Interim recommendations for use of the ChAdOx1-S [recombinant] vaccine against COVID-19 (AstraZeneca COVID-19 vaccine AZD1222 Vaxzevria™, SII COVISHIELD™)

Interim guidance

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World Health Organization

Background

This interim guidance has been developed on the basis of the advice issued by the Strategic Advisory Group of Experts (SAGE) on Immunization at its extraordinary meeting on 8 February 2021 (1), and updated on 21 April 2021 and 30 July 2021. A summary of the updates are presented in a table at the end of this document.

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[1] refer to a generic group of COVID-19 Vaccine (ChAdOx1-S [recombinant]) which all rely on the AstraZeneca core clinical data for regulatory evaluation for AZD1222 and are authorized under the emergency use listing procedure by WHO. The most commonly used trade names are Astra Zeneca COVID-19 vaccine Vaxzevria and COVISHIELD. Consequently, these vaccines are considered fully equivalent, even if produced at different manufacturing sites or assigned different product names, and the interim recommendations here apply universally to all ChAdOx1-S vaccines.

The guidance is based on the initial evidence summarized in the *Background document on the AZD1222 vaccine against COVID-19 developed by Oxford University and AstraZeneca* and the *Background paper on COVID-19 disease and vaccines* (2).

Annexes which include GRADE and evidence-to-recommendations (ETR) tables have also been updated to reflect the updated recommendations (3): https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-AZD1222-GRADE-ETR-2021.1 .

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.

[1] The recommendations contained in this publication are based on the advice of independent experts, who have considered the best available evidence, a risk–benefit analysis and other factors, as appropriate. This publication may include recommendations on the use of medicinal products for an indication, in a dosage form, dose regimen, population or other use parameters that are not included in the approved labelling. Relevant stakeholders should familiarize themselves with applicable national legal and ethical requirements. WHO does not accept any liability for the procurement, distribution and/or administration of any product for any use.

Methods

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

General goal and strategy for the use of the 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 main immediate goal of vaccination against COVID-19, more so in low- and middle-income countries (LMICs) with limited supply of vaccines, is to protect against severe COVID-19 and death.

Based on the phase 3 trials, the ChAdOx1-S [recombinant] vaccine against COVID-19 has an efficacy of 72% (95% CI: 63-79%) against symptomatic SARS-CoV-2 infection, as shown by the primary analysis of data irrespective of inter-dose interval (data cut off 14 January 2021) from trial participants who received 2 standard doses with an interval varying from about 4 to 12 weeks (6). Vaccine efficacy tended to be higher when the interval between doses was longer. This, together with the finding of higher antibody levels with increasing inter-dose interval, supports the conclusion that longer dose intervals within the 4–12 weeks range are associated with greater vaccine efficacy against COVID-19. No vaccinated persons were hospitalized from 22 days after dose 1, as compared to 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 may be found in the 1 March 2021 *Background document on the AZD1222 vaccine against COVID-19 developed by Oxford University and AstraZeneca* (2). The global phase 3 trial (US, Chile, Peru) enrolled 32 449 participants, with 24% of the trial population aged 65 years or older (7). The primary analysis included events from 15 days post second dose, with an inter dose interval of 29 days. The case definition of symptomatic SARS-CoV-2 infection differed slightly from the Oxford University led trials. The vaccine efficacy against symptomatic SARS-CoV-2 infection was 76% (95% CI: 68–82%). No severe or critically ill cases occurred in the vaccinated group; 8 cases occurred in the placebo group. Vaccine efficacy in trial participants aged 65 years or older was 85% (95% CI: 58–94%) as per press release (7). As the pandemic has evolved, variants of concern have emerged (8). A recent estimate of vaccine effectiveness against hospitalization with the Delta variant (B.1.617.2) was 71% (95% CI: 51-83%) after 1 dose and 92% (95% CI: 75-97%) after 2 doses of ChAdOx1[recombinant] vaccine. Vaccine effectiveness against hospitalization with the Alpha variant was 76% (95% CI: 61-85%) after 1 dose and 86% (95% CI: 53-96%) after 2 doses of ChAdOx1[recombinant] vaccine (9).

