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

7 May 2021

World Health Organization

Background

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

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

Population:	Adults (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 (18–59 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT	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).

[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.

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

Population:	Adults (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 (18–59 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2/ RCT	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.

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

Population:	Older adults (≥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 (≥60 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Not 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			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] 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] 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. 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 (≥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 (≥60 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		4/ RCT	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.

[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	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			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] 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] 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.

[c] 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. 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	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.

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 (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 pandemic. In the rapidly evolving field of COVID-19 vaccines, WHO has to date issued interim recommendations on the use of Pfizer–BioNTech, Moderna, AstraZeneca and Janssen vaccines (1-4).

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No*	*Uncertain*	*Yes*	*Varies by setting*	The cumulative number of COVID-19 cases globally has surpassed 132 730 691 with more than 2 880 726 deaths. Cases have been found in 190 different countries or territories throughout the world (status 9 April 2021). There has been collateral damage to other public health programmes.	The COVID-19 situation is evolving rapidly; the most recent epidemiological situation can be found on the following website: https://covid19.who.int/table
		☐	☐	☒	☐		

BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	Using 20 December 2020 as the data cut-off, primary efficacy analysis of 27 115 study participants 18 – 59 years of age showed that COVID-19 vaccine BIBP had a vaccine efficacy of 78.9% (95%CI: 65.8–87.0%) against symptomatic disease. Vaccine efficacy in this age group against hospitalization was 78.5% (95%CI: 25.2–93.8%).	Seroconversion rates by day 14 after the first dose in the 18–59-year age group was 87% in the 4 µg group (final formulation). Seroconversion rates on day 28 reached 100% in every vaccine group. No participants in the placebo group seroconverted. Neutralizing antibodies were detected in all vaccine recipients by day 42 after the second dose (5). A preliminary, high-level, unpublished summary report of a vaccine effectiveness study in the context of routine rollout in Bahrain suggests high effectiveness across age groups and gender (see background paper).
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	Data from clinical trials demonstrate that COVID-19 vaccine BIBP was well tolerated. From the phase 3 clinical trial data, by the time of the interim analysis for safety (data cut-off 31 December 2020), 14 624 trial participants had received at least one dose of COVID-19 vaccine BIBP. The safety follow-up for at least 28 days after the full vaccination was completed. Long-term safety follow-up is still ongoing.	The results from the phase 1 and 2 immunogenicity and safety trial suggest an acceptable safety profile in healthy adults 18–59 years of age.

							The most common injection site reaction was pain (18.3% of vaccine recipients aged 18–59 years). The most common systemic reaction was headache (12.3% of vaccine recipients aged 18–59 years). Other solicited injection site reactions reported were redness, swelling, and induration, and other common systemic adverse events reported were fever, fatigue, myalgia, arthralgia, cough, dyspnoea, nausea, diarrhoea, and pruritus. Serious adverse events (SAEs) were not specified. SAEs from all but two participants were assessed not to be related to the vaccine.	
	Balance between benefits and harms	*Favours intervention* ☒	*Favours comparison* ☐	*Favours both* ☐	*Favours neither* ☐	Unclear ☐	Efficacy data suggest benefit, and short-term safety data suggest minimal harms. Further ongoing studies will need to be undertaken as part of post-marketing surveillance.	
	What is the overall quality of this evidence for the critical outcomes?	**Effectiveness of the intervention** *No included studies* ☐	*Very low* ☐	*Low* ☐	*Moderate* ☐	*High* ☒	Please see the related GRADE tables.	
		Safety of the intervention *No included studies* ☐	*Very low* ☐	*Low* ☐	*Moderate* ☒	*High* ☐		
VALUES & PREFERENCES	How certain is the relative importance of the desirable and	*Important uncertainty or variability*	*Possibly important uncertainty or variability*	*Probably no important uncertainty*	*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.	

