

FDA Briefing Document

Vaccines and Related Biological Products Advisory Committee Meeting

June 28, 2022

SARS-CoV-2 strain composition of COVID-19 vaccines

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1. Meeting Objective

The ongoing COVID-19 pandemic continues to present an extraordinary challenge to global public health, and response to the pandemic has been complicated by the rapid evolution of the virus. While the development, authorization and deployment of safe and effective COVID-19 vaccines has been a critical component of the global response to the pandemic, uncertainties about the future course of the pandemic along with an incomplete understanding of SARS-CoV-2 immunology leave open scientific and policy questions regarding the optimal use and further development of COVID-19 vaccines. At a previous Vaccines and Related Biological Products Advisory (VRBPAC) meeting on April 6, 2022, the committee discussed considerations that should inform strain composition decisions to ensure that available COVID-19 vaccines continue to meet public health needs, when and how frequently to consider strain composition changes, and the process that should be used for making a recommendation for updating the vaccine strain composition. As a follow-up to the April 6th VRBPAC discussion, this June 28th, 2022 VRBPAC meeting is being held to discuss whether and how the SARS-CoV-2 strain composition of COVID-19 vaccines should be modified. The VRBPAC will consider information from presentations discussing: current data on the evolution of SARS-CoV-2 variants, effectiveness of currently available COVID-19 vaccines, and modeling predictions for the potential future evolution of the COVID-19 pandemic; recently released recommendations from the World Health Organization (WHO) on updates to the composition of COVID-19 vaccines; immunogenicity data from clinical studies evaluating COVID-19 vaccines with various strain compositions; and the US Food and Drug Administration (FDA) perspective on the considerations for strain composition modifications of COVID-19 vaccines. Following these presentations, the VRBPAC will be asked to discuss several questions regarding considerations for and data needed to support authorization of modified COVID-19 vaccines, and then the VRBPAC will be asked to vote on a recommendation for the COVID-19 vaccine strain composition to be used for booster doses.

2. Background

2.1 SARS-CoV-2 Pandemic

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of June 17, 2022, has caused approximately [536 million cases of COVID-19, including 6.3 million deaths](#) worldwide. In the United States (U.S.), more than [85.9 million cases and 1 million deaths](#) have been reported to the Centers for Disease Control and Prevention (CDC). In addition to case fatalities, COVID-19 has been responsible for significant short-term and long-term morbidity. Furthermore, the pandemic has caused significant challenges and disruptions in worldwide healthcare systems, economies, and many other aspects of human activity (e.g., travel, employment, and education).

Since the start of the pandemic caused by the original Wuhan strain of SARS-CoV-2 (ancestral or prototype strain), surges in SARS-CoV-2 activity and resultant COVID-19 cases, hospitalizations, and deaths have been associated with a combination of factors, including but not limited to: emergence of variants with greater transmissibility; greater virulence, and/or antigenic mutations, enabling at least partial escape from immunity conferred by prior vaccination or infection; relaxation of public health measures aimed at preventing transmission; and seasonal variation typical of respiratory viruses. Recent surges, both globally and in the U.S., have been associated with rapid spread of highly transmissible SARS-CoV-2 variants, e.g., Delta (B.1.617.2) and Omicron (B.1.1.529). The Omicron variant became the predominant variant circulating in the U.S. in December 2021, and while COVID-19 cases, hospitalizations, and deaths in the U.S. have declined since the peak of the Omicron surge in January 2022 ([CDC Data Tracker](#)), the Omicron variant continues to evolve into sublineages that have been associated with recent increases in COVID-19 case rates (see below) ([CDC Variant Proportions](#) and [CoVariants](#)). In addition, population-level evidence suggests an increased reinfection risk associated with the Omicron variant compared to earlier SARS-CoV-2 variants ([Pulliam et al, 2022](#)).

2.2 FDA Authorized and Approved COVID-19 Vaccines

Two COVID-19 vaccines (both based on an mRNA platform encoding the SARS-CoV-2 Spike (S) protein from the Wuhan strain containing a D614G mutation) have been approved by the FDA for use as a 2-dose primary series for active immunization to prevent COVID-19 caused by SARS-CoV-2. Comirnaty (manufactured by Pfizer Inc. for BioNTech Manufacturing GmbH) is approved for use in individuals 16 years of age and older, and Spikevax (manufactured for Moderna US, Inc.) is approved for use in individuals 18 years of age and older. These two vaccines have also received emergency use authorization (EUA) for additional uses related to active immunization to prevent COVID-19 caused by SARS-CoV-2.

The Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) is authorized for use as a: 3-dose primary series in individuals 6 months through 4 years of age; 2-dose primary series in individuals 5 years of age and older; third primary series dose in individuals 5 years of age and older with certain types of immunocompromise;¹ first booster dose in individuals 5-17 years of age at least 5 months after completion of a primary series; first booster dose in individuals 18 years of age and older after completion of primary vaccination with any authorized or approved COVID-19 vaccine (with the same interval as authorized for a booster dose with the vaccine used for primary vaccination); and second booster dose at least four months after a first booster dose of any authorized or approved COVID-19 vaccine in individuals 50 years of age and older and individuals 12-49 years of age with certain types of immunocompromise.

The Moderna COVID-19 Vaccine (mRNA-1273) is authorized for use as a: 2-dose primary series in individuals 6 months of age and older; third primary series dose in individuals 6 months of age and older with certain types of immunocompromise; first booster dose in individuals 18 years of age and older after completion of primary vaccination with any authorized or approved COVID-19 vaccine (with the same interval as authorized for a booster dose with the vaccine used for primary vaccination); and second booster dose at least four months after a first booster

¹ Individuals who have undergone solid organ transplantation or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

dose of any authorized or approved COVID-19 vaccine in individuals 50 years of age and older and individuals 18-49 years of age with certain types of immunocompromise.

In addition to the two authorized and approved mRNA COVID-19 vaccines, the Janssen COVID-19 Vaccine (based on a replication-deficient adenovirus type 26 vector platform encoding the SARS-CoV-2 S protein from the Wuhan strain with D614G mutation) is available under EUA for use in individuals 18 years of age and older for whom other FDA-authorized or approved COVID-19 vaccines are not accessible or clinically appropriate, and in individuals 18 years of age and older who elect to receive the Janssen COVID-19 Vaccine because they would otherwise not receive a COVID-19 vaccine. The Janssen COVID-19 Vaccine is authorized for use in these populations as a single primary vaccination dose and a single booster dose after completion of primary vaccination with any authorized or approved COVID-19 vaccine (with the same interval as authorized for a booster dose with the vaccine used for primary vaccination).

An EUA request for the Novavax COVID-19 Vaccine, Adjuvated (an adjuvanted protein subunit COVID-19 vaccine that contains purified, full-length SARS-CoV-2 recombinant S protein that is stabilized in its prefusion conformation, and saponin-based adjuvant, Matrix-M.) for use in individuals 18 and older as a 2-dose primary series has been submitted by Novavax, Inc. and was discussed at a VRBPAC meeting on June 7th, 2022. Other COVID-19 vaccines based on various platforms have been authorized or approved for use in other countries but are not authorized or approved for use in the U.S. ([WHO Vaccine Tracker](#)).

2.3 Current Information on FDA Authorized and Approved COVID-19 Vaccine Effectiveness

While the currently authorized and approved COVID-19 vaccines in the U.S. are based on the original Wuhan strain, recently and currently circulating SARS-CoV-2 variants harbor mutations in the S protein that confer at least partial antigenic escape from vaccine-elicited immunity.

Nonetheless, currently available vaccines have retained some level of effectiveness against all epidemiologically important SARS-CoV-2 variants that have emerged to date, with higher level effectiveness preserved against more serious outcomes (hospitalization and death) than against mild symptomatic disease ([Tseng, et al, 2022](#); [Andrews, et al, 2022](#); [Taylor, et al, 2022](#); [Korves,](#)

[et al, 2022](#); [Stowe, et al, 2022](#); [Ferdinands, et al, 2022](#); [Chemaitelly, et al, 2022](#); [Tenforde, et al, 2022](#); [Arbel, et al, 2022](#); [Bar-On, et al, 2022](#); [Gazit, et al, 2022](#)).

