Background document on the AZD1222 vaccine against COVID-19 developed by Oxford University and AstraZeneca

Background document to the WHO Interim recommendations for use of the AZD1222 (ChAdOx1-S [recombinant]) vaccine against COVID19 developed by Oxford University and AstraZeneca

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Contents

Background

This background document has been prepared by the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 Vaccines to inform the discussions of SAGE at its 8 February 2021 extraordinary meeting, which resulted in the issuance of the 10 February 2021 WHO Interim recommendations for use of the AZD1222 (ChAdOx1-S [recombinant]) vaccine against COVID19 developed by Oxford University and AstraZeneca. Both recommendations and background document are available on the SAGE Covid-19 webpage: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials.

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 webpage and SAGE Covid-19 Working Group webpage.

Context

Replication-deficient adenovirus vectors containing a pathogen-specific transgene have been used as novel vaccines because of their ability to induce strong humoral and cellular responses. However, pre-existing immunity might reduce the immunogenicity of vectors derived from human viruses, and so use of simian adenoviruses might be preferable. COVID-19 Vaccine AstraZeneca, also known as AZD1222 or ChAdOx1-S (recombinant), was developed by Oxford University, United Kingdom, and AstraZeneca, and is a replication-deficient chimpanzee adenovirus-vectored vaccine expressing the full-length SARS CoV-2 spike glycoprotein gene.

Characteristics of AZD1222 vaccine against COVID-19

AZD1222 vaccine is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus vector encoding the S glycoprotein of SARS-CoV-2 (ChAdOx1-S (recombinant). The SARS-CoV-2 S immunogen in the vaccine is expressed in the trimeric prefusion conformation; the coding sequence has not been modified, in order to stabilize the expressed S-protein in the prefusion conformation. Adenoviruses are non-encapsulated, icosahedral particles (virions), and contain a single copy of the double-stranded DNA genome. The expression cassette for the SARS-CoV-2 spike protein fused to the tissue plasminogen activator leader sequence uses a modified human cytomegalovirus promoter and a bovine growth hormone polyadenylation sequence.

The following information is derived from the product information approved by the European Medicine Agency`s Committee for Medicinal Products for Human Use (CHMP)(1).

Composition

One dose (0.5ml) contains 5 x 10^{10} ChAdOx1-S (recombinant) viral particles. The vaccine is produced in genetically modified human embryonic kidney (HEK) 293 cells. In addition to ChAdOx1-S (recombinant), this product also contains the excipients L-histidine, L-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, polysorbate 80, ethanol, sucrose, sodium chloride, disodium edetate dihydrate and water for injection. None of the excipients are of animal or human origin. The excipients are well established for pharmaceutical products.

Stability and Shelf-life

A shelf-life of 6 months is proposed. Chemical and physical in-use stability from the time of vial opening (first needle puncture) to administration is up to 48 hours in a refrigerator (2–8 ºC). Within this period, the product may be kept and used at temperatures up to 30 ºC for a single period of up to 6 hours, after which it must be discarded. It should not be returned to the refrigerator.

Drug product description

The product is a colourless to slightly opalescent solution provided in a multidose vial with an elastomeric stopper and aluminium overseal. The drug product vials are packaged in cartons of 10 vials.

Container

Different presentations of the multidose vial will be available in different regions. For example:

- In the European Union, the product will be available in 4-ml (8-dose) and 5-ml (10-dose) vials.
- 5 ml (10-dose) vials will be made available through COVAX.

- Covishield, produced by the Serum Institute of India (SII), is expected to be available in vials containing 1 dose (0.5 ml), 2 doses (1.0 ml), 5 doses (2.5 ml), 10 doses (5.0 ml) or 20 doses (10 ml).

Pharmacokinetics

Two biodistribution studies have been performed, which suggested that, after injection, the virus does not replicate or persist, and is not distributed in the body beyond the injection site in a way that would be clinically significant.

Developmental and reproductive toxicity

Animal developmental and reproductive toxicity (DART) studies are ongoing. A dose-range study and a GLP embryo-foetal development study were completed. In top-line results from the latter study, no test item-related effects were seen for dams in-life, including at the injection site, for female reproduction, foetal or pup survival or pup physical development, and there were no abnormal gross pathology findings in pups before or after weaning or in dams in either phase. There were no test item-related foetal external, visceral or skeletal findings. The audited report is due later in 2021.

Lactation

There have so far been no studies of the safety of this vaccine in women who are breastfeeding. Studies are planned to address this issue.

Preclinical studies

The following information is derived from scientific publications.

The efficacy of AZD1222 vaccine was assessed in rhesus macaque monkeys (2). Six animals per group were vaccinated intramuscularly with 2.5×10^{10} ChAdOx1-S (recombinant) virus particles each, using either a prime-only regimen (28 days before challenge) or a prime–boost regimen (56 and 28 days before challenge). As a control, six animals were vaccinated via the same route with the same dose of ChAdOx1-S (recombinant) green fluorescent protein (GFP) (one animal was vaccinated 56 and 28 days before challenge and five animals were vaccinated 28 days before challenge). No adverse events were observed after vaccination. Spike-specific antibodies were present as early as 14 days after vaccination and were significantly increased after the second vaccination (two-tailed signed-rank Wilcoxon test). Endpoint IgG titres of 400–6400 (prime) and 400–19 200 (prime–boost) were measured on the day of challenge. Virus-specific neutralizing antibodies were also significantly increased after the second vaccination (two-tailed signed-rank Wilcoxon test) and were detectable in all vaccinated animals before challenge (titres 5–40 (prime) and 10–160 (prime–boost)). No virus-specific neutralizing antibodies were detected in control animals. On the day of challenge, IgM antibodies were present in the serum of all six prime–boost animals and two of the six prime-only animals. SARS-CoV-2 spike-specific T-cell responses were detected on the day of challenge by gamma interferon (IFNγ) ELISpot assay, after stimulation of peripheral blood mononuclear cells with a peptide library that spanned the full length of the spike protein. No statistically significant difference in the magnitude of the response was found between the prime–boost and prime-only group (Mann–Whitney *U*-test, $P = 0.3723$). Vaccination with ChAdOx1-S (recombinant) has been shown to induce neutralizing antibodies against the vaccine vector itself within 28 days of vaccination. Nonetheless, a boost vaccination with ChAdOx1-S (recombinant) resulted in a significant increase in binding and neutralizing antibodies and an increase in the SARS-CoV-2 virus-neutralizing titre was not significantly correlated with the ChAdOx1-S (recombinant) virus-neutralizing titre (two-tailed Pearson correlation, $r^2 = 0.6493$ $P = 0.0529$).

After challenge, the animals were evaluated for the protection offered by the vaccine and the potential for vaccine-associated enhanced respiratory disease (VAERD) (2). The clinical disease score in vaccinated monkeys was lower than that in the controls, and the vaccine prevented damage to the lungs. The prime–boost regimen induced humoral immune responses. Viral loads in the lungs were lower than in controls, but there was no reduction in viral shedding from the nose with either the prime-only or the prime–boost regimen. This suggests that AZD1222 may not prevent infection or transmission of SARS-CoV-2, but may reduce illness. The immune responses were not skewed towards a Th2-type and there was no suggestion of enhanced disease following vaccination. While a single dose induced antigen-specific antibody and T-cell responses, a booster immunization enhanced antibody responses, with a significant increase in SARS-CoV-2 neutralizing titres (3).

Clinical studies

The pivotal safety, efficacy and immunogenicity data informing registration of the vaccine are derived from four ongoing studies:

- COV001, a phase 1/2 trial conducted in the United Kingdom;
- COV002, a phase 2/3 trial conducted in the United Kingdom:
- COV003, a phase 3 trial conducted in Brazil; and
- COV005, a phase 1/2 trial conducted in South Africa.

Smaller trials using the vaccine are planned or under way in other countries, including India, Japan, Kenya, Russian Federation and South Africa. In addition, a large phase 3 trial involving about 30 000 participants is taking place in Argentina, Chile, Colombia, Peru and the USA; interim results from this trial are expected shortly.

The primary analysis of vaccine efficacy is used here as the main source of data. These data were made available by AstraZeneca for review, and permission has been given for these data to be made public in this background document.

Immunogenicity studies in humans

COV001 study (4–6)

A total of 1077 participants were enrolled in this study, of whom 543 were randomized to receive AZD1222, while the rest received meningococcal group A, C, W and Y conjugate vaccine (MenACWY) as control. Subsequently, some AZD1222 recipients received boosters at different doses and dose intervals. Binding antibody responses, as measured by enzyme-linked immunosorbent assay (ELISA), were consistently detected after one dose and were substantially boosted following a second dose, correlating with neutralizing antibody titres. The latter were measured using several methods and were detectable in all subjects after two doses, reaching titres similar to those in convalescent sera. Both CD4+ and CD8+ T-cell responses were detected by ELISpot.

Antibody responses were predominantly of IgG1 and IgG3 subclasses, with low levels of IgG2 and little detectable IgG4, consistent with a Th1-biased response. Likewise, cytokine secretion from antigen-specific CD4+ T cells showed a Th1-bias with increased IFNγ and tumour necrosing factor (TNF) alpha on days 7 and 14 (rather than a Th2-bias (IL-4 and IL-13)).