	undesirable outcomes?	*or variability* ☐ ☒ ☐ ☐ ☐	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. Targeted studies should assess this aspect.	
RESOURCE USE	Are the resources required small?	*No* / *Uncertain* / *Yes* / *Varies* ☒ ☐ ☐ ☐	COVID-19 vaccine BIBP can be distributed and stored using existing cold-chain infrastructure and does not require ultra-cold-chain capacity. Nevertheless, considerable resources will be needed to ensure the implementation of a COVID-19 vaccination programme, especially given: (i) that COVID-19 vaccination is likely to be prioritized for populations (e.g. health care workers, older adults) without pre-existing robust immunization programmes in many settings, and (ii) the urgency of vaccination roll-out worldwide, which may necessitate additional surge resources to accelerate implementation with adequate infection prevention and control procedures in the context of COVID-19. Resources required include, but are not restricted to, human resources, vaccine costs,	An estimated US$15.9 billion is needed for the vaccines pillar (COVAX) of the Access to COVID-19 Tools Accelerator (ACT-A) for 2020–21, in order to deliver 2 billion doses. This does not include all delivery costs in all countries participating in COVAX, bilateral procurement deals, or research and development investments outside of COVAX (6). The World Bank has approved a financing window of up to US$12 billion to support low- and middle-income countries in purchasing and distributing vaccine (7).

						logistics, planning and coordination, training, social mobilization and communications, and immunization safety surveillance.	
	Cost-effectiveness	*No* ☐	*Uncertain* ☐	*Yes* ☐	*Varies* ☒	Formal global cost-effectiveness analyses have not been conducted, but the emerging evidence indicates that the benefits, including the impact on recovery of the global economy, are likely to outweigh the cost of COVID-19 vaccination in general at global level. No formal cost-effectiveness analyses of BCOVID-19 vaccine BIBP compared with other vaccines have been conducted. The ability to use BIBP COVID-19 vaccine in existing cold-chain infrastructure in all country settings may allow higher population-level coverage. Cost-effectiveness analyses should be conducted at country level; cost-effectiveness of COVID-19 vaccination may vary by country depending on COVID-19 burden, comparator interventions assessed, analysis perspective, and local cost-effectiveness thresholds used	The global economy is estimated to be losing US$375 billion per month because of the coronavirus pandemic. G20 countries have invested approximately US$10 trillion in domestic economic stimulus to mitigate the economic consequences of reduced business activity and unemployment due to the pandemic. Initial estimates suggest that COVID-19 vaccination will provide substantial economic value in terms of averted morbidity and mortality costs and averted losses in gross domestic product (6;8-14).
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 six core ethical principles that should guide distribution. If distributed fairly, COVID-19 vaccines may have considerable impact on reducing health inequities. Storage and distribution requirements of the COVID-19	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,

							vaccine BIBP are the same as those of many other vaccines currently in use globally. Existing vaccine cold-chain capacity, available in almost all countries, could be leveraged for vaccine distribution.	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*	As vaccination is an eagerly awaited tool to combat COVID-19, it is assumed that key stakeholders, in particular ministries of health and immunization managers, are strongly in favour of it.	The fact that 190 economies are participating in COVAX suggests a very high acceptability of COVID-19 vaccination in general.
		☒	☐	☐	☐	☐		
	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).	
		☒	☐	☐	☐	☐	Representative multicountry 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*	This vaccine is assumed to be easily implementable in settings, including low- and middle-income-countries, with existing vaccine logistics and delivery infrastructure. 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.

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

Question:	Should COVID-19 vaccine BIBP be administered to older adults to prevent COVID-19?
Population:	Older adults (≥60 years)
Intervention:	Two doses of COVID-19 vaccine BIBP
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 to date issued interim recommendations on the use of Pfizer–BioNTech, Moderna, AstraZeneca and Janssen vaccines (1-4).

