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Expert Review of Vaccines

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierv20

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To cite this article: Eddie Underwood, Lisa M. Dunkle, Shabir A. Madhi, Cynthia L. Gay, Paul T. Heath, Karen L. Kotloff, Katherine Smith, Gordon Chau, Shirley Galbiati, Alice McGarry, Wayne Woo, Iksung Cho, Katia Alves, Germán Áñez, Chijioke Bennett, Vivek Shinde, Louis Fries, Raburn M. Mallory, Gregory M. Glenn & Seth Toback (2023) Safety, efficacy, and immunogenicity of the NVX-CoV2373 vaccine, Expert Review of Vaccines, 22:1, 501-517, DOI: 10.1080/14760584.2023.2218913

To link to this article: https://doi.org/10.1080/14760584.2023.2218913

EXPERT REVIEW OF VACCINES
2023, VOL. 22, NO. 1, 501–517
https://doi.org/10.1080/14760584.2023.2218913

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Safety, efficacy, and immunogenicity of the NVX-CoV2373 vaccine

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ABSTRACT

Introduction: The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in significant morbidity and mortality worldwide. As SARS-CoV-2 moves into endemic status, vaccination remains a key element in protecting the health of individuals, societies, and economies worldwide.

Areas covered: NVX-CoV2373 (Novavax, Gaithersburg, MD) is a recombinant protein vaccine composed of SARS-CoV-2 spike trimer nanoparticles formulated with saponin-based Matrix-M™ adjuvant (Novavax, Gaithersburg, MD). NVX-CoV2373 is authorized for emergency use in adults and adolescents aged ≥12 years in the United States and numerous other countries.

Expert opinion: In clinical trials, NVX-CoV2373 showed tolerable reactogenicity and favorable safety profiles characterized by mostly mild-to-moderate adverse events of short duration and by low rates of severe and serious adverse events comparable to those seen with placebo. The two-dose primary vaccination series resulted in robust increases in anti-spike protein immunoglobulin G, neutralizing antibody titers, and cellular immune responses. NVX-CoV2373 vaccination was associated with complete protection against severe disease and a high (90%) rate of protection against symptomatic disease in adults, including symptomatic disease caused by SARS-CoV-2 variants. Additionally, the NVX-CoV2373 adjuvanted recombinant protein platform offers a means to address issues of COVID-19 vaccination hesitancy and global vaccine equity.

ARTICLE HISTORY
Received 19 January 2023
Accepted 24 May 2023

KEYWORDS
clinical trial; coronavirus; COVID-19, Matrix-M adjuvant; prevention; protein-based vaccine; SARS-CoV-2; vaccination; NVX-CoV2373

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), was first identified in Wuhan, China, in December 2019. Subsequently, more than 630 million SARS-CoV-2 confirmed cases, including 6.5 million deaths, have been recorded globally [1]. The actual death toll is likely much higher, as models addressing excess mortality metrics estimate 15–20 million lives lost [2,3]. Due to unprecedented global collaboration, vaccines became available in December 2020. Thereby, an estimated 20 million deaths were averted in the first year of vaccination against SARS-CoV-2 [4]. Nevertheless, full vaccination has not yet been achieved globally [1].

Eleven vaccines against SARS-CoV-2 have been granted emergency use listing by the World Health Organization (WHO) as summarized in Table 1 [9]. Six vaccines are currently available for use in the United States (US), with either emergency use authorization (EUA) or approval by the U.S. Food and Drug Administration (FDA) for primary series vaccination and, for some, as a monovalent or bivalent booster [6–8].

In July and August 2022, the recombinant protein-based NVX-CoV2373 vaccine (Novavax, Gaithersburg, MD) became the latest COVID-19 vaccine authorized for emergency use in individuals aged ≥12 years as a primary series and for adults 18 years of age and older as a first booster [5]. Its current indication is expected to broaden with future regulatory submissions. Whereas mRNA- and viral vector-based platforms are relatively new, protein-based vaccines are a familiar technology that has been used to protect against bacterial and viral diseases for decades, with the first vaccine containing a recombinant protein approved for human use in 1986 [10]. Due to increasing availability of NVX-CoV2373 globally, this review aims to summarize available data on the vaccine's safety, immunogenicity, and efficacy.

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/14760584.2023.2218913.

Article highlights

- The aim of this Vaccine Profile is to characterize the NVX-CoV2373 adjuvanted, recombinant protein vaccine and summarize available clinical and immunogenicity data.
- NVX-CoV2373 is an authorized COVID-19 recombinant protein vaccine composed of the full-length SARS-CoV-2 Wuhan-Hu-1 spike protein as self-assembling nanoparticles combined with the novel adjuvant, Matrix-M.
- Matrix-M is a saponin-based adjuvant that promotes a broad-based, robust humoral and cellular immune response and offers potential advantages over other adjuvants.
- The traditional recombinant protein-based platform and standard refrigeration storage conditions of NVX-CoV2373 offer a means to address global vaccine equity and provide an alternative for those who may be vaccine hesitant toward newer technologies.
- Reactogenicity and safety data gathered from Phase II and Phase III trials in which NVX-CoV2373 was given as a primary series and as a first or second homologous booster reveal well-tolerated reactogenicity and an overall favorable safety profile including a low incidence of severe and serious adverse events comparable to placebo in adolescents and young and older adults.
- In two large Phase III clinical trials, NVX-CoV2373 provided 100% protection against severe COVID-19 disease and approximately 90% vaccine efficacy against symptomatic disease, including symptomatic disease caused by then-circulating variants (mainly alpha and beta), in adults across various subpopulations, age ranges, and in those with comorbidities for high-risk disease; a *post hoc* analysis of data from the US Phase III trial also revealed 100% protection against hospitalization.
- NVX-CoV2373 was associated with a vaccine efficacy of 80% in adolescents 12-17 years old during a period of delta variant predominance.
- A two-dose primary series with NVX-CoV2373 elicits a robust increase in anti-spike IgG and neutralizing antibody titers regardless of SARS-CoV-2 serostatus, age, HIV status, or co-administration with an age-appropriate seasonal influenza vaccine.
- After a first or second homologous booster with NVX-CoV2373, antibody levels significantly increase to levels considerably higher than the post-primary series levels, and the magnitude of difference between the ancestral strain and VOCs, including Omicron BA.1, BA.2, and BA.4/BA.5, is reduced with each booster dose, suggestive of potential broad protection against newly-evolving variants.
- The well-characterized recombinant protein vaccine technology platform employed for the manufacture of NVX-CoV2373 plus Matrix-M adjuvant affords ongoing flexibility and timeliness to respond to evolving SARS-CoV-2 immune escape variants to meet the needs of future boosters.

2. Body of the review

2.1. Development and formulation

NVX-CoV2373 is produced using a well-characterized recombinant protein vaccine platform. Protein-based vaccines have an established history of safe and effective use in the prevention of viral and bacterial diseases, and have benefited from recent technological advancements [11]. NVX-CoV2373 is an adjuvanted, self-assembling nanoparticle vaccine composed of recombinant SARS-CoV-2 spike trimers. The development and manufacturing technologies used to make NVX-CoV2373 allow for the production of vaccine-quality antigens at a large-scale with excellent consistency and quality. Briefly, a genetic construct encoding the full-length SARS-CoV-2 Wuhan-Hu-1 spike protein, codon-optimized for expression and stability in *Spodoptera frugiperda* (Sf9) insect cells, was synthesized and cloned into a baculovirus vector (Figure 1) [12]. Notably, the flexibility of this step allows for the use of alternative genetic constructs as needed, such as the S-proteins from new SARS-CoV-2 variants. Next, the recombinant baculovirus is replicated in Sf9 cells and NVX-CoV2373 spike gene is transcribed, translated, and post-translationally modified (i.e. glycosylated), resulting in high-yield production of the recombinant SARS-CoV-2 S-protein in a native trimer conformation. Next, the trimers are harvested, purified by column chromatography and filtration, and dialyzed into a detergent-containing buffer solution wherein they self-assemble into ~60 nanometer particles arranged around a polysorbate 80 core. The rigorous steps of in-process and final production testing ensure consistent purity levels. In the final step, the S-protein nanoparticles are formulated with Matrix-M saponin-based adjuvant (Matrix-M™) (Novavax, Gaithersburg, MD) [13]. Though the production of protein-based vaccines requires complex methods and analytics, the pandemic-era refinement and improvement of these processes allows for the rapid response to expected COVID-19 variant-specific antigen updates in future.

Saponins are naturally occurring compounds that are sustainably derived from the bark of the *Quillaja saponaria*

Table 1. SARS-CoV-2 vaccines with emergency use status and/or approval [9].

			FDA emergency use authorization/approval population	
Vaccine	Reference	WHO emergency use listing	Primary series	Booster
NVX-CoV2373 (Nuvaxovid™, Novavax, and CovoVax™, Serum Institute of India)	[5]	✓	EUA for individuals ≥12 years	EUA for individuals ≥18 years
mRNA-1273 (SPIKEVAX®, Moderna)	[6]	✓	Approved for individuals aged ≥18 years EUA for children aged 6 months to 17 years	EUA for individuals ≥6 months (monovalent and bivalent vaccines)
BNT162b2 (Comirnaty®, Pfizer-BioNTech)	[7]	✓	Approved for individuals aged ≥ 12 EUA for children aged 6 months to 11 years	EUA for individuals >5 years (monovalent and bivalent)
Ad5-nCoV (Convidecia, CanSino)	-	✓	N/A	N/A
Ad26.COV2.S (Jcovden™, Janssen/Johnson & Johnson)	[8]	✓	EUA for individuals ≥18 years	N/A
AZD1222 (Vaxzevria®, Oxford/AstraZeneca, and Covishield™, Serum Institute of India)	-	✓	N/A	N/A
BBV152 (Covaxin™, Bharat Biotech)	-	✓	N/A	N/A
BBIBP-CorV (Covilo, Sinopharm)	-	✓	N/A	N/A
Sinovac COVID-19 vaccine (CoronaVac®, Sinovac)	-	✓	N/A	N/A

Note: EUA, emergency use authorization; FDA, U.S. Food and Drug Administration; N/A, not applicable; WHO, World Health Organization.

