Annexes to the recommendations for use of the CanSinoBIO Ad5-nCoV-S [recombinant] vaccine (Convidecia™) against COVID-19

Grading of evidence

Evidence to recommendation tables

First issuance: 19 May 2022

World Health Organization

Background

These are the annexes to the Interim recommendations for use of the CanSinoBIO Ad5-nCoV-S [recombinant] vaccine against COVID-19. Annexes 1–8 contain tables that summarize the grading of recommendations, assessment, development and evaluations (GRADE). Annexes 9–12 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 1 April 2022).

Contents

Annex 1. GRADE table: Efficacy of Ad5-nCoV-S recombinant vaccine in adults

Population:	Adults (aged 18–59 years)			
Intervention:	Single dose of Ad5-nCoV-S recombinant vaccine			
Comparison:	Placebo/active control			
Outcome:	COVID-19 (PCR-confirmed)			
What is the efficacy of a single dose of Ad5-nCoV-S recombinant vaccine compared with placebo/active control in preventing PCR-confirmed COVID-19 in adults (aged 18–59 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).**
	Conclusion			We are very confident that a single dose of Ad5-nCoV-S recombinant vaccine are efficacious in preventing PCR-confirmed COVID-19 in adults (18–59 years) up to approx. 1-2 months following vaccination in the context of pre- Delta 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 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 median participant follow-up of 45 days. 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 Ad5-nCoV-S recombinant vaccine in adults

Population:	Adults (aged 18–59 years)
Intervention:	Single dose of Ad5-nCoV-S recombinant vaccine
Comparison:	Placebo/active control
Outcome:	Serious adverse events following vaccination

What is the risk of serious adverse events following Ad5-nCoV-S recombinant vaccination compared with placebo/active control in adults (aged 18–59 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		4/ RCT *(1-4)*	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 that of the estimate of the effect on the health outcome (level 3).**
	Conclusion			We are moderately confident that the risk of serious adverse events following one dose of Ad5-nCoV-S recombinant vaccine in adults (aged 18–59 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] Downgraded for the following limitations: The trial was not adequately powered to detect rare adverse events. These may emerge only when large populations have been vaccinated.

Annex 3. GRADE table: Efficacy of Ad5-nCoV-S recombinant vaccine in older adults

Population:	Older adults (aged ≥60 years)
Intervention:	Single dose of Ad5-nCoV-S recombinant vaccine
Comparison:	Placebo/active control
Outcome:	COVID-19 (PCR-confirmed)

What is the efficacy of a single dose of Ad5-nCoV-S recombinant vaccine compared with placebo/active control in preventing PCR-confirmed COVID-19 in older adults (aged ≥60 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]	-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			**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 a dose of Ad5-nCov-S recombinant vaccine are efficacious in preventing PCR-confirmed COVID-19 in older adults (aged ≥60 years) up to approx. 1-2 months following vaccination in the context of pre- Delta 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 trial participants in the phase 3 trial, approximately 8% in the vaccine arm (n=839) were aged 60 years or older. Overall vaccine efficacy against symptomatic disease was 53% (95% CI: 1–78%). The evidence was downgraded for imprecision due to large confidence intervals and the limited sample size. Data on long-term protection emerging from the phase 3 clinical trial remain limited, as trial data have so far been reported only for a median participant follow-up of 38 days after dose 2. 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 Ad5-nCoV-S recombinant vaccine in older adults

Population:	Older adults (aged ≥60 years)			
Intervention:	Single dose of Ad5-nCoV-S recombinant vaccine			
Comparison:	Placebo/active control			
Outcome:	Serious adverse events following vaccination			
What is the risk of serious adverse events following Ad5-nCoV-S recombinant vaccination compared with placebo/active control in older adults (aged ≥60 years)?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		3/ RCT *(1, 3, 4)*	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 that of the estimate of the effect on the health outcome (level 3).**
	Conclusion			We are moderately confident that the risk of serious adverse events following a dose of Ad5-nCoV-S recombinant vaccine in older adults (aged ≥60 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] Downgraded for the following limitations: The trials were not adequately powered to detect rare adverse events. These may emerge only when large populations have been vaccinated.