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No*	*Uncertain*	*Yes*	*Varies by setting*	The cumulative number of COVID-19 cases globally has surpassed 132 730 691 with more than 2 880 726 deaths. Cases have been found in 190 different countries or territories throughout the world (status 9 April 2021). There has been collateral damage to other public health programmes.	The COVID-19 situation is evolving rapidly; the most recent epidemiological situation can be found on the following website: https://covid19.who.int/table
		☐	☐	☒	☐		

BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Uncertain* ☒	*Yes* ☐	*Varies* ☐	Clinical efficacy in adults ≥60 years has not been established. The proportion of adults aged ≥60 years in the COVIV-02 efficacy study was low (approx.2%, n=893, of these 294 were enrolled in the COVID-19 vaccine BIBP group). There were no cases of COVID-19 in participants over 60 years of age in any trial arm, and so no assessment of efficacy in this age group could be made.	Immunogenicity data from older adults ⩾ 60 years of age are available from the phase 1 study in China and the phase 3 study, with immunogenicity available for a total of 66 participants in this age group. Seroconversion reached 100% 14 days after the second dose in both studies. Neutralizing antibody GMTs were high 14 days after the second dose, although they were lower compared to the younger adult age group from the same study. In the phase 1 trial, GMTs in younger adults 18-59 years of age were 211.2 (95%CI 159.0, 280.6) compared with 131.5 (95%CI 108.2, 159.7) in older adults ⩾ 60 years of age (5). A preliminary, high-level, unpublished summary report of a vaccine effectiveness study in the context of routine rollout in Bahrain suggests high effectiveness across age groups and gender (see background paper).
		No	*Uncertain*	*Yes*	*Varies*	The number of participants in the phase 3 trial aged ≥60 years was small (294 vaccinated), limiting the	

	Harms of the intervention Are the undesirable anticipated effects small?	☐ ☐ ☒ ☐	ability to detect rare adverse events in this age group. The most common injection site reaction was pain (11.7% of recipients aged ≥60 years). The most common systemic reaction was headache (11.7% of recipients aged ≥60 years). Other solicited injection site reactions reported were redness, swelling and induration; other common systemic adverse events reported were fever, fatigue, myalgia, arthralgia, cough, dyspnoea, nausea, diarrhoea and pruritus. Serious AEs were not specified. SAEs in all but two participants were assessed not to be related to the vaccine. Long-term safety data are not yet available and follow-up time remains limited.	
	Balance between benefits and harms	*Favours intervention* ☐ | *Favours comparison* ☐ | *Favours both* ☐ | *Favours neither* ☐ | Unclear ☒	There is no evidence of efficacy in this age group; limited short-term safety data suggest no serious safety signals in this group. Further studies will be needed to establish safety, efficacy and effectiveness in those aged 60 years and over.	
	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* ☐	Please see the related GRADE tables.	

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 studies should assess this aspect. As more data on vaccine efficacy in older adults are generated, the uncertainty around the importance of the desirable effects of the intervention will probably be reduced.	
RESOURCE USE	Are the resources required small?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐					COVID-19 vaccine BIBP can be distributed and stored using existing cold-chain infrastructure and does not require ultra-cold-chain capacity. Nevertheless, considerable resources will be needed to ensure the implementation of a COVID-19 vaccination programme, especially	An estimated US$15.9 billion is needed for the vaccines pillar (COVAX) of the Access to COVID-19 Tools Accelerator (ACT-A) for 2020–21, in order to deliver 2 billion doses. This does not include all delivery costs

						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.	in all countries participating in COVAX, bilateral procurement deals, or research and development investments outside of COVAX (6). The World Bank has approved a financing window of up to US $12 billion to support low- and middle-income countries in purchasing and distributing vaccine (7).
	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 COVID-19 vaccine BIBP compared with other vaccines have been conducted. The ability to use COVID-19 vaccine BIBP 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,	The global economy is estimated to be losing US$375 billion per month because of the coronavirus pandemic. G20 countries have invested approximately US$10 trillion in domestic economic stimulus to mitigate the economic consequences of reduced business activity and unemployment due to the pandemic. Initial estimates suggest that COVID-19 vaccination will provide substantial economic value in terms of averted morbidity and mortality costs and averted GDP losses (6;8-13).