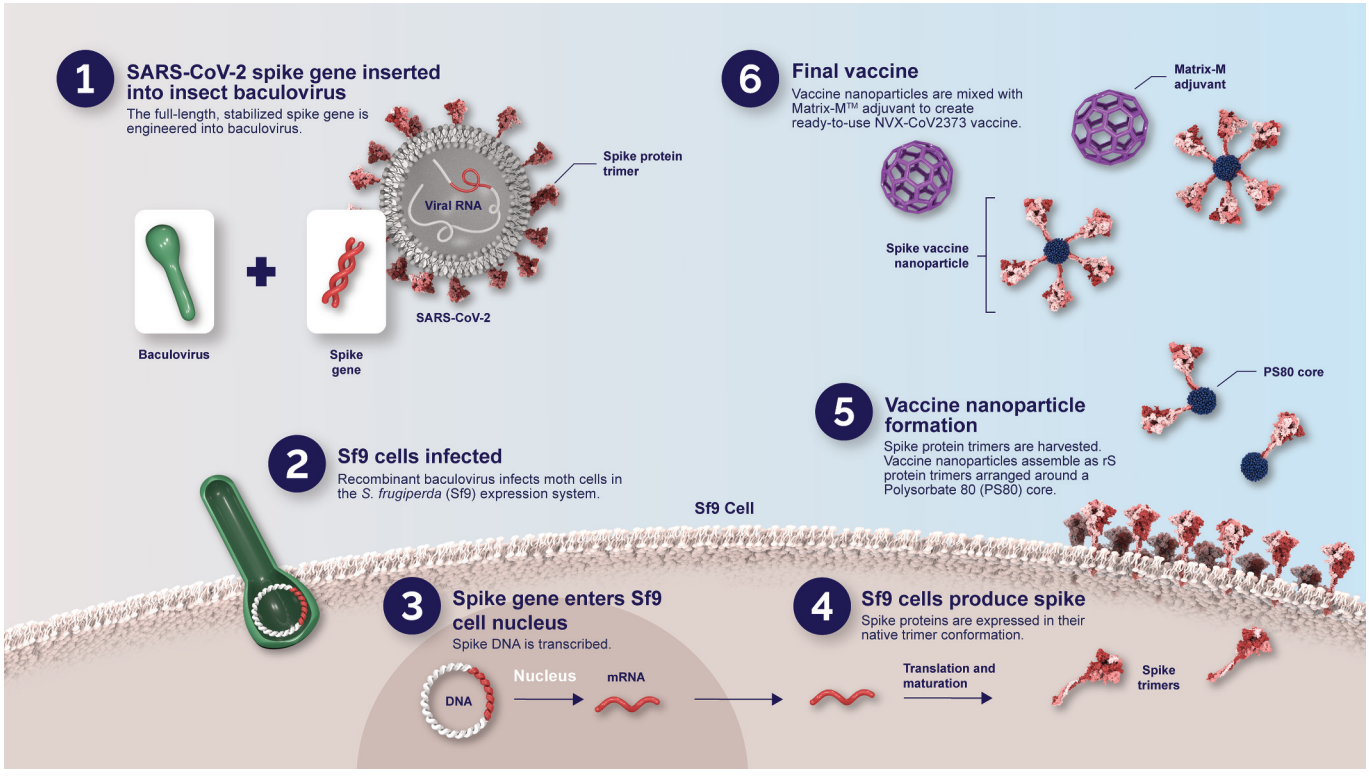

Figure 1. Mechanism of action of NVX-CoV2373. rS, recombinant spike; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Sf9, Spodoptera frugiperda.

(QS) tree. Saponins have been used extensively in traditional medicine across different cultures and in food industry products such as root beer, which benefits from the compounds' natural foaming properties [14–18]. Several iterations of saponin-based adjuvants have been studied. QS-21, known for its robust immunogenic properties but chemical instability in alkaline conditions, shows potential hemolytic activity, and may be associated with immediate pain at the site of injection [19,20]. The FDA-approved shingles vaccine Shingrix (GSK, London, UK) uses AS01, an adjuvant formulated with QS-21 mixed with liposomal cholesterol to attenuate its limitations [21]. Immune Stimulating Complexes (ISCOMs) are cage-like saponin structures of cholesterol, phospholipids, and physically incorporated antigens, however these faced manufacturing challenges [22]. ISCOMS were immunogenic without incorporated antigen, leading to the development of ISCOMATRIX, which was further developed by Novavax AB [14–16,23,24]. Matrix-M adjuvant utilizes a novel blend of cholesterol and phospholipids to eliminate hemolytic effects [25] along with two uniquely active and physically distinct saponin fractions: Matrix-A and Matrix-C [14,15]. Matrix-M adjuvant has previously produced enhanced humoral and T-cell responses to candidate vaccines for rabies, ebolavirus, influenza, and in a recently approved malaria vaccine [26–28]. The development, manufacturing, and immunologic activity of NVX-CoV2373, formulated with Matrix-M, provide several differentiating factors from other available COVID-19 vaccine platforms. First, Matrix-M allows substantial antigen dose sparing and promotes induction of a Th1-biased response [15,29–32]. A Th1-biased response is typically optimal for control of intracellular pathogens and alleviates concerns of potential vaccine-induced Th2 hypersensitivity or enhanced respiratory disease expressed in the FDA guidance on COVID-19 vaccine development [33]. In addition to Th1-type cytokine production, animal and human data suggest that the NVX-CoV2373 vaccine induces a complex immune response consisting of robust and polyfunctional CD4+ T-cell responses, along with a rapid emergence of circulating T follicular helper cells, essential for antibody response and support following infection or vaccination [12,34,35]. A modest CD8+ T-cell response has also been observed in a subset of human participants who received two doses of NVX-CoV2373 providing further evidence of the important immunological contribution of the Matrix-M adjuvant [13,34]. Matrix-M adjuvant may offer improvements over some of the common adjuvants found in other vaccines.

The NVXCoV2373 vaccine uniquely benefits from the use of protein-based nanoparticles and Matrix-M adjuvant. Clinical data have shown it induces a strong humoral and cellular immune response against ancestral SARS-CoV-2 and variants in humans and might demonstrate distinctive long-term behavior relative to mRNA vaccines [13,34,35]. The NVX-CoV2373 vaccine development did not utilize human fetal or embryonic cells, nor are human fetal or embryonic cells or tissue used during NVX-CoV2373 manufacturing or contained in the final product. In contrast to mRNA and viral vector-based vaccines, NVX-CoV2373 contains recombinant spike protein, rather than tasking the body to actively produce it from genetic material. On a practical note, NVX-CoV2373 has one dose (5 µg) for all authorized indications, does not require dilution prior to

administration, and stability of the preservative-free suspension is maintained at a standard refrigeration temperature range (2 to 8°C [36 to 46°F]) prior to use.

2.2. Reactogenicity and safety

2.2.1. Primary vaccination series studies

The primary vaccination series for NVX-CoV2373 consists of two doses of 5 µg rSARS-CoV-2 S-protein antigen adjuvanted with 50 µg Matrix-M administered intramuscularly 3 weeks apart. Data regarding the reactogenicity and safety of NVX-CoV2373 for primary vaccination are available from two phase III trials (Study 2019nCoV-302, completed; PREVENT-19 [Study 2019nCoV-301], ongoing) and two phase I-II trials (Study 2019nCoV-101 [ongoing] and Study 2019nCoV-501 [completed]) (Table 2) [31,32,36–42].

2.2.1.1. Study 2019nCoV-302. Study 2019nCoV-302 was a randomized, observer-blinded, phase III study in which 15,187 healthy adults aged 18–84 years from 33 United Kingdom (UK) sites were randomly assigned (1:1) to receive two doses of either NVX-CoV2373 ($n = 7593$) or placebo ($n = 7594$) spaced 21 days apart [38]. Solicited adverse event (AE) data were recorded within 7 days from vaccination for a subgroup of 2310 participants. Rates of solicited local and systemic AEs were greater with NVX-CoV2373 versus placebo and increased with the second vaccine dose. Following dose 1, 57.6% of participants who received NVX-CoV2373 reported a solicited local AE (i.e. injection site reaction) compared with 17.9% of participants who received placebo; following dose 2, these values were 79.6% and 16.4%, respectively. Among Study 2019nCoV-302 NVX-CoV2373 recipients, the most common local reactions of any severity were tenderness (dose 1: 53.3%; dose 2: 76.4%) and pain (dose 1: 29.3%; dose 2: 51.2%) (Figure 2a), lasting a median of 2–3 days and mostly of mild or moderate severity. Following dose 1, solicited systemic AEs (i.e. fatigue, headache, muscle pain, malaise, joint pain, nausea/vomiting, or fever) of any severity occurred in 45.7% of NVX-CoV2373 recipients and 36.3% of placebo recipients. Following dose 2, twice as many participants assigned to NVX-CoV2373 (64.0%) versus placebo (30.0%) experienced a systemic AE. The most common systemic AEs were mild or moderate headache, muscle pain, and fatigue that lasted a median of 1.6–1.8 days after dose 1 and 1.8–2.0 days after dose 2 (Figure 2a). Solicited local and systemic AEs occurred more frequently in those aged 18–64 than in those aged ≥65 years [38,39]. Unsolicited AE data were collected for all 15,139 participants who received at least one dose of NVX-CoV2373 or placebo for 21 days after the first vaccination and for 28 days after the second vaccination. Unsolicited treatment-emergent AEs (TEAEs) were reported in 25.3% and 20.5% of participants following administration of NVX-CoV2373 and placebo, respectively. Similar percentages of NVX-CoV2373 and placebo recipients experienced severe TEAEs (1.0% vs. 0.8%, respectively), serious AEs (SAEs) (0.5% vs. 0.5%, respectively), and medically attended AEs (MAAEs) (3.8% vs. 3.9%, respectively). One case of myocarditis male, age range 16–20 years, occurring 3 days after receipt of the second NVX-CoV2373 dose) and one case of pericarditis (female, age range 60–65 years, occurring 8 days after receipt of the first NVX-CoV2373 dose) were reported; both participants fully recovered (Table 3). There were no reports of anaphylaxis or vaccine-associated enhanced COVID-19. The favorable safety profile was maintained at completion of the placebo-controlled phase (median follow-up, 4.5 months) [39].

2.2.1.2. PREVENT-19 (Study 2019nCoV-301) - adults. PREVENT-19 is an ongoing randomized, observer-blinded, phase III study in which 29,949 healthy adults aged ≥18 years in the US and Mexico were randomly assigned (2:1) to receive two intramuscular doses of either NVX-CoV2373 ($n = 19,965$) or placebo ($n = 9,984$) spaced 21 days apart [40]. In total, 29,582 participants were included in the safety analysis (NVX-CoV2373, $n = 19,729$; placebo, $n = 9,853$). Of the 19,729 individuals in the NVX-CoV2373 group of the PREVENT-19 safety analysis set, a total of 17,251 (87.4%) were aged 18–64 years, and 2,478 (12.6%) were aged ≥65 years [40]. As with Study 2019nCoV-302, rates of solicited local and systemic AEs in PREVENT-19 were greater among individuals assigned to NVX-CoV2373 versus placebo, with higher incidences reported after the second dose. Following dose 1, 58.0% of NVX-CoV2373 recipients reported a solicited local AE versus 21.1% of placebo recipients; the respective values following dose 2 were 78.9% and 21.7%. The majority of solicited local AEs were mild to moderate in severity with the most common being tenderness and pain at the injection site (Figure 2b), lasting a median of 2 days or less. The rates of solicited systemic AEs were similar for NVX-CoV2373 (47.7%) and placebo (40.0%) recipients after dose 1. Following dose 2, the rate of solicited systemic AEs among NVX-CoV2373 recipients was higher than that among placebo recipients (69.5% vs. 35.9%). The most common solicited systemic AEs were headache, myalgia, fatigue, and malaise (Figure 2b), each of which had a median duration of 1 day in both treatment groups after either dose 1 or dose 2. As with local AEs, most solicited systemic AEs were mild or moderate in severity. The incidence rate per 100 person-years for any unsolicited AE among NVX-CoV2373 versus placebo recipients was 156.9 versus 133.2 among those aged 18–64 years and 152.8 versus 123.6 among those aged ≥65 years. Similar percentages of NVX-CoV2373 and placebo recipients experienced unsolicited AEs (16.3% vs. 14.8%, respectively), severe AEs (1.2% vs. 1.1%, respectively), SAEs (0.9% vs. 1.0%, respectively), and MAAEs (7.0% vs. 6.6%, respectively). In terms of AEs of prespecified special interest (AESIs), no imbalance in potential immune-mediated conditions was observed between the NVX-CoV2373 and placebo recipients. From first vaccination to the time of blinded crossover (approximately 3–4 months after the first vaccination series) or early termination, there were two reports of myocarditis, with one occurrence in each study arm (Table 3). There were no reports of pericarditis, Guillain-Barré syndrome, anaphylaxis, or vaccine-associated enhanced COVID-19 and there was no imbalance in vaccine-induced immune thrombosis with thrombocytopenia [40].

