CENTER DIRECTOR DECISIONAL MEMO

May 16, 2025

BLA:	125817
Product Name:	NUVAXOVID (COVID-19 Vaccine, Adjuvanted)
Indication:	Indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in adults 65 years of age and older and individuals 12 through 64 years who have at least one underlying condition that puts them at high risk for severe outcomes from COVID-19
Applicant:	Novavax, Inc
Author:	Vinayak Prasad, M.D., MPH., Director, Center for Biologics Evaluation and Research (CBER), FDA

Summary

This memorandum explains CBER's decision on the above submission. I have read the reviews and recommendations of the BLA review team. In addition to those I have read and reviewed pertinent portions of the sponsor's submission, as well as research on this topic in the peer reviewed literature.

The review team has done a commendable job in summarizing and analyzing the submission to date. Nevertheless, I disagree with certain aspects of their conclusions and instead reach the conclusion described below.

The decision to approve the Biologics License Application (BLA) for NUVAXOVID is for the following indication: for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 65 years of age and older and individuals 12 through 64 years who have at least one underlying condition that puts them at high risk for severe outcomes from COVID-19. Moreover, the company has agreed to a post marketing commitment (PMC) to assess the efficacy of the product among 50- to 64-year-old individuals in a randomized controlled trial. I concur with this approval and reach my decision based on the considerations outlined below.

Discussion

Reference is made to Novavax's original BLA (STN 125817/0) received on April 1, 2024, and subsequent amendments received on or before April 1, 2025, through which Novavax (Applicant) sought traditional approval of COVID-19 Vaccine, Adjuvanted (NUVAXOVID) for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. CBER has concluded, for the reasons outlined below, that the BLA be limited to the following individuals at high risk of severe COVID-19 outcomes: those age 65 and older and those from 12 to 64 years with at least one high risk feature listed by the Centers for

Disease Control and Prevention (CDC).[1] The Applicant submitted an amendment to the BLA revising their product labeling to align with this indication on May 12, 2025 and May 15, 2025. The Applicant's proposed changes are acceptable.

There are multiple reasons as to why CBER has decided to approve the BLA for individuals who are at high risk of severe outcomes from COVID-19 rather than a broad indication of all individuals 12 years and older. First, there are important limitations to the data submitted, including overreliance on potentially confounded observational data and a diminishing risk of severe outcomes from COVID-19 in the American population, coupled with known safety concerns, which fundamentally alters the benefit-risk calculation in non-high-risk individuals.

The randomized clinical trials of COVID-19 vaccines performed in 2020 and 2021 demonstrated acceptable efficacy against symptomatic COVID-19. Subsequent efficacy assessments for updated vaccine formulations against omicron subvariants have been based on immunogenicity data and observational or real-world data. Our ability to estimate clinical efficacy against novel COVID-19 variants from these types of studies is limited because the amount of protection conferred by an increase in neutralizing antibodies is unclear.[2] A 2025 observational study found antibody response to be significantly correlated with protection against self-reported repeat infection.[3] Although individuals with the highest neutralizing antibodies titers were found to have fewer repeat infections, it is unclear if the protection stemmed from factors innate to these individuals rather than from the absolute quantity of antibodies. Protection against future severe COVID-19 may predominantly come from other facets of the immune system, such as innate immunity or cell mediated immunity.[4,5] A causal relationship between a rise in neutralizing antibody titers and a diminished risk of severe COVID-19 outcomes has not been established, nor has the precise strength of such a relationship.