Annex 5. GRADE table: Efficacy of Ad5-nCoV-S recombinant vaccine in individuals with underlying conditions

Population:	Individuals with comorbidities or health states that increase risk for severe COVID-19			
Intervention:	Single dose of Ad5-nCoV-S recombinant vaccine			
Comparison:	Placebo/active control			
Outcome:	COVID-19 (PCR-confirmed)			
What is the efficacy of a single dose of Ad5-nCoV-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		1/ RCT *(1)*	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			We are moderately confident that a dose of Ad5-nCoV-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. 2 months following vaccination in the context of pre-Delta and pre-Omicron variants of concern.

Annex 6. GRADE table: Safety of Ad5-nCoV-S recombinant vaccine in individuals with underlying conditions

[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] Underlying comorbidities included diabetes, chronic lung disease, severe obesity or significant cardiovascular disease. Around 10% of the trial population were either obese or affected by comorbidities. Trial excluded pregnant and breastfeeding women, persons living with HIV and persons who were immunocompromised. SAGE will continue to review any emerging data and adjust its quality assessment as required.

Population:	Individuals with comorbidities or health states that increase risk for severe COVID-19
Intervention:	Single dose of Ad5-nCoV-S recombinant vaccine
Comparison:	Placebo/active control
Outcome:	Serious adverse events following vaccination

What is the risk of serious adverse events following Ad5-nCoV-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		1/ RCT	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 low level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 2).**
	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 a dose of Ad5-nCoV-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] Downgraded for the following limitations: the trial was not adequately powered to detect rare adverse events. These may emerge only when large populations have been vaccinated.

[c] The phase 3 trial excluded pregnant and breastfeeding women, persons living with HIV and persons who were immunocompromised.

Annex 7. SAGE evidence-to-recommendation framework: Ad5-nCoV-S recombinant vaccine use in adults

Question:	Should Ad5-nCoV-S recombinant vaccine be administered to adults to prevent COVID-19?
Population:	Adults (aged 18–59 years)
Intervention:	Single dose of Ad5-nCoV-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 pandemic. In the rapidly evolving field of COVID-19 vaccines, WHO has issued, to date, interim recommendations on the use of a number of COVID-19 vaccines .

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No*	*Uncertain*	*Yes*	*Varies by setting*	The COVID-19 situation is evolving rapidly. The cumulative number of COVID-19 deaths globally has surpassed 6 million. The most recent epidemiological situation can be found on the following website: https://covid19.who.int/table. There has been collateral damage to other public health programmes.	
		☐	☐	☒	☐		

BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	Primary efficacy analysis *(1)* shows that Ad5-nCoV-S recombinant vaccine beginning 28 days 61 (95% CI: 43–73) in approx. 20 000 participants aged ≤60 years and 65% (95% CI: 54–74%) efficacious in approx. 26 500 participants beginning 14 days post-vaccination (see Background paper).	The phase 1 trial included 108 volunteers aged 18–60 years for vaccination with Ad5-nCoV-S in China. Subjects vaccinated with three different dosages of Ad5-nCoV-S showed an acceptable safety profile and good immunogenicity, inducing humoral and cellular immune responses *(2)*. The phase 2 trial included 508 healthy adults aged ≥18 years, who were randomly assigned to the 1×1011 vp/dose group, the 5×1010 vp/dose group, and the placebo group at a 2:1:1 ratio. Both Ad5-nCoV-S vaccinated groups showed strong immune responses; the immunogenicity levels were roughly equivalent within 28 days between the low-dose group and the medium-dose group, and were superior to those of the placebo group *(3)*. During the phase 1 and 2 studies, the binding S-RBD antibody at day 28 after vaccination was found in at least 94% of study participants; the neutralizing antibody was found in at least 75% of study participants. Besides the humoral immunity, the cellular response was found in at least 91% of study