2.2.1.3. PREVENT-19 (Study 2019nCoV-301) - adolescent expansion study. An expansion of PREVENT-19 into pediatric participants evaluated NVX-CoV2373 in adolescents aged 12

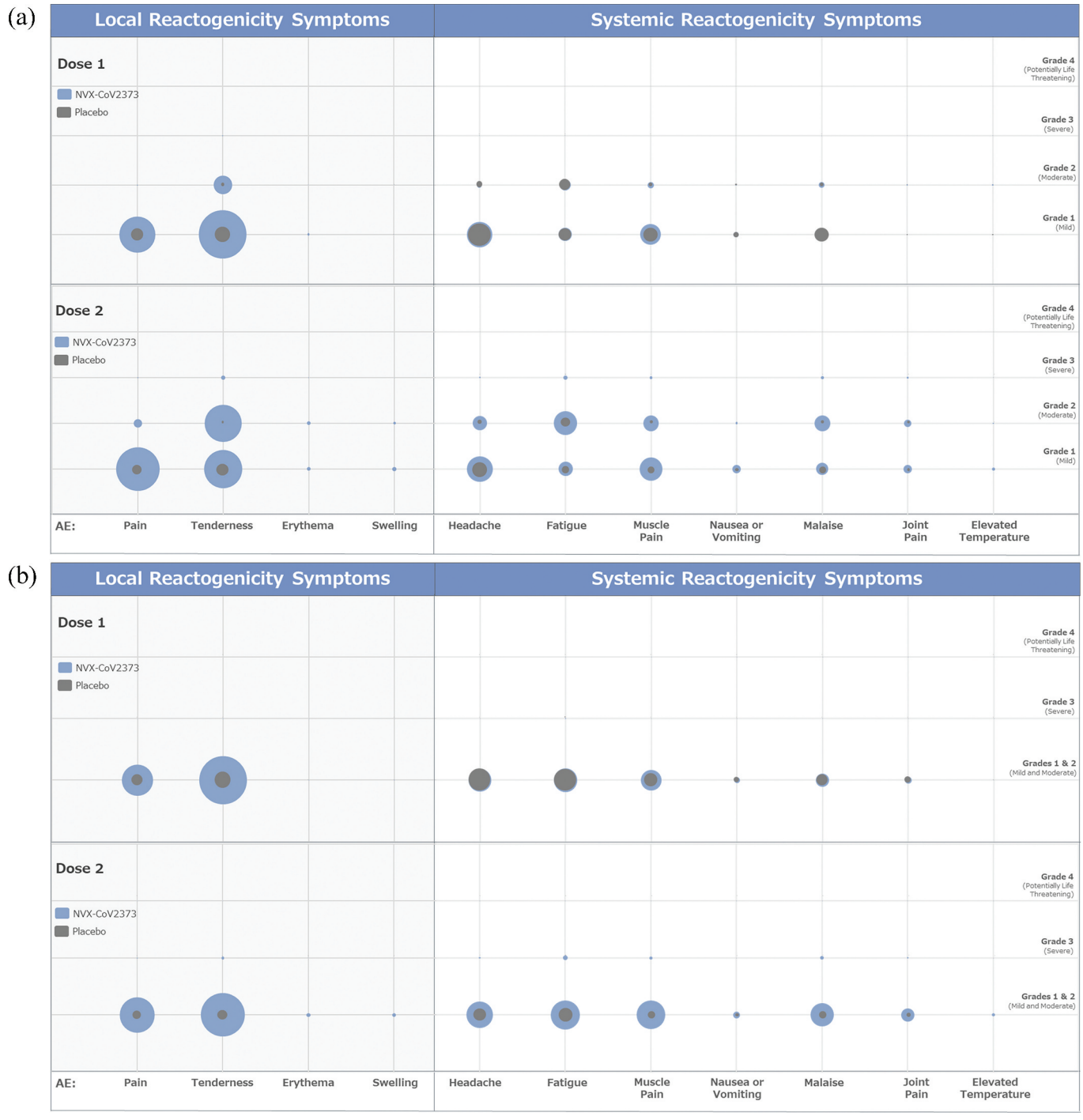

Figure 2. Solicited local and systemic adverse events (AEs) reported after primary vaccination in (a) Study 2019nCoV-302 [38], (b) PREVENT-19 [40]. (c) PREVENT-19 adolescents [42], and (d) Study 2019nCoV-501 [37,44]. Grade 1 and grade 2 reactogenicity events were reported separately for Study 2019nCoV-302 and Study 2019nCoV-501, whereas grades 1/2 were reported combined for PREVENT-19. Solicited AE data were recorded for a subgroup of 2310 participants for Study 2019nCoV-302 and for the entire Safety Analysis Set (all participants who received at least one dose of study vaccine/placebo) for PREVENT-19 ($n = 29,582$) and Study 2019nCoV-501 ($n = 4408$).

to <18 years [42]. A total of 2247 participants from 73 US sites were randomized (2:1) to receive two intramuscular doses of either NVX-CoV2373 ($n = 1491$) or placebo ($n = 756$) spaced 21 days apart. The safety analysis included 1487 recipients of NVX-CoV2373 and 745 placebo recipients. The median duration of safety follow-up after the second dose prior to blinded crossover was 71 days; solicited local and systemic AEs were collected for 7 days following each dose. Rates of solicited local and systemic AEs were higher in NVX-CoV2373 recipients following both doses 1 and 2 (65.5% and 75.3%, respectively) than in placebo recipients (28.5% and 20.6%, respectively). The most common solicited local AEs were tenderness and pain at the injection site (Figure 2c), which were mostly mild to moderate in severity and lasted a median of 2 days or less. The rates of solicited systemic AEs were also higher in NVX-CoV2373 recipients following doses 1 and 2 (55.2% and

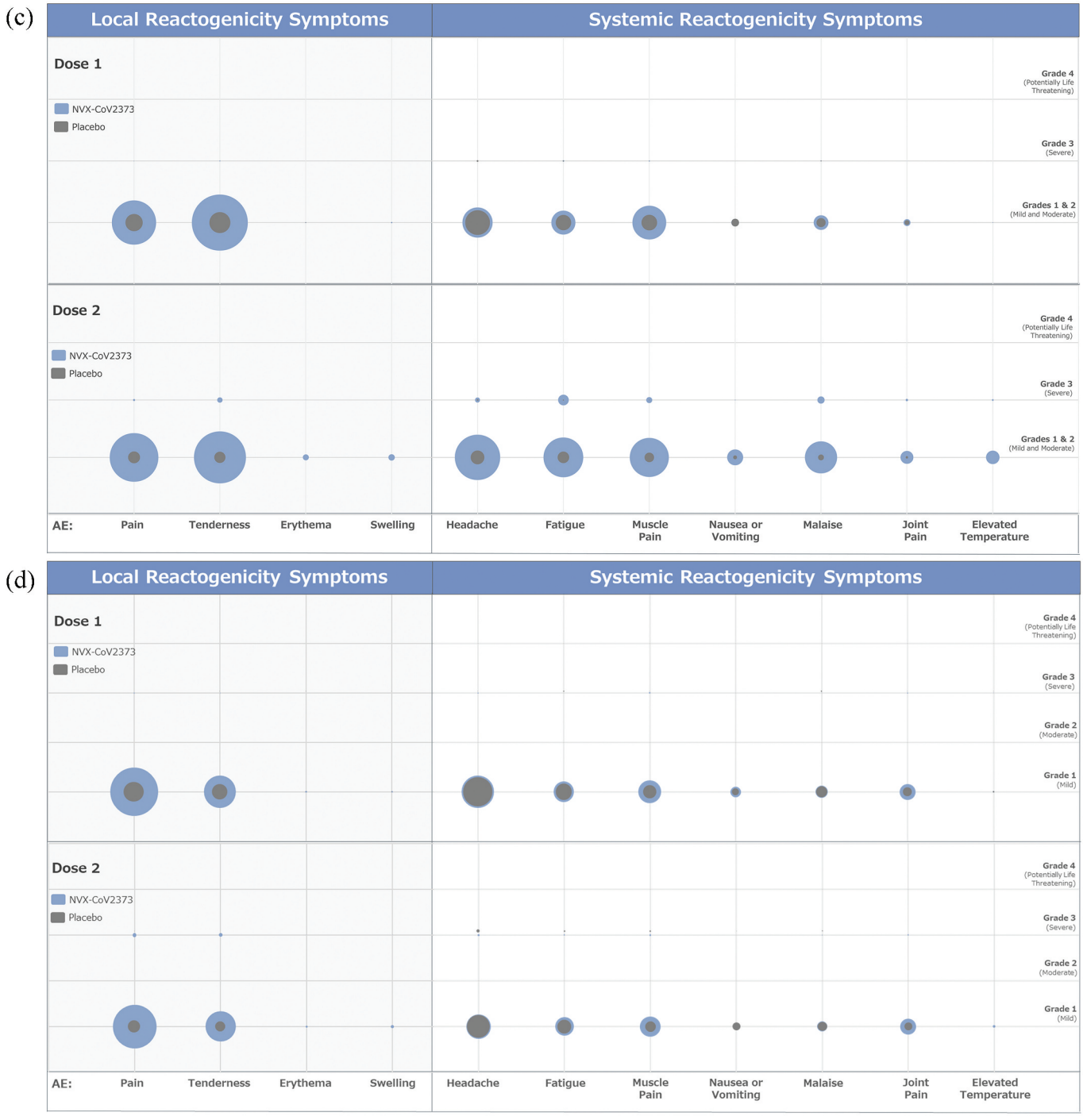

Figure 2. (Continued)

74.5%, respectively) than in placebo recipients (40.8% and 28.9%, respectively). The most common solicited systemic AEs were headache, fatigue, myalgia, and malaise (Figure 2c), which were mostly mild to moderate in severity and lasted a median of 2 days or less. Severe solicited systemic AEs, most commonly fatigue, occurred more frequently after dose 2 of NVX-CoV2373 (dose 1: NVX-CoV2373, 3.7%; placebo, 3.4%; dose 2: NVX-CoV2373, 22.0%; placebo, 3.4%). Similar percentages of NVX-CoV2373 and placebo recipients experienced unsolicited AEs (15.9% vs. 15.6%, respectively), severe TEAEs (0.4% vs. 0.3%, respectively), SAEs (0.5% vs. 0.3%, respectively), and MAAEs (6.5% vs. 6.8%, respectively). There were no reports of anaphylaxis, vaccine-enhanced COVID-19, Guillain-Barré syndrome, thrombosis with thrombocytopenia syndrome, or myocarditis/pericarditis [42].

