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

Interim guidance

First issued 17 March 2021

Updated 15 June 2021

Updated 9 December 2021

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)*.

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 is an urgent global need for effective and safe vaccines and to make them available at scale and equitably across all countries.

As sufficient vaccine supply will not be immediately available to immunize all who could benefit from it, countries are recommended to use the WHO Prioritization Roadmap *(8)* and the WHO Values Framework *(9)* as guidance for their prioritization of target groups. When vaccine supplies are very limited (stage I in the WHO Prioritization Roadmap), in settings with community transmission, the Roadmap recommends that priority be given initially to health workers at high risk and older people with and

without comorbidities. As more vaccine becomes available, additional priority groups should be vaccinated as outlined in the WHO Prioritization Roadmap *(8)*, taking into account national epidemiological data and other relevant considerations. Also, as a matter of global equity, as long as many parts of the world are facing extreme vaccine shortages, countries should continue to donate vaccines to COVAX.

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 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. The study will now also investigate the vaccine effectiveness of the newly emerged Omicron variant.

Two dose trials and immunogenicity studies:

The primary analysis results (cut-off 25 June 2021) of the ongoing phase 3 trial (ENSEMBLE 2; two doses) *(18)* 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 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.

To date, no vaccine effectiveness studies have been reported based on two doses.

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 the findings of another Phase 3 trial involving two doses, given 2 months apart, showed that 2 doses may have higher efficacy for all clinical endpoints compared to a single dose. Countries can choose to use Ad26.COV2.S as a schedule with a single or two doses taking the following considerations into account:

Many countries face severe vaccine supply constraints combined with a high disease burden. A single dose of the vaccine is efficacious and facilitates rapidly increasing vaccine coverage, which in turn will reduce the burden on health care systems by preventing severe disease outcomes. A single dose may also be a preferred option for vaccinating hard-to-reach populations.

As vaccine supplies or accessibility improve, countries should consider offering a second dose, beginning with high priority-use populations as outlined in the WHO Prioritization Roadmap. The administration of the second dose will result in increased individual-level protection against symptomatic infection, and against severe disease.

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), for adults aged 18–55 years and for those aged ≥65 years. The two-month interval increased responses by 4–6-fold and the six-month interval by 12-fold (latter study only done in younger age group). Countries could therefore consider an interval of up to 6 months.

WHO recommends an inter-dose interval of 2 to 6 months. The choice for the inter-dose interval depends on the epidemiological situation, and needs for certain subpopulations.

Booster doses beyond the second dose

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

Interchangeability with other vaccines

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 *(19, 20)*.

Ad26.COV.2 also 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 *(21)*.

Studies on heterologous primary series and boosting must be interpreted with caution given the lack of an established correlate of protection or duration of protection, and extensive safety data. No major safety concerns have been identified regarding the use of Ad26.COV2.S in heterologous schedules, although the overall study size is limited. No data are available on vaccine effectiveness following the use of Ad26.COV2.S in heterologous schedules.

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

Co-administration with inactivated influenza vaccines

Based on limited evidence mainly derived from other COVID-19 vaccines, it is acceptable to co-administer Ad26.COV2.S with an inactivated influenza vaccine. Different arms for injection should be used when both vaccines are delivered during the same visit. Continued pharmacovigilance monitoring is recommended.

Co-administration with vaccines other than inactivated influenza vaccines

No co-administration data are available for other live or inactivated vaccines. There should be a minimum interval of 14 days between administration of this vaccine and all other vaccines except inactivated influenza vaccine. This recommendation will be updated as data on co-administration with other vaccines, including live vaccines, become available.

Contraindications

A history of anaphylaxis to any component of the vaccine is a contraindication to vaccination.

Precautions

In 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 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 USA, 13.6 million doses in the European Economic Area, and 5.6 million doses in the rest of the world) *(18)*. Based on post-marketing safety surveillance, the following safety concerns were identified: thrombosis with thrombocytopenia syndrome (TTS), Guillain-Barre Syndrome (GBS) and capillary leak syndrome (CLS).

TTS was reported as approximately 2 per million doses administered. 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. The mean and median time-to onset (TTO) of the event was 16.5 and 12 days, respectively. .

GBS was reported as 7–8 per million doses administered, with the majority of the cases (64%) reported from the USA. The mean and median ages were 53.1 and 55 years, respectively with the range of 22 to 87 years, and involved more males (64%) than females (36%). The mean and median TTO of the event after vaccination was 36 days and 14 days, respectively. 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.

Very rare cases of CLS (0.21 per million doses administered) have been reported, some in persons with a prior history of CLS and some have had with fatal outcomes. The mean and median TTO was 1.3 days and 1 day, respectively.

In countries with ongoing SARS-CoV-2 transmission, the benefit of vaccination in protecting against COVID-19 far outweighs the risks of TTS, GBS and CLS. 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

Populations for which supportive data are available from immunogenicity and clinical trials

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. The comorbidities studied in the phase 3 clinical trial included hypertension, chronic lung disease, significant cardiac disease, obesity, diabetes, and human immunodeficiency virus (HIV) infection. Vaccination is recommended for persons with such comorbidities that have been identified as increasing the risk of severe COVID-19.

Populations for which limited or no data exist from the clinical trials

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 for 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 women

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. It may also be associated with an increased risk of maternal mortality *(22-24)*. 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.

Ad26.COV2.S is a nonreplicating 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. Further studies are planned in pregnant women in the coming months, including a pregnancy sub-study and a pregnancy exposure registry *(25)*. As data from these studies become available, recommendations on vaccination will be updated accordingly.

In the interim, WHO recommends the use of Ad26.COV2.S vaccine in pregnancy only if the benefits of vaccination to the pregnant person outweigh the potential risks. To help pregnant women and adolescents make this assessment, they should be provided with information about the risks of COVID-19 in pregnancy (including, for example, that some pregnant women are at increased risk of infection or have co-morbidities that add to their risk of severe disease), 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 women

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).[1] For more details, see *(26)*.

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 *(26)*. The emerging evidence suggests that an additional dose included in an extended primary series enhances immune responses in some ICPs *(27)*.

WHO recommends a second dose for ICPs aged 18 years and older. Available evidence *(26)* 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 the second 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 third dose. 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. Within 6–12 months after an initial natural infection, available data show that symptomatic reinfection is uncommon. The optimal time interval between a natural infection and vaccination is not yet known. Persons with PCR-confirmed SARS-CoV-2 infection may choose to delay vaccination for 6 months. However, emerging data indicate that breakthrough infections occur in settings where variants of concern

[1] **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.

are circulating. In these settings earlier immunization after infection is advisable, e.g. within 90 days. When more data on duration of immunity after natural infection become available, the length of this time period may be revised.

Persons with current acute COVID-19

Persons with acute PCR-confirmed COVID-19 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, but thought to be 3 months.

Persons who previously received passive antibody therapy for COVID-19

Currently there are no data on the safety or efficacy of vaccination in persons who received monoclonal antibodies or convalescent plasma as part of COVID-19 treatment. Hence, as a precautionary measure, vaccination should be deferred for at least 90 days to avoid interference of the antibody treatment with vaccine-induced immune responses.

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 (4), 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.

In the current period of very limited vaccine supply, preferential vaccination of international travellers would counter the principle of equity. WHO currently recommends that travellers should only be vaccinated if they are part of a high-risk group or in epidemiological settings identified in the WHO Prioritization Roadmap (4)). As vaccine supply increases, these recommendations will be revisited.

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