

Interim recommendations for use of the AZD1222 (ChAdOx1-S [recombinant]) vaccine against COVID-19 developed by Oxford University and AstraZeneca

Interim guidance
10 February 2021



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 8 February 2021 (1).

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](#).

These interim recommendations apply to AZD1222 (ChAdOx1-S [recombinant]) vaccine against COVID-19 developed by Oxford University (United Kingdom) and AstraZeneca as well as to ChAdOx1-S [recombinant] vaccines against COVID-19 produced by other manufacturers that rely on the AstraZeneca core clinical data, following demonstrated equivalence in their regulatory review and once emergency use listing (EUL) has been obtained from WHO.

The guidance is based on the evidence summarized in the *Background document on AZD1222 vaccine against COVID-19 developed by Oxford University and AstraZeneca* and the *Background paper on COVID-19 disease and vaccines*. Both these documents are available on the SAGE COVID-19 webpage: <https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials>.

Methods

SAGE applies the principles of evidence-based medicine and has set in place a thorough methodological process for issuing and updating recommendations (2). 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 (3). 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 AZD1222 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 is an urgent global need to develop effective and safe vaccines and to make them available at scale and equitably across all countries.

The AZD1222 vaccine against COVID-19 has an efficacy of 63.09% (95% CI 51.81; 71.73) against symptomatic SARS-CoV-2 infection, as shown by the primary analysis of data irrespective of interdose interval (data cut 7 December 2020) from trial participants in the United Kingdom, Brazil and South Africa who received 2 standard doses. Vaccine efficacy tended to be higher when the interval between doses was longer. This, together with the finding of higher antibody levels with increasing interdose interval, supports the conclusion that longer dose intervals within the 4–12 weeks range are associated with greater vaccine efficacy. No vaccinated persons were hospitalized as from 22 days after dose 1, compared with 14 unvaccinated persons who were hospitalized for COVID-19 in the same time frame. At the time of analysis, the median follow-up time after the second dose was 80 days. More detailed data on the efficacy and safety of this vaccine can be found in the *Background document on AZD1222 vaccine against COVID-19 developed by Oxford University and AstraZeneca* (<https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials>). The data reviewed by WHO support the conclusion that the known and

potential benefits of AZD1222 outweigh the known and potential risks. 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 (4) and the WHO Values Framework (5) as guidance for their prioritization of target groups. As long as 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 and older people with and without comorbidities. Protecting health workers has a threefold purpose: (i) to protect the individual health workers; (ii) to protect critical essential services during the COVID-19 pandemic; and (iii) to prevent onward transmission to vulnerable people. Protecting older people will have the greatest public health impact in terms of reducing the number of deaths. As more vaccine becomes available, additional priority groups should be vaccinated as outlined in the WHO Prioritization Roadmap (4), taking into account national epidemiological data, vaccine-specific characteristics as outlined in product information approved by regulatory authorities, and other relevant considerations.

Intended use

Persons aged 18 years and above.

Administration

The recommended schedule is two doses (0.5 ml) given intramuscularly into the deltoid muscle. According to the manufacturer's product label, the vaccine can be administered with an interval of 4-12 weeks (6). In light of the observation that two-dose efficacy and immunogenicity increase with a longer interdose interval, WHO recommends an interval of 8 to 12 weeks between the doses. If the second dose is inadvertently administered less than 4 weeks after the first, the dose does not need to be repeated. If administration of the second dose is inadvertently delayed beyond 12 weeks, it should be given at the earliest possible opportunity. It is recommended that all vaccinated individuals receive two doses.

Booster doses

There is currently no evidence indicating a need for further doses once an individual has received two doses. The need for, and timing of, additional doses will be evaluated as further data accumulate.

Interchangeability with COVID-19 vaccines

No data are available on the interchangeability of doses of this vaccine with other COVID-19 vaccines. It is currently recommended that the same product should be used for both doses. Recommendations may be updated as further information becomes available on interchangeability.

Co-administration with other vaccines

There should be a minimum interval of 14 days between administration of this vaccine and any other vaccine against other conditions. This recommendation may be amended as data on co-administration with other vaccines become available.

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 this vaccine should not receive a second dose of the same vaccine.

