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A Brighton Collaboration standardized template with key considerations for a benefit/risk assessment for the Novavax COVID-19 Vaccine (NVX-CoV2373), a recombinant spike protein vaccine with Matrix-M adjuvant to prevent disease caused by SARS-CoV-2 viruses

Bethanie Wilkinson [a], Kinjal S. Patel [a], Katherine Smith [a], Robert Walker [a], Chengbin Wang [a], Ann M. Greene [a], Gale Smith [a], Emily R. Smith [b,*], Marc Gurwith [b], Robert T. Chen [b], For the Benefit-Risk Assessment of VAccines by TechnolOgy Working Group BRAVATO; (ex-V3SWG)[1]

[a] Novavax, Inc., Gaithersburg, MD, USA
[b] Brighton Collaboration, a program of the Task Force for Global Health, Decatur, GA, USA

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ABSTRACT

Novavax, a global vaccine company, began evaluating NVX-CoV2373 in human studies in May 2020 and the pivotal placebo-controlled phase 3 studies started in November 2020; five clinical studies provided adult and adolescent clinical data for over 31,000 participants who were administered NVX-CoV2373. This extensive data has demonstrated a well-tolerated response to NVX-CoV2373 and high vaccine efficacy against mild, moderate, or severe COVID-19 using a two-dose series (Dunkle et al., 2022) [1], (Heath et al., 2021) [2], (Keech et al., 2020) [3], (Mallory et al., 2022) [4]. The most common adverse events seen after administration with NVX-CoV2373 were injection site tenderness, injection site pain, fatigue, myalgia, headache, malaise, arthralgia, nausea, or vomiting. In addition, immunogenicity against variants of interest (VOI) and variants of concern (VOC) was established with high titers of ACE2 receptor-inhibiting and neutralizing antibodies in these studies (EMA, 2022) [5], (FDA, 2023) [6]. Further studies on correlates of protection determined that titers of anti-Spike IgG and neutralizing antibodies correlated with efficacy against symptomatic COVID-19 established in clinical trials ($p < 0.001$ for recombinant protein vaccine and $p = 0.005$ for mRNA vaccines for IgG levels) (Fong et al., 2022) [7]. Administration of a booster dose of the recombinant protein vaccine approximately 6 months following the primary two-dose series resulted in substantial increases in humoral antibodies against both the prototype strain and all evaluated variants, similar to or higher than the antibody levels observed in phase 3 studies that were associated with high vaccine efficacy (Dunkle et al., 2022) [1], (Mallory et al., 2022) [4]. These findings, together with the well tolerated safety profile, support use of the recombinant protein vaccine as primary series and booster regimens.

1. Introduction

The Brighton Collaboration (https://www.brightoncollaboration.org) Viral Vector Vaccine Safety Working Group (V3SWG) was formed in 2008 in recognition of the increasing importance of viral vectors for the development of new vaccines and the need to understand their associated safety issues [8]. To better meet the needs of many other platform technologies used to develop vaccines to prevent COVID-19 beyond just vaccines using viral vectors, the V3SWG was renamed to Benefit-Risk Assessment of VAccines by TechnolOgy (BRAVATO) Working Group in July 2020. The BRAVATO WG has developed standardized templates to describe the key characteristics of several major vaccine platform technologies, including protein vaccines [9]. When completed (usually in a partnership between BRAVATO WG and the vaccine developer), the BRAVATO template helps answer key questions on the essential safety and benefit-risk issues of the intrinsic properties

* Corresponding author.
E-mail address: bc-coordinator@taskforce.org (E.R. Smith).
[1] See Acknowledgement for other BRAVATO members.

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of the candidate vaccine to facilitate scientific discourse among key stakeholders [10]. The World Health Organization (WHO) Global Advisory Committee on Vaccine Safety (GACVS) has endorsed the use of the template "as it is a structured approach to vaccine safety" [11,12].

This paper uses a BRAVATO protein template to review the features of Novavax's recombinant adjuvanted spike protein vaccine to prevent disease caused by SARS-CoV-2 viruses.

2. Background

A novel species of coronavirus, namely, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), caused the coronavirus disease 2019 (COVID-19) pandemic which began in December 2019. Effective vaccination against COVID-19 has provided protection against severe disease and mortality. However, transmissibility, emergence of variants, and waning immunity require the ongoing quest for vaccines with broader and more sustained protection. A new regimen of primary and periodic booster vaccinations to constrain SARS-CoV-2 and its variants has been established and may become the future method to control this virus and other emerging viruses in our population. In addition to mRNA vaccines, a recombinant protein vaccine with a more traditional vaccine platform has been introduced by Novavax, Inc and provides another tool in an expanding armamentarium of COVID-19 vaccines. One of the advantages of protein subunit vaccines is that they use a well-established technology that has been demonstrated to be effective and generally well tolerated and the traditional vaccines may encourage better compliance due to the extensive data of the safety profiles of recombinant proteins over the last 40 years (Hepatitis B vaccine composed of recombinant subunit proteins was introduced in 1986). In addition, protein vaccines can be relatively stable at refrigerated temperatures, thus providing ease of transport and storage, do not contain live components or require embryonic tissues for manufacture, are not comprised of genetic materials and have no vaccine-strain associated diseases. Purified protein vaccines allow precise examination and confirmation of the antigen structure and immunogenic potential; however, methods to characterize native and recombinant proteins can be complex and time consuming. Also, protein-based vaccines have been shown to induce robust and protective immune responses in relevant animal models and/or human clinical studies to various viral diseases, including quadrivalent influenza virus vaccine (qNIV), respiratory syncytial virus fusion (RSV F) protein, SARS-CoV spike protein and Middle East Respiratory Syndrome coronavirus (MERS-CoV) spike protein, and Zaire ebolavirus glycoprotein [13,14,15,16].

Novavax, Inc. has developed a recombinant protein vaccine formulated with the saponin-based Matrix-M™ adjuvant (referred to as NVX-CoV2373) to prevent disease caused by SARS-CoV-2 and its variants. SARS-CoV-2 recombinant spike (rS) nanoparticle consists of a highly purified protein constructed from the full-length, wild-type SARS-CoV-2 spike. This protein is based on the spike gene sequence from the original Wuhan-Hu-1 strain and is produced using a baculovirus-insect cell expression system. The recombinant spike protein was modified to contain amino acid substitutions in the S1/S2 furin cleavage and two proline substitutions in the S2 domain to confer protease resistance and to produce a stable prefusion conformation [17]. Antibodies against SARS-CoV-2 rS inhibit viral spike protein from binding to the human angiotensin-converting enzyme 2 (hACE2) receptor of host cells [17]. Additionally, formulation with Matrix-M, a potent and stable adjuvant studied in over 37,000 individuals, allows for antigen dose sparing and enhanced immune responses while maintaining a favorable safety profile [18].

In response to the emergence of SARS-CoV-2 variants, Novavax has initiated the production and investigation of various SARS-CoV-2 rS vaccines using the spike gene sequence from variant strains, including the B.1.351 (Beta), B.1.617.2 (Delta), and B.1.1.529 (Omicron) variant viruses, and a bivalent SARS-CoV-2 rS nanoparticle vaccine combining the antigens of prototype Wuhan-Hu-1 strain and variant strains. The SARS-CoV-2 rS nanoparticle of prototype and variant strains are administered with Matrix-M adjuvant [19].

In over 40 countries, NVX-CoV2373 is either authorized for emergency use or has received full approval for the prevention of COVID-19 disease. NVX-CoV2373 provides another tool in an expanding armamentarium of COVID-19 vaccines.

The initial COVID-19 vaccine Clinical development program consists of 5 clinical trials. Data was collected for the primary vaccination series (i.e., Day 0 and 21) and booster data was collected for all studies but one. Two phase 3 efficacy trials were conducted when variants non-identical with the Wuhan-Hu-1 prototype strain circulated. Collectively, these trials demonstrated that NVX-CoV2373 had a favorable safety profile, induced immune responses to prototype and variant strains, and was efficacious in preventing COVID-19 [1,2].

2.1. Pivotal phase 3 studies

NVX-CoV2373 vaccination induced protection against variants of the original SARS-CoV-2 isolate as demonstrated by the efficacy in the Novavax pivotal, phase 3 clinical trials 2019nCoV-301 and 2019nCoV-302.

In study 2019nCoV-301, 29,949 adult participants who received either NVX-CoV2373 (n = 19,714) or placebo (n = 9,868) demonstrated 90.4% (95% CI, 82.9–94.6, $p < 0.001$) overall efficacy [1].

In study 2019nCoV-302, 14,039 participants who received either NVX-CoV2373 (n = 7,020) or placebo (n = 7,019) demonstrated 89.7% (95% CI, 80.2–94.6) overall efficacy [2].

Overall efficacy against Variants of Concern (VOC) or Variants of Interest (VOI), in study 2019nCoV-301, was 92.6% (95% CI, 83–96.) [1]. The most common VOC identified were: Alpha with 31/61 cases (51%), Beta (2/61, 4%) and Gamma (2/61, 4%), while the most common VOI were Iota with 8/61 cases (13%), and Epsilon (3/61, 5%) [1].

