CENTER DIRECTOR DECISIONAL MEMO

7/9/2025

BLA:	125752/276
Product Name:	SPIKEVAX (COVID-19 Vaccine, mRNA)
Indication:	Indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SPIKEVAX is approved for use in • Children 2 through 11 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19 • Infants and children 6 months through 23 months of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19.
Applicant:	ModernaTX, 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 sBLA 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 feel differently about certain aspects of their conclusions and instead reach the conclusion described below.

The decision to approve this supplemental Biologics License Application (BLA) for SPIKEVAX 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) for use in individuals 6 months through 11 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19.

ModernaTx, Inc. (Applicant) submitted an amendment to the BLA on June 19, 2025, revising their product labeling to align with this indication. Moreover, the company has agreed to a postmarketing commitment (PMC), and submitted an PMC Protocol Concept Sheet on June 2nd, 2025, to assess the efficacy of their product in 50- to 64-year-old individuals in a randomized controlled trial. The milestones described are acceptable. In light of the revised indication and PMC, I concur with this approval and reach my decision based on the considerations outlined below.

Summary Discussion

The manufacturer's application forces FDA CBER to confront the question: is there substantial certainty of a net clinical benefit (benefits outweigh harms) to vaccinating healthy children with this mRNA vaccine? CBER OCDs answer is, at the present time, with best available information, no. At the same time, CBER's answer for children with risk factors is: yes.

First, consider that COVID-19 severe disease, hospitalization and death is extremely low at pediatric ages, and has fallen, according to US CDC data from 2021-22 to the present. These rates are lower in healthy kids than kids with risk factors. Notably, the Applicant has agreed to a revised submission that focuses on kids with risk factors and FDA CBER has granted this approval.

Second, the Applicant has never shown a reduction in severe COVID-19, hospitalization, ICU stays or death in a randomized study in children. One reason why this has not been shown in randomized trials is that these events are so infrequent, the sample size for such a study would be massive. Although observational studies and case control studies have suggested these endpoints may be improved—those studies have methodologic limitations. Specifically, families who choose to vaccinate kids are fundamentally different than those who don't, and we cannot easily separate the treatment effect from those underlying differences. Case control studies hinge on the fact that cases and controls are sampled from the same underlying population, and this assumption is often incorrect.

Third, the Applicant has not shown that COVID-19 vaccination reduces long covid or transmission in any setting at any age with high quality data. Neither has the applicant nor a third party shown fewer missed days of school with high quality data. These endpoints cannot be considered for regulatory purposes. The FDA primary review teams have never allowed any company to make these claims about any COVID-19 vaccine, including for the Applicant.

Fourth, many of the studies the Applicant has submitted occurred in a COVID-19 landscape much different than the present day. Whether these studies retain relevance with wider population immunity and mutational changes to the virus is debated. One important factor in vaccinating kids is the fraction who were previously exposed to the virus through normal life. The potential upper bound absolute benefit to a kid who had and recovered from COVID is lower than one that has not been exposed to the virus. Yet, from the darkest hours of the pandemic to today, these rates have changed. Kids have broadly returned to normal life, and many more will encounter COVID-19 as it circulates year-round, from the moment of their birth. Vaccinating these individuals (healthy kids with natural immunity) carries massive uncertainty as to whether benefits outweigh risks.

Fifth, although COVID-19 vaccines have been given to billions of individuals and the harms have been studied in depth, no one knows if these products have harms that only materialize 10 or 20 years later, as such is a necessary limit of time. It is ignorant to claim that unknown long-term risks are not possible.

Sixth, much of the Applicant's submission concerns immunogenicity or the body's ability to make antibodies that neutralize the virus. Make no mistake—antibody titers are a surrogate endpoint. They can and do correlate with improved clinical outcomes in some, but not all

circumstances. Antibodies are not gold standard science, and one cannot be certain of net-clinical benefit merely because antibodies are increased. The human body does not actively manufacture all antibodies it is capable of producing at all times. Instead, it mobilizes antibody production from memory cells when appropriate. Vaccine doses can increase antibodies, but fail to further improve clinical outcomes. The proper interpretation of surrogate endpoints is key to understanding this application. CBER has shown flexibility and will accept these surrogate endpoints for children at high risk of severe COVID-19 outcomes, but will not for healthy children.

Seventh, CBER OCD's risk based regulatory philosophy to COVID-19 vaccination is no secret, has been announced publicly, and discussed widely. The CBER OCD and FDA Commissioner have published the framework in the *New England Journal of Medicine* (further discussed below), which broadly holds that vaccines for COVID-19 will be made available for elderly individuals (>65 years old) and younger individuals with risk factors for severe COVID-19 based on immunogenicity data, but that randomized trials measuring clinical outcomes will be required to approve these products for healthy individuals.