2.2.1.4. Study 2019nCoV-501. Study 2019nCoV-501 was a randomized, observer-blinded, phase IIA/B study in which adults aged 18–84 years from 16 sites in South Africa were randomized (1:1) to receive two doses of either NVX-CoV2373

Table 2. Overview of clinical studies of NVX-CoV2373 included in this report.

Study name	Identifier	Phase	Population	Location	Design	Status
Study 2019nCoV-101	NCT04368988	I/II	Healthy adults (18–84 years)	Australia US	Randomized, observer-blinded, placebo-controlled	Ongoing
Study 2019nCoV-501	NCT04533399	II	Adults (18–84 years) with or without HIV	South Africa	Randomized, observer-blinded, placebo-controlled	Completed
PREVENT-19 (Study 2019nCoV-301)	NCT04611802	III	Healthy individuals aged ≥12 years	US and Mexico (≥18 years) US (≥12 years)	Randomized, observer-blinded, placebo-controlled	Ongoing
Study 2019nCoV-302	NCT04583995	III	Healthy adults (18–84 years)	UK	Randomized, observer-blinded, placebo-controlled	Completed

Note: UK, United Kingdom; US, United States.

Table 3. Overview of reports of myocarditis and/or pericarditis in PREVENT-19 and Study 302.

Study	Intervention	Gender	Age range, years	Preferred term	Time of onset	Comments	Outcome	FDA opinion
PREVENT-19 (Study 2019nCoV-301)	NVX-CoV2373	Male	65–70	Myocarditis (serious)	28 days after dose 1	Concomitant COVID-19 infection and acute kidney injury; peak troponin: 5329 ng/l	Resolved with sequelae	Relatively longer latency and diagnosis of COVID-19 support alternative etiology, although association with vaccine cannot be definitively excluded
		Male	20–25	Myocarditis and pericarditis (non-serious)	10 days after dose 1	Sore throat and fever 8 days prior; exposure to streptococcal pharyngitis; elevated anti-streptolysin O titers; troponin normal	Lost to follow-up	Although temporally related to vaccination, ARF and non-rheumatic streptococcal myocarditis are plausible alternative etiologies
		Male	15–20[a]	Myocarditis (serious)	2 days after dose 2	Preceding nonspecific viral illness and concomitant methylphenidate use; peak troponin: ~32,000 ng/l	Recovered/ resolved	Temporal relationship and lack of clear alternative etiology supports a concern for a causal relationship to vaccine
	Placebo	Female	30–35	Myocarditis (serious)	72 days after dose 2	Diarrhea and social history of alcohol intake; peak troponin: 0.33 ng/ml (normal <0.04)	Recovered/ resolved	Unrelated
Study 2019nCoV-302	NVX-CoV2373	Male	15–20	Myocarditis (serious)	2 days after dose 2	MRI consistent with myocarditis; peak troponin: ~7,800 ng/l; pharyngitis and lymphadenopathy reported 11 days later	Resolved	Temporal relationship and lack of clear alternative etiology supports a concern for a causal relationship to vaccine
		Female	60–65	Pericarditis (serious)	8 days after dose 1	Accompanied by fever, elevated white blood cell count and neutrophils; ECG consistent with pericarditis; troponin normal	Recovered/ resolved	Temporal relationship and lack of clear alternative etiology supports a concern for a causal relationship to vaccine

Note: [a]PREVENT-19 also includes an expansion cohort for adolescents aged 12–17 years.
AE, adverse event; ARF, acute rheumatic fever; COVID-19, coronavirus disease 2019; ECG, electrocardiogram; FDA, U.S. Food and Drug Administration; MI, myocardial infarction; MRI, magnetic resonance imaging.

or placebo spaced 21 days apart [37]. The safety analysis included 4164 HIV-negative participants (NVX-CoV2373, n = 2089; placebo, n = 2075) and 244 people living with HIV (PLWH) (NVX-CoV2373, n = 122; placebo, n = 122). Among NVX-CoV273 recipients that were seronegative for SARS-CoV -2 at baseline, frequencies of solicited local AEs were similar in HIV-negative individuals (dose 1, 30.6%; dose 2, 29.1%) and in PLWH (dose 1, 25.3%; dose 2, 32.1%). A similar pattern was observed for solicited systemic AEs (HIV-negative: dose 1, 28.7%; dose 2, 24.9%; PLWH: dose 1, 25.3%, dose 2: 15.4%). The most common solicited local and systemic AEs after doses 1 and 2 were pain, tenderness, headache, and fatigue (Figure 2d, Supplementary Figure s1). The frequencies of any unsolicited AEs (up to 49 days after the first dose) were similar in NVX-CoV2373 and placebo recipients, regardless of baseline SARS-CoV-2 or HIV status. Among participants seronegative for

SARS-CoV-2 at baseline, severe AEs occurred at a slightly higher frequency in PLWH (1.3%) versus in HIV-negative participants (0.4%); SAEs occurred in 0% and 0.1% of PLWH and HIV-negative participants, respectively, and MAAEs occurred in 3.8% and 0.9%, respectively. No myocarditis or pericarditis or potential immune-mediated conditions were reported.

2.2.2. Primary vaccination series co-administered with influenza vaccine

Initial evidence suggests the tolerable reactogenicity and favorable safety profile associated with the NVX-CoV2373 primary vaccination series is maintained when concomitantly administered with a seasonal influenza vaccine; a likely combination in preparation for future winter virus seasons. Study 2019nCoV-302 included a planned exploratory sub-study in which 217 NVX-CoV2373 recipients and 214 placebo recipients also received an age-appropriate seasonal influenza vaccine [41]. Participants were instructed to record local reactogenicity for only the NVX-CoV2373 or placebo injection site. Local and systemic AEs were more common following receipt of both vaccines. Local AEs occurred in 70.1% of participants who received both vaccines versus 39.4% of those who received placebo plus an influenza vaccine. In the main study, local injection site reactions occurred in 57.6% of those administered NVX-CoV2373 alone. Injection site tenderness was the most common local AE, reported in 64.9% of participants who received NVX-CoV2373 plus an influenza vaccine and in 53.3% of participants who received NVX-CoV2373 alone. Local reactogenicity events generally lasted 1 – 2 days in both treatment groups. Systemic AEs were reported in 60.1% of the NVX-CoV2373 plus influenza vaccine group, 47.2% of the placebo plus influenza vaccine group, and 45.7% of the group administered NVX-CoV2373 alone. The median duration of systemic AEs was approximately 1 day in both the NVX-CoV2373 plus influenza group and the NVX-CoV2373 alone group. The frequencies of unsolicited AEs (18.4%, 14.5%, and 17.6%, respectively), severe AEs (0.5%, 0%, and 0.4%, respectively), SAEs (0.5%, 0%, and 0.6%, respectively), and MAAEs (7.8%, 8.4%, and 3.8%, respectively) were generally low and balanced across the NVX-CoV2373 plus influenza vaccine, placebo plus influenza vaccine, and NVX-CoV2373 alone groups.

2.2.3. Homologous boosting

2.2.3.1. First booster (third dose). The reactogenicity and safety of NVX-CoV2373 given as a third (booster) dose have also been examined. Phase II of Study 2019nCoV-101 compared a two-dose, primary vaccination series of NVX-CoV2373 versus placebo in healthy adults aged 18–84 years in the US and Australia [32]. In a secondary analysis approximately 6 months later (day 189), 172 placebo recipients in the primary analysis received another dose of placebo (placebo/placebo/placebo), whereas those originally administered two doses of NVX-CoV2373 received either placebo (NVX-CoV2373/NVX-CoV2373/placebo; $n = 102$) or a booster dose of NVX-CoV2373 (NVX-CoV2373/NVX-CoV2373/NVX-CoV2373; $n = 105$) [36]. Solicited reactogenicity data were collected for 7 days following each dose of the primary vaccination series and the booster. The rate of solicited local AEs increased from 70% after the two-dose primary vaccination series to 82% after homologous boosting with NVX-CoV2373, with 5% and 13%, respectively, categorized as severe (grade ≥3). Solicited local AEs (any grade) persisted for a median of 1–2 days following the primary vaccination series and 2–2.5 days following the booster dose. In the week following the second versus third dose of NVX-CoV2373, the rates of any grade (53% vs. 77%, respectively) and grade ≥ 3 (6% vs. 15%, respectively) solicited systemic AEs also increased. During both post-vaccination periods, all solicited systemic AEs lasted a median of 1 day, except for muscle pain, which persisted a median of 2 days after the booster dose. Notably, the percentages of participants reporting an unsolicited AE in the 28 days following the booster dose were similar for the placebo/placebo/placebo (12%), NVX-CoV2373/NVX-CoV2373/placebo (14%), and NVX-CoV2373/NVX-CoV2373/NVX-CoV2373 (12%) groups, as were percentages with a severe AE (0%, 2%, and 0%, respectively), SAE (1%, 2.0%, and 1.0%, respectively), or MAAE (8%, 9%, and 6%, respectively). No case of myocarditis and/or pericarditis was reported.

2.2.3.2. Second booster (fourth dose). Study 2019nCoV-101 was extended to examine the reactogenicity and safety of a fourth NVX-CoV2373 dose as a second homologous booster to adults aged 18 – 84 years [43]. Forty-five recipients of the NVX-CoV2373 primary two-dose vaccination series and a booster (third dose) 6 months later (day 189), received a second NVX-CoV2373 booster (fourth dose) after another 6 months had elapsed (day 357). Solicited reactogenicity data were collected on the day the fourth dose was administered and for 6 days thereafter. Any-grade and grade ≥ 3 solicited local AEs were reported by 73% and 19% of participants, respectively, after the fourth NVX-CoV2373 dose compared to 82% and 13% after the third dose. Local reactions were short lived, with median durations of 2 days for pain, 3 days for tenderness and erythema, and 4 days for swelling. Solicited systemic reactions were reported by 68% (any grade) and 17% (grade ≥3) of participants following the fourth dose versus 77% and 15%, respectively, following the third dose. The incidence of fever was low (10%) with no grade ≥ 3 febrile events reported. Solicited systemic reactions were also short lived, with median durations of 1 day for fever and headache and 2 days for fatigue, malaise, joint pain, nausea/vomiting, and muscle pain. Unsolicited AEs occurred in 9% of participants in the 28 days following the second booster dose, none of which were severe or serious. No SAEs or MAAEs were reported after the fourth dose.

