Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
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EVIDENCE SUMMARY

Is NVX-Cov2373 (Novavax) effective and safe in the prevention of COVID-19 infection?

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RECOMMENDATIONS

We suggest the use of NVX-CoV2373 (Novavax), given as 5ug (with 50ug Matrix M1 adjuvant) two doses, intramuscular, 21 days apart, for the prevention of symptomatic and severe SARS-CoV-2 infection in healthy adults.
(Low certainty of evidence; Weak recommendation)

We suggest the use of NVX-CoV2373 (Novavax), given as 5ug (with 50ug Matrix M1 adjuvant) two doses, intramuscular, 21 days apart, for the prevention of symptomatic SARS-CoV-2 infection in older adults (>65 years old).
(Low certainty of evidence; Weak recommendation)

We suggest the use of NVX-CoV2373 (Novavax), given as 5ug (with 50ug Matrix M1 adjuvant) two doses, intramuscular, 21 days apart, for the prevention of symptomatic SARS-CoV-2 infection in adults with comorbidities.
(Moderate certainty of evidence; Weak recommendation)

We suggest against the use of NVX-CoV2373 (Novavax), for the prevention of symptomatic SARS-CoV-2 infection in the immunocompromised population (specifically HIV positive individuals).
(Very low certainty of evidence; Weak recommendation)

We suggest against the use of NVX-CoV2373 for the prevention of symptomatic SARS-CoV-2 infection among pregnant and lactating women.
(*No direct evidence; Weak recommendation)*

In areas where the Alpha variant is predominant, we suggest the use of the NVX-CoV2373 (Novavax) given as 5ug (with 50ug Matrix-M1 adjuvant), two doses, intramuscular, 21 days apart, to prevent symptomatic SARS-CoV-2 infection.
(Low certainty of evidence; Weak recommendation)

In areas where the Beta variant is predominant, we suggest against the use of the NVX-CoV2373 (Novavax) to prevent symptomatic SARS-CoV-2 infection.
(Low certainty of evidence; Weak recommendation)

There is insufficient evidence to recommend for or against the use of NVX-2373 for the prevention of symptomatic SARS-CoV-2 infection among children.

We recommend against the use of the NVX-CoV2373 (Novavax) in individuals who have known allergies to its contents/excipients, such as Matrix-M1. *(Best practice statement)*

Consensus Issues

The Panel highly considered equity issues in the recommendations for the use of NVX-2373 in the prevention of SARS-CoV-2 infection. However, in the case of populations who were at high risk of severe infection and are immunocompromised such as the HIV positive individuals and in the pregnant and lactating women, the Panel took into consideration the lower efficacy estimates and the wide confidence interval with the lower border breaching the 30% threshold combined with the signal of additional harm with the higher adverse reaction risk so that a recommendation against the use of the vaccine was given.

Key Findings

The evidence base on the efficacy and safety of NVX-Cov2373, as of November 12, 2021, includes five RCTs and one comparative cohort study. Results show that the vaccine provides excellent protection against symptomatic COVID-19 among healthy adults, among older persons above 65 years of age, among high-risk groups and those with comorbidities. The vaccine is highly immunogenic. Effectiveness is preserved against the Alpha variant, but one study showed potential loss of effect against the Beta variant. The vaccine is reactogenic.

Introduction

The NVX-Cov2373 vaccine (manufactured by US company Novavax) is a recombinant nanoparticle vaccine containing the spike glycoprotein of the prototype strain plus Matrix-M adjuvant. The vaccine is given intramuscularly in 2 doses, 21 days apart. It is stable and can be stored at temperatures 2-8°C.[1] It received its first authorization for emergency use from Indonesia last November 1, 2021.[2]

This review describes the current available evidence supporting the efficacy, effectiveness and safety of NVX-Cov2373 (Novavax) in the prevention of COVID-19.

Review Methods

Search Strategy

The search followed the strategy used for all the vaccine reviews in this series. Briefly, this covered PubMed, living COVID-19 evidence registries including the Living Overview Evidence platform, the COVID-NMA and the Metaevidence.org, the reference list of the WHO Situational reports, the WHO COVID-19 literature on coronavirus disease database and the VIEW-Hub Resource Library.

Assessment of Risk of Bias and Certainty of Evidence

The assessment of the risk of bias and certainty of evidence for this review followed that of the vaccine reviews in this series. Briefly, the risk of bias of randomized controlled trials was assessed using the Cochrane Risk of Bias tool version 1, which includes the following domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; and selective reporting.