							comparator interventions assessed, analysis perspective, and local cost-effectiveness thresholds used.	
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 six core ethical principles that should guide distribution. If distributed fairly, COVID-19 vaccines may have considerable impact on reducing health inequities. Storage and distribution requirements of BIBP COVID-19 vaccine are the same as those of many other vaccines currently in use globally. Existing vaccine cold-chain capacity, available in almost all countries worldwide, could be leveraged for vaccine distribution.	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* ☐	No scientific evidence is available. As vaccination is an eagerly awaited tool to combat COVID-19, it is assumed that key stakeholders, in particular ministries of health and immunization managers, are strongly in favour of COVID-19 vaccination.	The fact that 190 economies are participating in COVAX suggests a very high acceptability of COVID-19 vaccination in general, though not necessarily of this vaccine in particular.
	Which option is acceptable to target group?	*Intervention*	*Comparison*	*Both*	*Neither*	*Un-clear*	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). Representative multicountry 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* ☐	This vaccine is assumed to be easily implementable in settings, including low- and middle-income-countries, with existing vaccine logistics and delivery infrastructure. 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: COVID-19 vaccine BIBP use in individuals with comorbidities

Question:	Should COVID-19 vaccine BIBP be administered to individuals with comorbidities or health states that increase risk for severe COVID-19[a] to prevent COVID-19?
Population:	Individuals with comorbidities or health states that increase risk for severe COVID-19
Intervention:	Two doses of COVID-19 vaccine BIBP
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 to date issued interim recommendations on the use of Pfizer–BioNTech, Moderna, AstraZeneca and Janssen vaccines (1-4).

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	The cumulative number of COVID-19 cases globally has surpassed 132 730 691with more than 2 880 726 deaths. Cases have been found in 190 different countries or territories throughout the world (status 9 April 2021). There has been collateral damage to other public health programmes.	The COVID-19 situation is evolving rapidly; the most recent epidemiological situation can be found on the following website: https://covid19.who.int/table

[a] Comorbidity in the phase 3 trial was defined as BMI ≥ 30 kg/m^2, cardiovascular disorder, respiratory disease or diabetes.

BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	The phase 3 clinical trial to evaluate the efficacy, safety and immunogenicity ofCOVID-19 vaccine BIBP was conducted in healthy people aged 18 years old and above. Exclusion criteria included hypertension and diabetic complications, among others, limiting participation to relatively healthy individuals, although some subjects with hypertension and diabetes were enrolled. In the vaccine group, 374 participants had hypertension, while in the placebo group 367 had hypertension. No cases of COVID-19 occurred in the vaccine subgroup, compared with 4 in the placebo subgroup (VE:100%,no CI). In the vaccine group 300 participants had diabetes, while in the placebo group 308 had diabetes. Two cases of COVID-19 occurred in the vaccine subgroup, and 6 in the placebo subgroup (VE:63.7%,95% CI: –79.8, –92.7). In the vaccine group 3040 participants were obese (BMI≥30), while in the placebo group 3080 had diabetes. Seven cases of COVID-19 occurred in the vaccine subgroup, and 36 in the placebo subgroup (VE:80.7%,95% CI: –56.7, –91.4).	