A standard dose (SD) booster of 5×10^{10} viral particles (vp) administered 56 days after the priming dose induced a rise in polyfunctional antibody concentrations (7). These were higher than following low dose (LD) boosters of 2.2×10^{10} or 2.5×10^{10} vp, but not significantly higher than following booster doses given at 28 days. These boosters did not measurably increase the magnitude of the T-cell responses. While anti-adenoviral vector neutralizing antibody responses were detectable, their presence was not associated with reduced antibody or T cell anti-SARS CoV2 responses to booster vaccine doses.

Anti-spike neutralizing antibody titres, as well as Fc-mediated functional antibody responses, including antibody-dependent neutrophil/monocyte phagocytosis, complement activation and natural killer cell activation, were substantially increased by a booster dose of vaccine. A full SD booster induced stronger antibody responses than an LD boost, although the magnitude of T-cell responses did not increase with either dose. The booster dose of AZD1222 was found to be safe and better tolerated than the priming doses.

COV002 study (7)

In the first part of this phase 2/3 trial, 560 subjects in three different age groups (18–55, 56–69 and ≥70 years) were enrolled and received either one (older two groups) or two doses of AZD1222 or MenACWY (control) vaccine, 28 days apart. Two dose regimens were used (LD and SD).

The median anti-spike SARS CoV-2 IgG responses 28 days after the booster dose were similar across the three age cohorts, as were the neutralizing antibody titres. T-cell responses peaked on day 14 after a single SD and did not increase significantly after the booster vaccination.

The antibody response tended to be slightly lower with the LD regimen compared with the SD regimen on day 56.

The rate of seroconversion (a 4-fold or greater increase over baseline) to S-binding antibodies was over 98% 28 days after the first dose and over 99% 28 days after the second dose for participants who were seronegative at baseline. The rate of seroconversion, as measured in a live neutralization assay, was over 80% 28 days after the first dose and over 99% 28 days after the second dose for participants who were seronegative at baseline.

AZD1222 appeared to be better tolerated in older adults than in younger adults and had similar immunogenicity across all age groups after a booster dose.

In the COV002 study, some participants assigned to receive SD prime and booster doses in fact received a lower than intended priming dose (roughly equivalent to the LD given during the phase 2 part of the study). The interval between

priming and booster doses for all these LDSD subjects was also longer than initially foreseen, about 12 weeks. Among subjects who received SD prime and booster doses (SDSD), the dose intervals varied, mostly ranging between 4 and 12 weeks. In this group, observed immunogenicity (by immunoassay) (8) following the booster dose increased with longer dose interval. Immunogenicity was similar among those given the lower priming dose with a longer dose interval and those given the standard priming dose with a longer dose interval.

Efficacy

The efficacy analysis reported reflects data collected up to 7 December 2020 in the four studies, and includes patients who received two standard doses (SDSD) with any interval between doses (ranging from 3 to 23 weeks (21 to 159 days)).

COV001 (United Kingdom, phase 1/2). This study in adults aged 18–55 years was designed to evaluate various dosing regimens, and used a single dose or a 2-dose regimen of AZD1222 or MenACWY (control), different dose levels (SD and LD), and various dosing schedules.

COV002 (United Kingdom, phase 2/3). This study enrolled participants in 19 study sites and targeted individuals working in professions with a high possible exposure to SARS-CoV-2, such as those working in health and social care settings. The study began by enrolling participants aged 18–55 years. Only one vaccine dose was planned initially but this was increased to two on the basis of immunogenicity findings in phase 1/2 studies (COV001). Participants over 55 years of age were also enrolled subsequently and had a shorter interval between their first and second doses. Participants received a single dose or a 2-dose regimen of AZD1222 vaccine or MenACWY. Most participants had an interval between doses of 4–12 weeks and about 20% had an interval in excess of this.

COV003 (Brazil, phase 3). This study enrolled participants at high risk of exposure to the virus, including health care workers, in six sites across the country. Recruitment of participants in Brazil began a little later than the COV002 study in the United Kingdom, and they were offered two doses of the vaccine up to 12 weeks apart (target 4 weeks). Participants received either two doses of AZD1222 or a first dose of MenACWY and a second dose of saline placebo. For less than 2% of participants, the interval between doses was more than 12 weeks.

COV005 (South Africa, phase 1/2). This study enrolled adults living with or without HIV at seven sites in the country. The study started at approximately the same time as the study in Brazil; participants received two doses of AZD1222 vaccine or saline placebo at a dose interval between less than 4 weeks and 12 weeks. The dose interval was never more than 12 weeks.

Women who were pregnant or breastfeeding were excluded from all studies.

Baseline demographics were well balanced across the vaccine and control groups. In the pooled analysis of all four studies, among the participants who received two standard doses (SDSD) of the vaccine with any interval between doses (data cut-off 7 December 2020): 90.2% of participants were 18–64 years old and 9.8% were aged 65 or older; 54.4% of subjects were female; 71.8% were white, 11.8% were black and 3.4% were Asian. In total, 2592 participants (36.0%) had at least one pre-existing comorbidity (defined as a body mass index (BMI) ≥30 kg/m^2, cardiovascular disorder, respiratory disease or diabetes).

The primary analysis of the trial results was conducted when participants had been followed for a median of 133 days after the first dose and 80 days after the second dose.

Efficacy against COVID-19

The primary endpoint was specified as efficacy against symptomatic COVID-19 15 days or more after the second dose among participants who were seronegative at trial entry. A total of 14 380 participants were eligible for inclusion in the efficacy analysis (43% in the United Kingdom, 47% in Brazil, 10% in South Africa). There were 271 COVID-19 cases with onset 15 days or more after dose 2, with 74 cases in the vaccinated group and 197 in the control group. The estimate of vaccine efficacy (VE) was 63.09% (95% confidence interval (CI) 51.81–71.73%).

Only about 9.8% of participants were aged 65 years or older and among these there were only 12 cases of COVID-19, 4 in the vaccine group and 8 in the control group (VE 51.91%; 95% CI –59.98% to 85.54%).

Exploratory analyses were conducted of vaccine efficacy 15 days or more after the second dose, according to the interval between the first and second doses. For about 59% of participants the interval was 4–8 weeks, for 22% 9–12 weeks and for 16% more than 12 weeks. The estimates of VE increased significantly in these 3 groups, being 56%, 70% and 78%, respectively.

During the 21 days after the first dose, there was no difference between the vaccine and control groups in COVID-19 incidence. From 22 days after the first dose up to the time of the second dose or up to 12 weeks after the second dose, there were 18 cases of COVID-19 in the vaccine group and 63 cases in the control group (VE 71.42%; 95%CI 51.11–84.08%). The interval between first and second doses varied, but up to 12 weeks there was no evidence of a decline in efficacy.

Efficacy against COVID-19 hospitalization (WHO clinical progression scale ≥4)

In the total trial population, there were 24 patients who needed to be hospitalised for COVID-19, 2 in the vaccine group and 22 in the control group. During the period from 22 days after the first dose, there were no hospitalized cases in the vaccinated group and 14 in the control group. For the period from 15 or more days after dose 2, there were, respectively, 0 and 8 hospitalized cases.

Efficacy against severe COVID-19 (WHO clinical progression scale ≥ 6)

In the total population, there were only three cases of severe COVID-19, all in the control group.

Summary

Evidence of efficacy emerged from about 22 days after the first vaccine dose. The vaccine was efficacious against laboratory-confirmed COVID-19 from 22 days after the first dose and persisted until at least 12 weeks after a second dose was given (VE 71.42%). The primary trial endpoint was efficacy measured from 15 days after the second vaccine dose until data cut-off, which was, on average, about 2 months (mean 58 days; median 66 days) after the second dose. The vaccine continued to be efficacious during this period (VE 63.09%). Exploratory analyses indicated that efficacy following the second dose increased with increasing interval between the first and second doses.

A relatively small proportion of participants were aged 65 years or over and the number of cases of COVID-19 in this age group was too small to assess protection based on the efficacy data alone. There were no COVID-19 hospitalizations, severe COVID-19 disease, or COVID-19 deaths in participants ≥65 years of age who received AZD1222.

A summary of the main findings is presented in Table 1.