						participants, demonstrating the good immunogenicity profile of Ad5-nCoV-S. Heterologous schedules (1 or 2 primary series doses of CoronaVac) followed by a dose of Ad5-nCoV-S recombinant vaccine (as a booster dose) have demonstrated to be safe and more immunogenic than a homologous CoronaVac vaccination series *(5)*. WHO has summarized the available evidence and issued interim recommendations for heterologous COVID-19 vaccine schedules *(6)*.
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	Data from more than 36 000 participants demonstrate that Ad5-nCoV-S recombinant vaccine was well tolerated across all populations. There was no significant difference between the Ad5-nCoV-S or placebo groups in the incidence of serious adverse events (14 [0.1%] of 18 363 Ad5-nCoV-S recipients and 10 [0.1%] of 18 354 placebo recipients, p=0.54), or medically attended adverse events (442 [2.4%] of 18 363 Ad5-nCoV-S recipients and 411 [2.2%] of 18 354 placebo recipients, p=0.30), or any serious adverse events considered related to the study product (none in either Ad5-nCoV-S or placebo recipients). In the extended safety cohort, 1004 (63.5%) of 1582 Ad5-nCoV-S recipients, and 729 (46.4%) of	As of 31 December 2021, approx. 58 million doses of Ad5-nCoV-S have been distributed worldwide, of which around 13.8 million doses were administered in mainland China. Adverse events data were obtained from regulatory authorities (National Medical Products Association (NMPA), WHO-Uppsala Monitoring Centre (UMC), and regulatory authorities of other countries) and safety surveillance from the American Region, Chile, China, and Mexico (data from UMC). As of 31 December 2021, 47 cases of thrombosis with thrombocytopenia syndrome

				1572 placebo recipients reported a solicited systemic adverse event (p<0.0001), of which headache was the most common (699 [44%] of Ad5-nCoV-S recipients and 481 [30.6%] of placebo recipients; p<0.0001). A total of 971 (61.3%) of 1584 Ad5-nCoV-S recipients, and 314 (20.0%) of 1573 placebo recipients reported an injection-site adverse event (p<0.0001), of which pain at the injection site was the most frequent (939 [59%] of Ad5-nCoV-S recipients and 303 [19%] of recipients *(1)*.	(TTS) were reported worldwide (0.081 cases per 100 000 vaccinees), compared to the cumulative incidence of TTS following vaccination with a non-replicate adenovirus vector-based vaccine which ranges from 0.5 to 6.8 cases per 100 000 vaccinees. Of the 47 cases, 27 were males and 20 females; 25 cases were aged 18–59 years, 12 were aged ≥60 years, and information on the age of 10 cases was not available. Of the 47 cases of TTS, 33 occurred within 30 days following vaccination, 1 occurred more than 30 days after vaccination; for the remainder no data are available. A total of 28 cases with Guillain-Barre Syndrome were reported among 58 million vaccinated, corresponding to an incidence rate of 0.05 per 100 000 vaccinees, which is below or similar to the background rate. A total of 39 reports on anaphylaxis were received, with a reported incidence of 0.07 cases per 100 000 vaccinees. There is some concern that an Ad5-vectored vaccine could potentially increase the risk of HIV acquisition. Two

					placebo-controlled phase 2b trials in different populations that evaluated an Ad5-vectored HIV-1 vaccine found an increased risk of HIV acquisition among those vaccinated. In the first trial – the STEP study -the increased risk was observed in a subpopulation of uncircumcised men who had pre-existing Ad5 immunity, and in the second trial – the Phambili study – the increased risk was in heterosexual men *(7-9)*. However, seropositivity for Ad5 and circumcision were not found to increase susceptibility to HIV infection in the second trial, conducted in South Africa, and no increased HIV risk was observed in a third trial of a different Ad5-vectored HIV vaccine *(9-11)*. In a non-human primate challenge study of Ad5-infected rhesus macaques, vaccination with a replication-incompetent Simian Immunodeficiency Virus (SIV) Ad5-vaccine increased the risk of SIV acquisition from low-dose SIV penile challenge *(12)*, replicating the results observed in human trials. However, another study Ad5-seropositive rhesus macaques vaccinated with the empty Ad5 vector were