In study 2019nCoV-302, viral strain data were available for 95 of the 106 endpoint cases (90%). Sixty-six of 95 (69%) were identified as the VOC Alpha variant (B.1.1.7) with the other cases classified as non-Alpha. Vaccine efficacy against B.1.1.7 was 86.3% (95% CI, 71.3—93.5), and efficacy against the non-alpha variants (VOC or VOI) was 96.4% (95% CI, 73.8–99.5) [2].

2.2. Adolescents (12–17 years)

A pediatric expansion of Study 2019nCoV-301 was conducted, in which participants 12 to 17 years of age were vaccinated with active vaccine or placebo. In the interim data analysis, the primary endpoint for immunogenicity was met. Participants with confirmed infection or prior infection due to SARS-CoV-2 at the time of randomization were not included in the primary efficacy analysis, and the overall point estimate of efficacy was 79.5% (95% CI, 46.8—92.1) [20].

2.3. Concomitant vaccination

In the seasonal influenza vaccine co-administration substudy of 2019nCoV-302, the vaccine efficacy of NVX-CoV2373 was 74.8% (95% CI, −19.7–94.7) for all participants and 87.5% (95% CI, −0.2–98.4) for participants 18 to 64 years of age; all cases of COVID-19 were from the B.1.1.7 (Alpha) variant. Co-administration of NVX-CoV2373 was well-tolerated, did not perturb immune responses to the influenza vaccines, and induced robust immune responses to SARS-CoV-2, though these responses were attenuated in the older adult cohort (65–84 years of age) [21].

2.4. NVX-CoV2373 safety

NVX-CoV2373 safety has been assessed throughout the comprehensive non-clinical and clinical development programs and in post authorization safety surveillance. No risks were identified in the

nonclinical development program while data supported the dose and regimen approved for human use. The NVX-CoV2373 safety profile indicates this vaccine is well tolerated as demonstrated by data from over 31,000 participants receiving NVX-CoV2373 across 5 randomized controlled clinical trials.

The most frequent adverse reactions from the clinical trials were injection site tenderness, injection site pain, fatigue, myalgia, headache, malaise, arthralgia, nausea or vomiting. These adverse reactions were usually mild to moderate in severity with a median duration of less than or equal to 2 days. These local and systemic adverse reactions occurred more frequently after Dose 2 than after Dose 1 [5].

Additionally, there has been no evidence of vaccine-associated enhanced disease following administration in multiple animal species and in humans during clinical development and in the post authorization setting.

Myocarditis and/or pericarditis are safety concerns of interest with all COVID-19 vaccines. In clinical trials, 2 events of myocarditis were reported in the NVX-CoV2373 group, and 1 event was reported in the placebo group during the pre-crossover period, with a risk difference of 0 (95% CI, −0.02–0.02). Post-crossover from placebo to active vaccine, 2 participants reported 2 events of pericarditis and 1 event of myocarditis for NVX-CoV2373, and 1 event of myocarditis for placebo was reported, with a risk difference of 0 (95% CI, −0.02–0.05) for myocarditis and 0·02 (95% CI, 0.00–0.08) for pericarditis [22]. Onset was within 14 days after vaccine administration with signs and symptoms (such as acute and persisting chest pain, shortness of breath, or palpitations) similar to those seen with myocarditis or pericarditis from other etiologies [5]. Myocarditis and/or pericarditis is classified as an important identified risk based on reports received in the post-authorization setting and is closely monitored through both routine and additional pharmacovigilance activities [23].

Brighton Collaboration
Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Protein Vaccines

1. Authorship	**Information**
1.1 Author(s) and affiliation(s)	Bethanie Wilkinson, Kinjal Patel, Kathy Smith, Robert Walker, Chengbin Wang, Ann M. Greene, Gale Smith
1.2 Date completed/updated	16 May 2023
2. Basic Vaccine information	**Information**
2.1 Vaccine name	Nuvaxovid™ (NVX-CoV2373)Proprietary names and trademarks used herein, even when not specifically marked as such, are not to be considered unprotected by law.
2.2 Protein type (e.g., molecular clamp, virus-like particle, peptide) and any special characteristics	The particle consists of recombinant spike protein (virus antigen), modified to contain amino acid substitutions in the S1/S2 cleavage domain furin cleavage site and two proline substitutions in the S2 domain to confer protease resistance and to produce a stable prefusion conformation. The antigen is adjuvanted (to enhance immune response) and organized in a nanoparticle (to increase antigen processing by antigen-presenting cells and antigen deposition in lymph nodes and elicit more and/or better-quality neutralizing antibodies) [24]
2.3 Type of heterologous expression system used for antigen production (e.g., bacteria, yeast, plants, mammalian or insect cells, chemical synthesis)	Produced by recombinant DNA technology using a baculovirus expression system in an insect cell line that is derived from Sf9 cells of the *Spodoptera frugiperda* species
2.4 Adjuvant (if applicable)	Matrix-M
2.5 Final vaccine formulation components that may impact delivery into cells, stability, and safety (e.g., preservatives (e.g., thimerosal, phenol, benzethonium chloride, 2-phenoxyethanol), complexing with polymers, encapsulation within microparticles, liposomes, depot formulations)	NVX-CoV2373 is a dispersion for injection containing 5 ug surface antigen, recombinant spike protein from the Wuhan Strain of SARS-CoV-2 and 50 ug Matrix-M with the following ingredients to stabilize the formulation and adjust the pH of the vaccine to be compatible with human tissues. • Disodium hydrogen phosphate heptahydrate • Sodium dihydrogen phosphate monohydrate • Disodium hydrogen phosphate dihydrate • Sodium chloride • Polysorbate 80 • Cholesterol • Phosphatidylcholine (including all-rac-α-Tocopherol) • Potassium dihydrogen phosphate • Potassium chloride • Sodium hydroxide (for the adjustment of pH) • Hydrochloric acid (for the adjustment of pH)
2.6 Route and method of delivery (e.g., intramuscular injection, microneedles, skin patch, intranasal, other mucosal)	Intramuscular injection
3. Target Pathogen and Population	**Information**
3.1 What is the target pathogen?	SARS-CoV-2 and variants
3.2 What are the disease manifestations caused by the target pathogen in humans, for the following categories:	
● In healthy people	Clinical manifestations are wide ranging. Patients can experience mild symptoms to severe illness. Symptoms may appear 2-14 days after exposure to the virus and include the following [25]. • Fever or chills • Cough • Shortness of breath or difficulty breathing • Fatigue • Muscle or body aches • Headache • New loss of taste or smell • Sore throat • Diarrhea • Congestion or runny nose • Nausea or vomiting Serious manifestations of the SARS-CoV-2 infection include but are not limited to the following [26] • Pulmonary – Pneumonia, acute respiratory distress syndrome (ARDS), pulmonary embolism • Neurological – Guillain–Barre syndrome, reduced consciousness, acute cerebrovascular disease, ataxia, epilepsy

