Annexes to the recommendations for use of the Janssen AD26.COV2.S vaccine against COVID-19

Grading of evidence –

Evidence to recommendations tables

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World Health Organization

Background

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 Janssen AD26.COV2.S COVID-19 vaccine in adults

Population:	Adults (18–59 years)
Intervention:	Single dose of Janssen AD26.COV2.S vaccine
Comparison:	Placebo/active control
Outcome:	Moderate to severe/critical COVID-19 (PCR-confirmed)

What is the efficacy of a single dose of Janssen AD26.COV2.S vaccine compared with placebo/active control in preventing moderate to severe/critical PCR-confirmed COVID-19 in adults (18–59 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT (1, 2)	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 a single dose of Janssen AD26.COV2.S vaccine is efficacious in preventing moderate to severe/critical PCR-confirmed COVID-19 in adults (18–59 years).

[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 Janssen AD26.COV2.S COVID-19 vaccine in adults

Population:	Adults (18–59 years)
Intervention:	Single dose of Janssen AD26.COV2.S vaccine
Comparison:	Placebo/active control
Outcome:	Serious adverse events following immunization

What is the risk of serious adverse events following Janssen AD26.COV2.S vaccination compared with placebo/active control in adults (18–59 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 a single dose of Janssen AD26.COV2.S vaccine in adults (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 (i.e. fewer than about 1 in 2000). These may emerge only when large populations have been vaccinated. A very rare syndrome of blood clotting combined with low platelet counts has been reported about 3 to 15 days following vaccination with the Ad26.COV2.S vaccine, described as Thrombosis with Thrombocytopenia Syndrome (TTS). Most cases were in females 18-59 years.

Annex 3. GRADE table: Efficacy of Janssen AD26.COV2.S COVID-19 vaccine in older adults

Population:	Older adults (≥60 years)
Intervention:	Older adults (≥60 years)
Comparison:	Single dose of Janssen AD26.COV2.S vaccine
Outcome:	Moderate to severe/critical COVID-19 (PCR-confirmed)

What is the efficacy of a single dose of Janssen AD26.COV2.S vaccine compared with placebo/active control in preventing moderate to severe/critical PCR-confirmed COVID-19 in older adults (≥60 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT (1, 2)	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		Imprecision	Not serious[b]	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 confident that a single dose of JANSSEN AD26.COV2.S vaccine is efficacious in preventing moderate to severe/critical PCR-confirmed COVID-19 in older adults (≥60 years).

[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 40% of the trial participants were aged 60 years or over. 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 vaccine in older adults

Population:	Older adults (≥60 years)
Intervention:	Single dose of Janssen AD26.COV2.S vaccine
Comparison:	Placebo/active control
Outcome:	Serious adverse events following immunization

What is the risk of serious adverse events following Janssen AD26.COV2.S vaccination compared with placebo/active control in older adults (≥60 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ 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[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 the risk of serious adverse events following a single dose of Janssen AD26.COV2.S vaccine in older adults (≥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 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 40% of the trial participants were aged 60 years or over. This was not considered as constituting a limitation that leads to downgrading of the evidence.

Annex 5. GRADE table: GRADE table: Efficacy of Janssen AD26.COV2.S COVID-19 vaccine in individuals with underlying conditions

Population:	Individuals with comorbidities or health states that increase risk for severe COVID-19
Intervention:	Single dose of Janssen AD26.COV2.S vaccine
Comparison:	Placebo/active control
Outcome:	Moderate to severe/critical COVID-19 (PCR-confirmed)

What is the efficacy of a single dose of Janssen AD26.COV2.S vaccine compared with placebo/active control in preventing moderate to severe/critical 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, 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 a single dose of Janssen AD26.COV2.S vaccine is efficacious in preventing moderate to severe/critical 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. 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 and diabetes. Approximately 40% 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.

