Annexes to the recommendations for use of the Valneva VLA2001 vaccine against COVID-19

Grading of evidence

Evidence to recommendations tables

First issued 18 August 2022

World Health Organization

Background

These are the annexes to the Interim recommendations for use of the Valneva VLA2001 vaccine against COVID-19.

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

Contents

Annex 1. GRADE table: Efficacy of VLA2001 COVID-19 vaccine in adults

Population:	Adults (18–50 years)
Intervention:	Two doses of VLA2001 vaccine
Comparison:	Placebo/active control
Outcome:	COVID-19 (PCR-confirmed)

What is the efficacy of two doses of VLA2001 vaccine compared with placebo/active control in preventing PCR-confirmed COVID-19 in adults (18–50 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	Serious[b]	-2
		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).**
	Conclusion			Vaccine efficacy in adults (18–50 years) is inferred by demonstrating a non-inferior immune response between VLA2001 vaccine and ChAdOx1-S vaccine for which efficacy against PCR-confirmed COVID-19 has been estimated. The confidence in the quality of evidence is limited due to indirectness of the data.

[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] No efficacy estimates were obtained. Protection of VLA2001 vaccine is inferred by immunobridging to ChAdOx1-S vaccine. Participants ⩾30 years were randomized to either vaccine, participants aged <30 years received two doses of VLA2001 open label. This was considered as constituting a limitation that leads to downgrading of the evidence.

Annex 2. GRADE table: Safety of VLA2001 vaccine in adults

Population:	Adults (18–50 years)			
Intervention:	One or two doses of VLA2001 vaccine			
Comparison:	Placebo/active control			
Outcome:	Serious adverse events following immunization			
What is the risk of serious adverse events following VLA2001 vaccination compared with placebo/active control in adults (18–50 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).**
	Conclusion			We are moderately confident that there is a very low risk of serious adverse events following one or two doses of VLA2001 vaccine in adults (18–50 years) .

Annex 3. GRADE table: Efficacy of VLA2001 COVID-19 vaccine in older adults

[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 (i.e. fewer than about 1 in 2000).

Population:	Older adults (≥50 years)
Intervention:	Two doses of VLA2001 vaccine
Comparison:	Placebo/active control
Outcome:	COVID-19 (PCR-confirmed)

What is the efficacy of two doses of VLA2001 vaccine compared with placebo/active control in preventing PCR-confirmed COVID-19 in older adults (≥50 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	Serious[b]	-2
		Imprecision	Serious[c]	-1
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**1**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports very low confidence that the true effect lies close to the estimate of the effect on the health outcome (level 1).**
	Conclusion			Vaccine efficacy in older adults (≥55 years) is inferred by demonstrating a non-inferior immune response between VLA2001 vaccine and ChAdOx1-S vaccine for which efficacy against PCR-confirmed COVID-19 has been estimated. The confidence in the quality of evidence is very low due to indirectness of the data and limited representation of older adults.

[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] No efficacy estimates were obtained. Protection of VLA2001 vaccine is inferred by immunobridging to ChAdOx1-S vaccine. This was considered as constituting limitations that lead to downgrading of the evidence.

[c] In the phase 3 trial, less than 1% of the population studied was older than 50 years leading to wide confidence intervals. This was considered as constituting a limitation that leads to downgrading of the evidence

Annex 4. GRADE table: Safety of VLA2001 COVID-19 vaccine in older adults

Population:	Older adults (≥50 years)
Intervention:	One or two doses of VLA2001 vaccine
Comparison:	Placebo/active control
Outcome:	Serious adverse events following immunization

What is the risk of serious adverse events following VLA2001 vaccination compared with placebo/active control in older adults (≥50 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT *(1)*	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Serious[c]	-2
		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			**1**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a very low level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 1).**
	Conclusion			We have very low confidence that the risk of serious adverse events following one or two doses of VLA2001 vaccine in older adults (≥50 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).

[c] In the phase 3 clinical trial, less than 1% of the population studied was older than 50 years. This was considered as constituting a limitation that leads to downgrading of the evidence.