Eight, although not a consideration in CBER's decision making, it is worth noting that real-world use of COVID-19 vaccines in healthy kids is incredibly low. Rates of vaccination and hospitalization were so low, the CDC was unable to calculate observational vaccine effectiveness data for 2024-2025 from such thin data. FDA is ultimately accountable to the American people, and Americans have overwhelmingly stated that they feel the evidence to vaccinate a healthy child with a COVID-19 mRNA product is not enough to compel them to act. CBER OCD, after careful examination of the scientific evidence, agrees with the vast majority of Americans. Again, though not a factor in my decision making, CBER OCD notes that no European peer nation advises healthy children to undergo COVID-19 vaccination, and the US has been a global outlier with its push to vaccinate healthy children with a novel mRNA product.

FDA has a statutory mandate to only approve products when we have substantial certainty benefits outweigh harms, and in cases we do not, sponsors are free to prove to the agency and the American people the worth of their products with randomized trials. We do not have substantial certainty benefits outweigh risks for healthy children based on the totality of data in this submission, and a careful consideration of the biomedical literature. In the meantime, CBER OCD will exercise regulatory flexibility in making products available to kids at high risk of severe disease of COVID-19.

Specific Discussion

Reference is made to Moderna Tx, Inc.'s supplemental BLA (125752/276) received on January 7, 2025 and subsequent amendments received on or before May 30, 2025, through which ModernaTx, Inc. (Applicant) sought approval of COVID-19 Vaccine, mRNA (SPIKEVAX) for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 6 months through 11 years of age. 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 6 months through 11 years of age with at least one high risk underlying condition as defined by the Centers for

Disease Control and Prevention (CDC).[1] The Applicant has agreed to the revised indication and submitted an updated label. The Applicant's proposed changes to the label are acceptable.

The estimated efficacy of the vaccine is based primarily on three clinical studies which are insufficient to characterize the current clinical benefit of the SPIKEVAX vaccine in the population of children without high-risk conditions.

First, mRNA-1273-P204[2] was a phase 2-3 randomized clinical trial of individuals 6 months to 11 years of age, which was performed when the delta variant was dominant and 7.7% of included children had a prior history of known SARS-CoV-2 infection. Thus, the relevance of this trial is unclear in today's epidemiological circumstances and for children under 6 years of age, where rates of pre-exposure may vary.

Second, mRNA-1273-P306 Part 1 and Part 2[3] was a phase 3 study to evaluate safety and immunogenicity in participants aged 6 months to <6 years while the Omicron variant was circulating but did not assess vaccine efficacy against any clinical endpoints; the study instead measured the change in antibody responses following vaccination, which has uncertain relevance in terms of clinical benefit.

Third, mRNA-1273-P203 Part 3[4] was a study of neutralizing antibody geometric mean concentration ratios against Omicron BA.4/BA.5 and Original (D614G) strains in seropositive adolescent participants post-Dose 1 compared with seronegative young adult participants post-Dose 2. This study was performed when the Omicron variant was dominant and included adolescents with a prior history of infection but has unclear implications for children under 12 years of age and, perhaps even more importantly, the study did not use a placebo control and was performed when the comparator vaccine's efficacy against clinical disease was not established.

As such, there is uncertainty about the current clinical benefit of SPIKEVAX vaccination in children 6 months to 11 years of age against Omicron sublineage variants independent of whether they have a history of SARS-CoV-2 infection.

In addition to the limitations of the original pediatric clinical trials, the amount of protection conferred by an increase in neutralizing antibodies, used as surrogate endpoints in the second two studies, is unclear.[5] A 2025 observational study found antibody response to be significantly correlated with protection against self-reported repeat infection.[6] Although individuals with the highest neutralizing antibodies titers were found to have fewer repeat infections, it is uncertain if the protection stemmed from factors innate to these individuals or 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.[6,7] A causal relationship between a rise in or the absolute amount of 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.

Additionally, the risk of severe outcomes from COVID-19 has decreased dramatically over the last four years.[8] Hospitalizations from COVID-19 have declined even in the age group 6 months to 23 months between 2021 and 2025.[9] The infection fatality rate is estimated to have decreased approximately 10-fold with the emergence of the Omicron subvariants.[8] Individuals who were previously at low risk of severe outcomes from COVID-19 now have even lower risks of death, hospitalization and severe disease due to COVID-19. The current infection fatality rate in non-high-risk children is challenging to calculate as death due to COVID-19 in this group is extremely rare.[8,10]

Due to this decrease in disease severity, any vaccination-related harms have a greater potential of outweighing potential benefits in low-risk populations. Although the FDA monitors the safety of all vaccines through post market surveillance, it is important to acknowledge circumstances in which the potential for benefit from vaccination among non-high-risk individuals is small and poorly defined. Although mRNA COVID-19 vaccines have been given to hundreds of millions, if not billions of individuals, the long-term safety profile of these products remains unknown.