The risk of bias of observational comparative studies will be assessed using the same domains as the Cochrane Risk of Bias v.1 tool. Sequence generation and allocation concealment will be assessed by default as ‘high risk of bias’ given the non-randomized nature of these studies. In addition to the Cochrane RoB tool item, assessment of the control of the following confounders

were done: age, presence of comorbidities and the risk of exposure, and if applicable, the prevailing variant of concern (for sampling performed at different time periods for the treatment groups). For each study, a pragmatic approach will used to assess the risk of confounding bias.

The following were considered in sequence:

- Was the prognostic confounder considered (yes/no)? If 'no', the study is at 'high' risk of bias for this confounder. If 'yes' go to question 2.
- Was the confounder balanced between the intervention(s) and control group(s) (yes/no)? If 'yes', the study is a 'low' risk of bias. If 'no', go to question 3.
- Was the confounder controlled for in the analysis, for example by statistical adjustment such as univariate or multivariate analysis or propensity score matching? If 'yes' the study was at 'low' risk of bias. If 'no' the study was 'high' risk of bias.

If majority or all the confounders were controlled for, the study was assessed as low risk for confounding but overall, the study were classified as being high risk or having serious risk of bias.

Non-comparative observational studies (e.g. case series, single cohort) were assessed to be of high/serious risk of bias.

General Search Results

As of November 12, 2021, six study reports were identified on the effect of NVX-CoV2373 on SARS-CoV-2 infection. Two were Phase 3 randomized controlled trials (RCT), three were Phase 1-2 RCTs and one was a comparative cohort study. Two studies provided clinical efficacy data, two reported on immunogenicity, four provided safety data, and two reported on the effect of the vaccine on the Alpha and Beta variants.

All the RCTs were assessed as low risk of bias.

Table 2 presents the risk of bias assessment of the included studies.

Results

Clinical Efficacy

Two Phase 3 RCTs reported sufficient protection provided by NVX-CoV2373 against symptomatic COVID-19 after a follow up of 2-3 months. Both studies were consistent in their reported vaccine effectiveness rates overall and in the different subgroups and settings.[1,3]

NVX-CoV2373 provides excellent protection against symptomatic COVID-19 with vaccine effectiveness of 89.7% (95% CI 80.2-84.6) and 90.4% (95% CI 82.9-94.6), measured at least 7 days after the second dose. All cases in the vaccine treatment groups for both studies were mild. Hence, VEs for moderate and severe were 100%, with wide confidence intervals for the VE for severe due to small event counts. Two deaths related to COVID-19 were reported in one trial, one in the vaccine group and one in the placebo group.[1] The death in the vaccine group occurred before the second dose. VEs for subgroups also showed good protection offered by NVX-CoV2373: VE for older persons aged 65 years and older was reported at 88.9% (95% CI 12.8-98.6), for high risk groups at 91.0% (95% CI 83.6-95.0) and for those with comorbidities at 90.9% (95%CI 70.2-97.2).

VE after the first dose was available from one study at 83.4% (95% CI 73.6-89.5).[1]

On the other hand, one Phase II RCT done which included 18- to 84-year old patients showed a lower overall VE at 49.4% (95% CI 6.1-72.8). Notable for this study was that it included stable HIV positive patients, and it was conducted during the Beta variant predominance in South Africa. Among the HIV negative patients, VE was observed to be 60.1% (95% CI 19.9-80.1).[4]

The detailed study characteristics of these Phase 3 trials are in Table 3. The Phase 2 study details are in Table 4.

Immunogenicity

Immunogenicity of NVX-CoV2373 was reported by the Phase 1 and 2 studies. Both were consistent in their findings that the vaccine is highly immunogenic, with significant geometric mean fold rises (GMFR) from baseline for anti-spike IgG and neutralizing antibodies compared to placebo. Seroconversion rates were uniformly high. Values were higher in the vaccine recipients when compared to the convalescent subpopulation. Lower GMFRs and seroconversion rates were observed in the older subpopulations. Minimal differences were seen between the low (5µg) and high (25µg) doses. ELISA anti-spike IgG geometric mean ELISA units (GMEUs) and neutralizing antibody geometric mean fold rises (GMFRs) were greater in the adjuvanted vaccine than those without the adjuvant. Strong T-cell response also demonstrated in the adjuvanted, with similar response levels reached regardless of dose.[5,6]

Real World Evidence: Effectiveness

No real-world evidence on NVX-CoV2373 was found.