2.2.4. Reactogenicity and safety summary

Data from the above studies illustrate that vaccination with NVX-CoV2373 is associated with tolerable reactogenicity and favorable safety profiles characterized by mostly mild-to-moderate AEs of short duration and low rates of severe and serious AEs comparable to those with placebo, including following NVX-CoV2373 as a homologous booster. Importantly, the reactogenicity and safety profile of NVX-CoV2373 is largely maintained in PLWH [37–40]. Solicited local and systemic AEs occurred less frequently in those aged ≥65 years than in those aged 18–64 years [38–40]. Importantly, fever was not a common event after vaccination with NVX-CoV2373.

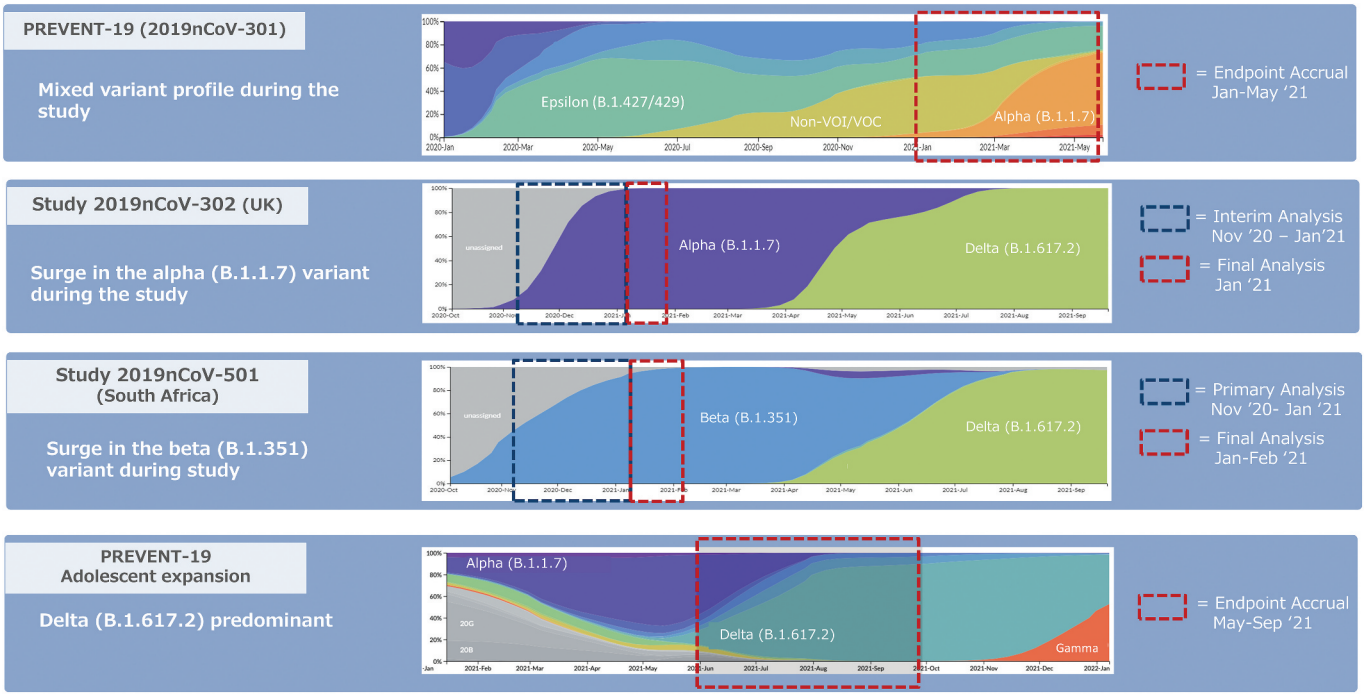

Figure 3. Evolution of SARS-CoV-2 variants during PREVENT-19 (adults and adolescent expansion) in the US, Study 2019nCoV-302, and Study 2019nCoV-501. Developed using nextrain.org. UK, United Kingdom; US, United States; VOC, variant of concern; VOI, variant of interest.

Corresponding incidence rates for unsolicited SAEs were lower for the younger versus older age group (3.68 vs. 8.48 events per 100 patient-years, respectively), with most SAEs in the older age group resulting from underlying conditions [40]. The favorable safety profile of NVX-CoV2373 was also preserved in study participants with comorbidities, such as obesity, chronic lung disease, diabetes, cardiovascular disease, and chronic kidney disease [38–40], and upon concomitant administration with an influenza vaccination [41].

2.3. Efficacy

2.3.1. Primary vaccination series studies

The efficacy of NVX-CoV2373 is especially noteworthy when considering the evolving viral epidemiology at the times the primary efficacy endpoint data were collected. As shown in Figure 3, variants of concern (VOCs) including alpha, beta, gamma, and delta, as well as unassigned variants, were circulating during the time of primary endpoint accrual where alpha was predominant during Study 2019nCoV-302 and PREVENT-19, beta was most prevalent during Study 2019nCoV-501, and delta was predominant during the PREVENT-19 adolescent expansion study.

2.3.1.1. Study 2019nCoV-302. In the per-protocol analysis of Study 2019nCoV-302 (NVX-CoV2373, $n = 7020$; placebo, $n = 7019$), 10 individuals randomized to NVX-CoV2373 and 96 randomized to placebo developed symptomatic COVID-19 over a median follow-up of 3 months, corresponding to a vaccine efficacy of 89.7% (95% confidence interval [CI], 80.2 – 94.6) (Table 4) [38]. Of the 10 cases of COVID-19 in NVX-CoV2373 recipients, one was mild, and nine were moderate in severity. In placebo recipients, 24, 57, and five individuals developed mild, moderate, and severe COVID-19, respectively. The efficacy of NVX-CoV2373 against alpha and non-alpha variants was 86.3% (95% CI, 71.3–93.5) and 96.4% (95% CI, 73.8–99.4), respectively. Study 2019nCoV-302 included a blinded crossover, and data from the start to the end of the placebo-controlled phase have also been reported [39]. By a median of 4.5 months post-vaccination (maximum, 7.5 months), 24 NVX-CoV2327 recipients and 134 placebo recipients developed COVID-19, yielding an efficacy rate of 82.7% (95% CI, 73.3 – 88.8) (Table 4). Vaccine efficacy was 100% (95% CI, 17.9–100.0) against severe disease (all six participants with severe COVID-19 received placebo), 79.2% (95% CI, 66.7–87.0) against moderate or severe disease, and 76.3% (95% CI, 57.4–86.8) against asymptomatic infection. A total of 231 participants (36 in the NVX-CoV2327 arm and 195 in the placebo arm) developed either symptomatic or asymptomatic infection, yielding a combined vaccine efficacy rate of 82.5% (95% CI, 75.0–87.7).

2.3.1.2. PREVENT-19 (Study 2019nCoV-301) – adults and adolescents. In the phase 3 PREVENT-19 study (median duration of placebo-controlled follow-up, 3 months), 14 cases of laboratory-confirmed COVID-19 occurred among the 17,312 NVX-CoV2373 recipients (mean incidence rate of 3.26/1000 patient years) compared with 63 cases among the 8140 placebo recipients (mean incidence rate of 34.01/1000 patient years) [40]. Thus, the NVX-CoV2373 efficacy against symptomatic disease in adults was 90.4% (95% CI, 82.9–94.6) (Table 4) at a time when alpha predominated with a mix of beta, gamma, epsilon, and iota SARS-CoV-2 variants in circulation (Figure 3). All 14 cases of COVID-19 in the NVX-CoV2373 arm were mild in severity. In the placebo arm, 49 cases were categorized as mild, 10 as moderate, and four as severe. NVX-CoV2373 efficacy against

Table 4. Efficacy of primary vaccination with NVX-CoV2373 in preventing symptomatic COVID-19.

Study name	Study reference	Population	Sub-study/ sub-population	Predominant viral variant	Per-protocol population	Symptomatic COVID-19 Cases, n	Symptomatic COVID-19 Vaccine efficacy, % (95% CI)
Study 2019nCoV-302	[38,39]	Healthy adults (18–84 years)	Main study: NVX-CoV2373 alone	Alpha	NVX-CoV2373 ($n = 7020$)	10	89.7 (80.2–94.6)[a]
					Placebo ($n = 7019$)	96	
					NVX-CoV2373 ($n = 7020$)	24	82.7 (73.3 – 88.8)[b]
					Placebo ($n = 7019$)	134	
			Sub-study: NVX-CoV2373 + influenza vaccine	Alpha	NVX-CoV2373 + influenza vaccine ($n = 191$)	2	80.6 (11.7–95.7)[b]
					Placebo + influenza vaccine ($n = 195$)	10	
PREVENT-19 (Study 2019nCoV-301)	[40]	Healthy adults and adolescents	Healthy adults (≥18 years)	Mixed	NVX-CoV2373 ($n = 17,312$)	14	90.4 (82.9–94.6)[c]
					Placebo ($n = 8140$)	63	
			Healthy adolescents (12 to <18 years)	Delta	NVX-CoV2373 ($n = 1491$)	6	79.5 (46.8 – 92.1)[c]
					Placebo ($n = 756$)	14	
Study 2019nCoV-501	[44]	Adults (18–84 years) ± HIV	HIV-positive	Beta	NVX-CoV2373 ($n = 76$)	4	Not reported
					Placebo ($n = 72$)	2	
			HIV-negative		NVX-CoV2373 ($n = 1281$)	11	60.1 (19.9–80.1)[d]
					Placebo ($n = 1255$)	27	

Note: [a]The median duration of follow-up was 3 months.
[b]The median duration of follow-up at completion of placebo-controlled phase was 4.5 months, with maximum of 7.5 months.
[c]The median duration of follow-up was 2 months.
[d]Data are preliminary, with follow-up occurring a median of 66 days after dose 1 and 45 days after dose 2. CI, confidence interval; COVID-19, coronavirus disease 2019.

moderate-to-severe COVID-19 was 100% (95% CI, 87.0–100). The efficacy of NVX-CoV2373 against any VOC or variant of interest was 92.6% (95% CI, 83.6–96.7); for the alpha variant specifically, NVX-CoV2373 was associated with an efficacy of 93.6% (95% CI, 81.7–97.8). In a *post hoc* analysis of data from PREVENT-19, vaccine efficacy against hospitalization in an expanded efficacy analysis population was 100% (95% CI, 83.1–100) [45].

In the per-protocol analysis of the PREVENT-19 adolescent expansion, the efficacy of NVX-CoV2373 in adolescents aged 12 to <18 years was 79.5% (95% CI, 46.8–92.1) (Table 4) at a time when delta was the predominant SARS-CoV-2 variant in circulation (Figure 3) [42]. All cases of COVID-19 (six in the NVX-CoV2373 arm, 14 in the placebo arm) were mild; thus, efficacy against moderate-to-severe COVID-19 could not be determined.