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 (10) and the WHO Values Framework (5) as guidance for their prioritization of target groups. As long as vaccine supplies are very limited, in settings with community transmission (stage I in the WHO Prioritization Roadmap), the Roadmap recommends that priority be given initially to health workers and older people with and without comorbidities. As more vaccine becomes available, additional target groups should be vaccinated as outlined in the WHO Prioritization Roadmap (10), 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 to 12 weeks (11). In light of the observation that two-dose efficacy and immunogenicity increase with a longer inter-dose interval, WHO recommends an interval of 8 to 12 weeks between the two 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.

Considerations for deferring the second dose in settings with limited vaccine supply

WHO acknowledges that a number of countries face vaccine supply constraints combined with high disease burden. Some countries have therefore considered delaying the administration of the second dose to allow for a higher initial coverage with one dose. Phase 3 clinical trial data show efficacy against symptomatic COVID-19 starts from 22 days after the first dose and thereafter is about 76%

(95% CI: 59–86%) between days 22 and 90, prior to the administration of a second dose. There is some waning of binding antibody levels by day 362 which is unlikely to be clinically significant (12). After administration of the second dose, both vaccine efficacy and antibody titres are higher in individuals who had longer intervals between doses, comparing 8-12 weeks with < 6 weeks. In vaccinees with the longer between-dose interval (≥12 weeks), efficacy at >14 days after the second dose was 81% (95% CI 60–91%), compared to 55% (95% CI: 33-70%) in those with an interval of <6 weeks (13). These findings are consistent with evidence that humoral and cellular immune responses are boosted more strongly with the longer interval between doses. There is little information on clinical protection beyond 12 weeks after a single dose. Effectiveness studies of national vaccination programmes are limited to an inter-dose interval of up to 16 weeks at this time. Binding antibodies elicited by one dose of the ChAdOx1-S [recombinant] vaccines against the COVID-19 spike protein have a slow decay over a period of 6 months.

Because ChAdOx1-S [recombinant] vaccines induce both a T cell and B cell response, it is likely that there is some degree of protection against clinical disease conferred by one dose beyond 12 weeks, in particular against hospitalization, severe disease, and death. However, data to confirm this are not currently available. Both seroconversion rates and antibody titres are only slightly lower in older adults (56 to 69 years and 70 plus years) after administration of one dose, compared with younger adults (18-55 years) (14).

Based on post-introduction vaccine effectiveness studies from countries using an inter-dose interval of 12 to 16 weeks, data on persistence of post dose 1 effectiveness are currently available in the context of the ancestral virus and the variant of concern Alpha (B.1.1.7) (15, 16). Evidence on the impact of variants of concern other than Alpha (B.1.1.7) on first and second dose vaccine effectiveness is only just emerging. Effectiveness against symptomatic disease after a single dose of vaccine against COVID-19 associated with Delta (B.1.617.2) was lower than that against Alpha (B.1.1.7), whilst two dose effectiveness was similar for these two variants (17). These data highlight the importance of providing a second dose of vaccine in the context of circulating variants of concern that may lower the effectiveness of a single dose.

Countries should take into account the following factors when considering deferral of the second dose beyond 8 to 12 weeks after the first dose. During an initial period of limited vaccine supply, prioritizing distribution of first doses of vaccine to as many highly vulnerable individuals as possible will avert more deaths than vaccinating fewer such people with two doses - so long as the effectiveness of a single dose against COVID-19 mortality is at least half that of two doses and does not wane below this level before receipt of the second dose. The optimal interval before offering second doses depends not only on vaccine effectiveness and waning but also on population vaccine coverage, supply projections, pre-existing naturally acquired immunity and country-specific vaccine prioritization plans (18-21). Furthermore, for settings with substantial circulation of variants of concern that have been shown to have reduced effectiveness associated with a single dose, the importance of providing the most vulnerable groups with 2 doses must be considered.