Table 1. Vaccine efficacy against virologically confirmed COVID-19 occurring 15 days or more after the second dose

Subgroup	Participants with events		VE (%)	95%CI (%)	P value
	AZD1222 No. (%)	Control No. (%)			
SDSD, any dose interval					
Overall	74/7201 (1.03)	197/7179 (2.74)	63.09	(51.81, 71.73)	<0.001
Age group					
≥ 65 years	4/703 (0.57)	8/680 (1.18)	51.91	(-59.98, 85.54)	0.233
18–64 years	70/6498 (1.08)	189/6499 (2.9)	63.47	(51.95;72.23)	<0.001
Presence of comorbidity at baseline					
Yes	28/2516 (1.11)	75/2540 (2.95)	61.87	(41.15, 75.29)	<0.001
No	46/4309 (1.07)	115/4227 (2.72)	61.62	(45.98, 72.73)	<0.001
Sex					
Male	24/3285 (0.73)	82/3237 (2.53)	71.34	(54.85, 81.81)	<0.001
Female	50/3916 (1.28)	115/3942 (2.92)	56.97	(40.04, 69.12)	<0.001
Country					
United Kingdom	23/3048 (0.75)	82/3136 (2.61)	71.70	(55.07, 82.17)	<0.001
Brazil	49/3414 (1.44)	112/3339 (3.35)	57.61	(40.73, 69.68)	<0.001
South Africa	2/739 (0.27)	3/704 (0.43)	37.13	(-276.69, 89.51)	0.611
Time interval between dose 1 and dose 2					
4–8 weeks	54/4796 (1.13)	117/4662 (2.51)	56.42	(39.86, 68.43)	<0.001
9–12 weeks	11/1053 (1.04)	39/1101 (3.54)	70.48	(42.41, 84.87)	<0.001
> 12 weeks	8/1146 (0.70)	38/1213 (3.13)	77.62	(51.98, 89.57)	<0.001

Safety

The safety analysis reported in this document reflects data obtained up to 4 November 2020.

The overall safety analysis of the AZD1222 vaccine is based on an interim analysis of pooled data from the four clinical trials. At the time of analysis, safety data were available for 23 745 participants aged 18 years and older. Of these, 12 021 subjects received at least one dose of the vaccine, and 8266 received two doses.

At the time of analysis the median follow up time after dose 1 was 105 days in the AZD1222 group and 104 days in the control group.

Demographic characteristics were generally similar in the vaccine and control groups. Among the participants who received AZD1222, 90.3% were aged 18–64 years and 9.7% were 65 years of age or older. The majority of recipients were white (75.5%), 10.1% were black and 3.5% were Asian; 55.8% were female and 44.2% male.

Adverse reactions

The majority of the adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination. Adverse reactions reported after the second dose were milder and less frequent than after the first dose. Reactogenicity was generally milder and less frequent in older adults (≥65 years old) than in younger adults (18–64 years). Analyses of safety data by age, comorbidity, baseline seropositivity and country did not raise any specific concerns.

The most frequently reported adverse reactions were injection site tenderness (63.7%), injection site pain (54.2%), headache (52.6%), fatigue (53.1%), myalgia (44.0%), malaise (44.2%), pyrexia (including feverishness (33.6%) and fever >38 °C (7.9%)), chills (31.9%), arthralgia (26.4%) and nausea (21.9%).

The incidence of subjects with at least one solicited local or systemic event after any vaccination was highest on day 1 following vaccination, decreasing to 4% and 13%, respectively, by day 7. The most common systemic solicited adverse events (AEs) on day 7 were fatigue, headache and malaise.

- Very common (≥10% of subjects): headache, nausea, myalgia, arthralgia, injection site tenderness, injection site pain, injection site warmth, injection site pruritus, fatigue, malaise, feverishness, chills.
- Common (1–10% of subjects): injection site swelling, injection site erythema, fever ≥ 38 °C.

Safety data are limited in older subjects, particularly those ≥ 65 years. The frequency and severity of the solicited AEs were lower in subjects ≥ 65 years, and the incidence of serious adverse events (SAEs) and adverse events of special interest (AESI) was similar in those under and over 65 years. There was no clinically relevant difference seen in the larger population of subjects that had at least one comorbidity.

Adverse events of special interest

Neuroinflammatory events

A very small number of neuroinflammatory events have been reported following vaccination. A causal relationship has not been established.

Neurological cases of interest

A new diagnosis of multiple sclerosis was seen in the vaccine arm of one subject, with symptom onset 10 days after the first dose. Magnetic resonance imaging (MRI) of the brain and spinal cord demonstrated multiple lesions. All but one of these lesions were not gadolinium-enhancing, suggesting that most lesions predated the vaccine dose.

A probable case of short segment inflammatory myelitis was seen in one subject in the vaccine arm, although the diagnosis is not certain. Symptom onset was 14 days after the second vaccine dose.

The available data do not allow a causal association between the vaccine and the two cases to be concluded with certainty.

One case of transverse myelitis was seen in the control group. Symptom onset was 54 days after the first control dose. Two cases of trigeminal neuralgia were also seen in the control group.

Facial palsies

Six cases of facial paralysis were seen, three each in the vaccine and control group. The three cases in the vaccine group were all one-sided facial nerve palsies, two had features suggesting they were not related to vaccination (one case is considered related to chronic suppurative otitis media/mastoiditis and the other occurred 80 days after vaccination).

Neuroinflammatory conditions are included in the risk management plan as an important potential risk and will be closely monitored through routine and additional pharmacovigilance activities.

Serious adverse events

Five SAEs were considered to be related to vaccination, of which two were in the vaccine group (pyrexia and transverse myelitis) and three were in the control group (autoimmune haemolytic anaemia, increased C-reactive protein and myelitis).

Special considerations

Pregnancy

Pregnancy was reported for 21 subjects: 12 in the vaccine group and 9 in the control group. Five cases ended in spontaneous abortion: 2 in the vaccine and 3 in the control group.

Animal studies of potential toxicity during reproduction and development are ongoing. Preliminary preclinical studies in mice do not indicate harmful effects on fertility, pregnancy, embryo-fetal development, parturition or postnatal development.

A pregnancy sub-study and pregnancy registry are planned.

Administration of vaccine in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.

Breastfeeding

It is unknown whether the vaccine is excreted in human milk.

Pediatric population

No data are available in subjects under 18 years of age.

Immunosuppression

No data are currently available in immunocompromised subjects, including those receiving immunosuppressant therapy. The efficacy of the vaccine may be lower in immunosuppressed individuals. Safety data are awaited in a subgroup of HIV-positive subjects.

Safety related to vaccine interactions

No data are available on use of the vaccine with concomitant vaccines, including influenza vaccines. Licensed seasonal influenza and pneumococcal vaccinations were permitted at least 7 days before or after the study vaccine.

Considerations for vaccinating older adults (age ≥ 65 years)

Vaccine efficacy in older adults aged 65 years or more is uncertain, because only 9.8% of the trial participants were in this age category. This sample size was too small to allow vaccine efficacy to be estimated in this age group with precision, since the infection rate in this age group was relatively low (e.g. as a result of shielding behaviour). Only 8 cases in the control arm and 4 cases in the vaccine arm were observed 15 days or more after the second dose of vaccine (based on the 7 December 2020 data cut), yielding a vaccine efficacy of 51.91% (95% CI: –59.98 to 85.54%). Efficacy was observed starting from day 22 after the first dose. While a longer interval between doses increased efficacy and immunogenicity in the study group as a whole, relevant data are not available for older persons as most of them received the second dose 4–6 weeks after the first. No cases of COVID-19 requiring hospitalization were recorded among those receiving two doses of vaccine, compared with two in the control group in this age group. Safety data from 1169 vaccine recipients in this age group indicate that the vaccine was well tolerated with no concerning safety signals. However, detection of rare outcomes will require continued safety monitoring during the ongoing phase 3 trials and programme use of the vaccine. Immunogenicity data from phase 1/2 studies indicate high seroconversion rates of S-binding antibodies after the first SD (97.8%) and the second SD (100%) in older adults; T-cell responses were comparable in older and younger age groups (3-7).

The infection fatality rate for COVID-19 rises exponentially with age and most deaths globally have been among adults aged over 65 years (9, 10). Older adults are therefore identified as a priority population in the WHO SAGE roadmap for prioritizing uses of COVID-19 vaccines in the context of limited supply (11). This prioritization is supported by vaccine impact modelling work, including scenarios with substantially reduced vaccine efficacy in older adults (12).

Emerging virus variants of concern

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.

AZD1222 was designed around the SARS-CoV-2 prototype virus identified in November 2019. Since then, the SARS-CoV-2 spike gene has accumulated mutations, including within the receptor-binding domain (RBD) and N-terminal domain (NTD), which are major targets of the immune response. The RBD mutations include the N501Y mutation, which is associated with increased affinity for the angiotensin-converting enzyme-2 (ACE2); the E484K and K417N RBD mutations and mutations in the NTD have been associated with neutralizing antibody escape (13).

The N501Y.V1 (B.1.1.7) lineage, first identified in the United Kingdom, includes an N501Y mutation, which has been associated with 53% increased transmissibly compared with earlier variants (14). The B.1.1.7 variant has now further evolved in the United Kingdom to include the E484K mutation.

The N501Y.V2 (B.1.351) lineage, first identified in South Africa, contains three RBD and one NTD mutations (L18F, D80A, D215G, R246I) and a three amino acid deletion from positions 242 to 244). Assessment of the sensitivity of

B.1.351 to neutralizing antibodies from convalescent donors infected with original lineage virus, using a spike-pseudotyped neutralization (PSVA) assay, demonstrated that 48% of the sera were unable to neutralize B.1.351, with the rest showing 3–86-fold lower neutralization capacity than with original lineage virus (15). This was corroborated using a live virus neutralization assay (LVNA), which showed a reduction in antibody activity ranging from 6-fold to knockout for the B.1.351 variant (16).