								not more susceptible to the SIV challenge, in contrast to those who received the Ad5-SIV vaccines, suggesting that the vector alone is not responsible for the heightened risk of HIV acquisition observed in some human studies *(13)*.
	Balance between benefits and harms	*Favours intervention* ☒	*Favours comparison* ☐	*Favours both* ☐	*Favours neither* ☐	Unclear ☐	A single dose of Ad5-nCoV-S recombinant confers high VE in the context of pre-Delta and pre-Omicron variants of concern. Safety data suggest minimal harms. Further data are needed as part of post-marketing surveillance.	In accordance with the WHO Prioritization Roadmap *(29)*, a booster dose may be required in the highest and high priority-use groups (i.e. older adults, health workers, persons with comorbidities).
	What is the overall quality of this evidence for the critical outcomes?	**Effectiveness of the intervention** *No included studies* ☐	*Very low* ☐	*Low* ☐	*Moderate* ☐	*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 varies on the relative importance of the intervention, as well as the relative weights that the target population attributes to the desirable outcomes (i.e. protection conferred by the vaccine) and the undesirable outcomes (i.e. the currently reported safety signals). 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 the target population assigns more weight to the desirable effects than to the undesirable effects related to COVID-19 vaccination.	Targeted studies should assess this aspect.
RESOURCE USE	Are the resources required small?	*No* ☒		*Uncertain* ☐	*Yes* ☐		*Varies* ☐	Considerable resources are needed to ensure the implementation of a COVID-19 vaccination programme, especially given the urgency of vaccination roll-out worldwide. This necessitates additional surge resources in many settings 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, the vaccine pillar of the Access to COVID-19 Tools Accelerator (ACT-Accelerator), has now shipped over 1 billion doses of COVID-19 vaccine to 144 countries and territories *(14)*. By January 2022, additional funding of at least US$ 5.2 billion was required for the Gavi COVAX Advance Market Commitment to establish a Pandemic Vaccine Pool of a minimum of 600 million additional vaccine doses to: address uncertainties and risks in the evolution of the virus; provide bundled finance to strengthen delivery systems in recipient countries; and cover essential ancillary costs *(15)*.

	Cost–effectiveness	*No* ☐	*Uncertain* ☐	*Yes* ☐	*Varies* ☒	Formal global cost–effectiveness analyses have not been conducted, but emerging evidence indicates that the benefits, including the impact on recovery of the global economy, are likely to outweigh the costs of COVID-19 vaccination in general at global level. Formal cost–effectiveness analyses of Ad5-nCoV-S recombinant, compared with other vaccines, have been conducted in some settings. The ability to use Ad5-nCoV-S recombinant 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.	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 *(16-22)*.
EQUITY	What would be the impact on health inequities?	*Increased* ☒	*Uncertain* ☐	*Reduced* ☐	*Varies* ☐	Equity and ethical considerations are critical. SAGE has produced a Values Framework *(23)*, 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.	Vaccine nationalism is seen as a threat to reducing health inequity, particularly 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 *(24)*.

ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Intervention*	*Comparison*	*Both*	*Neither*	*Unclear*	As vaccination is an important 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.
		☒	☐	☐	☐	☐		
	Which option is acceptable to target group?	*Intervention*	*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 receive a COVID-19 vaccine. Acceptance rates ranged from almost 55% to 87% *(25)*. Additionally, representative multi-country surveys are carried out periodically to assess the percentage of those willing to receive (or of those who have already 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 *(26, 27)*.	
		☒	☐	☐	☐	☐		

FEASIBILITY	Is the intervention feasible to implement?	*No* ☐	*Probably* No ☐	*Uncertain* ☐	*Probably* Yes ☐	*Yes* ☐	*Varies* ☒	Ad5-nCoV-S recombinant vaccine is assumed to be easily implementable in settings, including low- and middle-income countries, with existing vaccine logistics and delivery infrastructure. Storage and distribution requirements of the Ad5-nCoV-S recombinant vaccine are the same as those of many other vaccines currently in use globally. Therefore existing vaccine cold chain capacity, available in almost all countries worldwide could be leveraged for vaccine distribution. Administration of the vaccine to novel 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	We recommend the comparison ☐	We recommend against the intervention and the comparison ☐					

	☒ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations
RECOMMENDATION (TEXT)	Please see the interim recommendations.
IMPLEMENTATION CONSIDERATIONS	Please see the interim recommendations.
MONITORING, EVALUATION AND RESEARCH PRIORITIES	Please see the interim recommendations.