							In the entire study population, the protective efficacy against disease was 78.9% (95%CI 65.8%, 87.0%).	
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Uncertain* ☐	*Yes* ☒		*Varies* ☐	No data are currently available from subjects with comorbidities or underlying conditions that increase their risk for severe COVID-19 disease. Overall, the most common injection site reaction was pain (18.3% of vaccine recipients aged 18–59 years and 11.7% of recipients aged ≥60 years). The most common systemic reaction was headache (12.3% of vaccine recipients aged 18–59 years and 11.7% of recipients aged ≥60 years. Other solicited injection site reactions reported were redness, swelling, and induration; other common systemic adverse events reported were fever, fatigue, myalgia, arthralgia, cough, dyspnoea, nausea, diarrhoea, and pruritus. No long-term safety data are available yet and follow-up time remains limited.	
	Balance between benefits and harms	*Favours intervention* ☐	*Favours comparison* ☐	*Favours both* ☐	*Favours neither* ☐	Unclear ☒	Limited efficacy and safety data are available in these population groups. Further studies will need to be undertaken to establish safety and efficacy in this target population.	
	What is the overall quality of this	**Effectiveness of the intervention** *No included studies*		*Very low*	*Low*	*Moderate*	*High*	Please see the related GRADE tables.	

	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*	There is possibly important uncertainty regarding how the target population weighs the desirable and undesirable effects (i.e. the protection conferred by the vaccine weighed against the currently reported safety signals, related to COVID-19 vaccination. Different population groups may have different opinions regarding the relative weights attributed to desirable and undesirable outcomes.	
		☐	☒	☐	☐	☐		
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No*	*Probably No*	*Uncertain*	*Probably Yes*	*Yes*	*Varies*	Available scientific evidence suggests that the target population probably attaches more weight to the desirable effects than the undesirable effects related to COVID-19 vaccination. Targeted studies should assess this aspect.	
		☐	☐	☐	☒	☐	☐		
RESOURCE USE	Are the resources required small?	*No*		*Uncertain*		*Yes*	*Varies*	COVID-19 vaccine BIBP can be distributed and stored using existing cold-chain infrastructure and does not require ultra-cold-chain capacity. Nevertheless, considerable resources will be needed to ensure the implementation of a COVID-19 vaccination programme, especially	An estimated US$15.9 billion is needed for the vaccines pillar (COVAX) of the Access to COVID-19 Tools Accelerator (ACT-A) for 2020–21, in order to deliver 2 billion vaccine doses. This does not include all delivery
		☒		☐		☐	☐		

					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.	costs in all countries participating in COVAX, bilateral procurement deals, or research and development investments outside of COVAX (6). The World Bank has approved a financing window of up to US$12 billion to support low- and middle-income countries in purchasing and distributing vaccine (7).
	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 COVID-19 vaccine BIBP compared with other vaccines have been conducted. The ability to use COVID-19 vaccine BIBP 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,	The global economy is estimated to be losing US$375 billion per month because of the coronavirus pandemic. G20 countries have invested approximately US$10 trillion in domestic economic stimulus to mitigate the economic consequences of reduced business activity and unemployment due to the pandemic. Initial estimates suggest that COVID-19 vaccination will provide substantial economic value in terms of averted morbidity and mortality costs and averted GDP losses (6;8-13).

							comparator interventions assessed, analysis perspective, and local cost-effectiveness thresholds used.	
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 (13), which offers guidance on the fair allocation of COVID-19 vaccines based on six core ethical principles that should guide distribution. If distributed fairly, COVID-19 vaccines may have considerable impact on reducing health inequities. Storage and distribution requirements of COVID-19 vaccine BIBP are the same as for many other vaccines currently in use globally. Existing vaccine cold-chain capacity, available in almost all countries worldwide, could be leveraged for vaccine distribution.	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*	No scientific evidence is available. As vaccination is an eagerly awaited tool to combat COVID-19, it is assumed that key stakeholders, in particular ministries of health and immunization managers, are strongly in favour of COVID-19 vaccination.	The fact that 190 economies are participating in COVAX suggests a very high acceptability of COVID-19 vaccination in general, though not necessarily of this vaccine in particular.
		☒	☐	☐	☐	☐		
	Which option is acceptable to target group?	*Intervention*	*Comparison*	*Both*	*Neither*	*Un-clear*	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). Representative multicountry 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* ☐	This vaccine is assumed to be easily implementable in settings, including low- and middle-income countries, with existing vaccine logistics and delivery infrastructure. 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.			

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