Results from observational studies that have investigated the effectiveness of primary vaccination with authorized and approved vaccines have shown decreased effectiveness against certain variants (notably Omicron, for which neutralizing antibody titers are decreased compared with the Wuhan strain) and waning effectiveness over time ([Tseng, et al, 2022](#); [Andrews, et al, 2022](#); [Taylor, et al, 2022](#)). Although first booster doses have restored waning vaccine effectiveness (VE), including against severe disease and hospitalization associated with Omicron ([Tseng, et al, 2022](#); [Andrews, et al, 2022](#); [Taylor, et al, 2022](#); [Korves, et al, 2022](#)), observational studies have also indicated waning effectiveness of the first booster dose over time, mainly against mild disease, with some studies also suggesting waning effectiveness against hospitalization ([Tseng, et al, 2022](#); [Stowe, et al, 2022](#); [Ferdinands, et al, 2022](#); [Chemaitelly, et al, 2022](#)) and lower effectiveness among the immunocompromised ([Tenforde, et al, 2022](#)).

The Israeli experience with a second booster dose of the Pfizer-BioNTech COVID-19 Vaccine in adults 60 years of age and older indicates that a second booster dose improves VE overall, including through a reduction in mortality ([Arbel, et al, 2022](#); [Bar-On, et al, 2022](#); [Gazit, et al, 2022](#)), although effectiveness against mild disease decreased during a 10-week follow-up period.

Additional information on COVID-19 vaccine effectiveness will be presented at the VRBPAC meeting by staff from the CDC.

3. Considerations for Strain Composition of COVID-19 Vaccines

3.1 General Considerations

Currently authorized and approved COVID-19 vaccines are monovalent formulations based on the S protein from a SARS-CoV-2 virus that circulated early in the pandemic. Although a complete understanding of how emerging SARS-CoV-2 variants impact the effectiveness of current COVID-19 vaccines is lacking, the accumulating data suggest a current need to update COVID-19 vaccines to target circulating variants of concern (VOC) with the goal of improving vaccine effectiveness against these VOC. The decision to recommend changing the strain

composition of COVID-19 vaccines is complex and should be data driven. Implementing a strain composition change into practice will require FDA authorization or approval prior to deployment. The potential benefits offered by an updated vaccine containing a variant-specific component will have to be weighed against multiple uncertainties, including the future course of virus evolution, the lack of clinical efficacy data compared to earlier prototype vaccines, and potential manufacturing issues that might arise related to producing an updated vaccine formulation. A decision to modify the strain composition of COVID-19 vaccines would likely be supported by evidence that:

- Circulating SARS-CoV-2 virus variants are antigenically distinct from the strain included in current vaccines;
- Currently available vaccines are less effective against circulating virus variants than against previously circulating strains of virus;
- Candidate vaccines with an updated strain composition that is more closely matched to new circulating virus can be manufactured according to requirements for quality and consistency and in sufficient quantity to meet public health needs; and
- Candidate vaccines with such an updated strain composition would be more effective against circulating and potentially emerging virus variants and would have a more favorable benefit-risk balance than currently available vaccines.

3.2 April 6, 2022 VRBPAC Discussion

On April 6, 2022, the [172nd meeting of the VRBPAC](#) convened in open session to discuss considerations for future COVID-19 vaccine booster doses and the process for COVID-19 vaccine strain selection to address current and emerging variants. The committee heard presentations on: the epidemiology of SARS-CoV-2 strains (H Scobie, CDC); COVID-19 vaccine effectiveness (R Link-Gelles, CDC); the Israeli experience with a 2nd booster dose of Pfizer-BioNTech COVID-19 Vaccine in adults (S Alroy-Preis, Ministry of Health, Jerusalem and R Milo, the Weizmann Institute, Rehovot, Israel); future SARS-CoV-2 variants predictions (J Beigel, NIH and T Bedford, Fred Hutchinson Cancer Research Center); modeling of future U.S. COVID-19 outbreaks (C Murray, University of Washington); the WHO perspective on

variants for COVID-19 vaccine composition (K Subbarao, WHO Collaborating Center for Reference and Research on Influenza, Melbourne, Australia); and manufacturing timeline considerations (R Johnson, BARDA).

Following the FDA presentation of a proposed framework for addressing future COVID-19 vaccine strain composition, the committee was then asked to discuss the following questions:

1. What considerations should inform strain composition decisions to ensure that available COVID-19 vaccines continue to meet public health needs, e.g.:
 - a. Role of VRBPAC and FDA in coordinating strain composition decisions
 - b. Timelines needed to implement strain composition updates
 - c. Harmonization of strain composition across available vaccines
2. How often should the adequacy of strain composition for available vaccines be assessed?
3. What conditions would indicate a need for updated COVID-19 vaccine strain composition, and what data would be needed to support a decision on a strain composition update?
4. What considerations should guide the timing and populations for use of additional COVID-19 vaccine booster doses?