Annex 5. GRADE table: Efficacy of VLA2001 COVID-19 vaccine in individuals with underlying conditions

Population:	Individuals with comorbidities or health states that increase risk for severe COVID-19
Intervention:	Two doses of VLA2001 vaccine
Comparison:	Placebo/active control
Outcome:	COVID-19 (PCR-confirmed)

What is the efficacy of two doses of VLA2001 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]	-2
		Imprecision	Serious[c]	-1
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**1**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a very low level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 1).**
	Conclusion			Vaccine efficacy in individuals with comorbidities or health states that increase risk for severe COVID-19 is inferred by demonstrating a non-inferior immune response between VLA2001 vaccine and ChAdOx1-S vaccine for which efficacy against PCR-confirmed COVID-19 has been estimated. No data were obtained from the clinical trial on vaccination of pregnant or breastfeeding

[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] No efficacy estimates were obtained. Protection of VLA2001 vaccine is inferred by immunobridging to ChAdOx1-S vaccine. This was considered as constituting a limitation that leads to downgrading of the evidence.

[c] The phase 3 trial included mainly healthy adults. Few individuals with comorbidities were included, leading to wide confidence intervals. Underlying comorbidities included BMI ≥ 30 kg/m2, cardiovascular disorder, respiratory disease and diabetes. 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.

		women, or persons who were immunocompromised. The confidence in the quality of evidence is very low due to indirectness of the data and limited representation of older adults.

Annex 6. GRADE table: Safety of VLA2001 COVID-19 vaccine in individuals with underlying conditions

Population:	Individuals with comorbidities or health states that increase risk for severe COVID-19
Intervention:	One or two doses of VLA2001 vaccine
Comparison:	Placebo/active control
Outcome:	Serious adverse events following immunization

What is the risk of serious adverse events following VLA2001 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)*	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Serious[c]	-2
		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			**1**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a very low level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 1).**
	Conclusion			We have very low confidence that the risk of serious adverse events following one or two doses of VLA2001 vaccine in individuals with comorbidities or health states that increase risk for severe COVID-19 following one or two doses of VLA2001 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 2000).

[c] In the phase 3 clinical trial, very few individuals with comorbidities or health states that increase risk for severe COVID-19 were included. 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: VLA2001 vaccine use in adults

Question: Should VLA2001 vaccine be administered to adults to prevent PCR-confirmed COVID-19?

Population: Adults (18–50 years)

Intervention: Single dose of VLA2001 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 *(3)*.

	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* ☐	The phase 3 COV-COMPARE immuno-bridging trial was conducted in the UK. Participants aged ≥30 years were randomly assigned 2:1 to receive two doses of VLA2001 (n=1978) or ChAdOx1-S (n=997), 28 days apart; participants aged <30 years (n=1042) received two doses of VLA2001 open label. Sera from 990 participants aged ≥30 years and 210 participants aged <30 years were analysed for immunogenicity. VLA2001 induced higher neutralizing antibody geometric mean titres (GMTs) than ChAdOx1-S (803.5 [95% CI: 748.5, 862.6], vs. 576.6 [543.6, 611.7] respectively, GMT ratio 1.39, p<0.0001), and non-inferior seroconversion rates (>95% in both groups) *(1)*.	VLA2001 induced broad T-cell responses with anti-protein antigen-specific IFN-gamma producing T-cells against the Spike in 74.3% of participants, the Nucleocapsid in 45.9% and the Membrane in 20.3%.
	Harms of the intervention Are the undesirable anticipated	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	The phase 3 COV-COMPARE trial, a total of 4012 participants were included in the safety analysis *(1)*. Individuals who received VLA2001 reported significantly	In the COV-BOOST study *(4)*, a full dose of VLA2001 (n=219 participants in the VLA2001 group) was administered to

	effects small?						fewer solicited adverse events (AEs) up to 7 days after the 1st vaccination than those who received ChAdOx1-S, both with regards to local injection site reactions (59.7% vs 88.1%, p<0.0001) and systemic reactions (70.2% vs 91.1%, p<0.0001) respectively. The incidences of any serious adverse event (SAE), medically attended adverse events and adverse events of special interest were similar between the two groups (0.7% in the VLA2001 group and 1.0% in the ChAdOx1-S group) *(1)*. The phase 1/ 2 clinical trial supports a good safety profile of VLA2001 in healthy adults aged 18-55 years *(2)*.	individuals ≥30 years as a booster dose following the receipt of a 2 dose primary series of ChAdOx1-S or BNT162b2. The safety profile of VLA2001, any grade local and systemic reactions within 7 days after all vaccines, was similar to other administered COVID-19 vaccines, with fatigue and headache the most common systemic reactions, and pain being the most frequent local reaction.
	Balance between benefits and harms	*Favours intervention*	*Favours comparison*	*Favours both*	*Favours neither*	Unclear	Immunogenicity data suggest benefit, and safety data suggest minimal harms of two doses of both VLA2001 vaccine and CAdOx1-S vaccine. Further studies will need to be undertaken as part of post-marketing surveillance.	
		☐	☐	☒	☐	☐		
	What is the overall quality of this	**Effectiveness of the intervention**					Please see the related GRADE tables.	
		No included studies	*Very low*	*Low*	*Moderate*	*High*		