Clinical Efficacy and Effectiveness On Special Populations of Interest (Older persons, Children, Immunocompromised, Pregnant Women)

Older population

One Phase 3 trial reported sufficient protection given by NVX-CoV2373 for the older population, with VEs at 88.9% (95% CI 12-98).[1] The Phase 1-2 trials showed significantly lower immunogenic response among the older compared to the younger population.[5-6] However, high seroconversion rates after the 2-dose vaccine regimen (97% for anti-spike binding IgG and 100% for neutralizing antibodies) were still achieved, and the titers seen from the sera of vaccinated older persons were higher than titers from convalescent plasma.[5]

Immunocompromised: HIV Positive patients

One Phase 2 study, which included HIV positive patients, showed only an infection rate of 1.56% among vaccinated cases after a 35-day follow-up, against a 27.7% rate among the unvaccinated. Based on these rates, the calculated (unadjusted) VE for HIV positive patients is 94.4%.[4]

Children, pregnant and lactating women

No study was identified providing information on the effect of NVX-CoV2373 on children, pregnant and lactating women and the immunocompromised.

Safety

Regulatory Clinical Trial Evidence

The regulatory trials (Phase 1-3) of NVX-CoV2373 all provided safety information. Results were consistent in these regulatory trials.[1,3,5,6]

Solicited adverse events (local and systemic) were seen more frequently in the vaccine group compared to placebo. Most were mild to moderate and transient. Rates were higher in the young vaccine recipients compared to the older subgroup and in the second dose compared to the first. The most common local adverse event was injection site pain. The most common systemic adverse events reported were headache, myalgia, and fatigue.

Unsolicited adverse events were slightly higher in the vaccine group but not statistically significantly different. Serious adverse events, medically-attended adverse events, and discontinuation and death rates were low and similar between groups. Serious adverse events noted in the vaccine group were mostly assessed as non-vaccine related. One related serious adverse event (myocarditis) was reported in one vaccine recipient in one trial, which occurred 3 days after the second dose.[1]

Real World Evidence of Safety
As NVX-CoV2373 has not been authorized for use in any country, no real-world evidence is available.

Reports on Adverse Events of Interest
Apart from those stated in the clinical trials, no report on adverse events of interest was found.

Effectiveness Against Variants
Alpha
The two Phase 3 trials demonstrated adequate clinical efficacy of NVX-CoV2373 against symptomatic COVID-19 infection caused by the Alpha variant, with VE rates of 86.3% (95% CI 71.3-93.5)[1] and 93.6% (95% CI 81.7-97.8).[3]

Beta
One Phase 2 trial showed reduced and possible ineffectiveness of NVX-CoV2373 against the Beta variant, with a VE of 51% (95% CI -0.6 to 76.2).[4] One immunogenicity study based on sera from 23 vaccine recipients taken 14 days after the 2nd dose showed a 6.8- to 14.5-fold reduction in antibody titers with the Beta strain compared to D614G.[7]

Gamma, Delta
No report has been identified that studied the effect of NVX-CoV2373 on the Gamma and Delta variants.

Booster Vaccination
No study was identified using NVX-CoV2373 in a booster vaccination regimen.

Details of the study characteristics and results included in this review are presented in Table 4.

Authorizations
Indonesia is the first country to grant emergency use authorization for NVX-CoV2373 (Novavax) on November 1, 2021. The application for WHO EUL listing is under process as of November 13, 2021.

Research Gaps
The following are identified research gaps regarding NVX-Cov2373 vaccination for COVID-19 infection prevention: The efficacy/effectiveness of BBIBP-CorV in special populations such as the older and very old patients, children, immunocompromised (eg. HIV) populations; the

duration of protection / long term efficacy or effectiveness; its long-term safety; its clinical efficacy and effectiveness against infection with variants of concern such as the Delta variant; studies on heterologous primary vaccination; and its use in booster vaccinations.

Ongoing Trials

The search performed on November 12, 2021 of the Clinicaltrials.gov registry showed six active trials on NVX-Cov2373. Two of the trials have released interim reports. One trial is on children. Table 7 details these trials.

References

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[3] Dunkle L, Kotloff K, Gay C, Anez G, Adelglass J, Barrat Hernandez A. Efficacy and Safety of NVX-CoV2373 in Adults in the United States and Mexico [Internet]. MedRxiv. 2021 [cited 2021 Oct 31]. Available from: https://doi.org/10.1101/2021.10.05.21264567

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=10)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (10)					
Benefits	Large (8)	Moderate (2)	Small	Uncertain			• NVX-CoV2373 provides excellent protection against symptomatic COVID-19 with vaccine effectiveness of 89.7% (95%CI 80.2 to 84.6) and 90.4% (95%CI 82.9 to 94.6), measured at least 7 days after the second dose.
Harm	Large	Moderate	Small (6)	Trivial (2)	Varies (1)	Uncertain (1)	• Most adverse events were mild to moderate and transient, with higher rates among: (1) young vaccine recipients, and (2) after second dose. • Most common local adverse event: injection site pain. • Most common systemic adverse events: headache, myalgia and fatigue. • One related serious adverse event: myocarditis.