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	• Cardiac – arrhythmias, arterial and venous thromboembolism (VTE), cardiogenic shock, cardiac arrest, myocarditis • Gastrointestinal – Bowel ischemia • Renal – Acute renal failure
● In immunocompromised people	Accumulating evidence indicates immunocompromised people are at increased risk of severe illness from COVID-19. The manifestations are similar to those in healthy individuals but may be more severe and result in an increased risk of death due to the compromised immune system or immunosuppressants [27].
● In neonates, infants, children	Children are as likely to get COVID-19 as adults and less likely to become severely ill while experiencing the same manifestations as adults. Severe cases, hospitalizations and deaths occur in children at a lower frequency than in adults. Multisystem inflammatory syndrome in children (MIS-C) has been observed as a complication of COVID-19 infection; it is considered rare. A targeted surveillance of pediatric health centers from 15 March to 20 May 2020 identified 186 patients with MIS-C, of which 131 were positive for COVID-19. A meta-analysis demonstrated that the inflammatory markers, especially WBC, ALC, ANC, PLT, CRP, ferritin, D-dimer, LDH, fibrinogen, and ESR levels, were correlated with MIS-C [28]. Most patients with MIS-C (92%) had elevations in at least 4 biomarkers indicating inflammation [29,30].
● During pregnancy and in the fetus	Pregnant individuals are at an increased risk of severe COVID-19 and are more likely to be admitted to the intensive care unit, require invasive ventilation, require extracorporeal membrane oxygenation and experience a fatal outcome compared to non-pregnant individuals. The most common symptoms reported in pregnant individuals were cough and fever. Intrauterine SARS-CoV-2 transmission is rare. The risk of preeclampsia, preterm birth, and stillbirth is increased among pregnant individuals with SARS-CoV-2 infection than in those without SARS-CoV-2 infection. Severe COVID-19 disease in pregnant individuals was associated with preeclampsia, preterm birth, gestational diabetes, and low birthweight compared with those with mild disease [31].
● In elderly	The risk of severe disease from COVID-19 increases with age. Persons aged 65 or older had 7.7 times higher COVID-19 death rates than those between the ages of 55 and 64 years (IRR = 7.7, 95% CI, 7.4–7.9) and 62 times higher rate compared to those younger than 55 years (IRR = 62.1, 95% CI, 59.7–64.7) [32] More recent data [33] have demonstrated that breakthrough infections have occurred in vaccinated individuals; however, these infections are less likely to be severe or result in hospitalization or death in any age group [34,35]
● In any other special populations	Adults with the following underlying conditions are at an increased risk for severe illness from COVID-19: cancer, chronic kidney disease, chronic liver disease, chronic lung diseases, cystic fibrosis, dementia or other neurological conditions, diabetes (type 1 or 2), certain disabilities (e.g., Down syndrome, cerebral palsy, spinal cord injuries, etc.), cardiovascular diseases, HIV infection, mental health conditions (e.g. depression, schizophrenia, etc.), overweight, obesity, physical inactivity, sickle cell disease, thalassemia, smoking (current or former), solid organ or blood stem cell transplant, cerebrovascular disease, substance use disorders, and tuberculosis. Children with medical complexities, with genetic, neurologic, or metabolic conditions, or with congenital heart disease can be at increased risk for severe disease from COVID-19 [27]
3.3 Briefly, what are the key epidemiologic characteristics of the disease caused by the target pathogen (e.g., incubation period, communicable period, route/s of transmission, case fatality rate, transmissibility characteristics such as basic reproductive ratio (R_0), and spontaneous mutation)?	COVID-19 is a respiratory infection transmitted between humans through exposure to respiratory fluids with infectious virus, such as droplets and aerosols, by inhalation or direct mucosal contact [25] After contracting SARS-CoV-2 virus, the incubation period was estimated with an average of 6.4 days, ranging from 1 to 14 days [36,37]. The incubation period varies for different viral variants, and the average incubation periods for Delta and Omicron variants were reported to be as short as 4.8 days and 3.6 days, respectively [38] Manifestations of COVID-19 have a wide range from asymptomatic, to mild and severe illness. Over one-third of infections are asymptomatic, with lower prevalence of these asymptomatic infections among elderly [39,40]. In addition, infections from different viral strains may have different likelihood of severe disease. The latest strain -Omicron infection usually causes less severe disease than prior variants [41] As infectiousness of SARS-CoV-2 is associated with concentrations of viruses in upper respiratory specimens which decline after onset of symptoms, infectiousness peaks around one day before symptom onset and declines within a week of symptom onset, with an average period of infectiousness and risk of transmission between 2-3 days before and 8 days after symptom onset. However, for those with severe COVID-19, replication-competent infectious viruses still could be recovered even 10-20 days after symptom onset, particularly among immunocompromised patients [42]. In addition, persons with asymptomatic COVID-19 may still spread the virus to others [43]. Though asymptomatic patients have similar viral loads as symptomatic disease during the early disease course, asymptomatic patients have a rapid decrease in viral load with loss of infectivity [44]. A meta-analysis found that the secondary attack rate for asymptomatic index cases was 1.9%, but was 9.3% for pre-symptomatic and 13.6% for symptomatic index cases [45]. In addition to characteristics of the infection, different viral variants have different transmissibility and Omicron strain is more transmissible than other strains [46] Global summary estimates for the basic reproduction number (R0) ranged from 3.28 to 4.5 in the absence of interventions [47]. However, there is significant regional variability. For example, the estimates of (R0) from studies in China was 3.32 (95% CI: 2.81−3.82) [48], while it was 2.2 (95% CI: 1.9–2.6) in Western Europe with similar estimates from different countries there [49]. In contrast, substantial variations were observed across countries in Africa, with average of 3.67 and ranging from 1.98 to 9.66 [50]. Globally, the cumulative number of deaths related to COVID-19 is over 6.88 million as of March 10, 2023 [51]. In the US, the total cases and deaths due to COVID-19 reached 103,804,263, and 1.12 million, respectively, leading to overall case fatality rate of 1.08% in the US [51]. Case fatality rate of COVID-19 varied substantially over time as the result of changing dominant viral variant, case characteristics (age, underlying conditions, etc.), availability of effective treatment, and vaccine uptake. In one systematic review, the geographic variation in case fatality rate was mainly driven by difference in age distributions [52]
3.4 What sections of the population are most affected by the target pathogen (e.g., pediatric, pregnant, lactating women (breast feeding), adult, elderly)	Initial COVID-19 cases reported from China, the center of the initial outbreak, occurred in people ranging in age from 30 and 79 years old. In a review of 72,314 cases from China, only 2% of the cases were in people 19 years old or younger and 1% in children less than 10 years old [53]. While most of the COVID-19 cases occurred within the 18-29 year old group, the rate of hospitalization and death increased with age as seen in table below [54].

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Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Protein Vaccines

Age group rate ratios compared to ages 18 to 29 years									
Age group (years)	*0-4*	*5-17*	*18-29*	*30-39*	*40-49*	*50-64*	*65-74*	*75-84*	*85+*
Cases	0.5x	0.7x	Reference group	1x	0.9x	0.8x	0.6x	0.7x	0.8x
Hospitalization	0.7x	0.2x	Reference group	1.5x	1.8x	3.1x	5.0x	9.2x	15x
Death	0.3x	0.1x	Reference group	3.5x	10x	25x	60x	140x	360x

The risk of COVID-19 infection, hospitalization and death increases by the below amount in certain race/ethnicities compared to white, non-Hispanic persons [55].

- American Indian or Alaska Native, Non-Hispanic persons:
  - Cases 1.6×, Hospitalization 2.5×, and Death 2.1×
- Black or African American, Non-Hispanic persons:
  - Cases 1.1×, Hospitalization 2.2×, and Death 1.7×
- Hispanic or Latino persons:
  - Cases 1.5×, Hospitalization 1.9×, and Death 1.8×

CDC's Social Vulnerability Index (SVI), a composite measure of 4 subindices (socioeconomic status; household composition and disability; racial/ethnic minority status and English language proficiency status; housing type and transportation) was significantly associated with COVID-19 incidence rates and mortality. The SVI ranged from 0 to 1, with higher values indicative of greater vulnerability to a natural disaster. An increase of 0.1 point in SVI score was associated with a 14.3% increased risk (incidence rate ratio [IRR], 1.14; 95% CI: 1.13–1.16; $P < 0.001$) and 13.7% relative increase in mortality rate (IRR, 1.14; 95% CI: 1.12-1.16; $P < 0.001$), or an excess of 87 COVID-19 cases and 3 COVID-19 deaths per 100,000 population for a SVI score change from 0.5 to 0.6 in a midsize metropolitan county. The increased rates of COVID-19 result, in part, from barriers to social distancing due to socioenvironmental conditions (e.g. crowded housing and reliance on public transportation). Furthermore, a greater proportion of essential worker occupations are among low income and racial/ethnic minority community residents leading to a higher risk of SARS-CoV-2 exposure and transmission. In addition to these social factors, underlying disparities related to health outcomes (e.g., structural racism) contribute to the racial/ethnic disparities observed in COVID-19 incidence and mortality rates [56].

Please see section 3.2 for the risks posed by COVID-19 in special populations.

3.5 What is known about the immune responses, duration, and potential correlates of protective immunity to the target pathogen or to the disease?

Immune response

- SARS-CoV-2 infection and COVID-19 vaccination result in early production of serum IgA, IgM, and IgG antibodies, and also induce long-lasting memory B- and T-cell responses [57].
- SARS-CoV-2 infection early response [57]
  - IgM, IgA, and IgG can be detected in the blood 5–15 days following symptom onset
  - IgM peaks within first few weeks from symptom onset and falls below detectable levels after 2-3 months. IgA decreases to undetectable levels within 3 months of infection, while IgG is more durable with some waning. Memory B- and T-cells also appear within the first month following infection.
  - Variable immune response due to certain factors [57]
    - Severity of infection – Binding and neutralizing antibody titers rise faster and reach a higher peak in persons with more severe COVID-19 compared to those with mild or asymptomatic disease.
    - Low cycle threshold (Ct) value – correlates with higher antibody titers at the population level.
    - Increasing age- associated with decreased likelihood of seroconversion, but higher peak titers among those who do seroconvert.
    - Hematologic malignancy or immunosuppressant – associated with lower rates of seroconversion.
- Underlying medical conditions – Certain comorbidities (see section 3.2) are associated with more severe disease.
- Vaccination against SARS-CoV-2 [58]
  - COVID-19 vaccination results in early production of serum IgA, IgM, and IgG antibodies, and generate long-lasting memory B- and T-cell responses.
  - Factors leading to variable immune response with natural infection are similar to those following vaccination.

NVX-CoV2373

In general, resistance to viral replication and clinical illness in experimental animal models correlates with the presence of neutralizing antibodies [59]. However, Novavax has noted that immunized animals with even low, or undetectable levels of neutralization activity may show reduced viral replication and blunting of clinical impacts such as weight loss. This may imply the protective activity of antibodies at a level below that detectable in typical neutralization assays, or cellular immunity.

Correlate of protection

Recent publications have established that IgG levels and ACE-2 receptor binding site inhibition assays significantly correlate with efficacy against symptomatic COVID-19 established in clinical trials for vaccinated individuals ($p =<0.001$ for recombinant protein vaccine and $p=0.005$ for mRNA vaccine) [7]. Thus, these assays suggest levels of antibody that may provide some correlates of protection. Breakthrough infections caused by prototype variants are still being analyzed [7]

There is a paucity of evidence about the longevity of the antibody response to COVID-19 infection. It is known that antibodies to other human coronaviruses decrease over time and there are reports of reinfections with homologous coronaviruses within 90 days. Therefore, reinfection with COVID-19 is possible [60].