Precautions

No severe allergic reactions or anaphylaxis caused by AZD1222 have been recorded in the context of clinical trials. However, as for all vaccines, AZD1222 should be given under health care supervision, with the appropriate medical treatment available in case of allergic reactions. As for any other vaccine, an observation period of 15 min after vaccination should be ensured.

Anyone with an acute febrile illness (body temperature over 38.5 °C) should postpone vaccination until they are afebrile. However, the presence of a minor infection, such as a cold, or low-grade fever should not delay vaccination.

Vaccination of specific populations

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

Persons aged 65 years and over

Because a relatively small number of participants aged 65 years or over were recruited into the clinical trials, there were few cases of COVID-19 in either the vaccine or the control group in this age category, and thus the confidence interval on the efficacy estimate is very wide. More precise efficacy estimates for this age group are expected soon, from both ongoing trials and vaccine effectiveness studies in countries that are using this vaccine. Immune responses induced by the vaccine in older persons are well documented and similar to those in other age groups. This suggests it is likely that the vaccine will be found to be efficacious in older persons. The trial data indicate that the vaccine is safe for this age group. The risk of severe disease and death due to COVID-19 increases steeply with age. Older adults are identified as a priority group in the WHO SAGE Prioritization Roadmap. This prioritization is supported by vaccine impact modelling work, even for vaccine efficacy that is substantially below that observed among younger adults administered AZD1222. Taking the totality of available evidence into account, WHO recommends the vaccine for use in persons aged 65 years and older.

Persons with comorbidities

Certain comorbidities have been identified as increasing the risk of severe COVID-19 disease and death. The clinical trials 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 clinical trials included obesity, cardiovascular disease, respiratory disease and diabetes. Vaccination is recommended for persons with 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

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 recommended.

Pregnant women

Pregnant women are at higher risk of severe COVID-19 compared with women of childbearing age who are not pregnant, and COVID-19 has been associated with an increased risk of preterm birth. The available data on AZD1222 vaccination of pregnant women are insufficient to assess vaccine efficacy or vaccine-associated risks in pregnancy. However, it should be noted that AZD1222 is a nonreplicating vaccine.

Animal developmental and reproductive toxicity (DART) studies are ongoing. Preliminary findings show no indication of 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 registry. As data from these studies become available, recommendations on vaccination will be updated accordingly. In the interim, pregnant women should receive AZD 1222 only if the benefit of vaccination to the pregnant woman outweighs the potential vaccine risks, such as if they are health workers at high risk of exposure or have comorbidities that place them in a high-risk group for severe COVID-19. Information and, if possible, counselling on the lack of safety data for pregnant women should be provided.

WHO does not recommend pregnancy testing prior to vaccination. WHO does not recommend delaying pregnancy because of vaccination.

Lactating women

Breastfeeding offers substantial health benefits to lactating women and their breastfed children. Vaccine efficacy is expected to be similar in lactating women as in other adults. It is unknown whether AZD1222 is excreted in human milk. As the AZD1222 vaccine is a non-replicating vaccine, it is unlikely to pose a risk to the breastfeeding child. On the basis of these considerations, a lactating woman who is part of a group recommended for vaccination, e.g., health workers, should be offered vaccination on an equivalent basis. WHO does not recommend discontinuing breastfeeding after vaccination.

Persons living with HIV

Persons living with human immunodeficiency virus (HIV) may be at higher risk of severe COVID-19. Persons living with HIV were not included in the primary analyses of the trials and safety data in subgroups of HIV-positive subjects are awaited. Data on administration of the vaccine are currently insufficient to allow assessment of vaccine efficacy or safety for persons living with HIV. It is possible that the immune response to the vaccine may be reduced, which may lower its clinical effectiveness. In the interim, given that the vaccine is nonreplicating, persons living with HIV who are part of a group recommended for vaccination may be vaccinated. Information and, where possible, counselling should be provided to inform individual benefit–risk assessment. It is not necessary to test for HIV infection prior to vaccine administration.

Immunocompromised persons

Immunocompromised persons are at higher risk of severe COVID-19. Available data are currently insufficient to assess vaccine efficacy or vaccine-associated risks in severely immunocompromised persons, including those receiving immunosuppressant therapy. It is possible that the immune response to the vaccine may be reduced, which may lower its clinical effectiveness. In the interim, given that the vaccine is nonreplicating, immunocompromised persons who are part of a group recommended for vaccination may be vaccinated. Information and, where possible, counselling about vaccine safety and efficacy profiles in immunocompromised persons should be provided to inform individual benefit–risk assessment.