Annex 8. SAGE evidence-to-recommendation framework: Ad5-nCoV-S recombinant vaccine use in older adults

Question:	Should Ad5-nCoV-S recombinant vaccine be administered to older adults to prevent COVID-19?
Population:	Older adults (aged ≥60 years)
Intervention:	Single dose of Ad5-nCoV-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 pandemic. In the rapidly evolving field of COVID-19 vaccines, WHO has issued, to date, interim recommendations on the use of a number of COVID-19 vaccines *(28)*.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	The COVID-19 situation is evolving rapidly. The cumulative number of COVID-19 deaths globally has surpassed 6 million. The most recent epidemiological situation can be found on the following website: https://covid19.who.int/table. There has been collateral damage to other public health programmes.	
BENEFITS &		*No*	*Uncertain*	*Yes*	*Varies*	The mean age of trial participants was 39.2 years (interquartile range (IQR) 27–49) (10% were aged ≥60	The phase 2 trial included 508 healthy adults aged ≥18 years,

	Benefits of the intervention Are the desirable anticipated effects large?	☐	☐	☒	☐	years) in the vaccine group and 39.1 (IQR 27–49) (10.1% were aged ≥60 years) in the placebo group. Primary efficacy analysis *(1)* shows that Ad5-nCoV-S recombinant vaccine is 53% (1–78%) efficacious against disease, and 90% (22–99%) efficacious against severe disease in 1670 individuals aged ≥60 years against symptomatic COVID-19 beginning 14 days post vaccination. Vaccine efficacy beginning 28 was 18% (95%CI: -128—70) in those 60 years of age or older beginning 28 days post-vaccination*(1)*.	who were randomly assigned to the 1×1011 vp/dose group, the 5×1010 vp/dose group, and the placebo group at a 2:1:1 ratio. Both Ad5-nCoV-S vaccinated groups showed strong immune responses; the immunogenicity levels were roughly equivalent within 28 days between the low-dose group and the medium-dose group, and were superior to those of the placebo group *(3)*. During the phase 2 studies, the binding S-RBD antibody at day 28 after vaccination was found in at least 94% of study participants; the neutralizing antibody was found in at least 75% of study participants. Besides the humoral immunity, the cellular response was found in at least 91% of study participants, demonstrating the good immunogenicity profile of Ad5-nCoV-S. Heterologous schedules (1 or 2 primary series doses of CoronaVac) followed by a dose of Ad5-nCoV-S recombinant vaccine (as a booster dose) have demonstrated to be safe

						and more immunogenic than a homologous CoronaVac vaccination series *(5)*. WHO has summarized the available evidence and issued interim recommendations for heterologous COVID-19 vaccine schedules *(6)*.
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	There was no significant difference in the incidence of serious adverse events between the Ad5-nCoV-S or placebo groups (14 [0.1%] of 18 363 Ad5-nCoV-S recipients and 10 [0.1%] of 18 354 placebo recipients, p=0.54); or medically attended adverse events (442 [2.4%] of 18 363 Ad5-nCoV-S recipients and 411 [2.2%] of 18 354 placebo recipients, p=0.30); or any serious adverse events considered related to the study product (none in either Ad5-nCoV-S or placebo recipients). In the extended safety cohort, 1004 (63.5%) of 1582 Ad5-nCoV-S recipients, and 729 (46.4%) of 1572 placebo recipients reported a solicited systemic adverse event (p<0.0001), of which headache was the most common (699 [44%] of Ad5-nCoV-S recipients and 481 [30.6%] of placebo recipients, p<0·0001). A total of 971 (61.3%) of 1584 Ad5-nCoV-S recipients, and 314 (20.0%) of 1573 placebo recipients reported an injection-site adverse event (p<0.0001), of which pain at the injection site was the	As of 31 December 2021, approx. 58 million doses of Ad5-nCoV-S have been distributed worldwide, of which around 13.8 million doses were administered in mainland China. Adverse events data were obtained from regulatory authorities (NMPA, WHO-Uppsala Monitoring Centre (UMC) and regulatory authorities of other countries) and safety surveillance from the American Region, Chile, China and Mexico (data from UMC). As of 31 December 2021, 47 cases of thrombosis with thrombocytopenia syndrome (TTS) were reported worldwide (0.081 cases per 100 000 vaccinees), compared to the cumulative incidence of