	evidence for the critical outcomes?	☐	☐	☒	☐	☐		
		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 undesirable effects?	*No*	*Probably No*	*Uncertain*	*Probably Yes*	*Yes*	*Varies*	The target population probably assigns 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* ☐	VLA2001 vaccine can be distributed and stored using existing cold-chain infrastructure and does not require ultra-cold-chain capacity. Nevertheless, considerable resources are needed to ensure the implementation of a COVID-19 vaccination programme. 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 *(5)*. 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 *(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. No formal cost-effectiveness analyses of VLA2001 vaccine compared with other vaccines have been conducted. The ability to use VLA2001 in existing cold-chain infrastructure in all country settings may allow higher population-level coverage *(7)*. 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 e.g. reduced business activity and unemployment due to the pandemic, which is expected to amount up to US$13.8 trillion through 2024 *(8)*. Initial estimates suggest that timely rolled out COVID-19 vaccination will provide nomic value in terms of averted morbidity and mortality costs and averted losses in gross domestic product (GDP) *(9-14)*.
EQUITY	What would be the impact on	*Increased* ☐	*Uncertain* ☐	*Reduced* ☒	*Varies* ☐	Equity and ethical considerations are critical. SAGE has produced a Values Framework *(15)*, which offers	Vaccine nationalism is seen as a threat to reducing health inequity, in particular

	health inequities?						guidance on the fair allocation of COVID-19 vaccines based on 6 core ethical principles that should guide distribution. If distributed fairly, COVID-19 vaccines may have considerable impact on reducing health inequities.	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 *(16)*.
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Intervention*	*Comparison*	*Both*	*Neither*	*Un-clear*	Vaccination is an important tool to combat COVID-19 and key stakeholders, in particular ministries of health and immunization managers, are generally strongly in favour of COVID-19 vaccination.	190 economies are participating in COVAX suggesting a very high acceptability of COVID-19 vaccination in general.
		☒	☐	☐	☐	☐		
	Which option is acceptable to target group?	*Intervention*	*Comparison*	*Both*	*Neither*	*Un-clear*	COVID-19 vaccine acceptability in general varies between (sub)population groups and may be correlated with the perceived risk posed by the disease. In a global survey (19 countries) of acceptance rates in	
		☐	☐	☒	☐	☐		

								the general population of any COVID-19 vaccine product, 71.5% of participants reported that they would be very or somewhat likely to take a COVID-19 vaccine. Acceptance rates ranged from almost 55% to 87% *(17)*. 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. *(18, 19)*	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐	*Probably* No ☐	*Uncertain* ☐	*Probably* Yes ☐	*Yes* ☒	*<u>Varies</u>* ☐	The 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 VLA2001 vaccine are the same as those of many other vaccines currently in use globally. VLA2001 can be stored and transported at 2°C to 8°C within	

					the 12 months of shelf life. The chemical and physical in-use stability of the vaccine has been demonstrated for 6 hours in vial when stored at room temperature. Its shipping and storage fit into the existing medical supply infrastructure *(20)*.	
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 8. SAGE evidence-to-recommendation framework: VLA2001 vaccine use in older adults

Question: Should VLA2001 vaccine be administered to older adults to prevent PCR-confirmed COVID-19

Population: Older adults (≥50 years)

Intervention: Two doses of VLA2001 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 *(3)*.

	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. Older adults are particularly affected by COVID-19 and bear a significantly higher risk of severe COVID-19 outcomes and death.	
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Uncertain* ☒	*Yes* ☐	*Varies* ☐	Less than 1% of the study population in the primary analysis were aged 50 years or older *(1)*. In three participants >50 years of age who were included in the immunogenicity population, the neutralizing antibody GMT was 611.4 (95%CI: 158.91- 2352.01).	Due to the high coverage of the UK national vaccination campaign including all older age groups at the time of the phase 3 trial, the number of participants >55 years of age was very small.
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Uncertain* ☒	*Yes* ☐	*Varies* ☐	The phase 3 COV-COMPARE trial, a total of 24 participants aged >55 were included in the safety analysis (n=19 in VLA2001 and n=5 in the ChAdOx1-S group) *(1)*. Individuals aged ≥30 years who received VLA2001 reported significantly fewer solicited AEs up to 7 days after the 1st vaccination than those who received ChAdOx1-S, both with regards to local injection site reactions (59.7% vs 88.1%, p<0.0001) and systemic reactions (70.2% vs 91.1%, p<0.0001) respectively.	In the COV-BOOST study *(4)*, a full dose of VLA2001 (n=219 participants in the VLA2001 group) was administered to individuals ≥30 years (approx. 50% in the VLA2001 group was aged ≥70 years) as a booster dose following the receipt of a 2 dose primary series of ChAdOx1-S or BNT162b2. The safety profile of VLA2001, any grade local and systemic reactions