A preprint of work in progress reports that AZD1222 vaccine has similar efficacy against the B.1.1.7 coronavirus strain currently circulating in the United Kingdom as against previously circulating variants (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3779160). The protection against symptomatic infection was similar despite lower neutralizing antibody titres in vaccinated individuals against the B.1.1.7 variant than the original strain identified in Wuhan.

In the South African multisite, randomized, double-blind, placebo-controlled phase 1/2a trial (COV005) on safety and efficacy of AZD1222 vaccine in young healthy adults aged 18–65 years, dose two serum samples (n=26) were tested using PSVA and LVNA for neutralization activity against the B.1.351 variants. At the time of writing, this analysis had not been peer-reviewed, and was available only as a preprint. The B.1.351 variant showed high resistance to sera from vaccine recipients in the PSVA and LVNA. In the primary objective analysis, 23 (3.2%) of 717 placebo recipients and 19 (2.5%) of 750 vaccinees developed mild to moderate COVID-19; VE 21.9% (95%CI: –49.9 to 59.8). Of the 42 primary endpoint cases, 39 (92.9%) were due to the B.1.351 variant, against which VE was 10.4% (95% CI: –76.8 to 54.8).

Although this study indicates that AZD1222 vaccine does not protect against mild to moderate COVID-19 caused by the B.1.351 variant, extrapolating from immunological insights, it may still protect against severe COVID-19. Other vaccine-induced immune mediators, such as Th1 dominated cell-mediated immune responses, including T-helper cytotoxic CD8+ cells, may play a more central role in reducing the risk of severe COVID-19 rather than neutralizing antibodies alone.

Indirect evidence is compatible with protection against severe COVID-19; however, this remains to be demonstrated in ongoing clinical trials and post-implementation evaluations. 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.

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Annexes

Note:

Annexes 1–6 contain tables that summarize the grading of recommendations, assessment, development and evaluations (GRADE). Annexes 7–9 contain the SAGE evidence-to-recommendation framework tables (ETR tables). The ETR tables are based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel) (www.decide-collaboration.eu/, accessed 11 January 2021).

Annex 1. GRADE table: Efficacy of AZD1222 COVID-19 vaccine in adults

Population : Adults (18–64 years)

Intervention: Two doses of AZD1222 vaccine

Comparison: Placebo/active control

Outcome : COVID-19 (PCR-confirmed)

What is the efficacy of two doses of AZD1222 vaccine compared with placebo/active control in preventing PCR-confirmed COVID-19 in adults (18–64 years)?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT(1)	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious[b]	0
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		Imprecision	Not serious	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a high level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 4, or ⊕⊕⊕⊕).**
	Conclusion			We are very confident that 2 doses of AZD1222 vaccine are efficacious in preventing PCR-confirmed COVID-19 in adults (18–64 years).

Reference

1. Single dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine. (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3777268, accessed 3 February 2021).

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Data on long-term protection emerging from the ongoing phase 3 clinical trial remain limited, as trial data have so far been reported only for a follow-up of approximately 2 months. This was considered as not constituting a limitation that would lead to downgrading of the evidence. SAGE will continue to review any emerging data and adjust its quality assessment as required.

Annex 2. GRADE table: Safety of AZD1222 COVID-19 vaccine in adults

Population : Adults (18–64 years)

Intervention: One or two doses of AZD1222 vaccine

Comparison: Placebo/active control vaccination

Outcome : Serious adverse events following immunization

What is the risk of serious adverse events following AZD1222 vaccination compared with placebo/active control in adults (18–64 years)?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2/ RCT (1, 2)	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		Imprecision	Not serious	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a moderate level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 3, or ⊕⊕⊕).**
	Conclusion			We are moderately confident that the risk of serious adverse events following one or two doses of AZD1222 vaccine in adults (18–64 years) is low.

References

1. Single dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine. (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3777268, accessed 3 February 2021).
2. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet. 2020;396(10249):467-78.

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Downgraded for the following limitations. The trial was not adequately powered to detect rare adverse events (i.e. fewer than about 1 in 2000). These may emerge only when large populations have been vaccinated. The limited follow-up time of the clinical trial may not allow detection of adverse events occurring several months after vaccination.

Annex 3. GRADE table: Efficacy of AZD1222 COVID-19 vaccine in older adults

Population : Older adults (≥65 years)

Intervention: Two doses of AZD1222 vaccine

Comparison: Placebo/active control

Outcome : COVID-19 (PCR-confirmed)

What is the efficacy of two doses of AZD1222 vaccine compared with placebo/active control in preventing PCR-confirmed COVID-19 in older adults (≥65 years)?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT (1)	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		Imprecision	Serious[b]	-2
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a limited level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 2, or ⊕⊕).**
	Conclusion			Due to insufficient evidence, we have low confidence in the evidence indicating that 2 doses of AZD1222 vaccine are efficacious in preventing PCR-confirmed COVID-19 in older adults (≥65 years).

Reference

1. Single dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine. (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3777268, accessed 3 February 2021).

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Approximately 10% (1380) of the trial participants were aged 65 years or over. While supportive evidence (immunogenicity data in this age group) suggest that the vaccine elicits an immune response comparable to that in younger adults, the trial did not show a statistically significant vaccine efficacy in this age group. The very serious imprecision due to large confidence intervals and the limited sample size were considered as constituting a limitation that leads to downgrading of the evidence. Data on long-term protection emerging from the ongoing phase 3 clinical trial remain limited, as trial data have so far been reported only for a follow-up of approximately 2 months. This was considered as not constituting a limitation that would lead to downgrading of the evidence. SAGE will continue to review any emerging data and adjust its quality assessment as required.

Annex 4 GRADE table: Safety of AZD1222 COVID-19 vaccine in older adults

Population : Older adults (≥65 years)

Intervention: One or two doses of AZD1222 vaccine

Comparison: Placebo/active control

Outcome : Serious adverse events following immunization

What is the risk of serious adverse events following AZD1222 vaccination compared with placebo/active control in older adults (≥65 years)?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		4/ RCT(1, 2)	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		Imprecision	Serious[c]	-1
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a limited level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 2, or ⊕⊕).**
	Conclusion			We have low confidence in the quality of evidence that the risk of serious adverse events following one or two doses of AZD1222 vaccine in older adults (≥65 years) is low.

References

1. Single dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine. (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3777268, accessed 3 February 2021).
2. Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. Lancet 2021;396(10267):1979-93.

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Downgraded for the following limitations. The trial was not adequately powered to detect rare adverse events (i.e, about 1 in 250). These may emerge only when large populations have been vaccinated. The limited follow-up time of the clinical trial may not allow detection of adverse events occurring several months after vaccination.

[c] Approximately 10% (1380) of the trial participants were aged 65 years or over. This was considered as constituting a limitation that leads to downgrading of the evidence.

Annex 5. GRADE table: Efficacy of AZD1222 COVID-19 vaccine in individuals with underlying conditions

Population : Individuals with comorbidities or health states that increase risk for severe COVID-19

Intervention: Two doses of AZD1222 vaccine

Comparison: Placebo/active control

Outcome : COVID-19 (PCR-confirmed)

What is the efficacy of two doses of AZD1222 vaccine compared with placebo/active control in preventing PCR-confirmed COVID-19 in individuals with comorbidities or health states that increase risk for severe COVID-19?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		3/ RCT(1, 2)	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Serious[b]	-1
		Imprecision	Not serious[c]	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a moderate level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 3, or ⊕⊕⊕).**
	Conclusion			We are moderately confident that 2 doses of AZD1222 vaccine are efficacious in preventing PCR-confirmed COVID-19 in individuals with comorbidities or health states that increase risk for severe COVID-19 as included in the clinical trial. No data were obtained on vaccination of pregnant or breastfeeding women, or persons who were immunocompromised.

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Trial excluded pregnant and breastfeeding women, and persons who were immunocompromised. Although persons with HIV were included in the trial, they were not included in the analyses. This was considered as constituting a limitation that leads to downgrading of the evidence.

[c] Underlying comorbidities included BMI ≥ 30 kg/m^2, cardiovascular disorder, respiratory disease and diabetes. Approximately 36% of the trial population had at least one comorbidity. This was considered as not constituting a limitation that would lead to downgrading of the evidence. Data on long-term protection emerging from the ongoing phase 3 clinical trial remain limited, as trial data have so far been reported only for a follow-up of approximately 2 months. This was considered as not constituting a limitation that would lead to downgrading of the evidence. SAGE will continue to review any emerging data and adjust its quality assessment as required.

References

1. Single dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine. (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3777268, accessed 3 February 2021).
2. Public assessment report. Authorisation for temporary supply. COVID-19 Vaccine AstraZeneca, solution for injection in multidose container COVID-19 Vaccine (ChAdOx1-S [recombinant]). Medecines and Healthcare Products Regulatory Agency; 2021 (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/949772/UKPAR_COVID_19_Vaccine_AstraZeneca_05.01.2021.pdf , accessed 5 February 2021).