2.3.1.3. Study 2019nCoV-501. In a preliminary analysis of Study 2019nCoV-501 (NVX-CoV2373, $n = 1357$; placebo, $n = 1327$), the efficacy of NVX-CoV2373 in preventing mild-moderate symptomatic COVID-19 mainly due to the beta VOC was 49.4% (95% CI, 6.1–72.8) among participants who were seronegative for SARS-CoV-2 at baseline [44]. The substantially lower efficacy seen in this phase II trial relative to the PREVENT-19 and 2019nCoV-302 trials is likely due to several factors, including, but not limited to, the inclusion of PLWH ($n = 148$) and the predominance (>90%) of a SARS-CoV-2 neutralizing antibody escape variant (beta) in South Africa at the time of primary data collection (Figure 3). In the subgroup of participants who were HIV-negative and seronegative for SARS-CoV-2 at baseline (NVX-CoV2373, $n = 1281$; placebo, $n = 1255$), vaccine efficacy was 60.1% (95% CI, 19.9–80.1) (Table 4). In a *post hoc* analysis, efficacy against the beta variant was 51.0% (95% CI, −0.6 to 76.2) among HIV-negative participants and 43.0% (95% CI, −9.8 to 70.4) in the combined HIV-negative and PLWH population. Notably, all cases of COVID-19 reported in Study 2019nCoV-501 were mild or moderate, except for one case of severe disease in the placebo arm [44].

2.3.2. Primary vaccination series co-administered with influenza vaccine

Protective efficacy of NVX-CoV2373 appears to be maintained when co-administered with an influenza vaccine. In the per-protocol analysis of the Study 2019nCoV-302 sub-study, which involved dosing with an age-appropriate influenza vaccine plus either NVX-CoV2373 ($n = 191$) or placebo ($n = 195$), the efficacy against symptomatic COVID-19 was 74.8% (95% CI, −19.7% to 94.7%) at a median follow-up of 3 months (Table 4) [41] and was not significantly different from the efficacy of NVX-CoV2373 in the main study (i.e. without concurrent influenza vaccine) of 89.7% (95% CI, 80.2–94.6) at the same follow-up period [38]. Among study participants aged 18–64 years, the efficacy of NVX-CoV2373 was 87.5% (95% CI, −0.2 to 98.4) in the influenza sub-study and 89.8% (95% CI, 79.7–95.5) in the main study [41]. On completion of the placebo-controlled phase of this crossover study (median follow-up, 4.5 months), NVX-CoV2373 efficacy was 80.6% (95% CI, 11.7 – 95.7) [39].

2.3.3. Efficacy summary

In two large, geographically distinct, phase III clinical trials, a primary vaccination series with NVX-CoV2373 was associated with complete protection against severe disease and a high (~90%) level of protection against symptomatic disease in adults, including symptomatic disease caused by viral variants [38,40]. Moreover, the efficacy of NVX-CoV2373 was maintained in various demographic subpopulations. In PREVENT-19 and/or Study 2019nCoV-302, the protective efficacy of NVX-CoV2373 against symptomatic disease was 88.9% (95% CI, 12.8–98.6) in the elderly (65–84 years), 90.9% (95% CI, 70.4–97.2) in those with comorbidities, and 91% (95% CI, 83.6–95.0)

in those at high risk of COVID-19 (individuals aged ≥65 years, those with chronic health conditions, or those at increased risk of COVID-19 because of work or living conditions) [38,40]. The efficacy of NVX-CoV2373 in adolescents aged 12 to <18 years was 80%, with all cases of mild severity and caused by the delta variant [42]. In a preliminary analysis of phase IIA/B Study 501 in adults with and without HIV, the efficacy of NVX-CoV2373 was 49% overall and 60% in HIV-negative individuals; there were no severe cases in the vaccine group [44].

Although developed using the spike protein from the SARS-CoV-2 ancestral strain, the above studies show NVX-CoV2373 is also clinically effective against VOCs, including alpha, beta and delta. Importantly, a high rate of NVX-CoV2373 efficacy (80.6%) is maintained upon co-administration with an influenza vaccine [39].

2.4. Immunogenicity and neutralizing activity

2.4.1. Primary vaccination series studies

The immunogenicity of a primary vaccination series with NVX-CoV2373 was demonstrated to translate into high clinical efficacy [38–40,44].

2.4.1.1. Study 2019nCoV-302. Immunogenicity was assessed for per-protocol subsets of Study 2019nCoV-302 participants [39]. Serum anti-S-protein IgG levels were assessed for 831 participants (NVX-CoV2373, $n = 414$; placebo, $n = 417$). At day 35 (14 days after dose 2), geometric mean concentrations of anti-spike IgG were increased in the NVX-CoV2373 arm versus placebo across all age groups. For participants who received NVX-CoV2373 and were initially seronegative, anti-spike IgG levels increased 398-fold from baseline in participants aged 18 – 84 years, 425-fold in those aged 18 – 64 years, and 336-fold in those aged 65 – 84 years. Neutralizing antibody responses against the ancestral strain were assessed for 761 participants (NVX-CoV2373, $n = 381$; placebo, $n = 380$). At day 35 for participants who received NVX-CoV2373 and were initially seronegative, geometric mean titers of neutralizing antibodies had increased from baseline 112-fold, 124-fold, and 87-fold in those aged 18 – 84 years, 18 – 64 years, and 65 – 84 years, respectively.

2.4.1.2. Study 2019nCoV-501. The results from Study 2019nCoV-501 showed immunologic responses to NVX-CoV2373 are attenuated in PLWH relative to their HIV-negative counterparts [37]. In a per-protocol analysis performed at day 35 in the subgroup of NVX-CoV2373 recipients who were seronegative for SARS-CoV-2 at baseline, the geometric mean levels of anti-spike IgG were 14,420.5 ELISA Units (EU)/ml in PLWH ($n = 101$) and 31,631.8 EU/ml in those negative for HIV ($n = 1945$), corresponding to fold increases from baseline of 123 and 283.7, respectively. Despite the relative difference in antibody generation, the percentages of PLWH and HIV-negative patients who experienced seroconversion at day 35 were high and comparable (100% and 99.3%, respectively); seroconversion rates (percentage of participants with a ≥ 4-fold higher antibody level on day 35 vs day 0) for antibodies with neutralizing activity against the ancestral strain were 70.5% and 83.6%, respectively. Interestingly, in the subgroup of patients who were seropositive for SARS-CoV-2 at baseline, the geometric mean levels of anti-spike IgG at baseline were similar in PLWH and in HIV-negative individuals (1852.9 and 1713.0 EU units/ml, respectively). This similarity persisted following vaccination with NVX-CoV2373, as IgG levels at day 35 against the SARS-CoV-2 spike protein increased by 53.1-fold in PLWH and by 56.1-fold in the HIV-negative group. The seroconversion rates at day 35 were 92.3% and 97.3%, respectively, with neutralizing antibody seroconversion rates of 92.1% and 95.7%.

2.4.1.3. Study 2019nCoV-101. Study 2019nCoV-101 demonstrated that a two-dose, primary vaccination series with NVX-CoV2373 elicits a robust immunogenic response, as measured by IgG levels against the SARS-CoV-2 spike protein [31,32]. Phase I of Study 2019nCoV-101 examined the immunogenicity and neutralizing antibody activity elicited by vaccination regimens that included one or two doses, 5 µg or 25 µg rSARS-CoV-2 S-protein, and formulation with or without Matrix-M adjuvant, versus placebo [31]. By day 35, 14 days after the second dose, the largest IgG responses had occurred with regimens that included two doses of 5 µg or 25 µg rSARS-CoV-2 S-protein adjuvanted with Matrix-M. Geometric mean increases in anti-spike IgG levels relative to baseline were comparable for these two regimens (556.0- and 413.8-fold increases, respectively), highlighting the role of adjuvant sparing. The geometric mean concentration of anti-spike IgG over time with two doses of 5 µg rSARS-CoV-2 S-protein adjuvanted with Matrix-M (NVX-CoV2373) is summarized in Supplementary Figure S2A. Neutralizing antibodies were undetectable in all groups prior to vaccination. The geometric mean of neutralizing antibody titers over time among NVX-CoV2373 recipients is summarized in Supplementary Figure S2B. Relative to baseline, the neutralizing activity of antibodies against the ancestral strain of SARS-CoV-2 increased by five-fold at day 21 and by 195-fold at day 35 among NVX-CoV2373 recipients. To put these data into clinical perspective, the geometric mean titer of neutralizing antibody responses 2 weeks after the second dose of 5 µg adjuvanted rSARS-CoV-2 S-protein was approximately four-fold greater than that in serum from outpatients convalescing from symptomatic COVID-19 (geometric mean titer, 3906 vs. 837) and approximately two-fold lower than in convalescing hospitalized patients (geometric mean titer, 3906 vs. 7457).

In phase II of Study 2019nCoV-101, participants were administered one- or two-dose vaccination regimens formulated with Matrix-M and 5 µg or 25 µg rSARS-CoV-2 S-protein or two doses of placebo [32]. At day 35, participants in the per-protocol population who had received two doses of either 5 µg or 25 µg adjuvanted rSARS-CoV-2 S-protein had the largest and equivalent increases in anti-spike IgG geometric mean concentrations (385.6- and 384.9-fold increases from baseline, respectively, based on per-protocol analysis set) with seroconversion rates of 98.3% and 99.6%, respectively. Immunogenicity data for participants who received the formulation of NVX-CoV2373 now authorized for use (5 µg of adjuvanted SARS-CoV-2 S-protein) are summarized in Figure 4a. Although the immunogenicity of the two-dose NVX-CoV2373 formulation (5 µg adjuvanted rSARS-CoV-2 S-protein)