							most frequent (939 [59%] of Ad5-nCoV-S recipients and 303 [19%] of placebo recipients *(1)*).	TTS following vaccination with a non-replicate adenovirus vector-based vaccine which ranges from 0.5 to 6.8 cases per 100 000 vaccinees. Of the 47 cases, 27 were males and 20 females; 25 cases were aged 18–59 years, 12 cases were aged ≥60 years, and information on age for 10 cases was not available. Of the 47 cases, 33 occurred within 30 days following vaccination, 1 occurred more than 30 days after vaccination; for the remainder no data are available. A total of 28 cases with Guillain-Barre Syndrome were reported among 58 million vaccinated, corresponding to an incidence rate of 0.05 cases per 100 000 vaccinees, which is below or similar to the background rate. A total of 39 reports on anaphylaxis were received, with a reported incidence of 0.07 cases per 100 000 vaccinees.
	Balance between	*Favours intervention*	*Favours comparison*	*Favours both*	*Favours neither*	*Unclear*	A single dose of Ad5-nCoV-S recombinant vaccine in adults aged ≥60 years are efficacious in the	In accordance with the WHO Prioritization Roadmap *(29)*, a booster

	benefits and harms	☒	☐	☐	☐	☐	context of pre-Delta and pre-Omicron variants of concern., though confidence intervals are wide. Safety data suggest minimal harms. Further data are needed as part of post-marketing surveillance.	dose may be required in the highest and high priority-use groups (i.e. older adults, health workers, persons with comorbidities).
	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 (aged ≥65 years) 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:	*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	Targeted studies should assess this aspect.

	Are the desirable effects large relative to undesirable effects?	☐	☐	☐	☒	☐	☐	undesirable effects related to COVID-19 vaccination.	
RESOURCE USE	Are the resources required small?	*No* ☒		*Uncertain* ☐	*Yes* ☐	*Varies* ☐		Considerable resources are needed to ensure the implementation of a COVID-19 vaccination programme, especially given the urgency of vaccination roll-out worldwide. This necessitates additional surge resources in many settings 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, the vaccine pillar of the Access to COVID-19 Tools Accelerator (ACT-Accelerator), has now shipped over 1 billion doses of COVID-19 vaccine to 144 countries and territories *(14)*. By January 2022, additional funding of at least US$ 5.2 billion was required for the Gavi COVAX Advance Market Commitment to establish a Pandemic Vaccine Pool of a minimum of 600 million additional vaccine doses to: address uncertainties and risks in the evolution of the virus; provide bundled finance to strengthen delivery systems in recipient countries; and cover essential ancillary costs *(15)*.
	Cost–effectiveness	*No* ☐		*Uncertain* ☐	*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	The global economy is estimated to be losing US$ 375 billion per month because of the coronavirus pandemic. G20 countries have

						outweigh the costs of COVID-19 vaccination in general at global level. Formal cost–effectiveness analyses of Ad5-nCoV-S recombinant vaccine compared with other vaccines have been conducted in some settings. The ability to use Ad5-nCoV-S recombinant 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.	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 *(16-22)*.
EQUITY	What would be the impact on health inequities?	*Increased* ☒	*Uncertain* ☐	*Reduced* ☐	*Varies* ☐	Equity and ethical considerations are critical. SAGE has produced a Values Framework *(30)*, 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.	Vaccine nationalism is seen as a threat to reducing health inequity, particularly as high-income countries have arranged bilateral contracts with manufacturers. This has led to the establishment of ACT-Accelerator, and within this, the COVAX facility, which aims to ensure equitable access to vaccines for its participating member states *(24)*.

ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Intervention* ☒	*Comparison* ☐	*Both* ☐	*Neither* ☐	*Unclear* ☐		As vaccination is an important 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.
	Which option is acceptable to target group?	*Intervention* ☒	*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 receive a COVID-19 vaccine. Acceptance rates ranged from almost 55% to 87% *(25)*. Additionally, representative multi-country surveys are carried out periodically to assess the percentage of those willing to receive (or of those who have already 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 *(26, 27)*.	
FEASIBILITY	Is the intervention	*No*	*Probably No*	*Uncertain*	*Probably Yes*	*Yes*	*Varies*	Ad5-nCoV-S recombinant vaccine is assumed to be easily	

	feasible to implement?	☐	☐	☐	☐	☐	☒	implementable in settings, including low- and middle-income countries, with existing vaccine logistics and delivery infrastructure. Storage and distribution requirements of the Ad5-nCoV-S recombinant vaccine are the same as those of many other vaccines currently in use globally. Therefore existing vaccine cold chain capacity, available in almost all countries worldwide could be leveraged for vaccine distribution. Administration of the vaccine to novel 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)	Please see the interim recommendations.

