Annexes to the interim recommendations for use of the Bharat Biotech BBV152 COVAXIN® vaccine against COVID-19

Grading of evidence –

Evidence to recommendations tables

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World Health Organization

Background

These are the annexes to the Interim recommendations for use of the Bharat Biotech BBV152 COVAXIN® vaccine against COVID-19.

Annexes 1–6 contain tables that summarize the grading of recommendations, assessment, development and evaluations (GRADE) of Bharat Biotech BBV152 vaccine. 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 14 February 2022).

Contents

Annex 1. GRADE table: Efficacy of BBV152 COVID-19 vaccine in adults

Population:	Adults (aged 18–59 years)
Intervention:	Two doses of BBV152 vaccine
Comparison:	Placebo/active control
Outcome:	COVID-19 (PCR-confirmed)

What is the efficacy of two doses of BBV152 vaccine compared with placebo/active control in preventing PCR-confirmed COVID-19 in adults (18–59 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT*(1)*	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious[b]	0
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		Imprecision	Not serious	0
		Publication bias	Not serious	0
	Factors increasingconfidence	Large effect	Not applicable	0
		Dose–response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a high level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 4).**
	Conclusion			We are very confident that 2 doses of BBV152 vaccine are efficacious in preventing PCR-confirmed COVID-19 in adults (18–59 years) up to approx. 3 months following immunization in the context of wild-type and pre-Omicron variants of concern.

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

[b] Data 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 3 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 BBV152 COVID-19 vaccine in adults

Population:	Adults (aged 18–59 years)
Intervention:	Two doses of BBV152 vaccine
Comparison:	Placebo/active control
Outcome:	Serious adverse events following immunization

What is the risk of serious adverse events following BBV152 vaccination compared with placebo/active control in adults (18–59 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		3/ RCT *(1-3)*	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 increasingconfidence	Large effect	Not applicable	0
		Dose–response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 3).**
	Conclusion			We are moderately confident that the risk of serious adverse events following 1 or 2 doses of BBV152 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. less than about 1/2000). These may emerge only when large populations have been vaccinated. Limited follow-up time of clinical trial, which may not allow detection of adverse events occurring several months after vaccination.

Annex 3. GRADE table: Efficacy of BBV152 COVID-19 vaccine in older adults

Population:	Older adults (aged ≥60 years)
Intervention:	Two doses of BBV152 vaccine
Comparison:	Placebo/active control
Outcome:	COVID-19 (PCR-confirmed)

What is the efficacy of two doses of BBV152 vaccine compared with placebo/active control in preventing PCR-confirmed COVID-19 in older adults (≥60 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT *(1)*	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Serious[b]	-1
		Imprecision	Not serious[c]	0
		Publication bias	Not serious	0
	Factors increasingconfidence	Large effect	Not applicable	0
		Dose–response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 3).**
	Conclusion			We are moderately confident that 2 doses of BBV152 vaccine are efficacious in preventing PCR-confirmed COVID-19 in older adults (≥65 years) up to approx. 3 months following immunization in the context of wild-type and pre-Omicron variants of concern.

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

[b] Of the trial participants in the phase 3 clinical trial, 11% were aged over 60 years. While supportive evidence (immunogenicity data up to 65 years) suggest that the vaccine elicits an immune response,. The very serious imprecision due to the limited sample size was considered as a factor constituting a limitation that leads to downgrading of the evidence. SAGE will continue to review any emerging data and adjust its quality assessment as required.

[c] The confidence intervals are wide but this is related to sample size therefore not downgraded.

Annex 4. GRADE table: Safety of BBV152 COVID-19 vaccine in older adults

Population:	Older adults (aged ⩾60 years)
Intervention:	One or two doses of BBV152 vaccine
Comparison:	Placebo/active control
Outcome:	Serious adverse events following immunization

What is the risk of serious adverse events following BBV152 vaccination compared with placebo/active control in older adults (≥60 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2/ RCT *(1, 3)*	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Serious[c]	-1
		Imprecision	Not serious	0
		Publication bias	Not serious	0
	Factors increasingconfidence	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 that of the estimate of the effect on the health outcome (level 2).**
	Conclusion			We have low confidence in the evidence that the risk of serious adverse events following 1 or 2 doses of BBV152 vaccine in older adults (≥60 years) is low.