In conclusion, for countries that have not yet achieved high vaccine coverage rates in the high-priority groups and that are experiencing high incidence of COVID-19 cases combined with vaccine supply constraints, longer intervals i.e. up to 16 weeks can be considered (16). WHO recommends focusing on achieving high first dose coverage by extending the inter-dose interval, whilst continuing to maximize second dose coverage of vulnerable groups in the context of variants of concern, particularly the Delta variant.

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, booster doses with the same vaccine, other vaccines or variant-adapted vaccines will be evaluated as further data accumulate.

Interchangeability with other COVID-19 vaccines

All ChAdOx1-S [recombinant] products covered by this recommendation (AstraZeneca COVID-19 AZD1222 - Vaxzevria, SII COVISHIELD™) are considered equivalent and interchangeable for both ChAdOx1-S [recombinant] doses.

With regards to using ChAdOx1-S [recombinant] products with other COVID-19 vaccines, it is currently recommended that the same COVID-19 vaccine products be used for both doses of the two-dose schedule. If different COVID-19 vaccines are inadvertently administered in the two doses, no additional doses of either vaccine are recommended at this time.

Studies to date show that immune responses after a first dose of ChAdOx1-S [recombinant] products followed by an mRNA vaccine (i.e., BNT162b2 or mRNA-1273) show higher neutralising antibody levels and higher T cell mediated immune responses in comparison with two doses of the ChAdOx1-S [recombinant] products and similar levels to those of two mRNA vaccines and was better than a first dose mRNA vaccine followed by ChAdOx1-S [recombinant] (22-25). Results from an observational study using ChAdOx1-S [recombinant] products followed by mRNA-1273, also showed an increased but acceptable reactogenicity (25). While

these studies are encouraging, they require cautious interpretation given the limited sample size and lack of follow up especially related to safety data. There are currently no vaccine effectiveness studies on the use of heterologous schedules. More observational data will be forthcoming and further recommendations will be issued. In the interim, countries can consider using ChAdOx1-S [recombinant] products followed by a mRNA platform vaccine (i.e. BNT162b2, mRNA-1273), in particular in situations of interrupted supply; a heterologous schedule constitutes an off-label use of the respective vaccines. There are currently no data for heterologous priming with other vaccine products.

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

Co-administration with other vaccines

There should be a minimum interval of 14 days between administration of ChAdOx1-S [recombinant] 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. People who have had thrombosis with thrombocytopenia syndrome (TTS) following the first dose of this vaccine should not receive a second dose of the same vaccine.

Precautions

A history of anaphylaxis to any other vaccine or injectable therapy (i.e., intramuscular, intravenous, or subcutaneous vaccines or therapies) is not a contraindication to vaccination. For such persons, a risk assessment should be conducted by a health professional. It is uncertain if there is an increased risk of anaphylaxis, but counselling should be given about the potential risk of anaphylaxis and the risks should be weighed against the benefits of vaccination. Such persons should be observed for 30 minutes after vaccination in health care settings where anaphylaxis can be immediately treated.

In general, persons with an immediate non-anaphylactic allergic reaction to the first dose (i.e., urticaria, angioedema without respiratory signs or symptoms that occur within 4 hours of administration) should not receive additional doses, unless recommended after review by a health professional with specialist expertise. Subject to individual risk–benefit assessment, ChAdOx1-S [recombinant] could be provided under close medical supervision if it is the only available vaccine for persons at high risk of severe COVID-19. If a second dose is offered, the patient should be observed closely for 30 minutes after vaccination in a health care setting where severe allergic reactions can be immediately treated.

No severe allergic reactions or anaphylaxis caused by ChAdOx1-S [recombinant] vaccine have been recorded in the context of clinical trials, but rare cases have been reported following use in national vaccination programmes. As for all vaccines, ChAdOx1-S [recombinant] vaccine 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 minutes after vaccination should be ensured.