To date, FDA's regulatory approach for updated formulations of the SARS-CoV-2 vaccines has been similar to FDA's historical approach to updated yearly influenza vaccines. The SARS-CoV-2 virus and the influenza virus differ in important ways. First, infection with the SARS-CoV-2 virus has been shown to provide durable protection against future severe disease and death, which appears to outlast protection conferred by vaccination.[6] Second, the rate of viral evolution of SARS-CoV-2 is markedly slower than influenza. One analysis estimated SARS-CoV-2 has a replication rate 24-fold lower than influenza.[7] This slower rate of evolution is reflected in the

1. https://www.cdc.gov/covid/risk-factors/index.html
2 Zhang, B., Fong, Y., Fintzi, J. et al. Omicron COVID-19 immune correlates analysis of a third dose of mRNA-1273 in the COVE trial. Nat Commun 15, 7954 (2024). Zhang, B., Fong, Y., Fintzi, J. et al. Omicron COVID-19 immune correlates analysis of a third dose of mRNA-1273 in the COVE trial. Nat Commun 15, 7954 (2024).
3 Zhang B, Fong Y, Coronavirus Variant Immunologic Landscape Trial (COVAIL) Study Team. Neutralizing antibody immune correlates in COVAIL trial recipients of an mRNA second COVID-19 vaccine boost. Nat Commun. 2025 Jan 17;16(1):759.
4 Wang L, Nicols A, Turtle L, Richter A, Duncan CJ, Dunachie SJ, Klenerman P, Payne RP. T cell immune memory after covid-19 and vaccination. BMJ Med. 2023 Nov 22;2(1):e000468.
5 Neutralizing antibody immune correlates in COVAIL trial recipients of an mRNA second COVID-19 vaccine boost. Nat Commun. 2025 Jan 17;16(1):759. Zhang, 1 Coronavirus Variant Immunologic Landscape Trial (COVAIL) Study Team. Neutralizing antibody
6 COVID-19 Forecasting Team. Past SARS-CoV-2 infection protection against re-infection: a systematic review and meta-analysis. Lancet. 2023 Mar 11;401(10379):833-842.
7 Kawasaki Y, Abe H, Yasuda J. Comparison of genome replication fidelity between SARS-CoV-2 and influenza A virus in cell culture. Sci Rep. 2023 Aug 11;13(1):13105.

2025 World Health Organization's analysis and recommendation that updates in the JN.1 and KP.2 antigen targets are unlikely to be necessary for the upcoming 2025-2026 COVID-19 vaccine formulations.[8] The slower rate of viral evolution of SARS-CoV-2 is also consistent with the more robust protection against severe COVID-19 observed in subsequent seasons following prior infection[9] which may be mediated by cellular immunity[10] and is seen to a much lesser extent with the influenza virus.[11]

Observational data, which has generally been supportive of risk reduction from additional vaccine doses, is subject to multiple categories of bias, including, but not limited to the healthy vaccinee bias, which limits our ability to draw conclusions about vaccine efficacy. This bias is rooted in the fact that individuals seeking additional doses have different demographic characteristics, risk seeking, and health affirming behavior than those who do not, precluding reliable causal inference. This bias has been thoroughly documented for the COVID-19 and the influenza vaccine in numerous countries across the world. [12,13,14,15,16] Crucially, this bias was clearly demonstrated shown in one of the pivotal observational studies utilized to approve the initial COVID-19 booster shots, rendering its conclusions that boosters protected against COVID-19 mortality highly uncertain. [17,18]

Second, the risk of severe outcomes from COVID-19 has decreased dramatically over the last four years.[19,20] The infection fatality rate is estimated to have decreased approximately 10-fold

---

[8] https://www.who.int/news/item/15-05-2025-statement-on-the-antigen-composition-of-covid-19-vaccines#:~:text=As%20of%20May%202025%2C%20currently,to%20GISAID%20continues%20to%20increase.

[9] COVID-19 Forecasting Team. Past SARS-CoV-2 infection protection against re-infection: a systematic review and meta-analysis. Lancet. 2023 Mar 11;401(10379):833-842.

[10] Wang L, Nicols A, Turtle L, Richter A, Duncan CJ, Dunachie SJ, Klenerman P, Payne RP. T cell immune memory after covid-19 and vaccination. BMJ Med. 2023 Nov 22;2(1):e000468

[11] Patel MM, York IA, Monto AS, Thompson MG, Fry AM. Immune-mediated attenuation of influenza illness after infection: opportunities and challenges. Lancet Microbe. 2021 Dec;2(12):e715-e725.