Certainty of evidence	High (2)	Moderate (4)	Low (4)	Very low			• Low to high
Balance of effects	Favors vaccine (7)	Probably favors vaccine (3)	Does not favor diagnostic/treatment or no diagnostic/treatment	Probably favors no diagnostic/treatment	Favors no diagnostic/treatment	Don't know	
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (4)	Possibly NO important uncertainty or variability (4)	No important uncertainty or variability (1)			
Resources required	Uncertain	Large cost	Moderate Cost (6)	Negligible cost (3)	Moderate savings	Large savings (1)	• Novavax is priced at P366. Two doses are needed per individual. • Can be stored, transported and handled at standard refrigerator temperatures (2-8°C).
Certainty of evidence of resources required	No included studies (10)	Very low	Low	Moderate	High		
Equity	Uncertain	Probably reduced (2)	Probably no impact (1)	Probably increased (4)	Increased (1)	Varies (2)	• Addresses wide disparity in vaccine coverage: 85.1% fully-vaccinated senior citizens in NCR; only 28.3% in BARMM.
Acceptability	Uncertain	No	Probably no	Probably yes (4)	Yes (6)	Varies	• The Philippine FDA granted emergency use authorization for NVX-CoV2373 (Novavax) last November 18, 2021
Feasibility	Uncertain	No	Probably no	Probably yes (4)	Yes (6)	Varies	

Appendix 2. Risk of Bias Assessment of Included Studies

Study ID	Design	Randomization	Allocation Concealment	Blinding Particip	Blinding Carer/ Assessor	Followup	Selective Reporting	Others	Age	Comorbidities	Exposure	Confounding	OVERALL
Heath	RCT	LOW	LOW	UNCLEAR	LOW	HIGH [a]	LOW	NA	NA	NA	NA	NA	LOW
Dunkle	RCT	LOW	LOW	LOW	LOW	HIGH [a]	LOW	NA	NA	NA	NA	NA	LOW
Formica	RCT	LOW	LOW	LOW	LOW	LOW	LOW	NA	NA	NA	NA	NA	LOW
Keech	RCT	LOW	LOW	LOW	LOW	LOW	LOW	NA	NA	NA	NA	NA	LOW
Shinde	RCT	LOW	LOW	LOW	LOW	HIGH [b]	UNCLEAR	NA	NA	NA	NA	NA	LOW
Shen	Comparative cohort, immuno	HIGH	HIGH	UNCLEAR	UNCLEAR	LOW	UNCLEAR	NA	HIGH	HIGH	HIGH	HIGH	HIGH

a – interim report
b – interim report, safety data not reported for all

Appendix 3. Characteristics of the Randomized Controlled Trial (Ph3) on the Efficacy and Safety of NVX-Cor2373

Trial Identifier		**PREVENT-19**
Vaccine	**NVX-CoV2373**	
Data Sources	**Heath 2021 NEJM, supplem**	**Dunkle MedRxiv**
POPULATION		
Total Randomized	15,187	29,949
Inclusion Criteria		
• Age	18-84 years, healthy	At least 18 years
• Gender	Yes	Yes
• Race/ Ethnicity	Yes	Yes
• Immunocompromised	Excluded, but included stable HIV infection	Well controlled HIV infection
• Pregnant and breastfeeding	excluded	excluded
• With concomitant comorbidities	With stable chronic medical conditions	With stable chronic medical condition
• With previous COVID infection	excluded	excluded
• With known previous exposure to COVID	Not mentioned	excluded
• Seropositive at baseline	included	included
Exclusions	History of lab confirmed COVID-19 infection Participation in other COVID-19 studies Administration of immunoglobulins and other blood products within 3 months Immunosuppressive or immunodeficient state Pregnancy, lactation, willingness/intention Diagnosis/treatment for cancer Bleeding disorder, anticoagulant Received any live vaccine within 4 weeks or any vaccine Significant chronic cardiovascular, enod, medical problem, neurologic Any autoimmune or immunodeficiency disease/condition	Known previous lab-confirmed COVID infection or known immunosuppression
INTERVENTION (VACCINE)		
Type	Protein subunit	
Active substance	Spike protein nanoparticle	
Trial-specific considerations		
Dosing and administration	2 x 5ug SARS-CoV-2 rS with 50ug Matrix M1 adjuvant intramuscularly, 21 days apart	2 x 5ug SARS-CoV-2 rS with 50ug Matrix M1 adjuvant intramuscularly, 21 days apart

