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).

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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)*.

				ADDITIONAL INFORMATION
				s evolving umber of ally has he most iation can website: le damage to es.
				assess the enicity of a vaccine for	Seroconversion based on MNT50 at day 56 was reported in 171 (96·6%