Annex 6. GRADE table: Safety of AZD1222 COVID-19 vaccine in individuals with underlying conditions

Population : Individuals with comorbidities or health states that increase risk for severe COVID-19

Intervention: One or two doses of AZD1222 vaccine

Comparison: Placebo/active control

Outcome : Serious adverse events following immunization

What is the risk of serious adverse events following AZD1222 vaccination compared with placebo/active control in individuals with comorbidities or health states that increase risk for severe COVID-19?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		4/ RCT(1, 3)	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Serious[c]	-1
		Imprecision	Not serious	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a limited level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 2, or ⊕⊕).**
	Conclusion			We have low confidence in the quality of evidence that the risk of serious adverse events in individuals with comorbidities or health states that increase risk for severe COVID-19 following one or two doses of AZD1222 vaccine is low.

References

1. Single dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine. (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3777268, accessed 3 February 2021).
2. Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. Lancet 2021;396(10267):1979-93.

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Downgraded for the following limitations. The trial was not adequately powered to detect rare adverse events (i.e. fewer than about 1 in 800). These may emerge only when large populations have been vaccinated. The limited follow-up time of the clinical trial may not allow detection of adverse events occurring several months after vaccination.

[c] Trial excluded pregnant and breastfeeding women, and persons who were immunocompromised. Although persons with HIV were included in the trial, they were not included in the analyses. This was considered as constituting a limitation that leads to downgrading of the evidence.

Annex 7. SAGE evidence-to-recommendation framework: AZD1222 vaccine use in adults

Question: Should AZD1222 vaccine be administered to adults to prevent COVID-19?

Population: Adults (18–64 years)

Intervention: Two doses of AZD1222 vaccine

Comparison(s): Active control/placebo

Outcome: COVID-19 (PCR-confirmed)

Background: On 31 December 2019, WHO was alerted to several cases of pneumonia of unknown origin in Wuhan City, Hubei Province, China. The cause was found to be a novel coronavirus, SARS-CoV-2. The disease caused by this novel virus has been named COVID-19. The outbreak of COVID-19 was declared a public health emergency of international concern in January 2020. The disease has since spread, with an enormous impact on the health and well-being of individuals and populations worldwide. It has further caused major disruptions to various sectors of society and the economy across the globe.

Vaccines are a critical tool in combating the pandemic. In the rapidly evolving field of COVID-19 vaccines, WHO has to date issued interim recommendations on the use of Pfizer–BioNTech and Moderna COVID-19 vaccines (1, 2).

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No*	*Un-certain*	*Yes*	*Varies by setting*	The cumulative number of COVID-19 cases globally has surpassed 101 571 219 with more than 2 196 944 deaths. Cases have been found in 190 different countries or territories throughout the world (status 30 January 2021). There has been collateral damage to other public health programmes.	The COVID-19 situation is evolving rapidly; the most recent epidemiological situation can be found on the following website: https://covid19.who.int/table
		☐	☐	☒	☐		

BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Using 07 December 2020 as the data cut-off point, primary efficacy analysis shows that AZD1222 vaccine is 63.1% efficacious (95%CI 52.9–68.6%) across the study population. In those aged 18–64 years, vaccine efficacy was 63.5% (95%CI 52.0–72.2%). Vaccine efficacy in all participants varied by interval between first and second dose: <4 weeks interval: 66.56% (95%CI –221.8 to 96.5%) 4–8 weeks interval: 56.42% (95%CI 39.9–68.4%) 9–12 weeks interval: 70.48% (95%CI 42.4–84.9%) >12 weeks interval: 77.62% (95%CI 52–89.6%) Vaccine efficacy against COVID-19 occurring ≥ 22 days after the first dose (and before the second dose or up to 12 weeks after first dose) was 71.42% (95%CI 51.11–84.08%) in all participants.	The immunogenicity results from the phase 1/2 United Kingdom study, in 1077 healthy adults aged 18–55 years (3) and a phase 2 cohort in older adults (≥56 years)(4) showed the induction of binding and neutralizing antibodies, with higher antibody titres after a second dose of vaccine.(3, 4, 5) The vaccine further induced $CD4^+$ and $CD8^+$ T cells in adults aged 18–55 years, up to 8 weeks after vaccination with a single dose (6).
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Data from over 12 021 participants demonstrated that AZD1222 vaccine was well tolerated across all populations. Overall, 86% of subjects in the vaccine group (days 0-7 after any vaccination) experienced at least one solicited AE compared with 72% in the control group. The majority of solicited AEs were mild or moderate. Ten percent of subjects in the vaccine group experienced at least one local solicited AE of grade 3 or higher and 8% at least one systemic solicited event of grade 3 or higher, compared with 6% and 3% in the control group, respectively. Solicited AEs were milder and reported less frequently after the second dose than after the first.	The results from a phase 1/2 and a phase 2 immunogenicity and safety trial suggest an acceptable safety profile in healthy adults aged 18–55 years (3) as well as in older adults (≥56 years) (4)

			The most frequently reported systemic solicited AEs in the standard dose vaccine group after any vaccination were fatigue (53%) and headache (53%). Fewer than 1% of subjects reported a serious adverse event (SAE) and the reporting rate was balanced between the two study groups (0.7% vaccine group, 0.8% control). There were no clinically meaningful imbalances in SAE incidence for any subgroup (country, age, serostatus or comorbidity). There are no long-term safety data available yet and follow-up time remains limited.	
	Balance between benefits and harms	***Favours inter-vention*** ☒ ***Favours com-parison*** ☐ ***Favours both*** ☐ ***Favours neither*** ☐ **Unclear** ☐	Efficacy data suggest benefit, and short-term safety data suggest minimal harms. Further ongoing studies will need to be undertaken as part of post-marketing surveillance.	
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention ***No included studies*** ☐ ***Very low*** ☐ ***Low*** ☐ ***Mod-erate*** ☐ ***High*** ☒	Please see the related GRADE tables.	

		Safety of the intervention ***No included studies*** ☐ ***Very low*** ☐ ***Low*** ☐ ***Moderate*** ☒ ***High*** ☐		
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	***Important uncertainty or variability*** ☐ ***Possibly important uncertainty or variability*** ☒ ***Probably no important uncertainty or variability*** ☐ ***No important uncertainty or variability*** ☐ ***No known undesirable outcomes*** ☐	Available scientific evidence on the relative importance of the intervention, as well as the relative weights that the target population attributes to the desirable (i.e. protection conferred by the vaccine) and the undesirable outcomes (i.e. the currently reported safety signals), vary. Different population groups may have different opinions regarding the weights assigned to desirable and undesirable outcomes.	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐	Available scientific evidence suggests that target population probably assigns more weight to the desirable effects than to the undesirable effects related to COVID-19 vaccination. Targeted information campaigns should assess this aspect.	
RESOURCE	Are the resources	*No* *Uncertain* *Yes* *Varies*	AZD1222 can be distributed and stored using existing cold chain infrastructure (at 2–8 °C) (9)	An estimated US$15.9 billion is needed for the vaccines pillar

	required small?	☒	☐	☐	☐	and does not require ultra-cold chain capacity. In addition, as AZD1222 can be manufactured with widely available manufacturing capacity around the world (8), its price is expected to be lower than those of other COVID-19 vaccines that use new and less widely available manufacturing platforms. Prices for AZD1222 are also expected to be lower than those of many other COVID-19 vaccines because the supplier has committed to forego profits (9). Nevertheless, considerable resources will be needed to ensure the implementation of a COVID-19 vaccination programme, especially given: (i) that COVID-19 vaccination is likely to be prioritized for populations (e.g. health care workers, older adults) without pre-existing robust immunization programmes in many settings, and (ii) the urgency of vaccination roll-out worldwide, which may necessitate additional surge resources to accelerate implementation with adequate infection prevention and control procedures in the context of COVID-19. Resources required include, but are not restricted to, human resources, vaccine costs, logistics, planning and coordination, training, social mobilization and communications, and immunization safety surveillance.	(COVAX) of the Access to COVID-19 Tools Accelerator (ACT-A) for 2020–21, in order to deliver 2 billion doses. This does not include all delivery costs in all countries participating in COVAX, bilateral procurement deals, or research and development investments outside of COVAX (10). The World Bank has approved a financing window of up to US$12 billion to support low- and middle-income countries in purchasing and distributing vaccine (11).
	Cost-effectiveness	*No*	*Un-certain*	*Yes*	*Varies*	Formal global cost-effectiveness analyses have not been conducted, but the emerging evidence indicates that the benefits, including the impact on recovery of the global economy, are likely to outweigh the cost of COVID-19 vaccination in general at global level.	The global economy is estimated to be losing US$375 billion per month because of the coronavirus pandemic. G20 countries have invested approximately US$10 trillion in domestic economic stimulus to mitigate the economic consequences of reduced business activity and unemployment due to the pandemic. Initial estimates suggest that COVID-19 vaccination will provide substantial economic value in terms of averted morbidity and mortality costs and averted losses in gross domestic product (GDP) (10;12–18).
		☐	☐	☐	☒	No formal cost-effectiveness analyses of AZD1222 compared with other vaccines have been conducted. The AZD1222 vaccine is expected to be less costly than many other COVID-19 vaccines (see previous sub-criterion). Individual-level efficacy against COVID-19 may be lower than that of some other	