							The incidences of any SAE, medically attended adverse events and adverse events of special interest were similar between the two groups (0.7% in the VLA2001 group and 1.0% in the ChAdOx1-S group) (1, 2).	within 7 days after all vaccines, was similar to other administered COVID-19 vaccines, with fatigue and headache the most common systemic reactions, and pain being the most frequent local reaction.
	Balance between benefits and harms	*Favours intervention* ☐	*Favours comparison* ☐	*Favours both* ☐	*Favours neither* ☐	Unclear ☒	Due to currently very limited data, no meaningful conclusions on weighing of benefits and harms in this age group can be drawn at this time.	
	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	*Important uncertaint*	*Possibly important uncertaint*	*Probably no important*	*No important uncertain*	*No known undesirab*	The majority of severe disease occurs in older individuals.	

	relative importance of the desirable and undesirable outcomes?	*y or variability* ☐	*y or variability* ☒	*uncertainty or variability* ☐	*ty or variability* ☐	*le 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 undesirable effects?	*No* ☐	*Probably No* ☐	*Uncertain* ☒	*Probably Yes* ☐	*Yes* ☐	*Varies* ☐	The target population probably assigns 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* ☐			VLA2001 vaccine can be distributed and stored using existing cold-chain infrastructure and does not require ultra-cold-chain capacity. Nevertheless, considerable resources are needed to ensure the implementation of a COVID-19	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

					vaccination programme. 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.	countries and territories *(5)*. 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 *(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

					No formal cost-effectiveness analyses of VLA2001 vaccine compared with other vaccines have been conducted. The VLA2001 vaccine is expected to be less costly than other COVID-19 vaccines (see previous subcriterion). *(7)* The ability to use VLA2001 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.	mitigate the economic consequences of e.g. reduced business activity and unemployment due to the pandemic, which is expected to amount up to US$13.8 trillion through 2024*(8)*. Initial estimates suggest that timely rolled out COVID-19 vaccination will provide nomic value in terms of averted morbidity and mortality costs and averted losses in gross domestic product (GDP)*(9-14)*.
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 *(15)*, which offers guidance on the fair allocation of COVID-19 vaccines based on 6 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 equitable access to vaccines for its participating member states*(16)*.
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Intervention*	*Comparison*	*Both*	*Neither*	*Un-clear*	Vaccination is an important tool to combat COVID-19 and key stakeholders, in particular ministries of health and immunization managers, are generally 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*	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%. *(17)*	
		☐	☒	☐	☐	☐		

										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. *(18, 19)* Single-dose administration of this product may be favourable to some target groups.	
FEASIBILITY	Is the intervention feasible to implement?	*No*	*Probably* No	*Uncertain*	*Probably* Yes	*Yes*	*Varies*			The 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 VLA2001 vaccine are the same as those of many other vaccines currently in use globally. VLA2001 can be stored and transported at 2°C to 8°C within the 12 months of shelf life. The chemical and physical in-use stability of the vaccine has been	
		☐	☐	☐	☐	☒	☐				

			demonstrated for 6 hours in vial when stored at room temperature. Its shipping and storage fit into the existing medical supply infrastructure *(20)*.		
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: VLA2001 vaccine use in individuals with comorbidities

Question: Should VLA2001 vaccine be administered to individuals with comorbidities or health states that increase risk for severe COVID-19[a] to prevent PCR-confirmed COVID-19?

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

Intervention: Two doses of VLA2001 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 *(3)*.