Annex 6. GRADE table: Safety of Janssen AD26.COV2.S COVID-19 vaccine in individuals with underlying conditions

Population:	Individuals with comorbidities or health states that increase risk for severe COVID-19
Intervention:	Single dose of Janssen AD26.COV2.S vaccine
Comparison:	Placebo/active control
Outcome:	Serious adverse events following immunization

What is the risk of serious adverse events following Janssen AD26.COV2.S vaccination compared with placebo/active control in individuals with underlying conditions?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT(1, 2)	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Serious[c]	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			**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 a single dose of Janssen AD26.COV2.S 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 (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. This was considered as constituting a limitation that leads to downgrading of the evidence.

Annex 7. SAGE evidence-to-recommendation framework: Janssen AD26.COV2.S vaccine use in adults

Question: Should Janssen AD26.COV2.S vaccine be administered to adults to prevent moderate to severe/critical COVID-19?

Population: Adults (18–59 years)

Intervention: Single dose of JANSSEN AD26.COV2.S vaccine

Comparison(s): Active control/placebo

Outcome: Moderate to severe/critical 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 (3).

	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 164 523 894 with more than 3 412 032 deaths. Cases have been found in 190 different countries or territories throughout the world (status 21 May 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 &		*No*	*Uncertain*	*Yes*	*Varies*	The phase 3 study COV3001 demonstrated 63.7% efficacy (95%CI 53.9–71.6%) in people	In adults aged 18 years and over, vaccine effectiveness of the

	Benefits of the intervention Are the desirable anticipated effects large?	☐	☐	☒	☐	aged 18–59 years against confirmed moderate to severe/critical COVID-19 from 14 days after vaccination. In all participants, as from 14 days after vaccination, 2 COVID-19-related hospitalizations were observed in the vaccinated group compared with 29 in the placebo group (VE 93.1%, 95%CI 72.74–99.20).(1, 2)	Ad26.COV2.S vaccine was 76.7% (95% CI: 30.3-95.3%) in preventing SARS-CoV-2 infection with onset at least two weeks after vaccination.(4)
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	Ad26.COV2.S demonstrated an acceptable safety and reactogenicity profile in adults ≥18 years of age and in adults ≥60 years of age, including those with comorbidities associated with an increased risk of progressing to severe/critical COVID-19.(1, 2) All local and systemic adverse reactions were reported more frequently among younger (18–59 years) than among older (≥60 years) participants. In those aged 18–59 years, 4/14 564 (<0.1%) in the vaccine group reported related serious adverse events compared with 1/14 547 (<0.1%) in the placebo group. A very rare syndrome of blood clotting combined with low platelet counts has been reported about 3 to 15 days following vaccination with the Ad26.COV2.S vaccine, described as Thrombosis with Thrombocytopenia Syndrome (TTS). Most cases were in females 18-59 years.	

	Balance between benefits and harms	*Favours intervention* ☒	*Favours comparison* ☐	*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* ☐	*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 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), varies. 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	*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 to the undesirable effects related to COVID-19 vaccination.	

	undesirable effects?					Targeted studies should assess this aspect.	
RESOURCE USE	Are the resources required small?	*No* ☒	*Uncertain* ☐	*Yes* ☐	*Varies* ☐	Janssen AD26.COV2.S vaccine can be distributed and stored using existing cold-chain infrastructure and does not require ultra-cold-chain capacity. 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. (5) 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 (6).
	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 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

					No formal cost-effectiveness analyses of Janssen AD26.COV2.S vaccine compared with other vaccines have been conducted. The Janssen AD26.COV2.S vaccine is expected to be less costly than other COVID-19 vaccines (see previous subcriterion). (7) 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. The ability to use Janssen AD26.COV2.S 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.	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).(5, 8-13)
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 (16), 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, 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