3.6 Please describe any other key information about the target pathogen or population that may inform benefit-risk

See section 3.3-3.5

4. Characteristics of Antigen

Information

4.1 Is the vaccine likely to induce immunity to all strains/genotypes of the target pathogen? What is the evidence?

Mutations in virus Spike (S) protein of the original SARS-CoV-2 isolate (Wuhan-Hu-1) have produced variants of interest (VOI) and variants of concern (VOC); these variants incorporated amino acid substitutions or deletions in critical locations within the viral coding sequence of the spike protein [17]. The ability of sera to neutralize the SARS-CoV-2 spike protein (S) from Beta, Gamma, Delta, Epsilon and Omicron variants of concern (VOCs) relative to the ancestral Wuhan-Hu-1 strain was demonstrated [61].

NVX-CoV2373 induced immunity against variants of the original SARS-CoV-2 isolate as demonstrated by the efficacy in the Novavax clinical trials 301 and 302. These trials were conducted during the presence of variants non-identical with the

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Brighton Collaboration **Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Protein Vaccines**	
	Wuhan-Hu-1 prototype strain. In the pivotal phase 3 study 2019nCoV-301, sequencing data were available for 61 of the 77 endpoint cases (79%). Of these, 48 out of 61 (79%) were identified as Variants of Concern or Variants of Interest. The most common Variants of Concern identified were: Alpha with 31/61 cases (51%), Beta (2/61, 4%) and Gamma (2/61, 4%), while the most common Variants of Interest were Iota with 8/61 cases (13%), and Epsilon (3/61, 5%). In the second pivotal phase 3 study 2019nCoV-302, data were available for 95 of the 106 endpoint cases (90%). Of these, 66 out of 95 (69%) were identified as the Alpha variant with the other cases classified as non-Alpha. In the completed phase 2a/b study 2019nCoV-501, enrollment occurred when the B.1.351 (Beta) variant was circulating and completed in November 2020. More recently, efficacy data from the adolescent (12 to < 18 Years) expansion of study 2019nCoV-301 was collected during the widespread circulation of the Delta variant. Of the 20 primary endpoint cases in the Per-Protocol Efficacy Analysis Set, viral genetic sequences were available for 11 adolescent participants with all sequenced cases belonging to the Delta VOC.
4.2 What is known about the immune response to the vaccine in animals and/or humans (binding, functional, and neutralizing antibody, B-cell, T-cell memory, etc.)?	Novavax has completed nonclinical studies which have been used to support the development of our SARS-CoV-2 rS vaccine currently used in clinical trials. Immunogenicity of nonclinical studies in rodents and non-human primates overall demonstrate strong correlations between anti-S IgG, hACE2 binding inhibitory activity, and virus neutralization activity and contain sufficient internal controls and comparators to identify trends related to antigen construct, dose, formulation, and regimen within each experiment. In addition, challenge studies with SARS-CoV-2 variants in these animals correlated with immune response by parameters of immunogenicity measured. Mouse immunogenicity studies were conducted to evaluate several SARS-CoV-2 spike protein constructs. The candidate vaccine selected, NVX-CoV2373, was highly immunogenic and produced high levels of spike protein-specific IgG antibodies with human ACE-2 receptor binding domain blocking activity and SARS-CoV-2 wild-type virus neutralizing antibodies. Antibodies were measurable after a single immunization and increased 8- to 10-fold after a second dose. High titer neutralizing antibodies are generally accepted evidence that a vaccine is likely to be protective in humans. Intranasal SARS-CoV-2 challenge of hACE2-transduced mice that had been immunized with NVX-CoV2373 antigen with Matrix-M adjuvant showed protection of the animals against weight loss and a >100-fold reduction in viral load at optimal doses [17]. The selected candidate vaccine was also evaluated in a dose titration study using baboons, as results from this animal model are more predictive of responses in humans. A small sample of baboons demonstrated potentially valuable immune responses to NVX-CoV2373 as assessed by anti-S IgG, hACE2-binding inhibiting antibodies, and neutralizing antibodies. Matrix-M provided antigen-sparing and enabled the induction of strong functional antibody responses. Importantly, Matrix-M-adjuvanted NVX-CoV2373 also appeared to induce strong Th1 type CD4+ T cell responses to SARS-CoV-2 spike protein which included polyfunctional effector phenotypes. IL-4 producing cells (a Th2 marker) were not detected by ELISPOT. Furthermore, this study also lends support to the vaccine doses and need for Matrix-M as designed for the Phase 1 /2 trial [17]. Additional animal studies in rodents and non-human primates investigating immunogenicity and efficacy of the candidate vaccine, including animal challenge studies with wild type SARS-CoV-2 and variants of concern, are completed or ongoing. See section 8.1 for information about human immune responses to the vaccine.
4.3 Is there homology in the sequence of the vaccine antigen and human proteins?	In the S protein molecule, there are more than two dozen 7-/8-mers homologous to human proteins [62]. Fragments homologous to human proteins are scattered along the entire length of the S protein molecule, and some of them consists of fusion of sequences of considerable length, namely 7-8 mers and well as 10-mers All these n-mers stand out from the virus particles and may be involved in the effect of mimicry. With a high degree of probability, it can be argued that the S protein is involved in the process of mimicry. Mimicry may also take some part in provoking an autoimmune response. For example, there are 8-mers identified which may get involved in orchestrating the immune system's response (Nature reports,2021). The 8-mer RRARSVAS682-689 is homologous to the amiloride-sensitive sodium channel subunit alpha201-208, which is involved in salt taste perception(ref). Also, the native SARS-CoV-2 spike glycoprotein has been shown to share homology with the human epithelial sodium channel α-subunit in its unique RRARSVAS 8-mer at the S1/S2 furin cleavage site, which is not found in other coronaviruses. This sequence is specifically mutated in the "3Q" substitutions to eliminate the S1/S2 cleavage site and create protease resistance in the NVX-CoV2373 construct. We are unaware of any other currently described important homology with human sequences [62].
5. Adjuvant (if applicable)	**Information**
5.1 Describe the type of adjuvant, if it has been tested in humans, whether novel or commercialized, and if applicable, what other vaccines (preventive and therapeutic) are formulated with this adjuvant	The Matrix-M adjuvant is manufactured by mixing defined, partially purified extracts of the bark of the *Quillaja saponaria* Molina tree, termed Fraction A and Fraction C, with cholesterol and phosphatidylcholine in the presence of a detergent. The resulting spherical immune stimulating complexes are particles of approximately 40 nm diameter, are remarkably stable, held together by the strong affinity between saponin and cholesterol. The particle also provides chemical stability to the fragile saponin molecules under conditions where free saponins degrade quickly. The adjuvant designation, Matrix-M, refers generically to a blend of Matrix-A and Matrix-C particles together at any ratio. An 85:15 ratio (by weight) of Matrix-A and Matrix-C particles, respectively, yields the Matrix-M adjuvant. In humans, Matrix-M 50 μg is a component of the commercialized COVID-19 vaccine, NVX-CoV2373. It is also being studied with vaccines targeting Omicron-specific COVID-19 variants, seasonal influenza, COVID-19 + seasonal influenza combination, Respiratory syncytial virus, Malaria and Ebola.
5.2 What is the evidence that an adjuvant improves/boosts/enhances the immune response?	The adjuvanting property of saponins, to boost both humoral and cellular immune responses to antigens that are generally poor immunogens, in veterinary vaccines has precipitated the exploration of saponin-based adjuvants in human vaccines [63]. Matrix-M, in rodent, non-human primate, or human data, has been shown to increase the amplitude and speed of humoral immune responses, enhance the recognition of non-dominant epitopes on target protein antigens, amplify T follicular helper cell and germinal center B cell numbers, markedly enhance antigen-specific polyfunctional CD4+ T cell responses with a Th1 dominant phenotype, and, in mice, induce antigen-specific CD8+ T cell responses. In addition, Matrix-M is markedly antigen-sparing, allowing the induction of potent immunogenicity with at least 5- to 10-fold lower antigen doses [17].
5.3 What is the mechanism of action of the adjuvant (if known)?	The saponin-based Matrix-M adjuvant facilitates activation of the cells of the innate immune system, which enhances the magnitude of the spike protein-specific immune response. The two vaccine components elicit B- and T-cell immune responses to the spike protein, including neutralizing antibodies, which may contribute to protection against COVID-19 [18].
5.4 How is the adjuvant formulated with the antigen?	Current studies utilized premixed antigen and adjuvant as a co-formulated vaccine [64]. Phase 1 study used a bedside mix (antigen and adjuvant are formulated in separate vials and mixed prior to vaccination). The co-formulated vaccine is described below: Matrix-M adjuvant is processed through a unique process that results in very small, spherical particles that resemble a honeycomb or cage-like structure. After Novavax's process of protein purification, the recombinant spike protein trimers assemble into rosette like nanoparticles. The combination of both components is seen in the electron micrograph image below.

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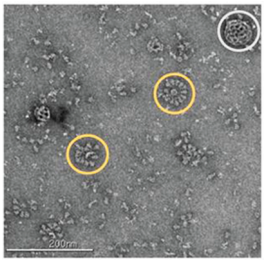
Brighton Collaboration
Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Protein Vaccines



The image shows individual spike nanoparticles (spike rosettes) circled in yellow and Matrix-M adjuvant cage-like structure are circled in white. Matrix-M does not appear to interact with spike nanoparticles. [see reference in comment field [64].
Matrix-M adjuvant is added to buffer, which is then added to obtain the desired protein concentration. The solution is filtered and aseptically filled into the United States Pharmacopeia (USP) type-I glass vials, stoppered, and sealed to produce SARS-CoV-2 rS vaccine. This final product is stored at 5 °C ± 3 °C.