				COVID-19 vaccines; more data are needed to assess efficacy against other endpoints (e.g. hospitalizations averted; see main text). The ability to use AZD1222 in existing cold chain infrastructure in all country settings may allow higher population-level coverage. Cost-effectiveness analyses should be conducted at country level; cost-effectiveness of COVID-19 vaccination may vary by country depending on COVID-19 burden, comparator interventions assessed, analysis perspective, and local cost-effectiveness thresholds used.	
EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐	*Un-certain* ☐	*Reduced* ☒	*Varies* ☐	Equity and ethical considerations are critical. SAGE has produced a Values Framework (19), which offers guidance on the fair allocation of COVID-19 vaccines based on six core ethical principles that should guide distribution. If distributed fairly, COVID-19 vaccines may have considerable impact on reducing health inequities. Storage and distribution requirements of the AZD1222 vaccine are the same as those of many other vaccines currently in use globally. Existing vaccine cold-chain capacity, available in almost all countries, could be leveraged for vaccine distribution.	Vaccine nationalism is seen as a threat to reducing health inequity, in particular as high-income countries have arranged bilateral contracts with manufacturers. This has led to the establishment of the Access to COVID-19 Tools (ACT) Accelerator and, within this, the COVAX facility, which aims to ensure equitable access to vaccines for its participating member states (20).
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health,	*Inter-vention*	*Com-parison*	*Both*	*Neither*	*Un-clear*	No scientific evidence is available. As vaccination is an eagerly awaited tool to combat COVID-19, it is assumed that key stakeholders, in particular ministries of health and immunization managers, are strongly in favour of it.	The fact that 190 economies are participating in COVAX suggests a very high acceptability of COVID-19 vaccination in general, though not necessarily of this vaccine in particular.

	immunization managers)?	☒	☐	☐	☐	☐		
	Which option is acceptable to target group?	*Inter-vention*	*Com parison*	*Both*	*Neither*	*Un-clear*	COVID-19 vaccine acceptability in general varies between (sub-)population groups and may be correlated with the perceived risk posed by the disease. In a global survey (19 countries) of acceptance rates in the general population of any COVID-19 vaccine product, 71.5% of participants reported that they would be very or somewhat likely to take a COVID-19 vaccine. Acceptance rates ranged from almost 55% to 87% (21).	
		☒	☐	☐	☐	☐	Representative multi-country surveys are carried out periodically to assess the percentage of those willing to receive (or of those who already have received) COVID-19 vaccination (non-product specific) . While these polls are limited to selected countries, they provide a certain degree of insight into vaccine acceptance and trends over time. (22, 23)	
FEASIBILITY	Is the intervention feasible to implement?	*No*	*Probably No*	*Un-certain*	*Probably Yes*	*Yes*	*<u>Varies</u>*	Administration of this vaccine is assumed to be easily implementable in settings – including low- and middle-income-countries – with existing vaccine logistics and delivery infrastructure. Administration of the vaccine to target groups that are currently not reached by national immunization programmes may pose a challenge in certain settings.	
		☐	☐	☐	☐	☒	☐		
Balance of consequences		Undesirable consequences *clearly outweigh*	Undesirable consequences *probably outweigh* desirable		The balance between desirable and undesirable consequences		Desirable consequences *probably outweigh* undesirable	Desirable consequences *clearly outweigh* undesirable	

	desirable consequences in most settings ☐	consequences in most settings ☐	*is closely balanced or uncertain* ☐	consequences in most settings ☐	consequences in most settings ☒
Type of recommendation	We recommend the intervention ☐	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☒ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐
Recommendation (text)	Vaccination with AZD1222 vaccine is recommended in persons aged 18 and above. 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.				
Implementation considerations					
Monitoring, evaluation and research priorities	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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Annex 8. SAGE evidence-to-recommendation framework: AZD1222 vaccine use in older adults

Question: Should AZD1222 vaccine be administered to older adults to prevent COVID-19?

Population: Older adults (≥65 years)

Intervention: Two doses of AZD1222 vaccine

Comparison(s): Active control/placebo

Outcome: COVID-19 (PCR-confirmed)

Background: On 31 December 2019, WHO was alerted to several cases of pneumonia of unknown origin in Wuhan City, Hubei Province, China. The cause was found to be a novel coronavirus, SARS-CoV-2. The disease caused by this novel virus has been named COVID-19. The outbreak of COVID-19 was declared a public health emergency of international concern in January 2020. The disease has since spread with an enormous impact on the health and well-being of individuals and populations worldwide. It has further caused major disruptions to various sectors of society and the economy across the globe.

Vaccines are a critical tool in combating the pandemic. In the rapidly evolving field of COVID-19 vaccines, WHO has to date issued interim recommendations on the use of Pfizer-BioNTech and Moderna COVID-19 vaccines (1, 2).

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No*	*Un-certain*	*Yes*	*Varies by setting*	The cumulative number of COVID-19 cases globally has surpassed 101 571 219 with more than 2 196 944 deaths. Cases have been found in 190 different countries or territories throughout the world (status 30 January 2021). There has been collateral damage to other public health programmes. Older adults are particularly affected by COVID-19 and bear a significantly higher risk of severe COVID-19 outcomes and death.	The COVID-19 situation is evolving rapidly; the most recent epidemiological situation can be found on the following website: https://covid19.who.int/table
		☐	☐	☒	☐		

BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☒	*Yes* ☐	*Varies* ☐	Around 10% of the study population in the primary analysis (data cut-off 7 December 2020; trials COV001, COV002, COV003, COV005) were aged 65 years or older. Primary efficacy analysis of 2 standard doses at any interval found a vaccine efficacy of 51.9% (95%CI –60.9–86.0%) in individuals aged 65 years and older against COVID-19, beginning 15 days after the second dose. A relatively small proportion of participants were aged 65 years or over and the number of cases of COVID-19 in this age group was too small to allow assessment of protection based on the efficacy data alone . There were no COVID-19 hospitalizations, no severe COVID-19 disease, and no COVID-19 deaths in participants ≥65 years of age who received the vaccine.	The immunogenicity results from the phase 1/2 United Kingdom study, in 1077 healthy adults aged 18–55 years (3) and a phase 2 cohort in older adults (≥56 years)(4) showed the induction of binding and neutralizing antibodies, with higher antibody titres after a second dose of vaccine (3, 4, 5). The vaccine further induced $CD4^+$ and $CD8^+$ T cells in adults aged 18–55 years, up to 8 weeks after vaccination with a single dose (6).
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Data from over 12 021 trial participants of all ages demonstrated that AZD1222 vaccine was well tolerated across all populations. Overall, 86% of subjects in the vaccine group (days 0–7 after any vaccination) experienced at least one solicited AE compared with 72% in the control group. The majority of solicited AEs were mild or moderate. Ten percent of subjects in the vaccine group experienced at least one local solicited AE of grade 3 or higher and 8% at least one systemic solicited event of grade 3 or higher, compared with 6% and 3% in the control group, respectively. Solicited AEs were milder and reported less frequently after the second dose than after the first.	The results from a phase 1/2 and a phase 2 immunogenicity and safety trial suggest an acceptable safety profile in healthy adults aged 18–55 years (3) as well as in older adults (≥56 years) (4)

								Reactogenicity was generally milder and less frequent in older adults (≥65 years old) compared with younger adults (18–64 years). The most frequently reported systemic solicited AEs in the standard-dose group after any vaccination were fatigue (53%) and headache (53%). Fewer than 1% of subjects reported a serious adverse event (SAE) and the reporting rate was balanced between the two study groups (0.7% vaccine group, 0.8% control). There were no clinically meaningful imbalances in SAE incidence for any subgroup (country, age, serostatus or comorbidity). There are no long-term safety data available yet and follow-up time remains limited.	
	Balance between benefits and harms	***Favours intervention***	***Favours comparison***	***Favours both***	***Favours neither***	**Unclear**		Efficacy data suggest some, though not significant, benefit of the intervention, and short-term safety data suggest limited harm. Further ongoing studies will need to be undertaken as part of post-marketing surveillance.	
		☒	☐	☐	☐	☐			

	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention ***No included studies*** ☐ ***Very low*** ☐ ***Low*** ☒ ***Moderate*** ☐ ***High*** ☐ Safety of the intervention ***No included studies*** ☐ ***Very low*** ☐ ***Low*** ☒ ***Moderate*** ☐ ***High*** ☐	Please see the related GRADE tables.	
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	***Important uncertainty or variability*** ☐ ***Possibly important uncertainty or variability*** ☒ ***Probably no important uncertainty or variability*** ☐ ***No important uncertainty or variability*** ☐ ***No known undesirable outcomes*** ☐	The majority of severe disease occurs in older individuals. Available scientific evidence suggests that the target population probably considers the desirable effects, i.e. the potential protection conferred by the vaccine, more important than the undesirable effects, i.e. the currently reported safety signals related to COVID-19 vaccination. Different population groups may have different opinions regarding the weights assigned to desirable and undesirable outcomes.	
	Values and preferences of the target population: Are the desirable	*No* *Probably No* *Uncertain* *Probably Yes* *Yes* *Varies*	Available scientific evidence suggests that the target population probably assigns more weight to the desirable effects than the undesirable effects related to COVID-19 vaccination.	