							Storage and distribution requirements of the Janssen AD26.COV2.S 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.	equitable access to vaccines for its participating member states.(14)
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Intervention*	*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 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.
		☒	☐	☐	☐	☐		
	Which option is acceptable to target group?	*Intervention*	*Comparison*	*Both*	*Neither*	*Un-clear*	Single-dose administration of this product may be favourable to the target group. 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%. (15) 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. (16, 17)	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐	*Probably* No ☐	*Uncertain* ☐	*Probably* Yes ☐	*Yes* ☒	*Varies* ☐	Single-dose 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. Ad26.COV2.S can be stored at 2°C to 8°C for 3 months within the 24 months of shelf life, and its shipping and storage fit into the existing medical supply infrastructure.(18) 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	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: Janssen AD26.COV2.S vaccine use in older adults

Question: Should Janssen AD26.COV2.S vaccine be administered to older adults to prevent moderate to severe/critical COVID-19

Population: Older adults (≥60 years)

Intervention: Single dose of Janssen AD26.COV2.S vaccine

Comparison(s): Active control/placebo

Outcome: Moderate to severe/critical 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 (3).

	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 164 523 894 with more than 3 412 032 deaths. Cases have been found in 190 different countries or territories throughout the world (status 21 May 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* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	Around 40% of the study population in the primary analysis were aged 60 years or older. The phase 3 study COV3001 demonstrated 76.3% efficacy (95%CI 61.1–86.0%) in those aged 60 years and above against confirmed moderate to severe/critical COVID-19 as from 14 days after vaccination. In all participants, as of 14 days after vaccination, there were 2 COVID-19-related hospitalizations in the vaccinated group compared with 29 in the placebo group (VE 93.1%, 95%CI 72.74–99.20).(1, 2)	A recent publication demonstrated, vaccine effectiveness of the Ad26.COV2.S vaccine was 76.7% (95% CI: 30.3-95.3%) in preventing SARS-CoV-2 infection with onset at least two weeks after vaccination. Around 50% of the vaccinees included were aged 65 and over.(4)
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	Ad26.COV2.S demonstrated an acceptable safety and reactogenicity profile in adults ≥18 years of age, and adults ≥60 years of age, including those with comorbidities associated with an increased risk of progressing to severe/critical COVID-19. All local and systemic adverse reactions were reported more frequently among younger (18–59 years) than among older (≥60 years) participants. In those aged 60 years and over, 3/7331 (<0.1%) in the vaccine group reported related serious adverse events compared with 1/7341 (<0.1%) in the placebo group.(1, 2)	

	Balance between benefits and harms	*Favours intervention* ☒	*Favours comparison* ☐	*Favours both* ☐	*Favours neither* ☐	Unclear ☐	Efficacy data 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* ☐		
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:	*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	

	Are the desirable effects large relative to undesirable effects?	☐	☐	☐	☒	☐	☐	undesirable effects related to COVID-19 vaccination. Targeted studies should assess this aspect. As more data on vaccine efficacy in older adults are 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* ☒	*Uncertain* ☐	*Yes* ☐	*Varies* ☐			Janssen AD26.COV2.S can be distributed and stored using existing cold-chain infrastructure and does not require ultra-cold-chain capacity. 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	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. (5) 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 (6).

						communications, and immunization safety surveillance.	
	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 cost of COVID-19 vaccination in general at global level. No formal cost-effectiveness analyses of Janssen AD26.COV2.S vaccine compared with other vaccines have been conducted. The Janssen AD26.COV2.S vaccine is expected to be less costly than other COVID-19 vaccines (see previous subcriterion). (7) 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. The ability to use Janssen AD26.COV2.S 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 (GDP).(5, 8-13)
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 (16), which offers guidance on the fair allocation	Vaccine nationalism is seen as a threat to reducing health inequity, in particular as high-