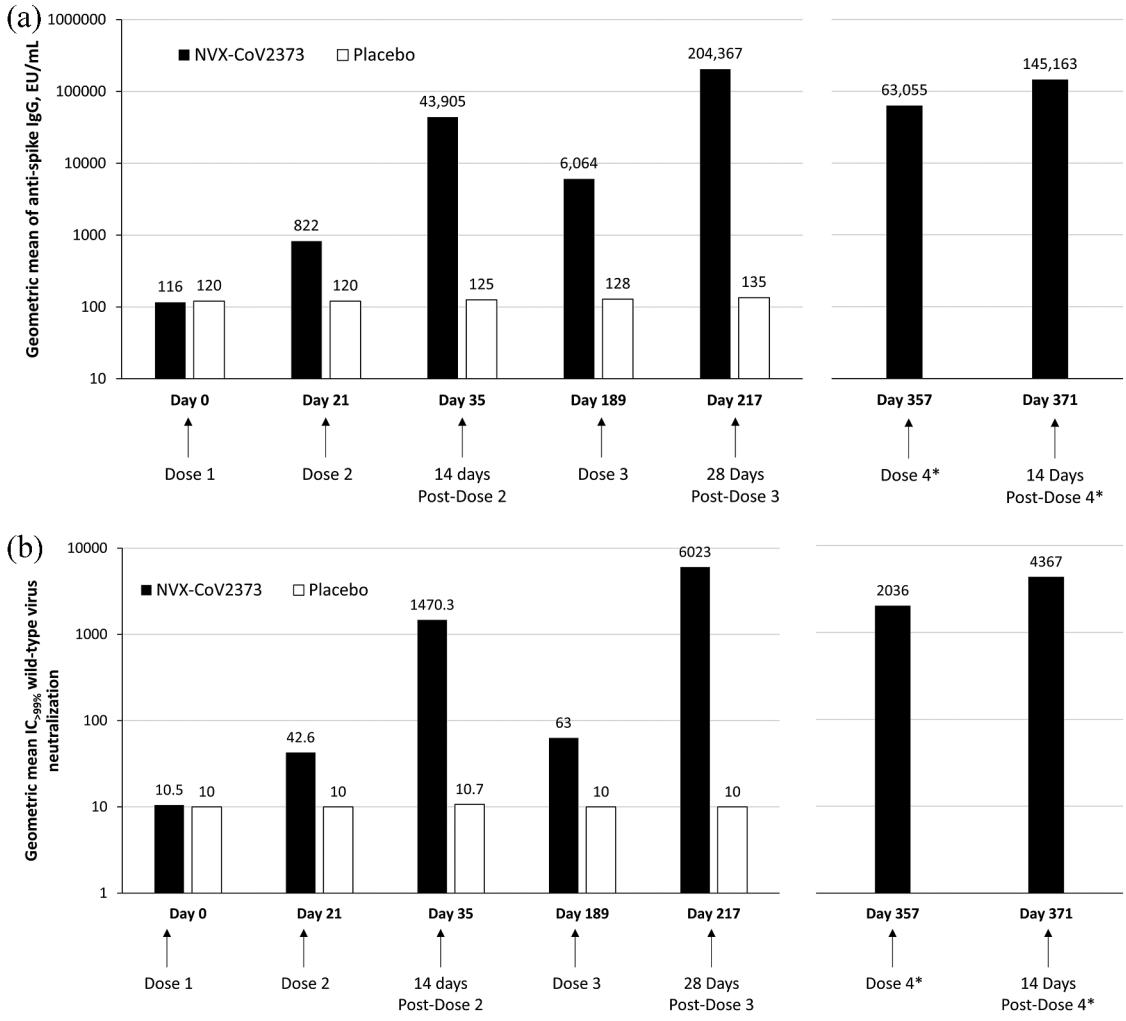

Figure 4. Study 2019nCoV-101 immunogenicity of NVX-CoV2373 over time [36,43]. (a) Geometric mean titer IgG response. (b) Geometric mean titer neutralizing antibody response. [a]Indicates that data were not reported for placebo. EU, enzyme-linked immunosorbent assay units; $IC_{>99\%}$, inhibitory concentration > 99%; IgG, immunoglobulin G; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

was greater in participants aged 18–59 years versus those aged 60–84 years, robust increases in anti-S protein IgG levels were seen in both age groups (18–59 years, 538.6-fold increase from baseline; 60–84 years, 257.7-fold increase from baseline). Neutralizing antibody responses against the ancestral strain at day 35 were also similar in participants who had received two doses of either 5 µg or 25 µg adjuvanted rSARS-CoV-2 S-protein. In NVX-CoV2373 recipients aged 18–59 years, neutralizing antibody titers increased 220-fold between baseline and day 35, with 100% seroconversion. Neutralizing antibody data for NVX-CoV2373 recipients who received the formulation now authorized for use (5 µg of adjuvanted SARS-CoV-2 S-protein) are summarized in Figure 4b. Although neutralizing antibody titer increases were not as large in participants aged 60–84 years (98-fold increase), the seroconversion rate (100%) was equivalent to that in the younger age group.

2.4.2. Homologous boosting

2.4.2.1. First booster (third dose). Homologous boosting with a third dose of NVX-CoV2373 has been shown to increase and broaden the immune response elicited by the two-dose, primary vaccination series [36]. In the secondary analysis of phase II of Study 2019nCoV-101, antibody levels against the SARS-CoV-2 spike protein were measured 2 weeks after completion of the primary vaccination series (day 35), approximately 6 months after completion of the primary vaccination series but prior to the booster dose (day 189), and 28 days following boosting (day 217). In a per-protocol analysis of the 101 participants who received three doses of NVX-CoV2373 (two primary doses and one booster dose), levels of IgG specific to the spike protein from the ancestral SARS-CoV-2 strain decreased from 43,905 EU/ml at day 35 to 6064 EU/ml at day 189 (Figure 4a). At day 217, anti-S IgG levels had increased to 204,367 EU/ml, a level approximately 4.7-fold higher than that measured 2 weeks after completion of the primary vaccination series (i.e. day 35), approximately 33.7-fold higher than levels observed prior to boosting (i.e. day 189), and consistent with levels associated with approximately 90% efficacy in phase III studies. Of note, the fold increases in SARS-CoV-2–specific antibodies between day 35 and day 217 were numerically greater in the older versus younger age group (5.1-fold vs. 4.1-fold). Vaccine-elicited neutralizing antibodies specific to the

ancestral strain increased 4.1-fold between day 35 and day 217 (Figure 4b), with similar increases in participants aged 60–84 years and 18–59 years (4.0-fold and 3.8-fold increase, respectively).

Phase II of Study 2019nCoV-101 enrolled from August to September 2020 [32,36]. Later that year, the first SARS-CoV-2 VOCs appeared [46]. Given the emergence of VOCs, additional immunogenicity tests were performed during the booster study [36]. Levels of IgG specific to the beta variant spike protein were assessed and found to increase approximately 40.6-fold from day 189 (4317 EU/ml) to day 217 (175,190 EU/ml); IgG levels at day 217 were 4.0-fold higher than levels measured against the ancestral strain at day 35. Neutralizing antibodies specific to the beta variant increased approximately 50.8-fold from day 189 to day 217, although titers were lower than those measured against the ancestral strain at day 35. An *in vitro* functional assay was also used to assess the ability of NVX-CoV2373–induced IgG to inhibit binding of the spike protein from the ancestral strain and VOCs to angiotensin-converting enzyme 2 (ACE2), a human transmembrane protein used by SARS-CoV-2 to enter cells. Between day 189 and day 217, titers of ACE2 binding-inhibitory antibodies increased 54-fold when measured with spike protein of the ancestral strain, 22-fold with spike protein of the alpha variant, 25-fold with spike protein of the beta variant, 24-fold with spike protein of the delta variant, and 20-fold with spike protein of omicron variant BA.1. Importantly, the NVX-CoV2373 booster dose increased titers of ACE2 binding-inhibitory antibodies against VOCs to levels higher than measured at day 35 following the two-dose primary vaccination series. These data suggest NVX-CoV2373 has the potential to confer broad cross-protection against new and emerging SARS-CoV-2 strains, and administration of a booster (third) dose increases that potential.

2.4.2.2. Second booster (fourth dose). The secondary analysis of phase II of Study 2019nCoV-101 was extended to examine the immunogenicity of a fourth NVX-CoV2373 dose administered as a second homologous booster to adults 18 – 84 years of age [43,47]. Forty-five participants who received the NVX-CoV2373 primary two-dose vaccination series and as a booster (third dose) 6 months later (day 189), were administered a second NVX-CoV2373 booster (fourth dose) after another 6 months (day 357). Following a moderate decrease in anti-spike IgG levels in the 6 months following the third dose, titers were restored by 2 weeks after the fourth dose (day 371) to those observed after the third dose (day 217) (Figure 4a). Neutralizing antibody titers following the fourth dose were also similar to those observed after the third dose (Figure 4b). For both the anti-spike protein IgG levels and the neutralizing antibody titers following the fourth dose, a similar response to the ancestral strain was observed in response to Omicron BA.1 and BA.4/BA.5 variants [43].

2.4.3. Primary vaccination series co-administered with influenza vaccine

The immunogenicity of primary vaccination with NVX-CoV2373 was somewhat reduced when co-administered with an influenza vaccine [41]. At day 35 (2 weeks after the second primary dose), the geometric mean concentration of IgG specific to the SARS-CoV-2 spike protein was 31,236.1 EU/ml in the per-protocol NVX-CoV2373 plus influenza vaccine group from the influenza sub-study of Study 2019nCoV-302 ($n = 178$) compared with 44,678.3 EU/ml in the per-protocol NVX-CoV2373 alone group from the main study ($n = 414$), corresponding to a ratio of 0.57 (adjusted for baseline EU, age, and treatment group). Although the geometric mean fold-rise in anti-spike IgG relative to baseline was lower in the NVX-CoV2373 plus influenza vaccine cohort than in NVX-CoV2373 alone cohort (268.6 vs. 398.4 EU/ml), robust increases over baseline occurred in both groups. The anti-spike IgG seroconversion rate at day 35 was 98% among participants who received both NVX-CoV2373 and an influenza vaccine. Based on hemagglutination inhibition titers at day 21 (3 weeks after co-administration of the first dose of NVX-CoV2373 and the influenza vaccine), the magnitude of the humoral response to influenza vaccination was not affected by co-administration with NVX-CoV2373.

2.4.4. Immunogenicity and neutralizing activity summary

Data from the above studies show the NVX-CoV2373 two-dose primary vaccination series results in a robust increase in neutralizing antibody titers and anti-spike protein IgG, regardless of baseline SARS-CoV-2 serostatus, HIV status, age, or co-administration with an influenza vaccine [31,32,37,39]. Administration of an NVX-CoV2373 booster (third dose) resulted in 4.7- and 4.1-fold increases, respectively, in anti-spike IgG levels and neutralizing antibody titers relative to peak levels 2 weeks following the two-dose primary vaccination series [36]. Although higher anti-spike levels were produced in younger versus older vaccine recipients, seroconversion rates were equivalent (99 – 100% in both age groups) [32,39]. In addition, ACE2 binding-inhibition assays demonstrate the capacity of NVX-CoV2373–induced IgG to prevent the high-affinity binding of ACE2 to the spike protein from alpha, beta, delta, and omicron VOCs [36].