	effects large relative to undesirable effects?	☐	☐	☐	☒	☐	☐	Targeted information campaigns should assess this aspect. With more data on vaccine efficacy in older adults being generated, the uncertainty around the importance of the desirable effects of the intervention will probably be reduced.	
RESOURCE USE	Are the resources required small?	*No*		*Un-certain*		*Yes*	*Varies*	AZD1222 can be distributed and stored using existing cold-chain infrastructure (at 2–8 °C) (7) and does not require ultra-cold chain capacity. In addition, as AZD1222 can be manufactured with widely available manufacturing capacity around the world (8), its price is expected to be lower than those of other COVID-19 vaccines that use new and less widely available manufacturing platforms. Prices are also expected to be lower for AZD1222 than for many other COVID-19 vaccines because the supplier has committed to forego profits (9). Nevertheless, considerable resources will be needed to ensure the implementation of a COVID-19 vaccination programme, especially given: (i) that COVID-19 vaccination is likely to be prioritized for populations (e.g. health care workers, older adults) without pre-existing robust immunization programmes in many settings, and (ii) the urgency of vaccination roll-out worldwide, which may necessitate additional surge resources to accelerate implementation with adequate infection prevention and control procedures in the context of COVID-19. Resources required include, but are not restricted to, human resources, vaccine costs, logistics, planning and coordination, training, social mobilization and communications, and immunization safety surveillance.	An estimated US$15.9 billion is needed for the vaccines pillar (COVAX) of the Access to COVID-19 Tools Accelerator (ACT-A) for 2020–21, in order to deliver 2 billion doses. This does not include all delivery costs in all countries participating in COVAX, bilateral procurement deals, or research and development investments outside of COVAX (10). The World Bank has approved a financing window of up to US $12 billion to support low- and middle-income countries in purchasing and distributing vaccine (11).
		☐		☐		☒	☐		
	Cost-effectiveness	*No*		*Un-certain*		*Yes*	*Varies*	Formal global cost-effectiveness analyses have not been conducted, but the emerging evidence	The global economy is estimated to be losing US$375 billion per month

		☐	☐	☐	☒	indicates that the benefits, including the impact on recovery of the global economy, are likely to outweigh the cost of COVID-19 vaccination in general at global level. No formal cost-effectiveness analyses of AZD1222 compared with other vaccines have been conducted. The AZD1222 vaccine is expected to be less costly than many other COVID-19 vaccines (see previous sub-criterion). Individual-level efficacy against COVID-19 may be lower than that of some other COVID-19 vaccines; more data are needed to assess efficacy against other endpoints (e.g. hospitalizations averted; see main text). The ability to use AZD1222 in existing cold-chain infrastructure in all country settings may allow higher population-level coverage. Cost-effectiveness analyses should be conducted at country level; cost-effectiveness of COVID-19 vaccination may vary by country depending on COVID-19 burden, comparator interventions assessed, analysis perspective, and local cost-effectiveness thresholds used.	because of the coronavirus pandemic. G20 countries have invested approximately US$10 trillion in domestic economic stimulus to mitigate the economic consequences of reduced business activity and unemployment due to the pandemic. Initial estimates suggest that COVID-19 vaccination will provide substantial economic value in terms of averted morbidity and mortality costs and averted losses in gross domestic product (GDP) (10;12–18).
EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐	*Un-certain* ☐	*Reduced* ☒	*Varie s* ☐	Equity and ethical considerations are critical. SAGE has produced a Values Framework (19), which offers guidance on the fair allocation of COVID-19 vaccines based on six core ethical principles that should guide distribution. If distributed fairly, COVID-19 vaccines may have considerable impact on reducing health inequities. Storage and distribution requirements of AZD1222 vaccine are the same as those of many other vaccines currently in use globally. Existing vaccine cold-chain capacity, which is available in	Vaccine nationalism is seen as a threat to reducing health inequity, in particular as high-income countries have arranged bilateral contracts with manufacturers. This has led to the establishment of the Access to COVID-19 Tools (ACT) Accelerator and, within this, the COVAX facility, which aims to ensure equitable access to vaccines for its participating member states (20).

		almost all countries, could be leveraged for vaccine distribution.		
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)? *Inter-vention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Un-clear* ☐	No scientific evidence is available. As vaccination is an eagerly awaited tool to combat COVID-19, it is assumed that key stakeholders, in particular ministries of health and immunization managers, are strongly in favour of COVID-19 vaccination.	The fact that 190 economies are participating in COVAX suggests a very high acceptability of COVID-19 vaccination in general, though not necessarily of this vaccine in particular.
	Which option is acceptable to target group? *Inter-vention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Un-clear* ☐	COVID-19 vaccine acceptability varies between (sub-) population groups and may be correlated with the perceived risk posed by the disease. In a global survey (19 countries) of acceptance rates in the general population of any COVID-19 vaccine product, 71.5% of participants reported that they would be very or somewhat likely to take a COVID-19 vaccine. Acceptance rates ranged from almost 55% to 87% (21). Representative multi-country surveys are carried out periodically to assess the percentage of those willing to receive (or of those who already have received) COVID-19 vaccination (non-product specific) . While these polls are limited to selected countries, they provide a certain degree of insight into vaccine acceptance and trends over time. (22,23)	
FEASIBILITY	Is the intervention feasible to implement? *No* *Probably No* *Uncertain* *Probably Yes* *Yes* *Varies*	Administration of this vaccine is assumed to be easily implementable in settings – including low- and middle-income countries – with existing vaccine logistics and delivery infrastructure.	

		☐ ☐ ☐ ☐ ☒ ☐	Administration of the vaccine to target groups currently not reached by national immunization programmes may pose a challenge in certain settings.			
Balance of consequences		Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☒	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐
Type of recommendation		We recommend the intervention ☐	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☒ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐
Recommendation (text)	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 that the vaccine will probably 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 a vaccine efficacy 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.					

Implementation considerations	
Monitoring, evaluation and research priorities	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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Annex 9. SAGE evidence-to-recommendation framework: AZD1222 vaccine use in individuals with comorbidities

Question: Should AZD1222 vaccine be administered to individuals with comorbidities or health states that increase risk for severe COVID-19[16] to prevent COVID-19?

Population: Individuals with comorbidities or health states that increase risk for severe COVID-19

Intervention: Two doses of AZD1222 vaccine

Comparison(s): Active control/placebo

Outcome: COVID-19 (PCR-confirmed)

Background: On 31 December 2019, WHO was alerted to several cases of pneumonia of unknown origin in Wuhan City, Hubei Province, China. The cause was found to be a novel coronavirus, SARS-CoV-2. The disease caused by this novel virus has been named COVID-19. The outbreak of COVID-19 was declared a public health emergency of international concern in January 2020. The disease has since spread, with an enormous impact on the health and well-being of individuals and populations worldwide. It has further caused major disruptions to various sectors of society and the economy across the globe.

Vaccines are a critical tool in combating the pandemic. In the rapidly evolving field of COVID-19 vaccines, WHO has to date issued interim recommendations on the use of Pfizer-BioNTech and Moderna COVID-19 vaccine (1, 2).

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No*	*Uncertain*	*Yes*	*Varies by setting*	The cumulative number of COVID-19 cases globally has surpassed 101 571 219 with more than 2 196 944 deaths. Cases have been found in 190 different countries or territories throughout	The COVID-19 situation is evolving rapidly; the most recent epidemiological situation can be found on the following website:

[16] Comorbidity in the phase 3 trial was defined as BMI ≥ 30 kg/m^2, cardiovascular disorder, respiratory disease or diabetes.

		☐	☐	☒	☐	the world (status 30 January 2021). There has been collateral damage to other public health programmes. Individuals with certain comorbidities are particularly affected by COVID-19 and bear a higher risk of severe COVID-19 outcomes and death. Identified risk factors include comorbidities such as hypertension, chronic cardiac disease, non-asthmatic chronic pulmonary disease, chronic kidney disease, liver disease and obesity (particularly a body mass index (BMI) >40). People with multiple comorbidities are at a higher risk of COVID-19-related adverse outcomes (3). Although the relative risk may be high for some conditions, the absolute risk for younger adults with comorbidities is typically lower than for healthy older adults (>75 years).	https://covid19.who.int/table
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Approximately 36% of participants in the primary efficacy study, as well as in the overall study population, had at least one comorbidity at baseline. The most common comorbid conditions were obesity (54.4%), hypertension (17.4%), and asthma (16.7%). Primary efficacy analysis showed that AZD1222 vaccine was 61.3% efficacious (95%CI 41.2–75.3%) against COVID-19 beginning 15 days after the second dose in adults with a comorbid condition at baseline.	The immunogenicity results from the phase 1/2 United Kingdom study, in 1077 healthy adults aged 18–55 years (4) and a phase 2 cohort in older adults (≥56 years) (5) showed the induction of binding and neutralizing antibodies, with higher antibody titres after a second dose of vaccine (4, 5, 6) The vaccine further induced $CD4^+$ and $CD8^+$ T cells in adults aged 18–55 years, up to 8 weeks after vaccination with a single dose (7).
	Harms of the intervention Are the undesirable	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Overall, 86% of all subjects in the vaccine group (days 0–7 after any vaccination), independent of comorbidity, experienced at least one solicited AE compared with 72% in the control group. The majority of solicited AEs were mild or moderate. Ten percent of subjects in the vaccine group experienced at least one local solicited adverse event (AE) of grade 3 or higher and 8% at least	