5.5 How might the adjuvant impact the safety profile of the vaccine?	Though the primary impact of Matrix-M adjuvantation on the safety profile of a protein vaccine is anticipated to be an increased frequency of local and systemic reactogenicity complaints typical of intramuscular vaccines, there is no evidence from animal or human data with NVX-CoV2373 or multiple other protein antigens for significant impact to the safety profile [23].
5.6 Summarize the safety findings (preclinical and clinical) with the adjuvant, formulated with any antigen	Matrix-M adjuvant administration was generally well tolerated in humans and animals. Toxicology data from animal studies to evaluate Matrix-M adjuvant, alone or co-administered with different vaccine antigens, did not demonstrate relevant systemic or organ-specific toxicities. There were transient and inconsistent reductions in body weight and red cell mass parameters, as well as temperature elevations in some studies but these findings tended to resolve following the recovery period. Local injection site inflammation and regional lymph node hyperplasia consistent with active immunization were present in acute necropsies but showed resolution at recovery time points. NVX-CoV2373 5μg with Matrix-M 50 μg was studied in 5 clinical trials with over 31,000 adults during clinical development and demonstrated a well-tolerated safety profile. The most frequent adverse reactions were injection site tenderness, injection site pain, fatigue, myalgia, headache, malaise, arthralgia, and nausea or vomiting. Adverse reactions were usually mild to moderate in severity with a median duration of ≤2 days for local events and ≤1 day for systemic events following vaccination. To supplement data from the NVX-CoV2373 clinical development program, longer-term (6 months – 1 year) safety data from 2,574 adult subjects exposed to 50 or 75 μg Matrix-M adjuvant in clinical trials with other nanoparticle vaccine antigens produced using the same manufacturing platform technology as the SARS-CoV-2 rS antigen (i.e. RSV F protein, Ebola, and qNIV) were reviewed [13,14,16]. The safety of other recombinant nanoparticle vaccine antigens with Matrix-M adjuvant showed that each antigen and adjuvant regimen was well tolerated and resulted in safety profiles similar to those seen in the clinical trials of NVX-CoV2373 with Matrix-M adjuvant [23,5].
6. Delivery and Administration	**Information**
6.1 How might the vaccine formulation (antigen and adjuvant already formulated in the same vial or combined prior to administration) impact the safety profile of the vaccine?	Based on mechanism, the immunostimulation from Matrix-M adjuvant may also contribute to immunotoxicity [65] NVX-CoV2373 which is co-formulated with the Matrix-M adjuvant has demonstrated a tolerable safety profile in 2 pivotal clinical trials (2019nCoV-302, and 2019nCoV-301 [1,2].
6.2 If the vaccine is part of a heterologous prime-boost regimen, describe the regimen that this vaccine is a part of and the possible impact on safety	Heterologous boosting vaccination with full (0.5 mL) and half (0.25 mL) doses of NVX-CoV2373 was evaluated in healthy adult participants in an independent study called The Evaluating COVID-19 Vaccination Boosters (COV-BOOST) trial. In this trial, 229 and 220 participants, respectively, received heterologous booster vaccination with full- (0.5 ml) and half-dose (0.25 ml) NVX-CoV2373 following primary vaccination with the AstraZeneca (ChAd/ChAd) and Pfizer-BioNTech (BNT/BNT) COVID-19 vaccines. Injection site pain was the most frequent solicited local AE, and fatigue and headache were the most frequent solicited systemic AEs. As expected, reactogenicity was more prevalent in relatively younger participants (30 to 69 years) than in older participants (≥ 70 years). Most participants reported, including those who received NVX-CoV2373, mild solicited local and systemic AEs following booster vaccination, and the majority of unsolicited AEs were mild or moderate in severity and not related to booster vaccine. There were no AESIs reported in NVX-CoV2373 recipients, and few NVX-CoV2373 recipients reported SAEs with none assessed as related to the booster vaccine [61].
6.3 Describe how components of the vaccine formulation that facilitate stability and delivery into cells (Section 2.5) may impact the safety profile of the vaccine	Vaccine excipients are not expected to impact safety profile because they are chemically inactive.
6.4 Describe how the mode of vaccine delivery may impact safety (e.g., intramuscular by needle injection, microneedles, intranasal, oral)	Novavax SARS-CoV-2 rS vaccine is administered intramuscularly by injection and may cause local injection site reactions.

* Stability is considered here in the context of any relevant intrinsic characteristic of the vaccine deemed important for safety purposes.

7. Toxicology and Nonclinical	**Information**
7.1 What is known about biodistribution of the antigen in its final formulation and mode of administration in animal models?	Non-clinical studies in rodents have been completed to determine the biodistribution of the adjuvant when administered IM in the final formulation, but biodistribution of the antigen has not been evaluated to date. We anticipate that the co-formulated vaccine will follow a conventional protein antigen trafficking pathway following intramuscular administration: the antigen taken up by dendritic cells will migrate to the draining lymph node where it is processed and presented to T cells by antigen-presenting cells and initiate the immune response. Therefore, we expect that detectable antigen distribution would mostly be limited to local lymph nodes. However, given the low microgram dose of rS antigen, the antigen is unlikely to be measurable within the immediate area of the site of injection [17].
7.2 How long does the vaccine antigen persist in vivo (may specify in tissue/serum; proximal/distal to site of administration)?	No studies have been performed to measure persistence in local or distal tissues due to the very low microgram doses of antigen, it will be difficult to detect in serum and tissues. It should be noted that the antigen is a purified protein and thus non-