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

[b] Downgraded for the following limitations: The trial was not adequately powered to detect rare adverse events. These may emerge only when large populations have been vaccinated. Limited follow-up time of clinical trial, which may not allow detection of adverse events occurring several months after vaccination.

[c] Of the trial participants in the phase 3 clinical trial, 11% were aged over 60 years. While supportive evidence (immunogenicity data up to 65 years) suggest that the vaccine elicits an immune response, the very serious imprecision due to the limited sample size was considered as a factor constituting a limitation that leads to downgrading of the evidence. SAGE will continue to review any emerging data and adjust its quality assessment as required.

Annex 5. GRADE table: Efficacy of BBV152 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 BBV152 vaccine
Comparison:	Placebo/active control
Outcome:	COVID-19 (PCR-confirmed)

What is the efficacy of two doses of BBV152 vaccine compared with placebo/active control in preventing PCR-confirmed COVID-19 in individuals with comorbidities or health states that increase risk for severe COVID-19?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT*(1)*	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Serious[b]	-1
		Imprecision	Not serious[c]	0
		Publication bias	Not serious	0
	Factors increasingconfidence	Large effect	Not applicable	0
		Dose–response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 3).**
	Conclusion			We are moderately confident that 2 doses of BBV152 vaccine are efficacious in preventing PCR-confirmed COVID-19 in individuals with comorbidities or health states that increase risk for severe COVID-19 as included in the clinical trial up to approx. 3 months following immunization in the context of wild-type and pre-Omicron variants of concern. No data were obtained on vaccination of pregnant or breastfeeding women, or persons who were immunocompromised.

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

[b] Trial excluded pregnant and breastfeeding women, people living with HIV and persons who were severly immunocompromised. This was considered as constituting a limitation that leads to downgrading of the evidence.

[c] Underlying comorbidities included BMI ≥35 kg/m2, cardiovascular disorder, respiratory disease, liver disease or diabetes and other stable co-morbidities. Approximately 27% of the trial population had at least one comorbidity. This was considered as not constituting a limitation that would lead to downgrading of the evidence. SAGE will continue to review any emerging data and adjust the quality assessment as required.

Annex 6. GRADE table: Safety of BBV152 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 BBV152 vaccine
Comparison:	Placebo/active control
Outcome:	Serious adverse events following immunization

What is the risk of serious adverse events following BBV152 vaccination compared with placebo/active control in individuals with comorbidities or health states that increase risk for severe COVID-19?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT *(1)*	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Serious[c]	-1
		Imprecision	Not serious	0
		Publication bias	Not serious	0
	Factors increasingconfidence	Large effect	Not applicable	0
		Dose–response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a low level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 2).**
	Conclusion			We have low confidence in the quality of evidence that the overall risk of serious adverse events in individuals with comorbidities or health states that increase risk for severe COVID-19 following 1 or 2 doses of BBV152 vaccine is low.

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

[b] Downgraded for the following limitations: the trial was not adequately powered to detect rare adverse events. These may emerge only when large populations have been vaccinated. Limited follow-up time of clinical trial, which may not allow detection of adverse events occurring several months after vaccination.

[c]Trial excluded pregnant and breastfeeding women, people living with HIV, and persons who were severely immunocompromised. This was considered as constituting a limitation that leads to downgrading of the evidence.

Annex 7. SAGE evidence-to-recommendation framework BBV152 COVID-19 vaccine use in adults

Question:	Should BBV152 vaccine be administered to adults to prevent COVID-19?
Population:	Adults (aged 18–59 years)
Intervention:	Two doses of BBV152 vaccine
Comparison(s):	Active control/placebo
Outcome:	COVID-19 (PCR-confirmed)

Background:

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

Vaccines are a critical tool in combating the COVID-19 pandemic. In the rapidly evolving field of COVID-19 vaccines, WHO has issued to date interim recommendations on the use of a number of COVID-19 vaccines *(4)*.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	The COVID-19 situation is evolving rapidly. The cumulative number of COVID-19 deaths globally has surpassed 6 million. The most recent epidemiological situation can be found on the following website: https://covid19.who.int/table There has been collateral damage to other public health programmes.	
BENEFITS &		*No*	*Uncertain*	*Yes*	*Varies*	For the phase 3 study to assess the efficacy, safety, and immunogenicity of a 2-dose regimen of BBV152 vaccine for	Seroconversion based on MNT50 at day 56 was reported in 171 (96·6%