	anticipated effects small?					one systemic solicited event of grade 3 or higher, compared with 6% and 3% in the control group, respectively. Solicited AEs were milder and reported less frequently after the second dose than after the first. The most frequently reported systemic solicited AEs in the standard-dose group after any vaccination were fatigue (53%) and headache (53%). Fewer than 1% of subjects reported a serious adverse event (SAE) and the reporting rate was balanced between the two study groups (0.7% vaccine group, 0.8% control). There were no clinically meaningful imbalances in SAE incidence for any subgroup (country, age, serostatus or comorbidity). No data are currently available in immunocompromised subjects or in subjects taking immunosuppressants. Safety data are awaited in a subgroup of HIV-positive subjects.	
	Balance between benefits and harms	***Favours intervention*** ☒	***Favours comparison*** ☐	***Favours both*** ☐	***Favours neither*** ☐	**Unclear** ☐	Efficacy data suggest benefit, and the short-term safety data suggest minimal harm. Further studies will need to be undertaken as part of post-marketing surveillance.	
		Effectiveness of the intervention					Please see the related GRADE tables.	

	What is the overall quality of this evidence for the critical outcomes?	***No included studies*** ☐ ***Very low*** ☐ ***Low*** ☐ ***Moderate*** ☒ ***High*** ☐ Safety of the intervention ***No included studies*** ☐ ***Very low*** ☐ ***Low*** ☒ ***Moderate*** ☐ ***High*** ☐		
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	***Important uncertainty or variability*** ☐ ***Possibly important uncertainty or variability*** ☒ ***Probably no important uncertainty or variability*** ☐ ***No important uncertainty or variability*** ☐ ***No known undesirable outcomes*** ☐	There is possibly important uncertainty regarding how the target population weighs the desirable and undesirable effects (i.e. the protection conferred by the vaccine weighed against the currently reported safety signals) related to COVID-19 vaccination. Different population groups may have different opinions regarding the relative weights attributed to desirable and undesirable outcomes.	
	Values and preferences of the target population: Are the desirable	*No* *Probably No* *Uncertain* *Probably Yes* *Yes* *Varies*	It is assumed that target population probably attaches more weight to the desirable effects than the undesirable effects related to COVID-19 vaccination.	

	effects large relative to undesirable effects?	☐	☐	☐	☒	☐	☐	Targeted information campaigns should assess this aspect.	
RESOURCE USE	Are the resources required small?	*No*		*Un-certain*	*Yes*		*Varies*	AZD1222 can be distributed and stored using existing cold-chain infrastructure (at 2–8 °C) (8) and does not require ultra-cold-chain capacity. In addition, as AZD1222 can be manufactured with widely available manufacturing capacity around the world (9), its price is expected to be lower than those of other COVID-19 vaccines that use new and less widely available manufacturing platforms. Prices are also expected to be lower for AZD1222 than for many other COVID-19 vaccines because the supplier has commited to forego profits (10). Nevertheless, considerable resources will be needed to ensure the implementation of a COVID-19 vaccination programme, especially given: (i) that COVID-19 vaccination is likely to be prioritized for populations (e.g. health care workers, older adults) without pre-existing robust immunization programmes in many settings, and (ii) the urgency of vaccination roll-out worldwide, which may necessitate additional surge resources to accelerate implementation with adequate infection prevention and control procedures in the context of COVID-19. Resources required include, but are not restricted to, human resources, vaccine costs, logistics, planning and coordination, training, social mobilization and communications, and immunization safety surveillance.	An estimated US$15.9 billion is needed for the vaccines pillar (COVAX) of the Access to COVID-19 Tools Accelerator (ACT-A) for 2020–21, in order to deliver 2 billion vaccine doses. This does not include all delivery costs in all countries participating in COVAX, bilateral procurement deals, or research and development investments outside of COVAX (11). The World Bank has approved a financing window of up to US$12 billion to support low- and middle-income countries in purchasing and distributing vaccine (12).
		☐		☐	☒		☐		
	Cost-effectiveness	*No*		*Un-certain*	*Yes*		*Varies*	Formal global cost-effectiveness analyses have not been conducted, but the emerging evidence	The global economy is estimated to be losing US$375 billion per month

		☐	☐	☐	☒	indicates that the benefits, including the impact on recovery of the global economy, are likely to outweigh the cost of COVID-19 vaccination in general at global level. No formal cost-effectiveness analyses of AZD1222 compared with other vaccines have been conducted. The AZD1222 vaccine is expected to be less costly than many other COVID-19 vaccines (see previous sub-criterion). Individual-level efficacy against COVID-19 may be lower than for some other COVID-19 vaccines; more data are needed to assess efficacy against other endpoints (e.g. hospitalizations averted; see main text). The ability to use AZD1222 in existing cold-chain infrastructure in all country settings may allow higher population-level coverage. Cost-effectiveness analyses should be conducted at country level; cost-effectiveness of COVID-19 vaccination may vary by country depending on COVID-19 burden, comparator interventions assessed, analysis perspective, and local cost-effectiveness thresholds used.	because of the coronavirus pandemic. G20 countries have invested approximately US$10 trillion in domestic economic stimulus to mitigate the economic consequences of reduced business activity and unemployment due to the pandemic. Initial estimates suggest that COVID-19 vaccination will provide substantial economic value in terms of averted morbidity and mortality costs and averted losses in gross domestic product (GDP) (10;12–18).
EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐	*Un-certain* ☐	*Reduced* ☒	*Varie s* ☐	Equity and ethical considerations are critical. SAGE has produced a Values Framework (20), which offers guidance on the fair allocation of COVID-19 vaccines based on six core ethical principles that should guide distribution. If distributed fairly, COVID-19 vaccines may have considerable impact on reducing health inequities. Storage and distribution requirements of AZD1222 vaccine are the same as for many other vaccines currently in use globally. Existing vaccine cold-chain capacity, available in almost	Vaccine nationalism is seen as a threat to reducing health inequity, in particular as high-income countries have arranged bilateral contracts with manufacturers. This has led to the establishment of the Access to COVID-19 Tools (ACT) Accelerator and, within this, the COVAX facility, which aims to ensure equitable access to vaccines for its participating member states (21).

		all countries worldwide, could be leveraged for vaccine distribution.		
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)? *Inter-vention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	No scientific evidence is available. As vaccination is an eagerly awaited tool to combat COVID-19, it is assumed that key stakeholders, in particular ministries of health and immunization managers, are strongly in favour of COVID-19 vaccination.	The fact that 190 economies are participating in COVAX suggests a very high acceptability of COVID-19 vaccination in general, though not necessarily of this vaccine in particular.
	Which option is acceptable to target group? *Inter-vention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	COVID-19 vaccine acceptability in general varies between (sub)population groups and may be correlated with the perceived risk posed by the disease. In a global survey (19 countries) of acceptance rates in the general population of any COVID-19 vaccine product, 71.5% of participants reported that they would be very or somewhat likely to take a COVID-19 vaccine. Acceptance rates ranged from almost 55% to 87% (22). Representative multi-country surveys are carried out periodically to assess the percentage of those willing to receive (or of those who already have received) COVID-19 vaccination (non-product specific) . While these polls are limited to selected countries, they provide a certain degree of insight into vaccine acceptance and trends over time. (23, 24).	

FEASIBILITY	Is the intervention feasible to implement?	*No* ☐	*Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☐	*Yes* ☒	*Varies* ☐	Administration of this vaccine is assumed to be easily implementable in settings – including low- and middle-income countries – with existing vaccine logistics and delivery infrastructure. Administration of the vaccine to target groups that are currently not reached by national immunization programmes may pose a challenge in certain settings.		
Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☒	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐					
Type of recommendation	We recommend the intervention ☐	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☒ Only with targeted monitoring and evaluation ☒ Only in specific contexts or specific (sub)populations		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐					

Recommendation (text)	**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 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. **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 alter its effectiveness. In the interim, given that the vaccine is not a live virus vaccine, 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. **Pregnant women** Pregnant women are at higher risk of severe COVID-19 than 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 the AZD1222 is non-replicating vaccine. Animal developmental and reproductive toxicity (DART) studies are ongoing. On the basis of preliminary findings, no harm is expected on the development of the fetus. Further studies are planned in pregnant women in the coming months, including a pregnancy substudy 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 pregnant women who are health workers at high risk of exposure and pregnant women with comorbidities that already place them in a high-risk group for severe COVID-19. Information and, if possible, counselling on the lack of safety and efficacy 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 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 HIV may be at higher risk of severe COVID-19. Persons living with HIV were not included in the primary analyses of the phase 3 trials and safety data are awaited in a subgroup of HIV-positive subjects. 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 alter its effectiveness. In the interim, given that the vaccine is a non-replicating vaccine, 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. **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 have no contraindications to vaccination may be vaccinated.
Implementation considerations	
Monitoring, evaluation and research priorities	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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