopenia syndrome), maternal and neonatal outcomes, and mortality in groups prioritized for vaccination;
  - incidence by WHO region, age and sex, and pathophysiology of TTS.
- Vaccine effectiveness:
  - vaccine effectiveness in relation to new virus variants;
  - vaccine effectiveness over time after two doses versus one dose;
  - booster studies with a second dose, heterologous or variant-adjusted vaccines;
  - studies to investigate whether this vaccine 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;
  - vaccine effectiveness against Post-COVID-19 conditions.
- Subpopulations:
  - prospective studies on the safety this vaccine in pregnant and lactating women;
  - immunogenicity and safety of vaccination in persons below the age of 18 years;
  - safety data on vaccination in immunocompromised persons, including persons living with HIV and persons with autoimmune disease.
- Vaccination logistics:
  - immunogenicity and safety studies of co-administration with other vaccines, including influenza and pneumococcal vaccines, to adults and older persons;
  - interchangeability and “mix and match” studies for boosters within and across COVID-19 vaccine platforms.
- Virus variants:
  - 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 for the use of vaccines with reduced effectiveness against emergent variants;
  - Booster studies with updated vaccine formulations.

Table of updates

2 June 2022

Section	Rationale for update
Second dose	The ENSEMBLE 2 trial and subsequent studies from South Africa showed improved vaccine performance with 2 doses. The Interim Recommendations were updated to reflect these findings.
Interchangeability between vaccine products and platforms	Recent emerging data from mix and match studies led to an update in this section to allow to also use heterologous schedules
Considerations for one or two-dose schedules, and for inter-dose intervals	Points for considerations for countries deciding between introducing a second dose including considerations for the inter-dose interval.
Safety	Safety data were updated to include data up to 27 April 2022
Vaccination logistics	Updated to reflect longer storage duration
Persons who previously received passive antibody therapy for COVID-19	An interval between antibody therapy and COVID-19 vaccination is no longer recommended.

9 December 2021

Section	Rationale for update
Second dose	Since the first issuance of this vaccine, the ENSEMBLE 2 trial was published which showed efficacy data for 2 doses given 2 months apart. The Interim Recommendations were updated to reflect these findings.
Interchangeability between vaccine products and platforms	Recent emerging data from mix and match studies led to an update in this section to allow to also use heterologous schedules
Considerations for one or two-dose schedules, and for inter-dose intervals	Points for considerations for countries deciding between introducing a second dose including considerations for the inter-dose interval.
Safety	As of 31 August 2021, an estimated 33.5 million doses of Ad26.COV2.S (5×10^{10} vp) have been administered worldwide (an estimated 14.3 million doses in the US, 13.6 million doses in the European Economic Area, and 5.6 million doses in the rest of the world. The section on safety and precautions was updated to reflect the most recent published data for Guillain-Barre Syndrome, Thrombosis with Thrombocytopenia Syndrome, and capillary leak syndrome.
Pregnant and breastfeeding women	Text was updated to reflect more recent evidence on vaccination of pregnant women.
Immunocompromised persons	Updated based on the WHO good practice statement on immunocompromised persons with regards to COVID-19
Co-administration with inactivated influenza vaccines	Updated to reflect the deliberations of SAGE in October 2021 on co-administration of COVID-19 vaccines with inactivated influenza vaccines

15 June 2021

Section	Rationale for update
Precautions	Post-introduction safety surveillance showed that a very rare syndrome of blood clotting combined with low platelet counts (thrombosis with thrombocytopenia syndrome) has emerged. The section under Precautions was therefore updated to reflect this safety signal.
Pregnancy	Compared to non-pregnant women, pregnancy is associated with higher rates of thrombosis, thrombocytopenia, and haemorrhage; however, it is currently not known whether pregnancy is associated with a higher risk of TTS. As data become available, recommendations on vaccination will be updated accordingly. In the interim, WHO recommends the use of Ad26.COV2.S in pregnant women only if the benefits of vaccination to the pregnant woman outweigh the potential risks.

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WHO continues to monitor the situation closely for any changes that may affect this interim guidance. Should any factors change, WHO will issue a further update. Otherwise, this interim guidance document will expire 2 years after the date of publication.

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