[12] Høeg TB, Duriseti R, Prasad V. Potential "Healthy Vaccinee Bias" in a Study of BNT162b2 Vaccine against Covid-19. N Engl J Med. 2023 Jul 20;389(3):284-285.

[13] Fürst T, Bazalová A, Fryčák T, Janošek J. Does the healthy vaccinee bias rule them all? Association of COVID-19 vaccination status and all-cause mortality from an analysis of data from 2.2 million individual health records. Int J Infect Dis. 2024 May;142:106976

[14] Chemaitelly, H et al. Assessing healthy vaccinee effect in COVID-19 vaccine effectiveness studies: A national cohort study in Qatar. medRxiv 2024.07.28.24311115

[15] Riedmann U, Chalupka A, Richter L, Werber D, Sprenger M, Willeit P, Rijksen M, Lodron J, Høeg TB, Ioannidis JP, Pilz S. Underlying health biases in previously-infected SARS-CoV-2 vaccination recipients: A cohort study. J Infect. 2025 Apr 30;90(6):106497.

[16] Remschmidt, C, Wichmann O, Harder T. Frequency and impact of confounding by indication and healthy vaccinee bias in observational studies assessing influenza vaccine effectiveness: a systematic review. BMC Infect Dis. 2015 Oct 17;15:429.

[17] Arbel R, Hammerman A, Sergienko R, Friger M, Peretz A, Netzer D, Yaron S. BNT162b2 Vaccine Booster and Mortality Due to Covid-19. N Engl J Med. 2021 Dec 23;385(26):2413-2420.

[18] Høeg TB, Duriseti R, Prasad V. Potential "Healthy Vaccinee Bias" in a Study of BNT162b2 Vaccine against Covid-19. N Engl J Med. 2023 Jul 20;389(3):284-285.

[19] Erikstrup C, Laksafoss AD, et al. Seroprevalence and infection fatality rate of the SARS-CoV-2 Omicron variant in Denmark: A nationwide serosurveillance study. Lancet Reg Health Eur. 2022 Oct;21:100479.

[20] Riedmann U, Chalupka A, Richter L, Sprenger M, Rauch W, Krause R, Willeit P, Schennach H, Benka B, Werber D, Høeg TB, Ioannidis JP, Pilz S. COVID-19 case fatality rate and infection fatality rate from 2020 to 2023: Nationwide analysis in Austria. J Infect Public Health. 2025 Apr;18(4):102698

with the emergence of the omicron subvariants coupled with increased prior immunity rates.[21] Therefore, individuals who were previously at low risk of severe outcomes from COVID-19 now have minimal risk of death due to COVID-19. Already in 2022, the infection fatality rate among adults <73 years old without medical comorbidities was estimated to be under 0.007%. [22] Cumulative 2024-2025 COVID-19 hospitalization rates in the United States were lower than the 2024-2025 influenza season.[23]

The decrease in the chance of developing severe COVID-19, means that the potential for absolute benefit from vaccination has simultaneously decreased. Even rare vaccination-related harms, both known and unknown, now have a higher chance of outweighing potential benefits in non-high-risk populations. Some harm-benefit analyses suggested net harm of ongoing vaccination of low-risk populations.[24,25] Post vaccination myocarditis is a known risk of the Novavax vaccine[26] and there have been unfavorable imbalances in rates of neurological, cardiac and thrombotic adverse events among vaccine recipients reported by the Applicant.[27] These adverse events could represent significant risks for which studies to date have been underpowered to confidently attribute to vaccination. Although the FDA monitors the safety of all vaccines through post-market surveillance, it is important to acknowledge times at which the potential for benefit from vaccination among non-high-risk individuals is small and poorly defined.