	Benefits of the intervention Are the desirable anticipated effects large?	☐	☐	☒	☐	the prevention of symptomatic COVID-19 in adults aged ⩾18 years, a total of 24 419 participants were vaccinated with either 2 doses of BBV152 or placebo. Results suggest a vaccine efficacy of 79% (95% Confidence Interval (CI): 66–88%) in those aged 18–59 years *(1)*. In the entire study population, vaccine efficacy against severe disease was 93% (95% CI: 57–99%). Two studies conducted in a context of Delta variant circulation, provide vaccine effectiveness estimates in health workers of 2 doses against symptomatic disease. Effectiveness in participants with no previous history of SARS CoV2 infection was 47% (95% CI 29-61) *(5)* and 87% (95% CI, 76%-93%) *(6)* in individuals previously infected, respectively. Effectiveness in the context of Omicron variant circulation remains to be assessed.	[95% CI: 92.8–98.8%]) of 177 participants aged 12–65 years. Seroconversion rates and geometric mean titres (GMTs) were similar across three age groups (≥12 to <18 years; ≥18 to <55 years; and ≥55 to ≥65 years) *(3)*. In a continuation of the Phase 2 trial, participants aged 18-64 years were rerandomized to receive a third dose of BBV152 or placebo. No vaccine efficacy data is available for this trial. Immunological testing for neutralising antibodies against homologous and heterologous SARS-CoV-2 variants (Alpha, Beta and Delta) increased 19- to 97-fold after a third vaccination (booster) *(7)*.
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	Among the 24 419 participants who received BBV152 in the pivotal phase 3 study, the median follow-up after vaccination was 146 days; 23 803 (92.3%) participants had at least 2 months (8 weeks) of follow-up at the time of the published analysis. The vaccine had a good reactogenicity profile with similar rates of solicited, unsolicited, and serious adverse events and adverse events of special interest in vaccine and placebo groups. Serious adverse events (SAEs) occurred in 99 participants; 39 (0·30%) received BBV152 and 60 (0·47%) received placebo. One related SAE was reported among BBV152 recipients *(1)*. Only 1 SAE (Immune thrombocytopenia) under the System Organ Class of “blood and lymphatic disorders” was considered related to BBV152 administration. Severe allergic (anaphylactic) reactions	The results from the phase 1 and 2 immunogenicity and safety trials suggest an acceptable safety profile in healthy adults *(2, 3)*. No safety concerns were identified in participants receiving a third dose *(7)*.

							have not been reported in BBV152 clinical studies to date.	
	Balance between benefits and harms	*Favours intervention* ☒	*Favours comparison* ☐	*Favours both* ☐	*Favours neither* ☐	Unclear ☐	Two doses of BBV-152 confer high vaccine efficacy in the 3 month following immunization. Observational data suggest limited vaccine effectiveness of two doses of BBV-152 in those with no history of previous infection and high effectiveness in those with previous infection *(5,6)*. An additional third dose of BBV-152 increases the level of neutralising antibodies against homologous and heterologous SARS-CoV-2 variants (Alpha, Beta and Delta). Safety data suggest no serious harms following administration of a first, second or third dose. Further data are needed 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 undesirable effects?	*No* ☐	*Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☒	*Yes* ☐	*Varies* ☐	Available scientific evidence suggests that the target population assigns more weight to the desirable effects than to the undesirable effects related to COVID-19 vaccination.	
RESOURCE USE	Are the resources required small?	*No* ☒		*Uncertain* ☐	*Yes* ☐		*Varies* ☐	BBV152 can be distributed and stored using existing cold chain infrastructure (at 2–8 °C), and does not require ultra-cold chain capacity *(1)*. Based on media reports and government procurement in India, prices for BBV152 are expected to be within the range of other COVID-19 vaccines with WHO EUL, with potential differential pricing by procurement mechanism (e.g. COVAX AMC vs. direct country procurement vs. private market). Nevertheless, considerable resources will be needed to ensure the implementation of a COVID-19 vaccination programme, especially given: (i) that COVID-19 vaccination is likely to be prioritized for populations (e.g. health-care workers, older adults) without pre-existing robust immunization programmes in many settings; and (ii) the urgency of vaccination roll-out worldwide, which may necessitate additional surge resources to accelerate implementation with adequate infection prevention and control procedures in the context of COVID-19. Resources required include, but are not restricted to, human resources, vaccine costs, logistics, planning and coordination, training, social mobilization and communications, and immunization safety surveillance.	COVAX, the vaccine pillar of the Access to COVID-19 Tools Accelerator (ACT-Accelerator), has now shipped over 1 billion doses to 144 countries and territories*(8)*. In January 2022, an additional funding of at least US$ 5.2 billion is required for the Gavi COVAX Advance Market Commitment to establish a Pandemic Vaccine Pool of a minimum of 600 million additional doses to address uncertainties and risks in the virus' evolution, provide bundled finance to strengthen delivery systems in recipient countries, and cover essential ancillary costs*(9)*.
	Cost–effectiveness	*No* ☐		*Uncertain* ☐	*Yes* ☐		*Varies* ☒	Formal global cost–effectiveness analyses have not been conducted, but the emerging evidence indicates that the benefits, including the impact on recovery of the global economy, are likely to outweigh the costs of COVID-19 vaccination in general at global level.	The global economy is estimated to be losing US$ 375 billion per month due to the coronavirus pandemic. G20 countries have invested approximately US$ 10