A very rare syndrome of blood clotting combined with low platelet counts, described as thrombosis with thrombocytopenia syndrome (TTS) (26), has been reported around 3 to 30 days following vaccination with the ChAdOx1-S [recombinant] vaccine (27). A causal relationship between the vaccine and TTS is considered plausible although the biological mechanism for this syndrome is still being investigated. Most of these cases were reported from the United Kingdom and the European Union (EU). There is considerable geographic variation with regards to the reported incidence, with very few cases reported from non-European countries, despite extensive use of the vaccine in these countries. Data from the United Kingdom (as of 14 June 2021 (28)) and the EU suggest the risk of TTS is estimated to be approximately 1 case per 100 000 vaccinated adults. Current data from Europe and other countries, e.g. Australia, suggest a higher risk in younger adults compared with older adults; no additional risk factors have yet been identified (27). An estimation of the risk in other countries needs further data collection and analysis.

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

It is currently unknown whether there is a risk of TTS following the second 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.

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

Guillain-Barré syndrome (GBS) has been reported very rarely following vaccination with ChAdOx1-S [recombinant] vaccine (29). However, a causal relationship with the vaccine has neither been confirmed nor ruled out and more rigorous studies are needed to fully assess the significance of these events. Based on the available data, the potential benefits of the ChAdOx1-S [recombinant] vaccine continue to outweigh any potential risk of GBS, particularly given the increase in the more transmissible Delta (B.1.617.2) variant. 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.

Vaccination of specific populations

Populations for which clinical trial and/or post-introduction data exist

Persons aged 65 years and over

The risk of severe COVID-19 and death increases steeply with age. Phase 3 clinical trials demonstrated an efficacy against symptomatic COVID-19 of 85% (95% CI: 58–94%) in individuals aged 65 years or older (7). The trial data also indicate that the vaccine is safe for this age group. Post-introduction vaccine effectiveness studies from the United Kingdom have shown high rates of protection against hospitalizations, severe COVID-19 and death in older persons, including those over the age of 80 years (30, 31). 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. Vaccine effectiveness data after two doses also suggests a similar safety and effectiveness profile for persons with comorbidities (32).

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 persons 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

Evidence suggests that pregnant women with COVID-19 are at higher risk of developing severe disease compared to non-pregnant women of reproductive age. COVID-19 in pregnancy has also been associated with an increased risk of preterm birth and of neonates requiring neonatal intensive care. 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 serious outcomes from COVID-19.

Completed developmental and reproductive toxicology (DART) studies in animals have not shown harmful effects of the vaccine in pregnancy. ChAdOx1-S [recombinant] vaccine is a replication-defective vaccine. Available data on vaccination of pregnant women are insufficient to assess vaccine efficacy or vaccine-associated risks in pregnancy; studies in pregnant women are planned in the coming months, including a pregnancy sub-study and a pregnancy registry. Based on previous experience with other vaccine use during pregnancy, the effectiveness of the ChAdOx1-S [recombinant] vaccine in pregnant women is expected to be comparable to that observed for non-pregnant women in similar age groups. Of note, compared with 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 ChAdOx1-S [recombinant] vaccine in pregnant women only if 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 (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 ChAdOx1-S [recombinant] vaccine is not a live virus vaccine, it is biologically and clinically unlikely to pose a risk to the breastfeeding child. On the basis of these considerations, WHO recommends the use of ChAdOx1-S [recombinant] vaccine in breastfeeding women as in other adults. WHO does not recommend discontinuing breastfeeding because of vaccination.

Persons living with HIV

Persons living with human immunodeficiency virus (PLWH) may be at higher risk of severe COVID-19. Safety and immunogenicity data of two doses of ChAdOx1-S [recombinant] vaccine products were comparable between PLWH with well-controlled HIV and HIV-negative individuals (33, 34). 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 ChAdOx1-S [recombinant] vaccine products 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 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 months after an initial natural infection, available data show that symptomatic reinfection due to the same variant is uncommon. Given limited vaccine supply, persons with PCR-confirmed SARS-CoV-2 infection in the preceding 6 months may therefore choose to delay vaccination until near the end of this period.