IMPLEMENTATION CONSIDERATIONS	Please see the interim recommendations.
MONITORING, EVALUATION AND RESEARCH PRIORITIES	Please see the interim recommendations.

Annex 9. SAGE evidence-to-recommendation framework: Ad5-nCoV-S recombinant vaccine use in individuals with comorbidities

Question:	Should Ad5-nCoV-S recombinant vaccine be administered to individuals with comorbidities[a] or health states that increase risk for severe COVID-19 to prevent COVID-19?
Population:	Individuals with comorbidities or health states that increase risk for severe COVID-19
Intervention:	Single dose of Ad5-nCoV-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 pandemic. In the rapidly evolving field of COVID-19 vaccines, WHO has issued, to date, interim recommendations on the use of a number of COVID-19 vaccines *(28)*.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	The COVID-19 situation is evolving rapidly. The cumulative number of COVID-19 deaths globally has surpassed 6 million. The most recent epidemiological situation can be found on the following website: https://covid19.who.int/table.	

[a] Comorbidities included were cardiovascular disease, hypertension, obesity and type 2 diabetes. Comorbidities for which there were too few data to evaluate were asthma, cancer, chronic kidney disease, chronic obstructive pulmonary disorder (COPD), HIV infection, immunocompromised, liver disease, and neurological conditions.

						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. 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 (i.e. aged >75 years). Pregnant women with COVID-19 are at higher risk of developing severe disease, with increased risk of intensive care unit admission and invasive ventilation, compared with non-pregnant women of reproductive age. COVID-19 in pregnancy is also associated with an increased risk of preterm birth, and of neonates requiring neonatal intensive care. It may also be associated with an increased risk of maternal mortality.	
BENEFITS &		*No*	*Uncertain*	*Yes*	*Varies*	Vaccine efficacy in those with comorbidities was 61% (95% CI: 36-76%) 14 days post-vaccination.	The phase 1 trial included 108 healthy volunteers aged 18–60

	Benefits of the intervention Are the desirable anticipated effects large?	☐	☐	☒	☐	Vaccine efficacy for the obesity subgroup (184 people in the vaccine group versus 161 people in the placebo group) was 61% (95% CI: 37– 76), while it was 55% (95% CI: -16–83) for the diabetes subgroup (495 people in the vaccine group versus 488 people in the placebo group), and 67% (95% CI: 30–85) for the hypertension subgroup (1016 people in the vaccine group and 1010 people in the placebo group) (see background paper).	years for vaccination with Ad5-nCoV-S in China. Subjects vaccinated with three different dosages of Ad5-nCoV-S showed an acceptable safety profile and good immunogenicity, inducing humoral and cellular immune responses *(2)*. The phase 2 trial included 508 healthy adults aged ≥18 years, who were randomly assigned to the 1×1011 vp/dose group, the 5×1010 vp/dose group and the placebo group at a 2:1:1 ratio. Both Ad5-nCoV-S vaccinated groups showed strong immune responses; the immunogenicity levels were roughly equivalent within 28 days between the low-dose group and the medium-dose group, and were superior to those of the placebo group *(3)*. During the phase 1 and phase 2 studies, the binding S-RBD antibody at day 28 after vaccination was found in at least 94% of study participants; the neutralizing antibody was found in at least 75% of study