					No formal cost–effectiveness analyses of BBV152 compared to other vaccines have been conducted. The BBV152 vaccine is expected to be less costly than some other COVID-19 vaccines (see previous sub-criterion). The ability to use BBV152 in existing cold chain infrastructure in all country settings may enable 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.	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 GDP losses *(10-17)*.
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 *(18)*, 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 *(19)*.
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Intervention* ☒	*Comparison* ☐	*Both* ☐	*Neither* ☐	*Unclear* ☐	As vaccination is an important tool to combat COVID-19, it is assumed that key stakeholders, , in particular ministries of health and immunization managers, are strongly in favour of it. Over 55 million doses have been administered in India.	The fact that 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* ☐ / *Unclear* ☐	COVID-19 vaccine acceptability, in general, varies between (sub-) population groups and may be correlated with the perceived risk posed by the vaccine versus 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% *(20)*. Polls have been launched (periodically), assessing vaccine acceptance in selected countries. These polls confirm overall, not product-specific, vaccine acceptance, with variations across countries *(21, 22)*.	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ / *Probably* No ☐ / *Uncertain* ☐ / *Probably* Yes ☐ / *Yes* ☒ / *Varies* ☐	The BBV152 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 BBV152 vaccine are the same as those of many other vaccines currently in use globally. Therefore existing vaccine cold chain capacity, available in almost all countries worldwide could be leveraged for vaccine distribution. Administration of the vaccine to novel target groups currently not reached by national immunization programmes may pose a challenge in certain settings.	

BALANCE OF CONSEQUENCES	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☒

TYPE OF RECOMMENDATION	We recommend the intervention ☐	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☒ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations	We recommend the comparison ☐	We recommend against the intervention and the comparison ☐
RECOMMENDATION (TEXT)	Please see the interim recommendations.			
IMPLEMENTATION CONSIDERATIONS	Please see the interim recommendations.			
MONITORING, EVALUATION AND RESEARCH PRIORITIES	Please see the interim recommendations.			

Annex 8. SAGE evidence-to-recommendation framework: BBV152 COVID-19 vaccine use in older adults

Question:	Should BBV152 vaccine be administered to older adults to prevent COVID-19?
Population:	Older adults (aged ≥60 years)
Intervention:	Two doses of BBV152 vaccine
Comparison(s):	Active control/placebo
Outcome:	COVID-19 (PCR-confirmed)

Background:

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

Vaccines are a critical tool in combating the COVID-19 pandemic. In the rapidly evolving field of COVID-19 vaccines, WHO has issued to date interim recommendations on the use of a number of COVID-19 vaccines *(4)*.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	The COVID-19 situation is evolving rapidly. The cumulative number of COVID-19 deaths globally has surpassed 6 million. The most recent epidemiological situation can be found on the following website: https://covid19.who.int/table There has been collateral damage to other public health programmes.	
BENEFITS &		*No*	*Uncertain*	*Yes*	*Varies*	In the phase 3 clinical trial, 11% of participants were aged >60 years *(1)*.	Seroconversion rates and GMTs across age groups (≥18 to <55 years, and ≥55