There was general agreement among committee members that given the complexities of changing COVID-19 vaccine strain composition, decisions on vaccine strain composition should be undertaken as a coordinated process led by FDA, with input from VRBPAC, and with consideration of any global recommendations that WHO might provide. The committee noted that any strain change decision should be data-driven, and that there should be evidence that the current vaccine strain composition is not adequately effective against severe disease caused by circulating variants coupled with compelling evidence that a proposed modified vaccine composition will provide improved vaccine effectiveness. There was relatively uniform agreement that a single vaccine composition to be used by all manufacturers was desirable. Committee members expressed that, ideally, a vaccine based on a modified strain composition could be used for both primary vaccination and booster. The April 6th meeting was not intended to make a specific recommendation for COVID-19 vaccine strain composition and the committee did not suggest specific strain recommendations. Rather, the committee acknowledged that

continued monitoring of vaccine effectiveness, virus variant epidemiology, and clinical immunogenicity evaluation of modified vaccines would be critical for decisions of the strain composition of COVID-19 vaccines.

3.3 WHO Recommendations for COVID-19 Vaccine Strain Composition

WHO has established the Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC) to review and assess the public health implications of emerging SARS-CoV-2 VOC on the performance of COVID-19 vaccines and to provide recommendations to WHO on COVID-19 vaccine strain composition. The TAG-CO-VAC issued an [interim statement](#) on March 8, 2022, in which it noted that in order to continue to provide optimal protection into the future, COVID-19 vaccines may need to be updated as antigenically distinct virus variants emerge. The TAG-CO-VAC encouraged COVID-19 vaccine manufacturers to generate and provide data on the performance of current and variant-specific COVID-19 vaccines so that the TAG-CO-VAC could provide more specific advice to WHO on adjustments needed to inform COVID-19 vaccine strain composition. Further guidance from the TAG-CO-VAC was provided in an updated [interim statement](#) on June 17, 2022. The key recommendations in this most recent interim statement are as follows:

- The use of currently available vaccines based on prototype virus strains from early in the pandemic provide a high level of protection against severe disease outcomes for all virus variants, including Omicron, if the primary vaccination series is supplemented with a booster vaccine dose.
- Broader immunity against recent circulating virus variants may be achieved by including an Omicron component in a booster vaccine dose to those who have previously received a COVID-19 vaccination primary series.
- The use of an Omicron-specific monovalent vaccine as a primary series was not advised because of the uncertainty of whether such a vaccine would elicit the same level of protection against severe illness as previously demonstrated for prototype COVID-19 vaccines.

The June 17, 2022, TAG-CO-VAC statement acknowledged the limited amount of data currently available and the considerable uncertainties that remain, including the course of SARS-CoV-2 evolution and the relative performance of variant-specific vaccine formulations. The TAG-CO-VAC continued to strongly encourage the generation of additional clinical immunogenicity data from Omicron-specific candidate vaccines from a variety of vaccine platforms.

3.4 Epidemiology and Antigenic Characterization of Current SARS-CoV-2 Variants of Concern

SARS-CoV-2 evolution was apparent within months after the beginning of the pandemic (e.g., D614G mutation) and has continued as the virus further adapts to replication in the human host. Some new genetic variants, classified as variants of interest (VOI) and VOC, are more infectious, transmissible, and antigenically distinct from earlier virus strains. To date there have been five designated VOCs – Alpha, Beta, Gamma, Delta, and Omicron. The Omicron VOC emerged in late 2021 and rapidly became the dominant circulating SARS-COV-2 virus variant. Omicron appears to have evolved independently from previous VOC and compared to early strains of SARS-CoV-2 (e.g., Wuhan) and the previous VOCs (e.g., Alpha, Beta, Gamma, and Delta) contains many more amino acid mutations.