	(subgroup received influenza vaccine with the first dose, given as open label)	
Number randomized	7569	19714 (17,312 per protocol)
COMPARATOR		
Type, dosing and administration	Saline, 0.5ml, intramuscular, 21 days apart	Saline, 0.5ml, intramuscular, 21 days apart
Number randomized	7020	9868 (8140 per protocol)
OUTCOMES		
Primary efficacy endpoints	Efficacy against occurrence of virologically confirmed symptomatic mild, moderate, or severe COVID-19 from 7 days after the second dose, as defined by the FDA	Preventing the first episode of PRT-PCR confirmed symptomatic mild, moderate, severe COVID-19 (as per FDA criteria) with onset of >=7 days after the second dose
Primary safety endpoints	Solicited local and systemic adverse events for 7 days after each dose Unsolicited adverse events through 28 days after 2nd dose Serious adverse events, adverse events of special interest, medically attended adverse events from first dose through 1 year after the 2nd dose (safety data excludes the 400 participants who were enrolled in the influenza vaccine substudy) ** SEE SUPPL TS3	-
Secondary endpoints Exploratory endpoints Immunogenicity	- VE against symptomatic COVID by SARS-CoV-2 strain (variants)	- Protection against RT-PCR confirmed COVID 19 due to non-VOC/VOI strains - Infection by subgroups - Safety, reactogenicity
Subgroups considered in the analysis		
● Age	Median age = 56 years, 27.9% were 65 years or older	Median age : 47 years 11.8% were 65 years or older
● Sex	48% females	48.2% females
● Ethnic groups	2.9% asians	
● Baseline seropositivity status / evidence of previous infection	4.2%	6.3% (NVX), 6.9% (pla)
● Medical comorbidities	44.6% had one or more comorbidity	47.3% with one or more comorbidity
● Immunocompromised / HIV disease	Not mentioned	
● Risk for acquiring COVID infection	Not mentioned	
● Risk for progression to severe COVID	44.6%	

Follow up		
• Planned	1 year	
• At data cutoff of interim report (first interim analysis)	Around 3 months (98 days)	Median 2 months?
Date of Data Cut-off date for latest available trial data	Not mentioned	April 19, 2021
METHODS / OTHER TRIAL PARAMETERS		
Risk of bias	Centralized IVRS Cases determined in a blinded fashion Observer-blind	Web based IVRS Blinded assessment ** blinded crossover for those who received placebo to get the vaccine (the report is prior to the crossover)
Study Sites	33 sites in the UK	113 cites in the US, 6 in Mexico
Study Sponsor	Novavax	Novavax
Type of report available as of this rapid review	Published interim report	Pre-print
Others		

Appendix 4. Characteristics and Results of Clinical Trials on NVX-Cov2373

Study ID	Design	Population	Intervention / Comparison	Outcome (Followup/Assessment) Result
Shinde	RCT (Ph2) Double-blinded Interim report at 35 days ffup (planned 1 year)	18 to 84 years, with a subgroup of 18 to 64 years with HIV infection (stable) N=4387 randomized Vac: 2199 Pla: 2188 30% seropositive at baseline 41 sera samples used for genomic sequencing	5ug NVX-CoV2373 with 50ug Matrix-M1 adjuvant, 2 doses, 21 days apart Placebo (saline)	Symptomatic COVID infection starting D8 after 2nd dose Vac: 15, mild to moderate Pla: 29, one severe VE = 49.4% (6.1 to 72.8) Subgroup: HIV negative: 60.1% (19.9 to 80.1) Seropositive at baseline: 52.2% (24.8 to 81.7) Effectiveness against Beta (41 samples) VE = 51.0% (-0.6 to 76.2) for HIV negative VE = 43% (-9.8 to 70.4) for HIV positive and negative Reactogenicity (7 days) - more severe local adverse events among seronegative participants in the vaccine group (4% vs 1%) - most common systemic adverse reaction: headache, muscle pain, fatigue - more common in vaccine group were medically attended AEs and serious A2 13. vs.6 / 2.vs 1
Shen	Comparative cohort (vs mRNA-1273 and convalescent plasma) Immunogenicity study	Randomly selected sera from convalescent persons and vaccine recipients mRNA-1273: 26 NVX-CoV2373: 23	Reference strain: D614G	GMT ID50 titer vs Beta 14.5 times lower for NVX GMT ID50 titer vs B.1.429 8.6x lower GMT ID80 vs Beta 6.8x lower