	Benefits of the intervention Are the desirable anticipated effects large?	☐	☒	☐	☐	Vaccine efficacy against symptomatic COVID-19 was 68% (95% CI: 8–91%) in those aged ≥60 years. To note, efficacy was estimated to be 72% (95% CI: -5–95%) in those aged ≥60 to ≤69 years, and 58% (95% CI: -16–96%) in those aged ≥70 to ≤79 years. Two studies conducted in a context of Delta variant circulation, provide vaccine effectiveness estimates in health workers of 2 doses against symptomatic disease. Effectiveness in participants with no previous history of SARS CoV2 infection was 47% (95% CI 29-61); a very small number of individuals were aged 60 years and older *(5)*. In previously infected individuals, effectiveness was 87% (95% CI, 76%-93%) *(6)*, though no data on older adults were available. Effectiveness in this age group, in particular in the context of Omicron variant circulation remains to be assessed.	to ⩽65 years) were similar, but only small numbers of participants were included in the oldest age groups (over 60 years) *(3)*. In a continuation of the Phase 2 trial, participants aged 18-64 years were rerandomized to receive a third dose of BBV152 or placebo. No vaccine efficacy data is available for this trial. Immunological testing for neutralising antibodies against homologous and heterologous SARS-CoV-2 variants (Alpha, Beta and Delta) increased 19- to 97-fold after a third vaccination (booster) *(7)*.
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	Among the 25 798 participants who received BBV152 in the pivotal phase 3 study, the median follow-up after vaccination was 146 days, and 23 803 (92.3%) participants had at least 2 months (8 weeks) of follow-up at the time of the published analysis. The vaccine had a good reactogenicity profile with similar rates of solicited, unsolicited, and serious adverse events and adverse events of special interest in vaccine and placebo groups. In general, similar reactogenicity was observed in older adults compared to younger adults. Serious adverse events occurred in 99 participants; 39 (0·30%) received BBV152 and 60 (0·47%) received placebo. One related SAE was reported among BBV152 recipients *(1)*. Only 1 SAE (Immune thrombocytopenia) under the System Organ Class of “blood and lymphatic disorders” was considered related to BBV152 administration.	

							Severe allergic (anaphylactic) reactions have not been reported in BBV152 clinical studies to date.	
	Balance between benefits and harms	*Favours intervention* ☒	*Favours comparison* ☐	*Favours both* ☐	*Favours neither* ☐	Unclear ☐	Two doses of BBV-152 confer high vaccine efficacy in the 3 month following immunization. Observational data suggest limited vaccine effectiveness of two doses of BBV-152 in those with no history of previous infection and high effectiveness in those with previous infection, though no age-specific data were generated. An additional third dose of BBV-152 increases the level of neutralising antibodies against homologous and heterologous SARS-CoV-2 variants (Alpha, Beta and Delta). Safety data suggest no serious harms following administration of a first, second or third dose. Further data are needed 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* ☐	The majority of severe disease occurs in older individuals. Available scientific evidence suggests that the target population probably considers the desirable effects (i.e. the potential protection conferred by the vaccine), more important than the undesirable effects (i.e. the currently reported safety signals related to COVID-19 vaccination). Different population groups may have different opinions regarding the weights assigned to desirable and undesirable outcomes.	

	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐	*Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☒	*Yes* ☐	*Varies* ☐	Available scientific evidence suggests that the target population probably assigns more weight to the desirable effects than the undesirable effects related to COVID-19 vaccination. Targeted information campaigns should assess this aspect.	
RESOURCE USE	Are the resources required small?	*No* ☐		*Uncertain* ☐	*Yes* ☒		*Varies* ☐	BBV152 can be distributed and stored using existing cold chain infrastructure (at 2–8 °C), and does not require ultra-cold chain capacity *(1)*. Based on media reports and government procurement in India, prices for BBV152 are expected to be within the range of other COVID-19 vaccines with WHO EUL, with potential differential pricing by procurement mechanism (e.g. COVAX AMC vs. direct country procurement vs. private market). Nevertheless, considerable resources will be needed to ensure the implementation of a COVID-19 vaccination programme, especially given: (i) that COVID-19 vaccination is likely to be prioritized for populations (e.g. health-care workers, older adults) without pre-existing robust immunization programmes in many settings, and (ii) the urgency of vaccination roll-out worldwide, which may necessitate additional surge resources to accelerate implementation with adequate infection prevention and control procedures in the context of COVID-19. Resources required include, but are not restricted to, human resources, vaccine costs, logistics, planning and coordination, training, social mobilization and communications, and immunization safety surveillance.	COVAX, the vaccine pillar of the Access to COVID-19 Tools Accelerator (ACT-Accelerator), has now shipped over 1 billion doses to 144 countries and territories*(8)*. In January 2022, an additional funding of at least US$ 5.2 billion is required for the Gavi COVAX Advance Market Commitment to establish a Pandemic Vaccine Pool of a minimum of 600 million additional doses to address uncertainties and risks in the virus' evolution, provide bundled finance to strengthen delivery systems in recipient countries, and cover essential ancillary costs*(9)*.
	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 due to the coronavirus pandemic. G20 countries have invested approximately US$ 10