Compared to the prototype strain spike (S) antigen used in currently available COVID-19 vaccines, the Omicron S protein has more than 30 mutations, 15 of which are in the spike receptor binding domain (RBD), the predominant target of neutralizing antibodies elicited by infection and vaccination. Even as the original form of Omicron (designated as BA.1 variant) spread rapidly around the world, the virus continued to evolve and at the present time, several sublineages of Omicron are in circulation in various parts of the world. In the U.S., by late December 2021 Omicron BA.1 had become the dominant virus variant, replacing the previously dominant Delta variant. By early April 2022, Omicron BA.2 became the dominant virus strain in the U.S, but by late April and early May, another Omicron sublineage virus, BA.2.12.1, began rapidly spreading and became the dominant strain in the U.S. Recently, two other Omicron sublineages, BA.4 and BA.5, which appeared in South Africa in March 2022, have spread to the U.S. and have begun to increase rapidly in proportion to the virus population.

The large number of mutations in the Omicron variant and its sublineages, compared to previous circulating VOCs, is of particular concern, primarily due to the large number of mutations in the S protein, including mutations in the RBD known to be important for ACE2 receptor binding and antibody recognition. Several studies documented that sera from previously infected or vaccinated individuals had substantially reduced neutralization titers to Omicron BA.1 and BA.2 compared to previously circulating virus strains (e.g., D614G) and most approved or authorized monoclonal antibodies have reduced activity to Omicron ([Mannar et al., 2022](#); [Zhou et al., 2022](#); [Iketani et al., 2022](#); [Lusvarghi et al., 2022](#)). Neutralization titers against recent Omicron sublineages (e.g., BA.2.12.1 and BA.4/BA.5) elicited by current COVID-19 vaccines appear to be further reduced ([Qu et al 2022](#); [Hachmann et al., 2022](#)). In addition, Omicron infection of previously unvaccinated individuals results in a neutralizing antibody response that is not extensively cross-reactive for other SARS-CoV-2 VOCs. On the other hand, however, Omicron infection following vaccination appears to improve neutralizing antibody titers against other VOCs ([Richardson et al., 2022](#)). Although the sublineages of Omicron are antigenically closer to each other than Omicron is to previously circulating variants, the amino acid changes among the different sublineages may still be significant in the context of cross-protection.

Within the S protein, BA.2 has an additional six amino acid changes relative to BA.1, two in the N-terminal domain (NTD) (T19I and V213G) and four in the RBD (S371F, T376A, D405N, and R408S) ([CoVariants](#)). There is also a nine-nucleotide deletion in the NTD of BA.2 that results in deletions of amino acids 24-26 and mutation A27S. The more recently characterized Omicron sublineages BA.2.12.1 and BA.4 and BA.5 share many of the S protein mutations present in BA.2 (the Spike amino acid sequences of BA.4 and BA.5 are identical and can be considered together for vaccine purposes). For example, BA.2.12.1 is identical to BA.2 with the exception of two additional amino acid changes at L452Q (in the RBD) and S704L (not in the RBD). The BA.4/BA.5 S protein sequence is also similar to that of BA.2 except that the Q493R change is absent, and additional changes are present at L452R and F486V (both in the RBD). The BA.4/BA.5 sublineages also share the deletions at H69 and V70 present in Omicron BA.1. Numerous studies to compare and contrast the cross-protection afforded by Omicron sublineages are ongoing.

3.5 Clinical Studies of Candidate COVID-19 Variant Vaccines to Inform Vaccine Strain Composition

As outlined in Guidance for Industry “[Emergency Use Authorization for Vaccines to Prevent COVID-19](#),” FDA recommends that the effectiveness of a modified COVID-19 vaccine against a particular VOC can be evaluated based on: efficacy of primary vaccination with the manufacturer’s authorized or approved prototype COVID-19 vaccine made by the same process and for which a clinical disease endpoint efficacy study has been conducted that met FDA pre-specified success criteria, and a comparison of immune responses (assessed by neutralizing antibody) induced by the modified vaccine and the prototype vaccine. The evaluation of modified vaccines for the purpose of vaccine strain composition decisions will need to rely mainly on comparative immunogenicity data due to the time constraints involved in vaccine manufacturing and clinical efficacy evaluation.

Toward that goal, several vaccine manufacturers have prepared various modified vaccine candidates for evaluation in clinical trials. Considering the current epidemiology, studies with candidate vaccines containing an Omicron variant Spike provide the most relevant information to inform a recommendation for a modified vaccine composition. The following sections are a summary of study analyses presented by sponsors of candidate vaccines containing an Omicron variant Spike.² Much of the data are derived from assays that have not completed validation and the data and the analyses have not yet been independently verified.

