Annexes to the interim recommendations for use of the Novavax NVX-CoV2373 vaccine against COVID-19

Grading of evidence –
Evidence to recommendations tables

20 December 2021

World Health Organization

Background

These are the annexes to the Interim recommendations for use of the Novavax NVX-CoV2373 vaccine against COVID-19 Trade names are Nuvaxovid and COVOVAX.

Annexes 1–6 contain tables that summarize the grading of recommendations, assessment, development and evaluations (GRADE) of Novavax NVX-CoV2373 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 30 November 2021).

Contents

Annex 1. GRADE table: Efficacy of NVX-CoV2373 vaccine in adults

Population:	Adults (aged 18–64 years)
Intervention:	Two doses of NVX-CoV2373 vaccine
Comparison:	Placebo/active control
Outcome:	COVID-19 (PCR-confirmed)

What is the efficacy of two doses of NVX-CoV2373 vaccine compared with placebo/active control in preventing PCR-confirmed COVID-19 in adults (18–64 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]	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 NVX-CoV2373 vaccine are efficacious in preventing PCR-confirmed COVID-19 in adults (18–64 years).

[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 NVX-CoV2373 vaccine in adults

Population:	Adults (aged 18–64 years)
Intervention:	Two doses of NVX-CoV2373 vaccine
Comparison:	Placebo/active control
Outcome:	Serious adverse events following immunization

What is the risk of serious adverse events following NVX-CoV2373 vaccination compared with placebo/active control in adults (18–64 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		5/ RCT *(1-5)*	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 NVX-CoV2373 vaccine in adults (18–64 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. These may emerge only when large populations have been vaccinated.

Annex 3. GRADE table: Efficacy of NVX-CoV2373 vaccine in older adults

Population:	Older adults (aged ≥65 years)
Intervention:	Two doses of NVX-CoV2373 vaccine
Comparison:	Placebo/active control
Outcome:	COVID-19 (PCR-confirmed)

What is the efficacy of two doses of NVX-CoV2373 vaccine compared with placebo/active control in preventing PCR-confirmed COVID-19 in older adults (≥65 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT*(1-3)*	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		Imprecision	Serious[b]	-1
		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 4).**
	Conclusion			We are moderately confident that 2 doses of NVX-CoV2373 vaccine are efficacious in preventing PCR-confirmed COVID-19 in older adults (≥65 years).

[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 UK trial, approximately 28% (vaccine arm: n=1953) were 65 years of age or older. Overall vaccine efficacy against symptomatic disease was 88.9% (95% CI, 12.8 to 98.6). While supportive evidence (immunogenicity data in this age group) suggest that the vaccine elicits an immune response comparable to older adults, the evidence was downgraded for imprecision due to large confidence intervals and the limited sample size. Data on long-term protection emerging from the phase 3 clinical trial remain limited, as trial data have so far been reported only for a follow-up of a median of 3 months after dose 2. 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 4. GRADE table: Safety of NVX-CoV2373 vaccine in older adults

Population:	Older adults (aged ⩾65 years)
Intervention:	One or two doses of NVX-CoV2373 vaccine
Comparison:	Placebo/active control
Outcome:	Serious adverse events following immunization

What is the risk of serious adverse events following NVX-CoV2373 vaccination compared with placebo/active control in older adults (≥65 years)?

			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]	-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 NVX-CoV2373 vaccine in older adults (≥65 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 trials were not adequately powered to detect rare adverse events. These may emerge only when large populations have been vaccinated.

Annex 5. GRADE table: Efficacy of NVX-CoV2373 vaccine in individuals with underlying conditions

Population:	Individuals with comorbidities or health states that increase risk for severe COVID-19
Intervention:	Two doses of NVX-CoV2373 vaccine
Comparison:	Placebo/active control
Outcome:	COVID-19 (PCR-confirmed)

What is the efficacy of two doses of NVX-CoV2373 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*(1-3)*	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 NVX-CoV2373 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. 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 and persons who were severly immunocompromised. This was considered as constituting a limitation that leads to downgrading of the evidence.

[c] Underlying comorbidities included HIV, BMI ≥30 kg/m2, chronic respiratory, cardiac, renal, neurologic, hepatic as well as immunocompromising conditions . The clinical trial 2019 nCoV-501, a Phase 2a/b in South Africa, included 244 medically stable HIV-positive participants ≥ 18 to ≤ 64 years of age though vaccine efficacy could not be assessed in this population group due to small sample size. 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 NVX-CoV2373 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 NVX-CoV2373 vaccine
Comparison:	Placebo/active control
Outcome:	Serious adverse events following immunization

What is the risk of serious adverse events following NVX-CoV2373 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		3/ 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 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 NVX-CoV2373 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.

[c] Underlying comorbidities included HIV, BMI ≥30 kg/m2, chronic respiratory, cardiac, renal, neurologic, hepatic as well as immunocompromising conditions. The clinical trial 2019 nCoV-501, a Phase 2a/b in South Africa, included 244 medically stable HIV-positive participants ≥ 18 to ≤ 64 years of age. Trial excluded pregnant and breastfeeding women 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 NVX-CoV2373 vaccine use in adults

Question:	Should NVX-CoV2373 vaccine be administered to adults to prevent COVID-19?
Population:	Adults (aged 18–64 years)
Intervention:	Two doses of NVX-CoV2373 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 *(6)*. .

	CRITERIA	JUDGEMENTS		RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	Is the problem		*Varies by*	The cumulative number of COVID-19 surpassed 5 318 216 und in 190 territories status 16 has been ublic health	The COVID-19 situation is evolving rapidly; the most recent epidemiological situation can be found on the following website: https://covid19.who.int/table
				ials 18 to a Phase 3 ne vaccine 0-95%) for derate, or et from 7 *(2)*. In the efficacy in was 92% ne efficacy firmed in a	