								participants. Besides the humoral immunity, the cellular response was found in at least 91% of study participants, demonstrating the good immunogenicity profile of Ad5-nCoV-S. Heterologous schedules (1 or 2 primary doses of CoronaVac) followed by a dose of Ad5-nCoV-S recombinant vaccine (as a booster dose) have demonstrated to be safe and more immunogenic than a homologous CoronaVac vaccination series *(5)*. WHO has summarized the available evidence and issued interim recommendations for heterologous COVID-19 vaccine schedules *(6)*.
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐	*Uncertain* ☐	*Yes* ☒		*Varies* ☐	Though pregnancy was an exclusion criteria, 92 pregnancies have been recorded in the phase 3 trial so far; none of the outcomes of special interest were significantly different between the two groups (see Background paper).	Developmental and reproductive toxicology (DART) studies of Ad5-nCoV-S recombinant have not shown harmful effects in pregnant animals and their offspring.
	Balance between	*Favours intervention*	*Favours comparison*	*Favours both*	*Favours neither*	*Unclear*	A single dose of Ad5-nCoV-S recombinant vaccine is efficacious	In accordance with the WHO Prioritization

	benefits and harms	☒	☐	☐	☐	☐	in individuals with comorbidities or health states that increase risk for severe COVID-19 in the context of pre-Delta and pre-Omicron variants of concern, though confidence intervals are wide. Currently available safety data suggest minimal harms in the general study population. An extended primary series including an additional (third) dose for ICPs may be required. Further studies will need to be undertaken as part of post-marketing surveillance.	Roadmap *(29)*, a booster dose may be required in the highest and high priority-use groups (i.e. older adults, health workers, persons with comorbidities).
	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*: ☐	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 effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐	Available scientific evidence suggests that the target population probably attaches more weight to the desirable effects than the undesirable effects related to COVID-19 vaccination.	Targeted studies should assess this aspect.
RESOURCE USE	Are the resources required small?	*No* ☒ *Uncertain* ☐ *Yes* ☐ *Varies* ☐	Considerable resources are needed to ensure the implementation of a COVID-19 vaccination programme, especially given the urgency of vaccination roll-out worldwide. This necessitates additional surge resources in many settings 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, the vaccine pillar of the Access to COVID-19 Tools Accelerator (ACT-Accelerator), has now shipped over 1 billion doses of COVID-19 vaccine to 144 countries and territories *(14)*. By January 2022, additional funding of at least US$ 5.2 billion was required for the Gavi COVAX Advance Market Commitment to establish a Pandemic Vaccine Pool of a minimum of 600 million additional vaccine doses to: address uncertainties and risks in the evolution of the virus; provide bundled finance to strengthen delivery systems in recipient countries; and cover essential ancillary costs *(15)*.

	Cost-effectiveness	*No* ☐	*Uncertain* ☐	*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 costs of COVID-19 vaccination in general at global level. Formal cost–effectiveness analyses of Ad5-nCoV-S recombinant compared with other vaccines have been conducted in some settings. The ability to use Ad5-nCoV-S recombinant 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.	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 *(16-22)*.
EQUITY	What would be the impact on health inequities?	*Increased* ☒	*Uncertain* ☐	*Reduced* ☐	*Varies* ☐	Equity and ethical considerations are critical. SAGE has produced a Values Framework *(30)*, 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.	Vaccine nationalism is seen as a threat to reducing health inequity, particularly 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 *(24)*.
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Intervention*	*Comparison*	*Both*	*Neither*	*Unclear*	As vaccination is an important 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.
		☒	☐	☐	☐	☐		
	Which option is acceptable to target group?	*Intervention*	*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 receive a COVID-19 vaccine. Acceptance rates ranged from almost 55% to 87% *(25)*. Additionally, representative multi-country surveys are carried out periodically to assess the percentage of those willing to receive (or of those who have already 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 *(26, 27)*.	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐	*Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☐	*Yes* ☐	*Varies* ☒	Ad5-nCoV-S recombinant vaccine is assumed to be easily implementable in settings, including low- and middle-income countries, with existing vaccine logistics and delivery infrastructure. Storage and distribution requirements of the Ad5-nCoV-S recombinant vaccine are the same as those of many other vaccines currently in use globally. Therefore existing vaccine cold chain capacity, available in almost all countries worldwide could be leveraged for vaccine distribution. Administration of the vaccine to novel 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	We recommend the comparison ☐	We recommend against the intervention and the comparison ☐

	☒ Only in specific contexts or specific (sub)populations
RECOMMENDATION (TEXT)	Please see the interim recommendations.
IMPLEMENTATION CONSIDERATIONS	Please see the interim recommendations.
MONITORING, EVALUATION AND RESEARCH PRIORITIES	Please see the interim recommendations.

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