3. Conclusion

Based on the available clinical data, collected from >25,000 adults in placebo-controlled, randomized clinical trials, NVX-CoV2373 has a tolerable reactogenicity profile and a favorable safety profile, is highly immunogenic, and it is effective in preventing SARS-CoV-2 infection and severe COVID-19. The most common AEs associated with NVX-CoV2373 were mild to moderate (grade 1–2), transient (1–2 days), local injection site reactions. NVX-CoV2373 was clinically effective against the ancestral strain of SARS-CoV-2, as well as VOCs, including the alpha and beta variants [38–40,44]. A two-dose primary vaccination series results in robust increases in neutralizing antibody titers and anti-spike protein IgG [31,32,37,39]. In addition, NVX-CoV2373–induced IgG inhibits binding of the spike protein from alpha, beta, delta, and the highly transmissible Omicron BA.1 and BA.2 subvariants to hACE2 [36]. Collectively, these data suggest that NVX-CoV2373 can provide broad protection against established and emerging SARS-CoV-2 variants. Notably, NVX-CoV2373 efficacy is maintained in various subpopulations (e.g. elderly, individuals with

chronic comorbidities). Based on data from PREVENT-19, NVX-CoV2373 was authorized by the FDA, European Medicines Agency, and other regulatory agencies for emergency use in adolescents aged 12–17 years [5,42,48]. Compared with titers measured after completion of the primary vaccination series, homologous boosting with NVX-CoV2373 provides increased levels of both binding and neutralizing antibodies against the SARS-CoV-2 spike protein [36]. In the sub-study of Study 2019nCoV-302, co-administration of NVX-CoV2373 and an age-appropriate influenza vaccine in opposite deltoids did not impact seroconversion rates for either vaccine, making co-administration a viable option [41]. EUA of NVX-CoV2373 marks the first adjuvanted recombinant protein-based COVID-19 vaccine available for use in the US. Produced using an established vaccine technology, NVX-CoV2373 has the potential to improve immunization rates by offering another choice to potential vaccine recipients.

4. Expert opinion

4.1. Efficacy and safety of COVID-19 vaccines available in the US

The efficacy of the several vaccines available in the US needs to be viewed in the context of the rapidly evolving pandemic during which the phase III studies were conducted. In 2020, when the studies of BNT162b2, mRNA-1273, and Ad26.COV2.S were conducted, the predominant circulating SARS-CoV-2 strain was the ancestral Wuhan-Hu-1 strain on which all of the vaccines were based. By early 2021, at the time the NVX-CoV2373 studies were conducted, new variants had begun to emerge, such that the alpha variant was the predominant circulating strain in the UK and the US/Mexico where Study 2019nCoV-302 and PREVENT-19 were conducted. The continued emergence of immune-evading variants has led to significant challenges in the understanding of relative vaccine efficacy among the available vaccines.

In the Study 2019nCoV-302 and PREVENT-19 phase III, two-dose primary vaccination studies, NVX-CoV2373 efficacy against confirmed symptomatic mild, moderate, or severe COVID-19 in adults aged ≥18 years was 89.7% (95% CI, 80.2 – 94.6) and 90.4% (95% CI, 82.9 – 94.6), respectively, at a median follow-up of 3 months, and 82.7% (95% CI, 73.3 – 88.8) at up to 7.5 months follow-up (median, 4.5 months) [38–40]. In phase III trials of two-dose primary vaccination series with the mRNA-based BNT162b2 (aged ≥16 years) and mRNA-1273 (aged ≥18 years) vaccines, efficacy was 95.0% (95% CI, 90.3 – 97.6) and 94.1% (95% CI, 89.3 – 96.8), respectively, at a median follow-up of 2 months, and 91.3% (95% CI, 89.0 – 93.2) and 93.2% (91.0 – 94.8), at 5- to 6-month median follow-up [49–51]. Efficacy with single-dose AD26.COV2.S primary vaccination was 66.9% (95% CI, 59.0 – 73.4) and 56.3% (95% CI, 51.3 – 60.8) at median follow-up of 2 and 4 months, respectively [52,53]. The estimated efficacy of NVX-CoV2373 against the ancestral SARS-CoV-2 strain was 96.4% (95% CI, 73.8 – 99.5) at 3-month median follow-up, similar to the efficacies reported for BNT162b2 (95.0%) and mRNA-1273 (94.1%) against this strain at 2-month median follow-up [38,49,50].

With all COVID-19 vaccines currently available in the US, mild to moderate local and systemic adverse effects are common and AESIs are rare [36,38–40,49–53]. Following post-marketing reports of myocarditis and pericarditis among recipients of the first generation of COVID-19 vaccines (mRNA- and viral vector-based), regulators and sponsors started looking more closely at these AESIs in clinical trials of investigational COVID-19 vaccines. Although there appears to be an increased risk of myocarditis and pericarditis with COVID-19 vaccines, it is small relative to that seen following infection with SARS-CoV-2, with most cases mild or moderate in clinical severity [54–57]. In a self-controlled analysis, 1–6 excess cases of myocarditis per 1 million individuals were estimated to occur in the 28 days following administration of the first dose of an mRNA-based (BNT162b2 or mRNA-1273) or adenovirus-vectored (ChAdOx1 [AstraZeneca-Oxford]) vaccine compared with 40 cases per 1 million individuals infected with SARS-CoV-2 [55]. Neither the first nor second dose of ChAdOx1 nCoV-19, BNT162b2, or mRNA-1273 was associated with an excess in pericarditis, whereas infection with SARS-CoV-2 was estimated to result in an additional 6 cases per 1 million patients. Therefore, health and regulatory authorities concluded that the benefits of vaccination against SARS-CoV-2 outweigh the risks [58–60]. To date, there have been five reports of myocarditis and/or pericarditis among clinical trial participants administered NVX-CoV2373, summarized in Table 3. However, determination of the true NVX-CoV2373–associated risk of these rare events requires ongoing evaluation in the post-marketing setting.

4.2. Advantages of NVX-CoV2373

The WHO's Global COVID-19 Vaccination Strategy set a goal to vaccinate 70% of the world's population by mid-2022 to 'protect people everywhere from disease, protect the health system, fully restart economies, restore the health of society, and lower the risk of new variants' [61]. Despite the success of COVID-19 vaccines in blunting the effects of the pandemic, much of the world has not reached this goal. Only 68% of the world population and 24% of people in low-income countries have received one or more COVID-19 vaccine doses [62]. In the US, only 69% of the population has completed a primary vaccination series, and only 10% have received an updated bivalent booster dose [63]. In addition to its high efficacy rate and favorable safety profile, NVX-CoV2373 provides several advantages in overcoming some barriers to vaccination. In the US, where COVID-19 vaccines are readily available, safety fears due to the novelty of the mRNA platform have been a cause of vaccine hesitancy [64]. A US-based survey of 400 individuals hesitant to receive any available COVID-19 vaccines in early 2022 revealed that 55% would likely receive a protein-based vaccine [11]. With its traditional protein-based platform, NVX-CoV2373 provides an alternative for those with hesitancy toward newer technologies. NVX-CoV2373 also provides a solution for those who are allergic to components of other COVID-19 vaccines. The freezing temperatures (as low as – 90°C) required to maintain stability of mRNA-based COVID-19

vaccines may be impracticable in remote and low-income regions. As vaccine storage requirements are an important component of global vaccine equity and sustainability, a shelf life of 9 months at 2 – 8°C with NVX-CoV2373 provides a means to increase global vaccination coverage [65]. Importantly, antigenic distance mapping of neutralization titers specific to multiple SARS-CoV-2 variants shows increased coverage against forward shift variants with each NVX-CoV2373 booster dose, in which the factor difference for ancestral vs Omicron BA.4 or BA.5 strains was 33.5 for dose 2, 7.1 for dose 3, and 3.5 for dose 4, indicating a decreasing antigenic distance with each booster dose [43]. NVX-CoV2373-induced antibodies have also shown neutralization of Omicron sub-lineages BA.1 and BA.4/BA.5 [66]. Thus, NVX-CoV2373 offers a potential alternative to mRNA-based bivalent boosters. Furthermore, the well-characterized recombinant protein vaccine technology used for manufacture of NVX-CoV2373 plus Matrix-M adjuvant affords ongoing flexibility and timeliness to respond to evolving SARS-CoV-2 immune escape variants. Currently, studies are ongoing to evaluate vaccine efficacy and immunogenicity against rapidly emerging VOCs, immunocompromised PLWH (NCT05112848), and the Hummingbird study in children down to 6 months of age (NCT05468736). Finally, post-authorization global safety monitoring and evaluation is ongoing including during pregnancy through evaluation of Phase III clinical trial data and the COVID-19 Vaccines International Pregnancy Registry (C-VIPER).

Abbreviation List

ACE2	angiotensin-converting enzyme 2
AE	adverse event
AESI	adverse event of special interest
ARF	acute rheumatic fever
CI	confidence interval
COVID-19	coronavirus disease 2019
ECG	electrocardiogram
EU	enzyme-linked immunosorbent assay units
EUA	emergency use authorization
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	U.S. Food and Drug Administration
hACE2	human angiotensin-converting enzyme 2
$IC_{>99\%}$	inhibitory concentration > 99%
IgG	immunoglobulin G
MAAE	medically attended adverse events
MI	myocardial infarction
MRI	magnetic resonance imaging
PACTR	Pan African Clinical Trials Registry
PLWH	people living with HIV
rS	recombinant spike
SAE	serious adverse events
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Sf9	*Spodoptera frugiperda*
TEAE	treatment-emergent adverse events
UK	United Kingdom
US	United States
VOC	variant of concern
VOI	variant of interest
WHO	World Health Organization

Acknowledgments

Medical writing support for the development of this review, under the direction of the authors, was provided by Tiffany DeSimone, PhD, CMPP; Carol Duffy, PhD, and Kelly Cameron, PhD, CMPP, of Ashfield MedComms (US), an Inizio company, which was funded by Novavax, Inc. The authors would like to thank Anthony Marchese, PhD, of Novavax, Inc. for his support and expertise updating the manuscript after peer review. Research support was provided by Sharon Glass of Novavax, Inc.

Funding

This manuscript was funded by Novavax, Inc.

Declaration of interest

R M. Mallory, S Galbiati, K Alves, S Toback, G Áñez, L M. Dunkle, A McGarry, W Woo, V Shinde, C Bennett, E Underwood, K Smith, L Fries, I Cho, G M. Glenn, and G Chau are or were all employees or contractors of Novavax and as such received compensation for their work, and might be shareholders of Novavax, Inc. S A. Madhi reports receiving grant support, paid to his institution, from Bill and Melinda Gates Foundation, Novavax, Pfizer, GlaxoSmithKline, and MinervaX, and receiving honoraria from Sanofi for lecture (unrelated to the current study). P T. Heath reports receiving grant support, paid to his institution, from Novavax, Pfizer, Moderna, Valneva, Astra Zeneca, and MinervaX. K L. Kotloff reports receiving grant support, paid to her institution, from NIAID for her work on the vaccine trial. C L. Gay reports receiving grant support, paid to her institution, from NIAID for her work on the vaccine trial. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or material discussed in the manuscript apart from those disclosed.

Information resources

Further information on NVX-CoV2373 clinical trials can be found at the study registration sites, including:

- ClinicalTrials.gov: https://clinicaltrials.gov/
- European Union Drug Regulating Authorities Clinical Trials Database (EudraCT): https://eudract.ema.europa.eu/
- Pan African Clinical Trials Registry (PACTR): https://pactr.samrc.ac.za/

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

Eddie Underwood developed the first draft of the manuscript. All other authors reviewed/revised the manuscript.

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