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Brighton Collaboration **Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Protein Vaccines**	
	replicating; and that the delivery in the context of a saponin adjuvant is designed to facilitate transport to the draining lymph nodes rather than formation of a local depot.
7.3 What is the possible risk of autoimmunity or a harmful immune response?	Though there is no known cause for autoimmunity, there are suggestions that viruses, bacteria or other pathogens, or even environmental factors may be linked to autoimmunity. There is also a theoretical possibility for any vaccine to produce a harmful immune response such as vaccine associated enhanced diseases [66].In addition, anaphylaxis is a severe, potentially life-threatening allergic reaction associated with vaccine administration in general. It has not been observed during clinical development but has been reported following administration of NVX-CoV2373 in the post marketing setting. Risk mitigation activities, such as instruction to observe closely for signs of anaphylaxis and to have medical treatment readily available following immunization, are communicated in the Product label and followed in clinical practice. Therefore, anaphylaxis does not have considerable impact on the risk/benefit balance [5].
7.4 Summarize the preclinical safety data that support the use of this product in humans including any related information from similar products	No risks have been identified from the animal toxicity studies.Studies across multiple species immunized with SARS-CoV-2 rS, including non-human primate models administered the intended human dose, have shown no evidence of vaccine-enhanced disease following challenge with live SARS-CoV-2 virus, even when administered at suboptimal vaccine doses (i.e., single doses and/or lower antigen/adjuvant doses).In a repeat-dose toxicity study in rabbits, 50 μg SARS-CoV-2 rS with or without 50 μg Matrix-M adjuvant was well tolerated with non-adverse findings limited to local injection site inflammation and serum chemical markers of inflammation, which were transient and considered consistent with immune system stimulation consequent to immunization [23].Data from a developmental and reproductive toxicity study in rats indicate that intramuscular administrations of NVX-CoV2373 or Matrix-M alone from prior to implantation through the end of pregnancy had no effect on mortality, physical examinations, cageside observations, body weights, body weight changes, estrous cyclicity, or food consumption during the pre-cohabitation, gestation, or developmental periods for dams. There was no difference between fetal body weights, survival, or in external, visceral, or skeletal examinations, nor were there differences in the number of male and female pups, pup body weights, survival, litter size and sex, developmental markers, or gross pathology findings.
7.5 Summarize the preclinical immunogenicity and efficacy data that support the use of this product in humans including any related information from similar products	Animals with ACE-2 receptors are suitable models for COVID-19 infection. Both rodent models (mice, hamsters) and non-human primate models (rhesus macaques, cynomolgus macaques, olive baboons) have served as immunogenicity and efficacy models. So far, the efficacy demonstrated by challenge studies in the animals is consistent with the efficacy in humans [17].
7.6 What is the evidence of disease enhancement or absence thereof *in vitro* or in animal models?[8]	Studies across multiple species immunized with SARS-CoV-2 rS, including non-human primate models administered at the intended human dose, have shown no evidence of vaccine-enhanced disease following challenge with live SARS-CoV-2 virus, even when administered at suboptimal vaccine doses (i.e., single doses and/or lower antigen/adjuvant doses) [23].
7.7 Would the vaccine in its final formulation have any impact on innate immunity? If so, what are the implications for benefit-risk?	NVX-CoV2373 is composed of purified full-length SARS-CoV-2 recombinant spike (S) protein that is stabilized in its prefusion conformation. The addition of the saponin-based Matrix-M adjuvant facilitates activation of the cells of the innate immune system, which enhances the magnitude of the S protein-specific immune response. The two vaccine components elicit B- and T-cell immune responses to the S protein, including neutralizing antibodies, which may contribute to protection against COVID-19 [5].
7.8 What is the evidence that the vaccine has generated a beneficial immune response in:	
• Small animal models?	See response to 4.2.
• Nonhuman primates (NHP)?	See response to 4.2.
8. Human Efficacy and Other Important Information	**Information**
8.1 What is the evidence that the vaccine would generate a protective immune response in humans (e.g., natural history, passive immunization, animal challenge studies)?	The basis for the testing the SARS-CoV-2-rS vaccine in humans is the immune response and protective effects demonstrated in animal studies (see response to section 4.2). In rodents and non-human primates, the SARS-CoV-2 rS protein with Matrix-M generates neutralizing antibodies, which block the high-affinity binding of SARS-CoV-2 spike to hACE2, and antigen-specific polyfunctional CD4+ T cells of Th1 phenotype. Murine studies also suggest induction of a CD8+ response. In mice transduced with hACE2, challenged of mice immunized with NVX-CoV2373 in the presence of Matrix-M show a dose-responsive reduction of viral load and attenuation of weight loss relative to unimmunized animals (see response to section 4.2). The clinical development program for prototype SARS-CoV-2 rS 5μg co-formulated with Matrix-M adjuvant comprised of 4 clinical trials: 2019nCoV-101 (part 2), 2019nCoV-501, 2019nCoV-302, and 2019nCoV-301. Enrollment and primary vaccination (i.e., Day 0 and 21) have been completed in all studies, and follow-up is ongoing. Six-month safety and immunogenicity data are available in Part 1 (Phase 1) of 2019nCoV-101, and 6- and 12-month booster dosing has been evaluated in Part 2 (Phase 2) of 2019nCoV-101. Final primary efficacy endpoint analyses have been conducted in 2019nCoV-501 (Phase 2a/b), 2019nCoV 302 (Phase 3), and 2019nCoV-301 (Phase 3) and are summarized below. For the latter 3 studies, participants are receiving blinded crossover vaccinations to ensure all participants receive active study vaccine. The NVX-CoV2373 clinical trials demonstrated immunogenicity against variants circulating at the time of trial conduct [5]. **Overall efficacy in adults (≥18 years) – primary series** In 2019nCoV-301, overall efficacy of NVX-CoV2373 (n=17,312) compared to placebo (n= 8,140) to prevent the onset of COVID-19 from seven days after Dose 2 was 90.4% (95% CI, 82.9-94.6) [1]. In 2019nCoV-302, 14,039 participants who received either NVX-CoV2373 (n = 7,020) or placebo (n = 7,019) demonstrated 89.7% (95% CI, 80.2-94.6) overall efficacy [2]. Overall efficacy of NVX-CoV2373 in study 2019nCoV-501 which included 2,770 participants [NVX-CoV2373 (n = 1,408) versus placebo (n = 1,362)] who were HIV positive or negative was 48.6% (95% CI: 28.4, 63.1). This data was not unexpected since immune dysfunction of HIV+ patients has been shown to have more breakthrough infections than healthier fully vaccinated populations [67].**Overall efficacy in adolescents (12-17 years) – primary series**A pediatric expansion is ongoing in Study 2019nCoV-301, in which participants 12 to < 18 years of age are being vaccinated with active vaccine or placebo. In the interim data analysis, the primary endpoint for immunogenicity was met. Participants with confirmed infection or prior infection due to SARS-CoV-2 at the time of randomization were not included in the primary efficacy analysis. However, the overall point estimate of efficacy was 79.5% (95% CI, 46.8-92.1) [20].**Immunogenicity in adults (≥18 years) – after booster dose**In study 2019nCoV-101 – Part 2, 104 participants who received a NVX-CoV2373 booster 6 months after completing the NVX-CoV2373 primary vaccine series had an approximate 96-fold increase in neutralizing antibodies on day 217 compared to day 189 (pre-booster). Peak neutralizing antibody GMT was 1470, an approximate 4.1-fold increase from a peak 14 days post-Dose 2. In study 2019nCoV-501, 1,173 participants (healthy HIV-negative adult participants 18 to 84 years of age and medically stable patients living with HIV) who received a NVX-CoV2373 booster 6 months after completing the NVX-CoV2373 primary vaccine series had an approximate 52-fold increase in neutralizing antibodies on day 236 compared to day 201 (pre-booster). Peak neutralizing antibody GMT was 694, an approximate 5.2-fold increase from a peak 14 days post-Dose 2 [5].

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Brighton Collaboration
Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Protein Vaccines

	In an independent, multicenter, randomized, controlled, Phase 2 investigator-initiated trial (CoVBOOST), a NVX-CoV2373 booster dose was given to adults aged 30 years and older who completed a primary vaccination series with ChAdOx1 nCov-19 (Oxford–AstraZeneca) or BNT162b2 (Pfizer– BioNtech). NVX-CoV2373 demonstrated a booster response regardless of the vaccine used for primary vaccination [61].
8.2 Describe other key information that may impact benefit-risk	Novavax clinical trials on immunogenicity and safety in humans are ongoing and are important to informing the benefit-risk profile of NVX-CoV2373. Other factors that may impact the benefit-risk balance of NVX-CoV2373 are the emergence of COVID-19 virus variants (see section 4.1 for efficacy against variants), populations not studied/or with limited exposure in clinical trials, interaction with other vaccines and long-term safety. These concerns are being assessed through clinical trials and post marketing safety and effectiveness studies.
9. Adverse Event (AE) Assessment of the Vaccine Platform:	**Information**
9.1 Approximately how many humans have received this vaccine to date? If variants of the vaccine platform, please list separately.	Across 5 clinical trials (2019nCoV-101 p1, 2019nCoV-101 p2, 2019nCoV-501, 2019nCoV-301, and 2019nCoV-302), 30,058 participants who were 18 years and older received at least one dose of NVX-CoV2373 [5]. In addition, 1,487 adolescent participants (12-17 years of age) were exposed to at least 1 dose of NVX-CoV2373 in the pediatric expansion cohort of study 2019nCoV-301 [5].
9.2 Method(s) used for safety monitoring:	
● Spontaneous reports/passive surveillance	● Collection, processing and analysis of individual case safety reports from the clinical trials and post-authorization phase, including targeted follow-up for specific important safety concerns. ● Review and reporting on aggregate data via Safety Summary Reports and Periodic Safety Update Reports ● Implementation of periodic qualitative and quantitative signal detection methods for enhanced surveillance [23].
● Diary	Novavax active and planned studies include the use of subject diaries to collect adverse event data 7 days after vaccination [1,2,4,13].
● Other active surveillance	The safety surveillance from the ongoing or completed clinical trials listed below is a priority with data collection for up to 2 years to provide further characterization of the NVX-COV2373 safety profile. ● Study 2019nCoV-101 (Part 1) ● Study 2019nCoV-101 (Part 2) ● Study 2019nCoV-501 ● Study 2019nCoV-302 ● Study 2019nCoV-301 ● Study 2019nCoV-311 ● Study 2019nCoV-505 Vaccine safety and efficacy have been demonstrated in clinical trials. However, vaccine safety and effectiveness in the "real world" setting with exposure to a wider variety of populations over a period beyond the follow up time of clinical trials is yet to be established. Therefore, the following post marketing studies are planned or ongoing. ● 2019nCoV-404: US Post-authorization Safety Study Using a Claims and/or her Database Outline ● 2019nCoV-402: UK Post-authorization Safety Study Using the Clinical Practice Research Datalink (CPRD) Outline ● 2019nCoV-405: Global Pregnancy and Infant Outcomes Study Using the COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER) Outline ● 2019nCoV-403: US Post-authorization Effectiveness Study Using a Claims and/herEHR Database Outline ● 2019nCoV-401: EU/EEA Post-authorization Effectiveness Study Based on a Test-Negative Design Using the COVIDRIVE Platform Outline [23]
9.3 What criteria were used for grading the AEs?	
● 2007 US FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials	Yes
● If no criteria were used for grading, or if other metrics were employed, please describe:	Not Applicable
9.4 List and provide frequency of any or possibly related serious* AEs and well as any severe expected or unexpected AEs observed: (*see Instructions):	Upon review of available safety data (including serious related events and serious unexpected events,) the following events are considered related in patients ≥12 years of age [5].

Table 1: Adverse reactions from Nuvaxovid clinical trials and post–authorisation experience in individuals 12 years of age and older

MedDRA System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy	
Immune system disorders				Anaphylaxis
Nervous system disorders	Headache			Paraesthesia Hypoaesthesia
Cardiac disorders				Myocarditis Pericarditis
Vascular disorders			Hypertension[d]	
Gastrointestinal disorders	Nausea or vomiting[a]			
Skin and subcutaneous tissue disorders			Rash Erythema Pruritus Urticaria	
Musculoskeletal and connective tissue disorders	Myalgia[a] Arthralgia[a]			
General disorders and administration site conditions	Injection site tenderness[a] Injection site pain[a] Fatigue[a] Malaise[a,b]	Injection site redness[a,c] Injection site swelling[a] Pyrexia[e] Chills Pain in extremity	Injection site pruritus	

a Higher frequencies of these events were observed after the second dose.
b This term also included events reported as influenza-like illness
c This term includes both injection site redness and injection site erythema (common).
d Hypertension was not reported in adolescents aged 12 through 17 years in the clinical study.
e Pyrexia was observed more frequently in adolescents aged 12 through 17 years compared to adults, with the frequency being very common after the second dose in adolescents.