However, emerging data indicate that symptomatic reinfection may occur in settings where variants of concern are circulating that are associated with markedly reduced protection conferred by previous natural infection and reduced vaccine effectiveness (for example, Beta B.1.351). In these settings, earlier immunization after infection is advisable, e.g. within 90 days following natural infection. When more data on duration of immunity after natural infection and against different virus variants 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 occurrence 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. The optimal minimum interval between a natural infection and vaccination is not yet known.

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, WHO recommends that 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 (10), 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 enable equitable access to vaccines.

Other considerations

SARS-CoV-2 variants

SARS-CoV-2 continues to evolve. Variants may emerge with higher transmissibility, disease severity, risk of reinfection, and/or a change in antigenic composition resulting in lower effectiveness of vaccines or control measures, or performance of diagnostics or therapeutics.

Preliminary analyses have shown a slightly reduced vaccine effectiveness of ChAdOx1-S [recombinant] vaccine against Alpha (B.1.1.7) in the United Kingdom, which is also associated with only a limited reduction in neutralizing antibody (6, 30) . Studies of antibodies following immunization with ChAdOx1-S [recombinant] vaccine against Beta (B.1.351), Gamma (P.1) and Delta (B.1.617.2) show that neutralizing activity is variably lower than against the ancestral strain (35-37). A two-dose regimen of the ChAdOx1 nCoV-19 vaccine did not show protection against mild-to-moderate COVID-19 due to the Beta (B.1.351) variant in a trial in South Africa (38) The young-age group (median 30 years) and low prevalence of underling medical conditions did not allow a specific assessment of vaccine efficacy against severe COVID-19. Recent estimates of vaccine effectiveness against hospitalization with Delta (B.1.617.2) were 71% (95% CI 51-83%) after 1 dose and 92% (95% CI: 75-97%) after 2 doses of ChAdOx1[recombinant] vaccine. Vaccine effectiveness against hospitalization with Alpha was 76% (95% CI: 61-85%) after 1 dose and 86% (95% CI: 53-96%) after 2 doses of ChAdOx1[recombinant] vaccine (9). There are no data currently on Lambda or other newer variants of interest.

In view of these findings, WHO currently recommends the use of ChAdOx1-S [recombinant] vaccine according to the Prioritization Roadmap (10) even if virus variants are present in a country. Countries should conduct a benefit-risk assessment according to the local epidemiological situation, including the extent of different circulating virus variants.

These preliminary findings highlight the urgent need for a coordinated approach for surveillance for variants and their 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 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 at an individual level is currently not recommended to assess immunity to COVID-19 following ChAdOx1-S [recombinant] vaccination.

Role of vaccines among other preventive measures

As there is not yet sufficient evidence as to the effect of the vaccine on transmission, 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. This advice will be updated as information on the impact of vaccination on virus transmission and indirect protection in the community is assessed.

Transmission of SARS-CoV-2 in educational settings appears to reflect transmission in the surrounding community. Countries' strategies related to COVID-19 control should be designed to minimise disruption to children's participation in education and other aspects of social life (22).

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 (AESIs) 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 policy on opened multidose vaccines 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. The open vaccine vials should also be kept at cooled temperatures between 2 °C to 8 °C during the in-use period (39, 40).

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 ChAdOx1-S [recombinant] 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 such as thrombosis with thrombocytopenia syndrome (TTS) (41), anaphylaxis and other serious allergic reactions, Bell's palsy, and 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 (including thromboembolic events, cerebral venous sinus thrombosis, and TTS), 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 time interval between the first and second dose;
  - vaccine effectiveness in relation to current and future variants of concern;
  - vaccine effectiveness over time and whether protection can be prolonged by booster doses;
  - second doses and 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;
  - vaccine effectiveness against post-COVID-19 conditions;
  - impact against transmission and indirect protection of unvaccinated populations;
- Subpopulations:
  - studies on the safety of ChAdOx1-S [recombinant] vaccine in pregnant and breastfeeding women;
  - immunogenicity and safety studies 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, including older persons;
  - safety, immunogenicity, and impact of a delayed second dose, as currently implemented by certain countries; 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 possible update of vaccines;
  - modelling to determine the trade-offs for the use of vaccines with reduced effectiveness against emergent variants;
  - booster studies with original and updated vaccine formulations.

