Annexes to the interim recommendations for use of the inactivated COVID-19 vaccine BIBP developed by China National Biotec Group (CNBG), Sinopharm

Grading of evidence

Evidence to recommendation tables

First issued 7 May 2021
Updated 28 October 2021
Last updated 15 March 2022

World Health Organization

Background

These are the annexes to the Interim recommendations for use of the inactivated COVID-19 vaccine BIBP developed by China National Biotec Group (CNBG), Sinopharm.

Annexes 1–6 contain tables that summarize the grading of recommendations, assessment, development and evaluations (GRADE). Annexes 7–9 contain the SAGE evidence-to-recommendation framework tables (ETR tables). The ETR tables are based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel) (www.decide-collaboration.eu/, accessed 11 January 2021).

Contents

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

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

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

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

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

[b] Data on long-term protection emerging from the ongoing phase 3 clinical trial remain limited, as trial data have so far been reported only for a follow-up of approximately 2 months. This was considered as not constituting a limitation that would lead to downgrading of the evidence. SAGE will continue to review any emerging data and adjust its quality assessment as required. These data are reflected in the evidence to recommendation tables below, but were not considered for grading of the evidence given the limitations and lack of peer-reviewed publications. Further data on long term protection were provided by the company.

Annex 2. GRADE table: Safety of COVID-19 vaccine BIBP in adults

Population:	Adults (aged 18–59 years)
Intervention:	Two doses of COVID-19 vaccine BIBP
Comparison:	Placebo/active control
Outcome:	Serious adverse events following immunization

What is the risk of serious adverse events following COVID-19 vaccine BIBP compared with placebo/active control in adults (aged 18–59 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2/ RCT *(1, 2)*	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		Imprecision	Not serious	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a moderate level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 3).**
	Conclusion			We are moderately confident that the risk of serious adverse events following one or two doses of COVID-19 vaccine BIBP 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 https://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. The limited follow-up time of the clinical trial may not allow detection of adverse events occurring several months after vaccination. Further data on safety were provided by the company. These data are reflected in the evidence to recommendation tables below, but were not considered for grading of the evidence given the limitations and lack of peer-reviewed publications.

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

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

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

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT *(1)*[a]	4
	Factors decreasing confidence	Limitation in study design[b]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Not 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			**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			No efficacy estimates are available in older adults (≥60 years) as no cases of COVID-19 were reported in the limited number of participants aged ≥60 years in either group. On the basis of efficacy estimates from adults aged 18–59 years and immunogenicity data, we have low confidence that the vaccine is efficacious in this age group.

[a] Additional data that have emerged since 24 May 2021 indicate that the immune response following the standard two dose primary series compared to younger individuals is deemed likely to be insufficient.

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

[c] In the phase 3 efficacy trial, 893 participants were aged 60 years or older. Of these 294 were enrolled in the COVID-19 vaccine BIBP group . While supportive evidence (immunogenicity data in this age group) suggests that the vaccine elicits an immune response, the trial did not show any vaccine efficacy in this age group. The very serious imprecision due to the limited sample size was considered as constituting a limitation that leads to downgrading of the evidence. Further data on efficacy in older adults were provided by the company. These data are reflected in the evidence to recommendation tables below, but were not considered for grading of the evidence given the limitations and lack of peer-reviewed publications. SAGE will continue to review any emerging data and adjust its quality assessment as required.

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

Population:	Older adults (aged ≥60 years)
Intervention:	Two doses of COVID-19 vaccine BIBP
Comparison:	Placebo/active control
Outcome:	Serious adverse events following immunization

What is the risk of serious adverse events following COVID-19 vaccine BIBP compared with placebo/active control in older adults (aged ≥60 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		4/ RCT *(1, 3)*	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		Imprecision	Serious[c]	-2
		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 in the quality of evidence that the risk of serious adverse events following one or two doses of COVID-19 vaccine BIBP in older adults (≥60 years) is low.

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see http://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. The limited follow-up time of the clinical trial may not allow detection of adverse events occurring several months after vaccination. Further data on safety were provided by the company. These data are reflected in the evidence to recommendation tables below, but were not considered for grading of the evidence given the limitations and lack of peer-reviewed publications.

[c] Only approximately 2% (893) of the trial participants were aged 60 years or over. Of these 294 were enrolled in the COVID-19 vaccine BIBP group. This was considered as constituting a limitation that leads to downgrading of the evidence.

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

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

What is the efficacy of two doses of COVID-19 vaccine BIBP 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		3/ RCT *(1-3)*[a]	4
	Factors decreasing confidence	Limitation in study design[b]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Serious[c]	-2
		Imprecision	Serious[d]	-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			No efficacy estimates are available for this group. On the basis of efficacy estimates from adults aged 18–59 years and immunogenicity data, we have very low confidence that the vaccine is efficacious in this age group.

[a] Additional data that have emerged since 24 May 2021 indicate that the immune response following the standard two dose primary series in immunocompromised individuals (ICPs) is deemed likely to be insufficient.

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

[c] Trial excluded individuals with hypertension, diabetic complications, pregnant and breastfeeding women, persons who were immunocompromised, and persons living with HIV, among others, limiting participation to relatively healthy individuals. Although some subjects with hypertension and diabetes were enrolled, this was considered as constituting a limitation that leads to downgrading of the evidence.

[d] Data on efficacy among participants with comorbidities are not available from the phase 3 clinical trial, although it is likely that the number of participants with comorbidities will be small given the exclusion criteria. This was considered as constituting a limitation that led to downgrading of the evidence. Further data on long term protection were provided by the company . These data are reflected in the evidence to recommendation tables below, but were not considered for grading of the evidence given the limitations and lack of peer-reviewed publications. SAGE will continue to review any emerging data and adjust its quality assessment as required.

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

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

What is the risk of serious adverse events following COVID-19 vaccine BIBP 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		4/ RCT *(1-3)*	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 in the quality of evidence that the risk of serious adverse events in individuals with comorbidities or health states that increase risk for severe COVID-19 following one or two doses of COVID-19 vaccine BIBP is low.

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

[b] Downgraded for the following limitations. The trial was not adequately powered to detect rare adverse events (i.e. fewer than about 1 in 800). These may emerge only when large populations have been vaccinated. The limited follow-up time of the clinical trial may not allow detection of adverse events occurring several months after vaccination.

[c] Trial excluded individuals with hypertension, diabetic complications, pregnant and breastfeeding women, persons who were immunocompromised and persons living with HIV, among others, limiting participation to relatively healthy individuals. Although some subjects with hypertension and diabetes were enrolled, this was considered as constituting a limitation that leads to downgrading of the evidence. Further data on efficacy in individuals with diabetes and obesity were provided by the company. These data are reflected in the evidence to recommendation tables below, but were not considered for grading of the evidence given the limitations and lack of peer-reviewed publications.

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

Question:	Should COVID-19 vaccine BIBP be administered to adults to prevent COVID-19?
Population:	Adults (aged 18–59 years)
Intervention:	Two doses of COVID-19 vaccine BIBP
Comparison(s):	Placebo/active control
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
				evolving mber of has nost ation ving le. l damage rammes	
				0 as the efficacy rticipants	Seroconversion rates by day 14 after the first dose in the 18–59-year age