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Brighton Collaboration **Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Protein Vaccines**	
9.5 List and provide frequency of any serious, unexpected significantly increased AE or lab abnormality in vaccine vs. control groups:	There are no unexpected events that were statistically significant.In clinical trials, 2 events of myocarditis were reported in the NVXCoV2373 group, and 1 event was reported in the placebo group during the pre-crossover period, with a risk difference of 0 (-0·02, 0·02). Post-crossover, two participants reported two events of pericarditis and one event of myocarditis for NVX-CoV2373, and one event of myocarditis for placebo were reported, with a risk difference of 0 (-0·02, 0·05) for myocarditis and 0·02 (0·00, 0·08) for pericarditis [22].
● Describe the control group:_____.	Across 5 clinical trials, 19,892 participants who were 18 years and older received at least one dose of placebo. In the pediatric expansion cohort of study 2019nCoV-301, 745 adolescent participants received placebo [5].There were no serious unexpected AEs in the placebo groups that were statistically significant compared to the vaccinee groups.
9.6. List and provide frequency of Adverse Events of Special Interest	See 9.4
9.7 Did a Data Safety Monitoring Board (DSMB) or its equivalent oversee the study?	Yes
● Did it identify any safety issue of concern?	No
● If so describe:	Not Applicable
10. Overall Risk Assessment	**Information**

10.1 Please summarize key safety issues of concern identified to date, if any:	NVX-CoV2373 was well tolerated in clinical trials. Unsolicited adverse events were balanced between the NVX-CoV2373 and placebo arms.**Adult primary series**In the participants ≥18 years of age, pooled reactogenicity data, in the two phase 3 studies who received any dose of NVX-CoV2373 (n=20,055) or placebo (n=10,561), the most frequent adverse reactions were injection site tenderness (75%), injection site pain (62%), fatigue (53%), myalgia (51%), headache (50%), malaise (41%), arthralgia (24%), and nausea or vomiting (15%) [5].Adverse reactions were usually mild to moderate in severity with a median duration of ≤2 days for local events and ≤1 day for systemic events following vaccination. Local and systemic adverse reactions were more frequently reported after Dose 2 than after Dose 1. There was also a higher incidence of adverse reactions in adults aged 18 to <65 years than in those aged 65 years and above [5,6].**Adolescent primary series**The most frequent adverse reactions observed in adolescent patients aged 12 through to 17 years who received at least 1 dose of NVX-CoV2373 (n=1,487) were injection site tenderness (71%), injection site pain (67%), headache (63%), myalgia (57%), fatigue (54%), malaise (43%), nausea or vomiting (23%), arthralgia (19%), injection site swelling (19%), pyrexia (17%), and injection site redness (17%). Fever was observed more frequently in adolescents aged 12 through to 17 years compared to adults, with the frequency being very common after the second dose in adolescents.Similar to the adult patients, adverse reactions were usually mild to moderate in severity with a median duration of ≤2 days for local events and ≤1 day for systemic events following vaccination.**Homologous and heterologous booster dose**In 104 participants from study 2019nCoV-101 (Part 2), who received a NVX-CoV2373 booster dose after completing the primary series with NVX-CoV2373, solicited adverse reactions occurred at higher frequencies and with higher grade after the booster dose compared to after the primary two-dose series. The most frequent solicited adverse reactions were injection site tenderness (81%), fatigue (63%), injection site pain (55%), muscle pain (51%), malaise (47%) and headache (46%), joint pain (29%), and fever (17%) with a median duration of 1 to 3 days following vaccination.In the independent CoV-BOOST study evaluating the use of a NVX-CoV2373 booster dose in individuals who had completed primary vaccination with an authorized mRNA COVID-19 vaccine or adenoviral vector COVID-19 vaccine, no new safety concerns were identified.**Myocarditis and pericarditis**Similar to other COVID-19 vaccines, myocarditis and pericarditis have been rarely reported in the NVX-CoV2373 clinical trials [68]. In post authorization passive surveillance, 35 myocarditis and pericarditis cases were reported from 744,235 doses of NVX-CoV2373 administered in Australia, Canada, the European Union, New Zealand, and South Korea [69].section 9.2.	
● how should they be addressed going forward	Communication of safety information, including taking specific actions to minimize risk, is done via the product label.	
10.2 What is the potential for causing serious unwanted effects and toxicities in:	**Describe the toxicities**	**Please rate risk as: none, minimal, low, moderate, high, or unknown**
• healthy humans?	Based on available evidence generated to-date with NVX-CoV2373, Novavax expects a minimal potential for serious unwanted effects and toxicities in healthy humans. See response in 10.1 for potential toxicities.	Minimal
• immunocompromised humans?	Based on available evidence generated to-date with NVX-CoV2373, Novavax expects a low potential for serious unwanted effects and toxicities in immunocompromised humans.See response in 10.1 for potential toxicities	Low
• human neonates, infants, children?	Based on available evidence generated to-date with NVX-CoV2373, Novavax expects a low potential for serious unwanted effects and toxicities in neonates, infants, and children.See response in 10.1 for potential toxicities.	Low
● pregnancy and in the fetus in humans?	Based on available evidence generated to-date with NVX-CoV2373, Novavax expects a low potential for serious unwanted effects and toxicities in pregnant women and fetuses.See response in 10.1 for potential toxicities.	Low
● elderly?	Based on available evidence generated to-date with NVX-CoV2373, Novavax expects a low potential for serious unwanted effects and toxicities in the elderly.See response in 10.1 for potential toxicities.	Minimal
● in any other special populations (e.g., institutionalized population, individuals with associated chronic comorbidity)?	Based on available evidence, Novavax does not believe there are other special populations which would be more susceptible for serious unwanted effects and toxicities.See response in 10.1 for potential toxicities.	Minimal

3. Disclaimer

The findings, opinions, conclusions, and assertions contained in this consensus document are those of the authors. They do not necessarily represent the official positions of any participant's organization (e.g., government, university, or corporations) and should not be construed to represent any Agency determination or policy.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The Brighton Collaboration BRAVATO authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Novavax authors are current employees of Novavax, Inc., a for-profit organization, who own stock or hold stock options.

Data availability

The data that has been used is confidential.