Keech	RCT Ph1-2	18 to 59 years old, healthy N = 133	NVX-CoV2373, 5ug and 25 ug, with or without Matrix M1 adjuvant, 2 doses, 21 days apart Placebo (83 received the vaccine with adjuvant, 25 without adjuvant, 23 placebo)	Antispike titers at days 0,7,21,28 and 35 - Geometric mean fold rises (GMFR) of vaccine recipients with adjuvant exceeded those without at day 21, further increase at day 35 - Responses in the 2-dose 5 and 25-ug adjuvanted regimen were similar NAB titers – response similar to above Reactogenicity at 7 days - absent or mild in the majority, similar across groups - 2 participants in the vaccine groups have severe AEs (headache, fatigue and malaise) Adverse events through day 35 - no serious AE or AE of special interest

Formica	RCT Ph 2 Observer blinded	18 to 84 y/o stable medical condition n= 1288 randomized placebo = 255 5ug 2 doses = 257 5ug one dose = 257 25ug 2 doses = 258 25ug 1 dose = 256	NVX-CoV2373, 5ug and 25 ug, with or without Matrix M1 adjuvant, 2 doses, 21 days apart Placebo	Antispike IgG titers and seropositivity at 0, 21, 35 GMFRs similar in both doses Seroconversion rates similar 98 vs 100 Responses significantly lower in the older age group Neutralizing Ab Similar pattern of response as in IgG Reactogenicity within 7 days - local AEs more in high dose for tenderness and pain - local AEs higher in younger - no grade 4 events - systemic more frequent in vaccine group Unsolicited AEs Similar rates: pla (17%), low dose (17%), high dose (18%) 7 discontinuations, 2 in placebo, 5 in vaccine 8 SAEs in vaccine group, all unrelated Authors conclusion: Matrix-M1 adjuvanted rSARS-CoV-2 nanoparticle vaccine was highly immunogenic and well tolerated in younger and older participants.

Heath	RCT Ph 3 Randomized, observer-blinded, placebo-controlled	18 to 84 yrs.old 27.9% aged 65 and older 44.6% with comorbidities conducted in the UK N = 15,187	NVX-CoV2372 5ug x 2 doses, 21 days apart Vs placebo	Virologically confirmed symptomatic COVID-19 at least 7 days after 2nd dose VE against symptomatic COVID-19 89.7% (95% CI 80.2, 94.6) all 5 severe cases occurred in the placebo group VE in participants 65 years old and over: 88.9% (95% CI 12.8, 98.6) VE against Alpha: 86.3% (95% CI, 71.3 to 93.5) VE against non-Alpha: 96.4% (95% CI, 73.8 to 99.4) Solicited and unsolicited local and systemic AE more frequently reported in vaccine group
Dunkle	RCT Ph3 Randomized, observer-blinded, placebo-controlled	United States and Mexico N = 29,949 12.6% 65 years or older		VE against RT-PCR confirmed symptomatic COVID-19 in naïve participants at least 7 days from 2nd dose All moderate to severe cases occurred in placebo group VE against VOC/VOI 92.6% (95% CI 83.6, 96.7) – mainly alpha variant VE against symptomatic COVID-19 90.4% (95% CI 82.9, 94.6) VE against moderate- to- severe COVID-19 100% (87, 100) VE against severe COVID-19 100% (34.6, 100) post hoc analysis

Appendix 5. Summary of Findings Table of Efficacy of NVX-CoV2373

Efficacy Outcome (at >7 days after dose2)	N Study design	Quality Assessment					Summary of Findings			Certainty
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine n/N (%)	Control n/N (%)	Vaccine Efficacy (CI)	
1: Symptomatic COVID-19 infection, seronegative at baseline	3 RCT	Serious (short ffup)	Serious (1 study with low VE)	Not serious	Not serious	Serious	10/7020 (0.1%)[a] 14/17312 (0.08%)[b] 15/1357 (1.1%)[c]	96/7019 (1.4%)[a] 63/8140 (0.78%)[b] 29/1327 (2.2)[c]	89.7% (80.2, 94.6)[a] 90.4% (82.9, 94.6)[b] 49.4% (6.1, 72.8)[c]	++ Low
2: Severe COVID-19 infection,	2 RCT	Serious (short ffup)	Not serious	Not serious	Serious	Serious	0/7207 (0%)[a] 0/17312(0%)[b]	5/7019 (.07%)[a] 4/8140(4.2%)[b]	90.9% (-0.64, 100)[a] 100% (34.6, 100%)[b]	++ Low
3: Asymptomatic COVID-19 infection, seronegative at baseline	0	Not available	na	na	na	na	na	na	na	na
4: Any COVID-19 infection, seronegative at base line	0	Not available	na	na	na	na	na	na	na	na
5: Symptomatic COVID-19 infection after first dose, before the second dose	1 RCT	Serious (short ffup)	Not assessed	Not serious	Not serious	Serious	na	na	83.4% (73.6, 89.5)[a]	na
6: Symptomatic COVID-19 infection, older adults (>=65yo), seronegative at baseline	1 RCT	Serious (short ffup)	Not assessed	Not serious	Serious	Serious	1/1953 (0.05%)[a]	9/1957 (0.5%)[a]	88.9 (20.2, 99.7)[a]	++ Low
7: Symptomatic COVID-19 infection, with pre-existing medical condition	2 RCT	Serious (short ffup)	Not serious	Not serious	Not serious	Serious	3/3117 (0.09%)[a]	33/3143 (1.0%)[a]	90.9 (70.4, 97.2)[a]	+++ Moderate