Tables of updates

Update 30 July 2021

Section	Rationale for update
Interchangeability with other COVID-19 vaccines	This section was updated based on new preliminary data using heterologous schedules (i.e. ChAdOx1-S [recombinant] vaccine followed by an mRNA vaccine (BNT162b2 or mRNA-1273).
Considerations for deferring the second dose in settings with limited vaccine supply	This section has been added to provide guidance to Member States facing vaccine supply shortages which result in an inability to readily administer second doses.
Pregnant and breastfeeding women	To reflect updates in data and insights with regards to the use of COVID-19 vaccines in pregnancy and breastfeeding women.
Contraindications and Precautions	To reflect updated data related to TTS and GBS related to ChAdOx1-S [recombinant] vaccine.

Update 21 April 2021

Section	Rationale for update
Background, booster and interchangeability	Since the issuance of the 10 February 2021 Interim recommendations, WHO has determined the equivalence of the vaccine products based on ChAdOx1-S. Hence these products are considered as equivalent and interchangeable.

Precautions	Since March 2021, a very rare syndrome of blood clotting combined with low platelet counts, described as thrombosis with thrombocytopenia syndrome (TTS),[2] has been reported following vaccination with the ChAdOx1-S [recombinant] vaccine.
Persons aged 65 and above	Since the issuance of the 10 February 2021 Interim recommendations, post-introduction data have emerged which provide more robust data with regards to the vaccine efficacy/effectiveness in persons aged 65 and above. The following sentence was added: "Post-introduction, vaccine effectiveness studies from the United Kingdom showed high rates of protection against hospitalizations, severe COVID-19 and death in older persons." Furthermore, interim analyses of the United States phase 3 trial of the AstraZeneca COVID-19 AZD 1222 showed statistically significant high clinical efficacy against COVID-19 in persons aged 65 years and above.
Persons who have previously had SARS-CoV-2 infection	This document was updated to harmonize with the most recent Interim recommendations for other COVID-19 vaccines where SAGE had decided to update the wording to reflect the concerns of reduced protection after natural infections in areas where variants of concern are circulating.
Pregnant and lactating women	To reflect updates in data and insights with regards to the use of COVID-19 vaccines in pregnancy and lactating women.
Persons living with HIV	To reflect recent data: *ChAdOx1 nCoV-19 (AZD1222) vaccine in people living with and without HIV*. Madhi S, et al. 2021 Epub ahead of print: DOI**:** 10.21203/rs.3.rs-322470/v1
Special settings	This document was updated to harmonize with language used in the most recent Interim recommendations for other COVID-19 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 offered vaccination against COVID-19 if they are also part of a high-risk group or in epidemiological settings identified in the WHO Prioritization Roadmap. The joint statement on prioritization of searfarers and aircrew was added.
Vaccination logistics	This section was updated to reflect WHO's open vial policy.
Recommendations on addressing current knowledge gaps through further research	(1) Thromboembolic events and TTS were added under safety monitoring. (2) Given that various stringent regulatory authorities have indicated that immunobridging including safety data would suffice for extending the age indication to adolescents and children, the recommendation was rephrased to "immunogenicity and safety studies" to replace the previous recommendation for randomized controlled trials. (3) To harmonize the list for research recommendations with more recent Interim recommendations for other COVID-19 vaccines,

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[2] https://www.who.int/news/item/16-04-2021-global-advisory-committee-on-vaccine-safety-(gacvs)-review-of-latest-evidence-of-rare-adverse-blood-coagulation-events-with-astrazeneca-covid-19-vaccine-(vaxzevria-and-covishield).

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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