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References

[1] Dunkle LM, et al. Efficacy and safety of NVX-CoV2373 in adults in the United States and Mexico. NEJM 2022;386(6):531–43.
[2] Heath PT, et al. Safety and efficacy of NVX-COV2373 Covid-19 vaccine. NEJM 2021;17(2):e0264455.
[3] Keech C, et al. Phase 1–2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine. NEJM 2020;383(24):2320–32.
[4] Mallory RM, et al. Safety and immunogenicity following a homologous booster dose of a SARS-CoV-2 recombinant spike protein vaccine (NVX-CoV2373): a secondary analysis of a randomised, placebo-controlled, phase 2 trial. Lancet Infect Dis 2022;22(11):1565–76.
[5] EMA. Summary of Product Characteristics (SmPC) Nuvaxovid. [Online]. Available: https://www.ema.europa.eu/en/documents/product-information/nuvaxovid-epar-product-information_en.pdf. [Accessed 28 September 2022].
[6] FDA. U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, Novavax COVID-19 Vaccine, Adjuvanted, for active immunization to prevent COVID-19 in individuals 12 years of age; 2023. [Online]. Available: https://www.fda.gov/media/159897/download.
[7] Fong Y, et al. Immune correlates analysis of the prevent-19 COVID-19 vaccine efficacy clinical trial, medRxiv 2022. [Online]. Available: 10.1101/2022.06.22.22276362. [Accessed 28 September 2022].
[8] Bonhoeffer J, et al. The Brighton Collaboration: addressing the need for standardized case definitions of adverse events following immunization (AEFI). Vaccine 2002;21(3–4):298–302.
[9] Kochhar S, et al. The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of protein vaccines. Vaccine 2020;38(35):5734–9.
[10] Chen RT, et al. The Brighton Collaboration Viral Vector Vaccines Safety Working Group (V3SWG). Vaccine 2015;33(1):73–5.
[11] WHO. Weekly Epidemiological Record No. 28. Online Print 2019; 94: 310–312.
[12] WHO. Weekly Epidemiological Record. No. 4. Online Print 2020; 95: 29–30.
[13] Shinde V, et al. Comparison of the safety and immunogenicity of a novel Matrix-M-adjuvanted nanoparticle influenza vaccine with a quadrivalent seasonal influenza vaccine in older adults: a phase 3 Randomised Controlled Trial. Lancet 2022;22:73–84.
[14] Fries L, et al. Immunogenicity and safety of a respiratory syncytial virus fusion protein (RSV F) nanoparticle vaccine in older adults. Immun Ageing 2017;14(8).
[15] Coleman C, et al. MERS-CoV spike nanoparticles protect mice from MERS-CoV infection. Vaccine 2017;35(12):1586–9.
[16] Bengtsson CL, et al. Matrix-M adjuvant enhances antibody, cellular and protective immune responses of a Zaire Ebola/Makona virus glycoprotein (GP) nanoparticle vaccine in mice. Vaccine 2016;34(16):1927–35.
[17] Tian JH, et al. SARS-CoV-2 spike glycoprotein vaccine candidate NVX-CoV2373 immunogenicity in baboons and protection in mice. Nat Commun 2021;12(1):372.
[18] Stertman L, et al. The Matrix-M™ adjuvant: A critical component of vaccines for the 21st century. Hum Vaccin Immunother 2023.
[19] Bhiman JN, et al. Novavax NVX–COV2373 triggers neutralization of Omicron. Nat Sci Rep 2023;13:1222.
[20] Áñez G, et al. Safety, immunogenicity, and efficacy of the NVX-CoV2373 COVID-19 vaccine in adolescents: a Randomized Clinical Trial. JAMA Netw Open 2023;6(4):e239135.
[21] Toback S, et al. Safety, immunogenicity, and efficacy of a COVID-19 vaccine (NVX-cov2373) co-administered with seasonal influenza vaccines: An exploratory substudy of a randomised, observer-blinded, placebo-controlled, phase 3 trial. Lancet Respir Med 2022;10(2):167–79.
[22] Smith K, et al. Safety of the NVX-CoV2373 COVID-19 Vaccine in Randomized Placebo-Controlled Clinical Trials. MedRxIV 2023.
[23] EMA. Risk Management Plan (RMP) Nuvaxovid [Online]. Available: https://www.ema.europa.eu/en/documents/rmp-summary/nuvaxovid-epar-risk-management-plan_en.pdf. [Accessed 28 September 2022].
[24] Vu M, et al. Current and future nanoparticle vaccines for COVID-19. EBioMedicine 2021;74:1–10.
[25] CDC. Symptoms of COVID-19. 11 August 2022. [Online]. Available: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. [Accessed 28 September 2022].
[26] Albanesi M, et al. Systematic emergencies in COVID-19 patient: a pictoral review. Tomography 2022;8(2):1041–51.
[27] CDC. People with Certain Medical Conditions. 2 September 2022. [Online]. Available: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fneed-extra-precautions%2Fgroups-at-higher-risk.html. [Accessed 28 September 2022].
[28] Zhao Y, et al. The inflammatory markers of multisystem inflammatory syndrome in children (MIS-C) and adolescents associated with COVID-19: A meta-analysis. J Med Virol 2021;93(7):4358–69.
[29] Feldstein LR, et al. Multisystem inflammatory syndrome in US children and adolescents. NEJM 2020;383:334–46.
[30] Havers FP, et al. COVID-NET surveillance team. Hospitalization of adolescents aged 12–17 years with laboratory-confirmed COVID-19—COVID-NET, 14 states, March 1, 2020–April 24, 2021. MMWR Morb Moral Wkly Rep 2021;70:851–7.
[31] Jamieson DJ, et al. An update on COVID-19 and pregnancy. Am J Obstet Gynecol 2022;226(2):177–86.
[32] Yanez ND, et al. COVID-19 mortality risk for older men and women. BMC Public Health 2020.
[33] CDC. COVID-19 after vaccination: possible breakthrough infection, 23 June 2022. [Online]. Available: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fneed-extra-precautions%2Fgroups-at-higher-risk.html. [Accessed 22 September 2022].
[34] Alcendor DJ, et al. Breakthrough COVID-19 infections in the US: Implications for prolonging the pandemic. Vaccines 2022; 10(755).
[35] Sun J, et al. Association between immune dysfunction and COVID-19 breakthrough infection after SARS-CoV-2 vaccination in the US. JAMA Intern Med 2022;182(2):153–62.
[36] Elias C, et al. The incubation period of COVID-19: A meta-analysis. Int J Infect Dis 2021;104:708–10.
[37] WHO. Coronavirus disease (COVID-19), 13 May 2021. [Online]. Available: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/coronavirus-disease-covid-19. [Accessed 22 September 2022].
[38] Du Z, et al. Shorter serial intervals and incubation periods in SARS-CoV-2 variants than the SARS-CoV-2 ancestral strain. J Travel Med 2022;29(6). p. taac052.
[39] CDC. Science Brief:SARS-CoV-2 Transmission, 7 May 2021. [Online]. Available: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/sars-cov-2-transmission.html. [Accessed 28 September 2022].
[40] Sah P, et al. Asymptomatic SARS-CoV-2 infection: A systematic review and meta-analysis. Proc Natl Acad Sci USA 2021;118(34):e2109229118.
[41] CDC. Variants of the Virus, 11 August 2022. [Online]. Available: https://www.cdc.gov/coronavirus/2019-ncov/variants/index.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fvariants%2Fomicron-variant.html#print. [Accessed 28 September 2022].
[42] CDC. Ending isolation and precautions for people with COVID-19: Interim Guidance, 31 August 2022. [Online]. Available: https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html#:~:text=Infectiousness%20peaks%20around%20one%20day,8%20days%20after%20symptom%20onset. [Accessed 28 September 2022].
[43] CDC. COVID-19 science update asymptomatic transmission, 12 June 2022. [Online]. Available: https://www.cdc.gov/library/covid19/061220_covidupdate.html. [Accessed 28 September 2022].

[44] Bae S, et al. Dynamics of viral shedding and symptoms in patients with asymptomatic or mild COVID-19. Viruses 2021;13(11):2133.
[45] Thompson HA, et al. Acute respiratory syndrome coronoavirus 2 (SARS-CoV-2) setting-specific transmission rates: a systematic review and meta-analysis. Clin Infect Dis 2021;73(3):e754–64.
[46] Torjesen I, et al. Covid-19: Omicron may be more transmissible than other variants and partly resistant to existing vaccines, scientists fear. BMJ 2021;375:n2943.
[47] Katul GG, et al. Global convergence of COVID-19 basic reproduction number and estimation from early dynamics. PLoS One 2020;15(9):e0239800.
[48] Alimohamadi Y, et al. Estimate of the basic reproduction number for COVID-19: a systematic review and meta-analysis. J Prev Med Public Health 2020;53(3):151–7.
[49] Locatelli I, et al. Estimating the basic reproduction number for COVID-19 in Western Europe. PLoS One 2021;16(3):e0248731.
[50] Iyaniwura SA, et al. The basic reproduction number of COVID-19 across Africa. PLoS One 2022;17(2):e0264455.
[51] Johns Hopkins University, "Coronavirus Resource Center," [Online]. Available: https://coronavirus.jhu.edu/. [Accessed 20 May 2022].
[52] Levin AT, et al. Assessing the age specificity of infection fatality rates for COVID-19: systematic review, meta-analysis, and public policy implications. Eur J Epidemiol 2020;35(12):1123–38.
[53] CCDC. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020. CCDCWeekly, 2020.
[54] CDC. Risk for COVID-19 Infection, Hospitalization, and Death By Age Group, 25 April 2023. [Online]. Available: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-age.html#print. [Accessed 1 May 2023].
[55] CDC. Risk for COVID-19 Infection, Hospitalization, and Death by Race/Ethnicity, 8 November 2022. [Online]. Available: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html#print. [Accessed 8 November 2022].
[56] Karmakar M. Association of social and demographic factors with COVID-19 incidence and death rates in the US. JAMA Netw Open 2021;4(1):e2036462.
[57] CDC. Science Brief: SARS-CoV-2 Infection-induced and Vaccine-induced Immunity, 29 October 2021. [Online]. Available: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/vaccine-induced-immunity.html. [Accessed 28 September 2022].
[58] Kellam P, Barclay W. The dynamics of humoral immune responses following SARS-CoV-2 infection and the potential for reinfection. J Gen Virol 2020.
[59] Karbiener M, et al. Calibrated comparison of SARS-CoV-2 neutralizing antibody levels in response to protein-, mRNA-, and vector-based COVID-19 vaccines. Vaccines 2022; 7(22).
[60] CDC. Reinfection, 19 October 2022. [Online]. Available: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/clinical-considerations-reinfection.html#print. [Accessed 30 March 2023].
[61] Munro APS, et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. Lancet 2021;398(10318):2258–76.
[62] Khavinson V, et al. Homology between SARS-CoV-2 and human proteins, 2021. [Online]. Available: 10.1038/s41598-021-96233-7.
[63] Wang P, et al. Natural and synthetic saponins as vaccine adjuvants. Vaccines 2021; 9(3):222.
[64] Bangaru S. Structural analysis of full-length SARS-CoV-2 spike protein from an advanced vaccine candidate. Science 2020;370(6520):1089–94.
[65] Batista-Duharte A, et al. Efficacy and safety of immunological adjuvants. Where is the cut-off? Biomed Pharmacother 2018;105:616–24.
[66] Munoz FM, et al. Brighton Collaboration Vaccine-associated Enhanced Disease Working Group. Vaccine-associated enhanced disease: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2021;39(22):3053–66.
[67] Shinde V, et al. Efficacy of NVX-CoV2373 Covid-19 vaccine against the B.1.351 Variant. N Engl J Med 2021;384(20):1899–909.
[68] Australian Govt. Dept. of Health and Aged Care, Nuvaxovid (Novavax), 2022. [Online]. Available: https://www.health.gov.au/initiatives-and-programs/covid-19-vaccines/approved-vaccines/novavax#rare-side-effects. [Accessed 8 November 2022].
[69] Twentyman E, et al. Interim recommendation of the advisory committee on immunization practices for use of the Novavax COVID-19 vaccine in persons aged ≥18 years — United States, July 2022. MMWR Morb Mortal Wkly Rep 2022;71:988–92.