				No formal cost–effectiveness analyses of BBV152 vaccine compared to other vaccines have been conducted. The BBV152 vaccine is expected to be less costly than many other COVID-19 vaccines (see previous sub-criterion). The ability to use BBV152 vaccine in existing cold chain infrastructure in all country settings may enable 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.	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 GDP losses *(10-17)*.
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 *(18)*, 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 *(19)*.
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Intervention* ☒	*Comparison* ☐	*Both* ☐	*Neither* ☐	*Unclear* ☐	No scientific evidence is available. As vaccination is an important tool to combat COVID-19, it is assumed that key stakeholders, in particular ministries of health and immunization managers are strongly in favour of COVID-19 vaccination.	A total of 190 economies are participating in COVAX which suggests a very high acceptability of COVID-19 vaccination in general, although not the BBV152 vaccine in particular.

	Which option is acceptable to target group?	*Intervention* ☒ / *Comparison* ☐ / *Both* ☐ / *Neither* ☐ / *Unclear* ☐	COVID-19 vaccine acceptability in general varies between (sub-) population groups and may be correlated with the perceived risk posed by the vaccine versus 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% *(20)*. Polls have been launched, (periodically) assessing vaccine acceptance in selected countries. These polls confirm overall, not product-specific, vaccine acceptance, with variations across countries *(21, 22)*.	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ / *Probably* No ☐ / *Uncertain* ☐ / *Probably* Yes ☐ / *Yes* ☒ / *Varies* ☐	The BBV152 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 BBV152 vaccine is shared by many other vaccines currently in use globally. Therefore existing vaccine cold chain capacity, available in almost all countries worldwide, could be leveraged for vaccine distribution. Administration of the vaccine to novel target groups currently not reached by national immunization programmes may pose a challenge in certain settings.	
BALANCE OF CONSEQUENCES	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☒

TYPE OF RECOMMENDATION	We recommend the intervention ☐	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☒ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations	We recommend the comparison ☐	We recommend against the intervention and the comparison ☐
RECOMMENDATION (TEXT)	Please see the interim recommendations.			
IMPLEMENTATION CONSIDERATIONS	Please see the interim recommendations.			
MONITORING, EVALUATION AND RESEARCH PRIORITIES	Please see the interim recommendations.			

Annex 9. SAGE evidence-to-recommendation framework: BBV152 COVID-19 vaccine use in individuals with comorbidities

Question:	Should BBV152 vaccine be administered to individuals with comorbidities[a] or health states that increase risk for severe COVID-19 to prevent COVID-19?
Population:	Individuals with comorbidities or health states that increase risk for severe COVID-19
Intervention:	Two doses of BBV152 vaccine
Comparison(s):	Active control/placebo
Outcome:	COVID-19 (PCR-confirmed)

Background:

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

Vaccines are a critical tool in combating the COVID-19 pandemic. In the rapidly evolving field of COVID-19 vaccines, WHO has issued to date interim recommendations on the use of a number of COVID-19 vaccines *(4)*.