							7/8109 (0.08%)[b]	34/3910 (0.9%)[b]	90.8 (79.2, 95.9)[b]	
8: Symptomatic COVID-19 infection, children (<18yo)	0	Not available	na	na	na	na	na	na	na	na
9: Symptomatic COVID-19 infection, HIV positive adults	1 RCT	Serious (short ffup)	Not assessed	Not serious	Very serious (wide CI)	Very Serious	4/76 (5.27%)[c]	2/72 (2.78%)[c]	-89.0% (-903.0, 64.21)[c]	+ Very Low
10: Any COVID-19 infection, B.1.1.7/Alpha variant	2 RCT	Serious (short ffup)	Not assessed	Not serious	Not serious	Serious	8/7020 (0.1%)[a] 4/17312 (0.02%)[b]	58/7020 (0.8%)[a] 27/8140 (0.33%)	86.3 (71.3, 93.5)[a] 93.6% (81.7, 97.8)[b]	+++ Moderate
11. Any COVID-19 infection, B.1.151/Beta variant	1 RCT	Serious (short ffup)	Not assessed	Not serious	Serious	Serious			43% (-9.8, 70.4)[a]	++ Low
12. Any COVID-19 infection, B.167.2/Delta variant	0	Not available	na	na	na	na	na	na	na	na

Appendix 6. Summary of Findings Table on the Safety of NVX-CoV2373

Safety Outcome	N Study design	Quality Assessment					Summary of Findings			Certainty
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine	Control	Relative Risk (95%CI)	
1: Solicited adverse reaction	0	Not available	na	na	na	na	na	na	na	na
2: Local adverse reaction	2 RCT	Not serious	Not assessed	Not serious	Not serious	Not serious	57.6% (D1)[a] 76.6% (D2)[a] 58.0% (D1)[b] 78.0% (D2)[b]	17.9% (D1)[a] 16.4% (D2)[a] 21.1% (D1)[b] 21.7% (D2)[b]	3.2 (2.8, 3.7)[a] 4.7 (4.0,5.4)[a] 2.7 (2.4, 3.1)[b] 3.6 (3.2, 4.1)[b]	++++ High
3: Systemic adverse reaction	2 RCT	Not serious	Not serious	Not serious	Not serious	Not serious	45.7% (D1)[a] 64.0% (D2) [a] 47.7% (D1) [b] 69.5% (D2) [b]	36.3% (D1)[a] 30.0% (D2)[a] 40.0% (D1)[b] 35.9% (D2)[b]	1.3 (1,1, 1.4)[a] 2.1 (1.6, 2.9)[a] 1.2 (1.1, 1.3) [b] 1.9 (1.8, 2.1) [b]	++++ High
4. Unsolicited adverse event (28d)	3 RCT	Not serious	Not serious	Not serious	Not serious	Not serious	25.3% [a] 21.8 [b] 17% [c]	20.5% [a] 18.2% [b] 17% [c]	1.2 (1.0, 1.5)[a] 1.4 (0.9,1.4) [b] 1.0	++++ High
5. Severe adverse event	1 RCT	Serious (short ffup)	Not serious	Not serious	Serious	Not serious	76/7569 (1.0%)[a]	64/7570 (0.8%)[a]	1.2 (0.85, 1.65)	++ Low
6: Serious adverse event	2 RCT	Serious (short ffup)	Not serious	Not serious	Serious	Not serious	0.6% [a] 1.2%[b]	0.6% [a] 1.3%[b]	1.0 (0.65,1.5)[a] 0.9 (0.7, 1.1)[b]	++ Low
7: Medically attended adverse events (MAAEs)	1 RCT	Serious (short ffup)	Not serious	Not serious	Not serious	Not serious	285/7569 (3.8%)[a]	295/7570 (3.9%)[a]	0.97 (0.8,1.1)[a]	+++ Moderate
7: Withdrawals due to adverse event	1 RCT	Serious (short ffup)	Not assessed	Not serious	Serious	Serious	17/7569 (0.2%)[a] 0.3%	16/7570 (0.2%) 0.1%	1.1 (0.5, 2.1)[a] 3.0 (0.3, 28.8)	++ Low

