Annexes to the recommendations for use of the Sinovac-CoronaVac vaccine against COVID-19

Grading of evidence

Evidence to recommendation tables

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World Health Organization

Background

These are the annexes of the Interim recommendations for use of the inactivated COVID-19 vaccine, CoronaVac, developed by Sinovac.

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 15 February 2021).

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Annex 1. GRADE table: Efficacy of Sinovac-CoronaVac vaccine in adults

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

What is the efficacy of two doses of Sinovac-CoronaVac 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		2/ RCT(1, 2)	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious[b,c]	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 Sinovac-CoronaVac vaccine 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-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 2 months. This was not considered to constitute a limitation that would lead to downgrading of the evidence. Recent data on longer term protection are referenced in the evidence to recommendation framework.

[c] Different case definitions were used in the various clinical trials protocols and the analysis conducted by Sinovac-CoronaVac. However, since all case definitions were set before the data were unblinded, this was not considered to constitute a limitation that would lead to downgrading of the evidence.

Annex 2. GRADE table: Safety of Sinovac-CoronaVac vaccine in adults

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

What is the risk of serious adverse events following Sinovac-CoronaVac 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,c]	-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 Sinovac-CoronaVac 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. fewer than about 1 in 2000). 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] Different case definitions were used in the various clinical trials protocols and the analysis conducted by Sinovac-CoronaVac. However, since all case definitions were set before the data were unblinded, this was not considered to constitute a limitation that would lead to downgrading of the evidence.

Annex 3. GRADE table: Efficacy of Sinovac-CoronaVac vaccine in older adults

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

What is the efficacy of two doses of Sinovac-CoronaVac 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		3/ RCT (1, 3, 4)[a]	4
	Factors decreasing confidence	Limitation in study design[b]	Not serious[c]	0
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		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			**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 2 doses of Sinovac-CoronaVac vaccine are efficacious in preventing PCR-confirmed COVID-19 in older adults (≥60 years) up to approx. 2 months following immunization in the context of wild-type and pre-Omicron variants of concern.

[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 individual 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 www.covid-nma.com/vaccines.

[c] Different case definitions were used in the various clinical trials protocols and the analysis conducted by the manufacturer. However, since all case definitions were set before the data were unblinded, was this was not considered to constitute a limitation that would lead to downgrading of the evidence.

[d] Of the trial participants, approximately 600 in the vaccine group were aged 60 years or above. While supportive evidence (immunogenicity and effectiveness data from Chile in this age group) suggest that the vaccine elicits an immune response comparable to that in younger adults, the trial did not show a statistically significant vaccine efficacy in this age group. The serious imprecision resulting from large confidence intervals and the limited sample size were considered to constitute a limitation that led to downgrading of the evidence. Recent data on longer term protection are referenced in the evidence to recommendation framework.

Annex 4. GRADE table: Safety of Sinovac-CoronaVac vaccine in older adults

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

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

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		3/ RCT (1, 3, 4)	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b,c]	-1
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		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			**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			We have low confidence in the quality of evidence that the risk of serious adverse events following one or two doses of Sinovac-CoronaVac vaccine 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 www.covid-nma.com/vaccines.

[b] Downgraded for the following limitations: The trial was not adequately powered to detect rare adverse events (i.e. about 1 in 250). Preliminary post-licensure safety data are available from Brazil, Chile, China and Indonesia. The limited follow-up time of the clinical trial may not allow detection of adverse events occurring several months after vaccination.

[c] Different case definitions were used in the various clinical trials protocols and the analysis conducted by the manufacturer. However, since all case definitions were set before the data were unblinded, not considered to constitute a limitation that would lead to downgrading of the evidence.

[d] Of the trial participants, approximately 10% (1380) were aged over 60 years. This was considered to constitute a limitation that leads to downgrading of the evidence.

Annex 5. GRADE table: Efficacy of Sinovac-CoronaVac vaccine in individuals with underlying conditions

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

What is the efficacy of two doses of Sinovac-CoronaVac 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		3/ RCT (1, 3, 4)[a]	4
	Factors decreasing confidence	Limitation in study design[b]	Not serious[c]	0
		Inconsistency	Not serious	0
		Indirectness	Serious[d]	-1
		Imprecision	Not serious[e]	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 2 doses of Sinovac-CoronaVac 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. 2 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] 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 www.covid-nma.com/vaccines.

[c] Different case definitions were used in the various clinical trials protocols and the analysis conducted by the manufacturer. However, since all case definitions were set before the data were unblinded, this was not considered to constitute a limitation that would lead to downgrading of the evidence.

[d] The trial excluded pregnant and breastfeeding women, and persons who were immunocompromised. Although persons with HIV were included in the trial, they were not included in the analyses. This was considered to constitute a limitation that leads to downgrading of the evidence. Recent post-licensure data suggest that CoronaVac is effective in pregnant women.

[e] Underlying comorbidities included obesity, cardiovascular disorder, respiratory disease and diabetes. Approximately 62% of the trial population had at least one comorbidity. Data on long-term protection from the ongoing phase 3 clinical trial remain limited, and have so far been reported only for a follow-up of approximately 2 months. Post-licensure data from Chile are available, where 30% of the population had one or more comorbidities. This was not considered to constitute a limitation that would lead to downgrading of the evidence. Recent data on longer term protection are referenced in the evidence to recommendation framework.

Annex 6. GRADE table: Safety of Sinovac-CoronaVac vaccine in individuals with underlying conditions

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

What is the risk of serious adverse events following Sinovac-CoronaVac 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		4/ RCT (1-4)	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b,c]	-1
		Inconsistency	Not serious	0
		Indirectness	Serious[d]	-1
		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			We have 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 Sinovac-CoronaVac vaccine is low.

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

[b] Downgraded for the following limitations. The trial was not adequately powered to detect rare adverse events (i.e. less 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] Different case-definitions were used in the various clinical trials protocols and the analysis conducted by the manufacturer. However, since all case definitions were defined before the data were unblinded, this was not considered to constitute a limitation that would lead to downgrading of the evidence.

[d] The trial excluded pregnant and breastfeeding women, and persons who were immunocompromised. Post-licensure data are available from Chile, where 30% of the population had one or more comorbidities. This was considered to constitute a limitation that leads to downgrading of the evidence. Recent post-licensure data suggest that CoronaVac is safe to use in pregnant women.

Annex 7. SAGE evidence-to-recommendation framework: Sinovac-CoronaVac vaccine use in adults

Question:	Should Sinovac-CoronaVac vaccine be administered to adults to prevent COVID-19?
Population:	Adults (18–59 years)
Intervention:	Two doses of Sinovac-CoronaVac vaccine
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 (9).

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
			s evolving umber of ally has he most ation can website: le l damage rammes.	