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

Grading of evidence -

Evidence to recommendations tables

First issued 10 February 2021

Updated 21 April 2021

Updated 30 July 2021

Last updated 15 March 2022

World Health Organization

Background

These are the annexes to the Interim recommendations for use of the ChAdOx1-S [recombinant] AZD1222 vaccine against COVID-19.

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).

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Annex 1. GRADE table: Efficacy of ChAdOx1-S recombinant COVID-19 vaccine in adults

Population:	Adults (18–64 years)
Intervention:	Two doses of ChAdOx1-S recombinant vaccine
Comparison:	Placebo/ active control
Outcome:	COVID-19 (PCR-confirmed)

What is the efficacy of two doses of ChAdOx1-S recombinant 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		3/ RCT *(1-4)*	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 that of the estimate of the effect on the health outcome (level 4).**
	Conclusion			We are very confident that 2 doses of ChAdOx1-S recombinant vaccine are efficacious in preventing PCR-confirmed COVID-19 in adults (18–64 years) up to approx. 4 months following immunization in the context of wild-type and pre-Omicron variants of concern.

[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 from post-licensure use in selected countries suggests high vaccine effectiveness. SAGE will continue to review any emerging data and adjust the quality assessment as required.

Annex 2. GRADE table: Safety of ChAdOx1-S recombinant COVID-19 vaccine in adults

Population:	Adults (18–64 years)
Intervention:	Two doses of ChAdOx1-S recombinant vaccine
Comparison:	Placebo/ active control
Outcome:	Serious adverse events following immunization

What is the risk of serious adverse events following ChAdOx1-S recombinant vaccination compared with placebo/ active control in adults (18–64 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		7/ RCT *(1, 2, 5-10)*	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 that of the estimate of the effect on the health outcome (level 4).**
	Conclusion			While very rare thromboembolic events following immunization have been reported, we are very confident that the overall risk of serious adverse events following one or two doses of ChAdOx1-S recombinant vaccine in adults (18–64 years) is low.

[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] The trial was not adequately powered to detect rare adverse events (i.e. fewer than about 1/2000). Data from post-licensure use suggest a very low risk of thrombocytopenic thrombotic serious adverse events following immunization. SAGE will continue to review any emerging data and adjust the quality assessment as required.

Annex 3. GRADE table: Efficacy of ChAdOx1-S recombinant COVID-19 vaccine in older adults

Population:	Older adults (≥65 years)
Intervention:	Two doses of ChAdOx1-S recombinant vaccine
Comparison:	Placebo/ active control
Outcome:	COVID-19 (PCR-confirmed)

What is the efficacy of two doses of ChAdOx1-S recombinant 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		3/ RCT *(1-4)*	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 that of the estimate of the effect on the health outcome (level 4).**
	Conclusion			We are very confident that 2 doses of ChAdOx1-S recombinant vaccine are efficacious in preventing PCR-confirmed COVID-19 in older adults (≥65 years) up to approx. 4 months following immunization in the context of wild-type and pre-Omicron variants of concern.

[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] Of the participants in phase III clinical trials in Brazil, South Africa, and the United Kingdom, approximately 10% (n=1380) were aged over 65 years.. Recent data from a phase III clinical trial in the Americas, n=5615 were aged 65 or over and vaccine efficacy was 85% (95%CI: 58-94%). Immunogenicity data in this age group suggest that the vaccine elicits an immune response comparable to younger adults.

Annex 4. GRADE table: Safety of ChAdOx1-S recombinant COVID-19 vaccine in older adults

Population:	Older adults (≥65 years)
Intervention:	One or two doses of ChAdOx1-S recombinant vaccine
Comparison:	Placebo/ active control
Outcome:	Serious adverse events following immunization

What is the risk of serious adverse events following ChAdOx1-S recombinant vaccination compared with placebo/ active control in older adults (≥65 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		7/ RCT *(1, 2, 5-10)*	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 that of the estimate of the effect on the health outcome (level 4).**
	Conclusion			While very rare thromboembolic events following immunization have been reported, mainly in adults aged <60 years, we are very confident that the risk of serious adverse events following one or two doses of ChAdOx1-S recombinant vaccine in older adults (≥65 years) is low.

[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] The trial was not adequately powered to detect rare adverse events (i.e, about 1/250). Data from post-licensure use suggest a very low risk of thrombocytopenic thrombotic serious adverse events following immunization. SAGE will continue to review any emerging data and adjust the quality assessment as required.

Annex 5. GRADE table: Efficacy of ChAdOx1-S recombinant 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 ChAdOx1-S recombinant vaccine
Comparison:	Placebo/ active control
Outcome:	COVID-19 (PCR-confirmed)

What is the efficacy of two doses of ChAdOx1-S recombinant 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 *(1-4)*	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 that of the estimate of the effect on the health outcome (level 3).**
	Conclusion			We are moderately confident that 2 doses of ChAdOx1-S recombinant 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 up to approx. 4 months following immunization in the context of wild-type and pre-Omicron variants of concern. 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. Comparable immunogenicity was shown between people living with and without HIV. This was considered as constituting a limitation that leads to downgrading of the evidence.

[c] Underlying comorbidities included BMI ≥ 30 kg/m2, cardiovascular disorder, respiratory disease or 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. SAGE will continue to review any emerging data and adjust tge quality assessment as required.

Annex 6. GRADE table: Safety of ChAdOx1-S recombinant 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 ChAdOx1-S recombinant vaccine
Comparison:	Placebo/ active control
Outcome:	Serious adverse events following immunization

What is the risk of serious adverse events following ChAdOx1-S recombinant 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		5/ RCT *(1, 2, 5, 9-11)*	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Serious[b]	-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			**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).**
	Conclusion			While very rare thromboembolic events following immunization have been reported, we have moderate confidence in the quality of evidence that the overall 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 ChAdOx1-S recombinant vaccine is low.

[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. Comparable safety profiles were seen in people living with and without HIV. This was considered as constituting a limitation that leads to downgrading of the evidence.

Annex 7. SAGE evidence-to-recommendation framework ChAdOx1-S recombinant COVID-19 vaccine use in adults

Question:	Should ChAdOx1-S recombinant vaccine be administered to adults to prevent COVID-19?
Population:	Adults (18–64 years)
Intervention:	Two doses of ChAdOx1-S recombinant 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 COVID-19 pandemic. In the rapidly evolving field of COVID-19 vaccines, WHO has issued to date

	ADDITIONAL INFORMATION
s evolving umber of ally has ost recent be found website: damage to es.	
ata cut-off, f trials in he United	The immunogenicity results from the phase 1/2 United Kingdom study, in 1077