8: Death	1 RCT	Serious (short ffup)	Not assessed	Not serious	Serious	Serious	2/7569 (0.02%)[a]	1/7570 (0.01%)	2.0 (0.18, 22.1) [b]	++ Low

a – Heath b – Dunkle c - Formica

Appendix 7. Ongoing Trials Registered at the Clinicaltrials.gov Registry on NVX-CoV2373 (as of Nov 12 2021)

NCT Number	Title	Status	Interventions	Sponsor/Collaborators	Age	Phases	Study Type	Study Designs	Start Date	Completion Date
NCT05112848	A Study to Evaluate Safety and Immunogenicity of a COVID-19 Vaccine in People Living with HIV at Risk for SARS-CoV-2 (COVID-19)	Not yet recruiting	Biological: NVX-CoV2373	Novavax	18 Years to 65 Years (Adult, Older Adult)	Phase 2	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) |Primary Purpose: Prevention	Nov-21	Jul-22
NCT04533399	A Study Looking at the Effectiveness and Safety of a COVID-19 Vaccine in South African Adults	Recruiting	Biological: SARS-CoV-2 rS/Matrix-M1 Adjuvant|Other: Placebo	Novavax|Bill and Melinda Gates Foundation	18 Years to 84 Years (Adult, Older Adult)	Phase 2	Interventional	Allocation: Randomized|Intervention Model: Sequential Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) |Primary Purpose: Prevention	17-Aug-20	Nov-21
NCT04583995	A Study Looking at the Effectiveness, Immune Response, and Safety of a COVID-19 Vaccine in Adults in the United Kingdom	Active, not recruiting	Biological: SARS-CoV-2 rS/Matrix M1-Adjuvant|Other: Placebo|Biological: Licensed seasonal influenza vaccine	Novavax	18 Years to 84 Years (Adult, Older Adult)	Phase 3	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) |Primary Purpose: Prevention	28-Nov-20	14-Jan-22

NCT04611802	A Study to Evaluate the Efficacy, Immune Response, and Safety of a COVID-19 Vaccine in Adults 18 Years With a Pediatric Expansion in Adolescents (12 to < 18 Years) at Risk for SARS-CoV-2	Active, not recruiting	Biological: SARS-CoV-2 rS/Matrix-M1 Adjuvant (Initial Vaccination Period) |Other: Placebo (Initial Vaccination Period) |Biological: SARS-CoV-2 rS/Matrix-M1 Adjuvant (Crossover Vaccination period)|Other: Placebo (Crossover Vaccination period)	Novavax|Department of Health and Human Services	12 Years and older (Child, Adult, Older Adult)	Phase 3	Interventional	Allocation: Randomized|Intervention Model: Crossover Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) |Primary Purpose: Prevention	27-Dec-20	30-Jun-23
NCT04368988	Evaluation of the Safety and Immunogenicity of a SARS-CoV-2 rS Nanoparticle Vaccine With/Without Matrix-M Adjuvant	Active, not recruiting	Biological: SARS-CoV-2 rS - Phase 1|Biological: SARS-CoV-2 rS/Matrix-M Adjuvant - Phase 1|Other: Normal saline solution (NSS), Placebo - Phase 1|Other: Normal saline solution (NSS), Placebo - Phase 2|Biological: SARS-CoV-2 rS/Matrix-M Adjuvant, Day 0 - Phase 1|Other: Normal saline solution (NSS),	Novavax|Coalition for Epidemic Preparedness Innovations	18 Years to 84 Years (Adult, Older Adult)	Phase 1|Phase 2	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) |Primary Purpose: Prevention	25-May-20	21-May-22

			Placebo, Day 21 - Phase 1|Biological: SARS-CoV-2 rS/Matrix-M Adjuvant - Phase 2							
NCT04834869	COVID-19 Vaccines Safety Tracking (CoVaST)	Recruiting	Biological: BNT162b2|Biological: mRNA-1273|Biological: AZD1222|Biological :CoronaVac|Biological:Sinopharm|Biological Gam-COVID-Vac|Biological: JNJ-78436735|Biological :CVnCoV|Biological: NVX-CoV2373|Biological: BBV152	Masaryk University	18 Years and older (Adult, Older Adult)		Observational	Observational Model: Other|Time Perspective: Prospective	1-Apr-21	31-Jan-22