Observational data, which has generally been supportive of risk reduction from initial and 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—or children whose parents choose to vaccinate them-- 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.[11,12,13,14,15] Crucially, this bias was clearly demonstrated in one of the pivotal observational studies used to approve the initial COVID-19 booster shots, rendering its conclusions that boosters protected against COVID-19 mortality highly uncertain.[11,16]

The decrease in the chance of developing severe COVID-19, means that the potential for absolute benefit from vaccination has simultaneously decreased. While not a factor in my decision making, it is worth noting that the COVID-19 vaccine schedule of United States (prior to May 2025) diverged from international consensus in recommending annual COVID-19 vaccinations for children.[17,18] This was highlighted at the April 2025 ACIP meeting[17] and discussed in the FDA's framework for COVID-19 vaccine approvals, "An Evidence-Based Approach to Covid-19 Vaccination" published in the *New England Journal of Medicine* on May 20th, 2025.[18]

Because the absolute potential for benefit among non-high-risk children is, at best, marginal

and because there is substantial uncertainty about vaccine efficacy against omicron variants coupled with higher rates of some adverse events among vaccine recipients[2] and, although rare, the possibility of serious harms from mRNA vaccination in this age group[19], including unknown long term risks, CBER OCD favors focusing the indication on a patient population for whom the clinical benefits of initial or ongoing vaccination have a greater potential of outweighing the known and unknown risks, in line with our statutory responsibility and duty.

We have also requested 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. The rationale for this study has also been outlined publicly in the aforementioned May 20th, 2025, *New England Journal of Medicine* publication.[15] A successful outcome from the agreed-upon study may be submitted to the BLA to support future labeling changes. There is equipoise for such a study in individuals 50 through 64 years of age without risk factors, as illustrated by varying practice patterns among peer nations.[18]

I acknowledge that the USPI includes safety and immunogenicity data in individuals 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.

Additionally, although not a factor in my decision making, at the May 25, 2025 Vaccines and Related Biological Products Advisory Committee (VRBPAC), the CDC noted that uptake of COVID-19 vaccines in children is extremely low. Moreover, due to methodologic limitations, observational vaccine effectiveness was not calculated in children for the 2024-25 season, and only data from adult recipients were presented. Parents and doctors do not appear convinced most children should receive COVID-19 vaccines to healthy children without additional substantive evidence of benefit.

FDA has a regulatory duty to only grant marketing authorization in settings where we have substantial certainty the benefits outweigh the risks. For healthy children that standard is not met. This view is in line with the majority of the globe that does not pursue vaccination in healthy children. Future randomized trials measuring clinical endpoints and safety are needed to alter this position.

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.

References:

1. CDC, People with Certain Medical Conditions and COVID-19 Risk Factors, June 2025. https://www.cdc.gov/covid/risk-factors/index.html
2. Creech CB, Anderson E, et al; KidCOVE Study Group. Evaluation of mRNA-1273 Covid-19 Vaccine in Children 6 to 11 Years of Age. N Engl J Med. 2022 May 26;386(21):2011-2023.
3. Dixit A, Bennett R, et al; ROVER Study Investigators. Interim safety and immunogenicity of COVID-19 omicron BA.1 variant-containing vaccine in children in the USA: an open-label non-randomised phase 3 trial. Lancet Infect Dis. 2024 Jul;24(7):687-697.
4. BLA Clinical Review Memorandum https://www.fda.gov/media/172357/download
5. 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).
6. 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.
7. 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.
8. 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
9. Thornburg, N. 2024-2025 Update on Current Epidemiology of COVID-19 and SARS-CoV-2 Genomics. CDC May 2025 https://www.fda.gov/media/186593/download
10. Hani E, Bertran M, Powell A, Williams H, Birrell P, DeAngelis D, Ramsay ME, Oligbu G, Ladhani SN. Significantly lower infection fatality rates associated with SARS-CoV-2 Omicron (B.1.1.529) infection in children and young people: Active, prospective national surveillance, January-March 2022, England. J Infect. 2023 Apr;86(4):397-398. doi: 10.1016/j.jinf.2023.01.032.
11. 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.RCA_Tox_Chem_Google-tbhv2
12. 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
13. 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.
14. 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
15. 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.
16. 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.
17. CDC, Use of 2025–2026 COVID-19 Vaccines:Work Group Considerations, April 2025 https://www.cdc.gov/acip/downloads/slides-2025-04-15-16/05-Panagiotakopoulos-COVID-508.pdf
18. Prasad V, Makary MA. An Evidence-Based Approach to Covid-19 Vaccination. N Engl J Med.

2025 May 20. doi: 10.1056/NEJMsb2506929
19. Su, John R. Adverse events among children ages 5–11 years after COVID-19 vaccination: updates from v-safe and the Vaccine Adverse Event Reporting System (VAERS).December 2021. https://stacks.cdc.gov/view/cdc/112668