Persons with autoimmune conditions

No data are currently available on the safety and efficacy of AZD1222 in persons with autoimmune conditions. Persons with autoimmune conditions who are part of a group recommended for vaccination may be vaccinated.

Persons who have previously had SARS-CoV-2 infection

Vaccination may 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. Available data from the pooled analyses indicate that AZD1222 is safe in people with evidence of prior SARS-CoV-2 infection. In participants who were seropositive at baseline, antibody levels were boosted after dose 1, with no further boosting after dose 2. The added protection of vaccinating previously infected individuals is yet to be established. Currently available data indicate that symptomatic reinfection within 6 months after an initial infection is rare. Thus, persons with PCR-confirmed SARS-CoV-2 infection in the preceding 6 months may delay vaccination until near the end of this period. 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, including those with onset of PCR-confirmed infection between doses, should not be vaccinated until after they have recovered from acute illness and the criteria for discontinuation of isolation have been met. Persons with PCR-confirmed SARS-CoV-2 infection may delay vaccination for 6 months. When more data on duration of immunity after natural infection become available, the length of this delay may be revised.

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. Because of this and the lack of evidence on whether vaccination reduces the risk of transmission, WHO currently does not recommend COVID-19 vaccination of travellers (unless they are also 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.

Preliminary analyses have shown a slightly reduced vaccine effectiveness of AZD1222 against B.1.1.7 in the V002 trial in the United Kingdom which is associated with only a limited reduction in neutralizing antibody. Preliminary analyses from the Phase 1/2a trial (COV005) in South Africa indicate marked reduction in vaccine effectiveness against mild and moderate disease due to B.1.351 based on a small sample size and substantial loss of neutralizing antibody activity. This study was designed to assess efficacy against disease of any severity, but the small sample size did not allow a specific assessment of vaccine efficacy against severe COVID-19. Indirect evidence is compatible with protection against severe COVID-19; however, this remains to be demonstrated in ongoing clinical trials and post-implementation evaluations.

In view of this, WHO currently recommends the use of AZD1222 vaccine according to the Prioritization Roadmap (4) 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.

These preliminary 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 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 AZD1222 vaccine, 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 AZD1222 vaccination.

Role of vaccines among other preventive measures

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

Community engagement, effective communication, and legitimacy

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 presented as a 10-dose vial with stopper (elastomeric with aluminium overseal), delivered in packs containing 10 multidose vials. Unopened multidose vials should be stored in a refrigerator (2 °C to 8 °C) and should not be frozen. Once a vial has been opened (first needle puncture), it should be handled according to the WHO open vial policy and be discarded at the end of the immunization session or within six hours of opening, whichever comes first. Within this period, the product may be kept and used at temperatures up to 30 °C (6, 7).

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.

When scheduling vaccination for occupational groups, e.g., health workers, consideration should be given to the reactogenicity profile of AZD1222 vaccine observed in clinical trials, which may occasionally lead to 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, anaphylaxis and other serious allergic reactions, Bell’s palsy, transverse myelitis, cases of multisystem inflammatory syndrome following vaccination, cases of COVID-19 following vaccination that result in hospitalization or death;
 - background rates of AESIs, maternal and neonatal outcomes, and mortality in groups prioritized for vaccination.
- Vaccine effectiveness:
 - vaccine effectiveness in older persons;
 - vaccine effectiveness in relation to time interval between the first and second dose;
 - vaccine effectiveness in relation to new virus variants;
 - vaccine effectiveness over time and whether protection can be prolonged by booster doses;
 - booster studies with heterologous 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.
- Subpopulations:
 - prospective studies on the safety of AZD1222 vaccine in pregnant and lactating women;
 - randomized controlled trials on efficacy 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;
 - safety, immunogenicity, and impact of a delayed second dose, as currently implemented by certain countries;
 - interchangeability and “mix and match” studies within and across COVID-19 vaccine platforms;
 - stability of vaccine under alternative cold-chain distribution and storage conditions.

- 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.

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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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