	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. Individuals with certain comorbidities are particularly affected by COVID-19 and	
		☐	☐	☒	☐		

[a] "Comorbidity" within the phase 3 trial was defined as BMI ⩾30 kg/m2, cardiovascular disorder, respiratory disease, or diabetes.

					present a higher risk of severe COVID-19 outcomes and death. Identified risk factors include comorbidities such as hypertension, chronic cardiac disease, non-asthmatic chronic pulmonary disease, chronic kidney disease, liver disease, and obesity (particularly a body mass index (BMI) >40). People with multiple comorbidities are at a higher risk of COVID-19-related adverse outcomes *(23)*. 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 (aged >75 years).	
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	Approximately 29% of participants in the phase 3 study population had at least 1 comorbidity at baseline (cardiovascular, diabetes, or any other chronic stable condition), or a BMI ⩾ 35 kg/m2. The most common comorbid conditions were other stable comorbidities (7% of vaccine recipients); controlled diabetes (6% of vaccine recipients); stable vascular disease (4% of vaccine recipients); and respiratory disease (1% of vaccine receipients). Primary efficacy analysis shows that BBV152 vaccine is 66% (95% CI: 34–84%) efficacious against COVID-19 beginning 14 days after dose 2 in adults with a comorbid condition at baseline (see background paper). Recent data suggest that vaccine effectiveness and immunogenicity of COVID-19 vaccines in general (not product-specific) are lower in moderately and severely immunocompromised persons (ICPs) [a] compared to persons without immunocompromising conditions *(24)*.	In a continuation of the Phase 2 trial, in healthy participants aged 18-64 years were rerandomized to receive a third dose of BBV152 or placebo. No vaccine efficacy data is available for this trial. Immunological testing for neutralising antibodies against homologous and heterologous SARS-CoV-2 variants (Alpha, Beta and Delta) increased 19- to 97-fold after a third vaccination (booster) *(7)*.

[a] **Active cancer:** Active immunosuppressive treatment for solid tumour or hematologic malignancy (including leukaemia, lymphoma, and myeloma), or within 12 months of ending such treatment. **Transplant recipients**: Receipt of solid organ transplant and taking immunosuppressive therapy; receipt of stem cell transplant (within 2 years of transplantation, or taking immunosuppressive therapy). **Immunodeficiency:** Severe primary immunodeficiency; chronic dialysis. **HIV/AIDS** with a current CD4 count of <200 cells/µl and/or lacking viral suppression. **Immunosuppressives:** Active treatment causing significant immunosuppression (including high-dose corticosteroids), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents, tumour-necrosis factor (TNF) blockers, and other drugs that are significantly immunosuppressive; or treatment in the previous 6 months of immunosuppressive chemotherapy or radiotherapy.

					Two studies conducted in a context of Delta variant circulation, provide vaccine effectiveness estimates in health workers of 2 doses against symptomatic disease. Effectiveness in participants with no previous history of SARS CoV2 infection was 47% (95% CI 29-61); with no data on comorbidities *(5)*. In previously infected individuals, effectiveness was 87% (95% CI, 76%-93%) *(6)*, obesity and comorbidity were reported by 9.9% and 20.8% participants, respectively. Effectiveness in this population group, in particular in the context of Omicron variant circulation remains to be assessed.	
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	Among the 25 798 participants who received BBV152 in the pivotal phase 3 study, the median follow-up after vaccination was 146 days; 23 803 (92%) participants had at least 2 months (8 weeks) of follow-up at the time of the published analysis. The vaccine had a good reactogenicity profile with similar rates of solicited, unsolicited, and serious adverse events and adverse events of special interest in vaccine and placebo groups. Serious adverse events occurred in 99 participants; 39 (0.30%) received BBV152 and 60 (0.47%) received placebo. One related SAE were reported among BBV152 recipients *(1)*. Only 1 SAE (Immune thrombocytopenia) under the System Organ Class of “blood and lymphatic disorders” was considered related to BBV152 administration. Severe allergic (anaphylactic) reactions have not been reported in BBV152 clinical studies to date. No data are currently available in immunocompromised subjects, in subjects taking immunosuppressants, in persons living with HIV, in pregnant or in breastfeeding women. The TLR 7/8 adjuvant IMDG has not been used in any other licensed vaccine.	Developmental and Reproductive Toxicology (DART) studies have been conducted. No safety signal was observed.