							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 Janssen AD26.COV2.S vaccine are the same as those of many other vaccines currently in use globally. Existing vaccine cold-chain capacity, which is available in almost all countries, could be leveraged for vaccine distribution.	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.(14)
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Intervention*	*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?	*Intervention*	*Comparison*	*Both*	*Neither*	*Un-clear*	Single-dose administration of this product may be favourable to the target group. 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%. (15) 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. (16, 17)	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐	*Probably* No ☐	*Uncertain* ☐	*Probably* Yes ☐	*Yes* ☒	*Varies* ☐	Single-dose 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. Ad26.COV2.S can be stored at 2°C to 8°C for 3 months within the 24 months of shelf life, and its shipping and storage fit into the existing medical supply infrastructure.(18)	
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	We recommend the comparison		We recommend against the intervention and the comparison			

	☐	☒ Only in the context of rigorous research ☐ 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 9. SAGE evidence-to-recommendation framework: Janssen AD26.COV2.S vaccine use in individuals with comorbidities

Question: Should Janssen AD26.COV2.S vaccine be administered to individuals with comorbidities or health states that increase risk for severe COVID-19[a] to prevent moderate to severe/critical COVID-19?

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

Intervention: Single dose of JANSSEN AD26.COV2.S vaccine

Comparison(s): Active control/placebo

Outcome: Moderate to severe/critical 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 (3).

	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 164 523 894 with more than 3 412 032 deaths. Cases have been found in 190 different countries or territories throughout the world (status 21 May 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

[a] Comorbidity in the phase 3 trial was defined as asthma, cancer, chronic kidney disease, cardiovascular disorder, respiratory disease, obesity, neurological conditions, immunocompromised from blood transplant, HIV infection or diabetes type 2.

					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 diabetes, hypertension, cardiac disease, chronic lung disease, cerebrovascular disease, dementia, mental disorders, chronic kidney disease, immunosuppression, obesity and cancer. People with multiple comorbidities are at a higher risk of COVID-19-related adverse outcomes (22) 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).	
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	At least one comorbidity was present for 39.9% of participants. The phase 3 study COV3001 demonstrated 64.2% efficacy (95%CI 52.7–73.1) in those with comorbidities against confirmed moderate to severe/critical COVID-19 as from 14 days after vaccination.(1, 2)	
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	Ad26.COV2.S demonstrated an acceptable safety and reactogenicity profile in adults ≥18 years of age, and adults ≥60 years of age, including those with comorbidities associated with an increased risk of progressing to severe/critical COVID-19.(1, 2)	

	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.	
	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* ☐		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* ☐	It is assumed that 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* ☐	Janssen AD26.COV2.S can be distributed and stored using existing cold-chain infrastructure and does not require ultra-cold-chain capacity. 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. (5) 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 (6).
	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 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

					No formal cost-effectiveness analyses of Janssen AD26.COV2.S vaccine compared with other vaccines have been conducted. The Janssen AD26.COV2.S vaccine is expected to be less costly than other COVID-19 vaccines (see previous subcriterion). (7) 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. The ability to use Janssen AD26.COV2.S 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.	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).(5, 8-13)
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 (16), 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, 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)

							Storage and distribution requirements of Janssen AD26.COV2.S vaccine are the same as for many other vaccines currently in use globally. Existing vaccine cold-chain capacity, available in almost all countries worldwide, could be leveraged for vaccine distribution.	Accelerator and within this, the COVAX facility, which aims to ensure equitable access to vaccines for its participating member states.(14)
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Intervention*	*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?	*Intervention*	*Comparison*	*Both*	*Neither*	*Un-clear*	Single-dose administration of this product may be favourable to the target group. 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%. (15) 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. (16, 17)	
FEASIBILITY	Is the intervention feasible to implement?	*No*	*Probably* No	*Uncertain*	*Probably* Yes	*Yes*	*Varies*	Single-dose 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. Ad26.COV2.S can be stored at 2°C to 8°C for 3 months within the 24 months of shelf life, and its shipping and storage fit into the existing medical supply infrastructure.(18)	
		☐	☐	☐	☐	☒	☐		

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	We recommend the comparison	We recommend against the intervention and the comparison
	☐	☐ Only in the context of rigorous research ☒ 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.

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