	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	

[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.

					found on the following website: https://covid19.who.int/table. 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 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 *(21)* 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	Benefits of the intervention Are the desirable anticipated	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	For baseline seronegative individuals, with obesity (BMI>30) population, at day 43 neutralizing antibody titres GMTs for VLA2001 (n=119) was 689.3 (95%CI 591.0, 803.9) compared to 640.1 (95%CI	

	effects large?				565.3, 724.8) for the ChAdOx1-S group (n=125), p-value 0.534 (see background paper). In individuals with specific risk factors (COPD, cardiovascular risk or diabetes), GMTs for VLA2001 (n=8) was 785.0 (95%CI: 451-1366) compared to 344 (95%CI:N/A) for the ChAdOx1-S group (n=1).	
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐	*Uncertain* ☒	*Yes* ☐	*Varies* ☐	The phase 3 COV-COMPARE trial enrolled healthy individuals. No safety data stratified by comorbidities or health states that increase risk for severe COVID-19 are currently available. In the entire study population, individuals aged ⩾30 years who received VLA2001 reported significantly fewer solicited adverse events (AEs) up to 7 days after the 1st vaccination than those who received ChAdOx1-S vaccine, both with regards to local injection site reactions (59.7% vs 88.1%, p<0.0001) and systemic reactions (70.2% vs 91.1%, p<0.0001) respectively. The incidences of any SAE, medically attended adverse events and adverse events of special interest were similar	In the COV-BOOST study *(4)*, a full dose of VLA2001 (n=219 participants in the VLA2001 group) was administered to individuals ≥30 years (including individuals with comorbidities) as a booster dose following the receipt of a 2 dose primary series of ChAdOx1-S or BNT162b2. The safety profile of VLA2001, any grade local and systemic reactions within 7 days after all vaccines, was similar to other administered COVID-19 vaccines, with fatigue and headache the most common systemic reactions,

							between the two groups (0.7% in the VLA2001 group and 1.0% in the ChAdOx1-S group) (1, 2).	and pain being the most frequent local reaction. A developmental and reproductive toxicity (DART) study in female rats VLA2001 did not affect reproductive parameters, delivery or fetal development *(20)*.
	Balance between benefits and harms	*Favours intervention* ☐	*Favours comparison* ☐	*Favours both* ☐	*Favours neither* ☐	Unclear ☒	Due to currently very limited data, no meaningful conclusions on weighing of benefits and harms in this population group can be drawn at this time.	
	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		*Important uncertaint*	*Possibly important*	*Probably no*	*No important*	*No known undesirab*		

	How certain is the relative importance of the desirable and undesirable outcomes?	*y or variability* ☐	*uncertainty or variability* ☒	*important uncertainty or variability* ☐	*uncertainty or variability* ☐	*le 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 undesirable effects?	*No* ☐	*Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☒	*Yes* ☐	*Varies* ☐	The target population probably assigns 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* ☐			VLA2001 vaccine can be distributed and stored using existing cold-chain infrastructure and does not require ultra-cold-chain capacity. Nevertheless, considerable resources are needed to ensure the	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

					implementation of a COVID-19 vaccination programme. 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.	countries and territories *(5)*. 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 *(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

					No formal cost-effectiveness analyses of VLA2001 vaccine compared with other vaccines have been conducted. The VLA2001 vaccine is expected to be less costly than other COVID-19 vaccines (see previous subcriterion). *(7)*. The ability to use VLA2001 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.	consequences of e.g. reduced business activity and unemployment due to the pandemic, which is expected to amount up to US$13.8 trillion through 2024*(8)*. Initial estimates suggest that timely rolled out COVID-19 vaccination will provide nomic value in terms of averted morbidity and mortality costs and averted losses in gross domestic product (GDP)*(9-14)*.
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 *(15)*, which offers guidance on the fair allocation of COVID-19 vaccines based on 6 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 equitable access to vaccines for its participating member states *(16)*.
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Intervention*	*Comparison*	*Both*	*Neither*	*Un-clear*	Vaccination is an important tool to combat COVID-19 and key stakeholders, in particular ministries of health and immunization managers, are generally 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*	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%. *(17)*	
		☐	☒	☐	☐	☐		

								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*(18, 19)*.	
FEASIBILITY	Is the intervention feasible to implement?	*No*	*Probably* No	*Uncertain*	*Probably* Yes	*Yes*	*Varies*	The 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 VLA2001 vaccine are the same as those of many other vaccines currently in use globally. VLA2001 can be stored and transported at 2°C to 8°C within the 12 months of shelf life. The chemical and physical in-use stability of the vaccine has been demonstrated for 6 hours in vial when stored at room temperature. Its shipping and storage fit into the existing	
		☐	☐	☐	☐	☒	☐		

			medical supply infrastructure *(20)*.		
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.				

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