	Balance between benefits and harms	*Favours intervention* ☒	*Favours comparison* ☐	*Favours both* ☐	*Favours neither* ☐	Unclear ☐	Two doses of BBV-152 confer high vaccine efficacy in those individuals with comorbidities or health states that increase risk for severe COVID-19 for which there are data in the 3 month following immunization. Observational data suggest limited vaccine effectiveness of two doses of BBV-152 in those with no history of previous infection and high effectiveness in those with previous infection. An additional third dose of BBV-152 increases the level of neutralising antibodies against homologous and heterologous SARS-CoV-2 variants (Alpha, Beta and Delta). Safety data suggest no serious harms following administration of a first, second or third dose. An extended primary series including an additional (third) dose for ICPs may be required *(24)*. Further data are needed 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 related to the target population weighing of desirable and undesirable effects (i.e. the protection conferred by the vaccine weighed against the currently reported safety signals) related to COVID-19 vaccination. Different population groups may have different opinions regarding the relative weights attributed to desirable and undesirable outcomes.	

	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐	*Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☒	*Yes* ☐	*Varies* ☐	Available scientific evidence suggests that the target population probably attached more weight to the desirable effects than the undesirable effects related to COVID-19 vaccination.	
RESOURCE USE	Are the resources required small?	*No* ☐		*Uncertain* ☐	*Yes* ☒		*Varies* ☐	BBV152 can be distributed and stored using existing cold chain infrastructure (at 2–8 °C), and does not require ultra-cold chain capacity *(1)*. Based on media reports and government procurement in India, prices for BBV152 are expected to be within the range of other COVID-19 vaccines with WHO EUL, with potential differential pricing by procurement mechanism (e.g. COVAX AMC vs. direct country procurement vs. private market). Nevertheless, considerable resources will be needed to ensure the implementation of a COVID-19 vaccination programme, especially given: (i) that COVID-19 vaccination is likely to be prioritized for populations (e.g. health-care workers, older adults) without pre-existing robust immunization programmes in many settings; and (ii) the urgency of vaccination roll-out worldwide, which may necessitate additional surge resources to accelerate implementation with adequate infection prevention and control procedures in the context of COVID-19. Resources required include, but are not restricted to, human resources, vaccine costs, logistics, planning and coordination, training, social mobilization and communications, and immunization safety surveillance.	COVAX, the vaccine pillar of the Access to COVID-19 Tools Accelerator (ACT-Accelerator), has now shipped over 1 billion doses to 144 countries and territories*(8)*. In January 2022, an additional funding of at least US$ 5.2 billion is required for the Gavi COVAX Advance Market Commitment to establish a Pandemic Vaccine Pool of a minimum of 600 million additional doses to address uncertainties and risks in the virus' evolution, provide bundled finance to strengthen delivery systems in recipient countries, and cover essential ancillary costs*(9)*
	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 due to the coronavirus pandemic. G20 countries have invested approximately US$ 10

					No formal cost–effectiveness analyses of BBV152 vaccine compared to other vaccines have been conducted. The BBV152 vaccine is expected to be less costly than many other COVID-19 vaccines (see previous sub-criterion). The ability to use BBV152 in existing cold chain infrastructure in all country settings may enable 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.	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 GDP losses *(10-17)*.
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 *(18)*, 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 *(19)*.
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Intervention* ☒	*Comparison* ☐	*Both* ☐	*Neither* ☐	*Unclear* ☐	No scientific evidence is available. As vaccination is an important tool to combat COVID-19, it is assumed that key stakeholders, in particular ministries of health and immunization managers are strongly in favour of COVID-19 vaccination	The fact that 190 economies are participating in COVAX suggests a very high acceptability of COVID-19 vaccination in general, although not the BBV152 vaccine in particular.

	Which option is acceptable to target group?	*Intervention* ☒	*Comparison* ☐	*Both* ☐	*Neither* ☐	*Unclear* ☐		COVID-19 vaccine acceptability in general varies between (sub-) population groups and may be correlated with the perceived risk posed by the vaccine versus 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% *(20)*. Polls have been launched, (periodically) assessing vaccine acceptance in selected countries. These polls confirm overall, not product-specific, vaccine acceptance, with variations across countries *(21, 22)*.	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐	*Probably* No ☐	*Uncertain* ☐	*Probably* Yes ☐	*Yes* ☒	*Varies* ☐	Th 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 BBV152 vaccine is shared by many other vaccines currently in use globally. Therefore existing vaccine cold chain capacity, available in almost all countries worldwide, could be leveraged for vaccine distribution. Administration of the vaccine to novel target groups currently not reached by national immunization programmes may pose a challenge in certain settings.	

BALANCE OF CONSEQUENCES	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☒	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐
TYPE OF RECOMMENDATION	We recommend the intervention	We suggest considering recommendation of the intervention	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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