While not a factor in my decision making, it is worth noting that the COVID-19 vaccine schedule of United States diverges from international consensus in recommending annual COVID-19 vaccinations to children and non-high-risk adults under the age of 65.[28] This was highlighted at the April 2025 ACIP meeting.[29]

Because the absolute potential for benefit among non-high-risk groups is minimal and there is substantial uncertainty about current vaccine efficacy, CBER is approving an indication in a patient population for whom the clinical benefits of ongoing vaccination are likely to outweigh

---

[21] Riedmann U, Chalupka A, Richter L, Sprenger M, Rauch W, Krause R, Willeit P, Schennach H, Benka B, Werber D, Høeg TB, Ioannidis JP, Pilz S. COVID-19 case fatality rate and infection fatality rate from 2020 to 2023: Nationwide analysis in Austria. J Infect Public Health. 2025 Apr;18(4):102698

[22] Erikstrup C, Laksafoss AD, et al. Seroprevalence and infection fatality rate of the SARS-CoV-2 Omicron variant in Denmark: A nationwide serosurveillance study. Lancet Reg Health Eur. 2022 Oct;21:100479. doi: 10.1016/j.lanepe.2022.100479. Epub 2022 Aug 5. PMID: 35959415; PMCID: PMC9355516.

[23] https://www.cdc.gov/resp-net/dashboard/index.html

[24] Krug A, Stevenson J, Høeg TB. BNT162b2 Vaccine-Associated Myo/Pericarditis in Adolescents: A Stratified Risk-Benefit Analysis. Eur J Clin Invest. 2022 May;52(5):e13759.

[25] Bardosh K, Krug A, Jamrozik E, Lemmens T, Keshavjee S, Prasad V, Makary MA, Baral S, Høeg TB. COVID-19 vaccine boosters for young adults: a risk benefit assessment and ethical analysis of mandate policies at universities. J Med Ethics. 2024 Jan 23;50(2):126-138.

[26] Macías Saint-Gerons D, Ibarz MT, Castro JL, Forés-Martos J, Tabarés-Seisdedos R. Myopericarditis Associated with the Novavax COVID-19 Vaccine (NVX-CoV2373): A Retrospective Analysis of Individual Case Safety Reports from VigiBase. Drugs Real World Outcomes. 2023 Jun;10(2):263-270.

[27] https://www.fda.gov/media/159897/download?attachment

[28] https://www.cdc.gov/acip/downloads/slides-2025-04-15-16/05-Panagiotakopoulos-COVID-508.pdf

[29] ibid, https://www.cdc.gov/acip/downloads/slides-2025-04-15-16/05-Panagiotakopoulos-COVID-508.pdf

the known risks. We have also requested and reached concurrence on a PMC study, in which a prospective, randomized, saline placebo-controlled clinical study will be conducted to determine if there are additional patient populations for whom a favorable benefit-risk profile exists. A successful outcome from the agreed-upon study may be submitted to the BLA to support future labeling changes. The Applicant and CBER agree that there is equipoise for such a study in individuals 50-65 years of age without risk factors, as illustrated by varying practice patterns among peer nations. The applicant's proposed PMC study and milestones are acceptable.

I acknowledge that the USPI includes safety and immunogenicity data in individuals 12 years of age and older, with and without high-risk conditions. Although the indication has been revised to exclude some of these individuals, I concur with inclusion of this additional information within the USPI. I believe availability of this additional information will facilitate transparency and ensure that all available safety and immunogenicity data is available to the US public.

Finally, and although this is not a factor in my decision making, I note that there is emerging consensus in the American medical community with regards to the approach and reasoning presented in this memorandum. On February 25, 2025 former FDA commissioner, Robert Califf, indicated in the Journal of the American Medical Association: "Covid vaccine uptake is now low enough that large RCTs are feasible to evaluate the efficacy and safety of new updated boosters."[30] He confirmed this view on May 9th, 2025, on his personal Substack[31] writing: “In the case of COVID-19 I believe it would now be quite reasonable, and even advisable, to conduct placebo-controlled trials for ‘boosters’ using updated versions of the vaccine in people who are not high-risk.”

In light of the considerations detailed here, I have concluded that this application should be approved under section 351(a) of the Public Health Service Act.

[30] Consequences and Opportunities From Poor Uptake of COVID Vaccinations Despite Strong Evidence | Medical Education and Training | JAMA | JAMA Network

[31] https://robcaliff272993.substack.com/p/thoughts-on-placebo-controlled-trials