Studies with Moderna mRNA vaccine candidate mRNA-1273.214 (bivalent, prototype plus Omicron)³

Previously uninfected subjects (adults, 18 years of age and older) received a 2nd booster (4th dose) of either mRNA-1273 (N=260; 50 µg mRNA encoding prototype S protein) or candidate

² Novavax will be presenting data on the use of their Novavax COVID-19 Vaccine, Adjuvated as a booster to address SARS-CoV-2 variants. This vaccine was developed against the prototype virus.

³ [See Moderna Press Release: 06/08/2022](#)

vaccine mRNA-1273.214 (N=334; bivalent vaccine containing 25 µg each of mRNA encoding prototype S protein and mRNA encoding Omicron/BA.1 S protein).

Compared to the prototype booster, the bivalent mRNA-1273.214 booster elicited a non-inferior neutralizing antibody response against prototype (ancestral) SARS-CoV-2 with a higher neutralizing antibody geometric mean titer (GMT) for mRNA-1273.214 (5977; 95% CI: 5322, 6713) compared to mRNA-1273 (5649; 95% CI: 5057, 6311); the GMT ratio (mRNA-1273.214 over mRNA-1273) was 1.22 (95% CI: 1.08, 1.37).

Compared to the prototype booster, the bivalent mRNA-1273.214 booster elicited a statistically superior neutralizing antibody response against Omicron/BA.1 SARS-CoV-2. The GMT for mRNA-1273.214 was 2372 (95% CI: 2071, 2718) compared to 1473 (95% CI: 1271, 1708) for mRNA-1273. The GMT ratio (mRNA-1273.214 over mRNA-1273) was 1.75 (95% CI: 1.49, 2.04).

The data from this study suggest that inclusion of an Omicron component in the 2nd booster vaccination (4th dose) improves the neutralizing antibody response against Omicron/BA.1 compared to the prototype vaccine and does not negatively affect the neutralizing antibody response against the ancestral strain of virus against which the prototype vaccine was designed. There are caveats to be noted relevant to the interpretation of these data that will be discussed at the advisory committee meeting.

Studies with Pfizer and BioNTech Omicron mRNA vaccine candidate BNT162b2 OMI

In one study, subjects (18 to 55 years of age with or without evidence of prior infection) received a 2nd booster (4th dose) of either BNT162b2 (30 µg prototype mRNA vaccine) or candidate vaccine BNT162b2 OMI (30 µg Omicron mRNA).

In the primary immunogenicity analysis of participants without evidence of prior infection, BNT162b2 OMI (N=132) elicited a superior neutralizing antibody response to the Omicron SARS-CoV-2 virus compared to the prototype booster (N=141). The BNT162b2 OMI GMT against Omicron was 1929 (CI: 1632, 2281) compared to a BNT162b2 GMT of 1100 (CI: 932, 1297); GMT ratio 1.75 (95% CI: 1.39, 2.22).

Compared to the prototype booster, BNT162b2 OMI elicited a similar neutralizing antibody response to the prototype (ancestral) SARS-CoV-2 virus. The BNT162b2 OMI GMT was 11997 (CI: 10554, 13638) compared to a BNT162b2 GMT of 12009 (CI: 10744, 13425).

In a second study in subjects ≥ 55 years of age, vaccine dose levels of 30 and 60 μg of monovalent vaccine BNT162b2 OMI and bivalent (BNT162b2 + BNT162b2 OMI) vaccine at 30 and 60 μg were compared to prototype BNT162b2 vaccine (30 μg). Approximately 300 previously vaccinated subjects were randomized into each group.

In the evaluable immunogenicity analysis of participants without evidence of prior infection, the GMT ratios for the 30 μg (N=169) and 60 μg (N=174) of monovalent vaccine BNT162b2 OMI (GMT 1015 and 1435, respectively) to the 30 μg (N=163) BNT162b2 prototype vaccine (GMT 456) were 2.23 (CI: 1.65, 3.00) and 3.15 (CI: 2.38, 4.16), respectively. The neutralizing antibody response to prototype virus are available from a sentinel group and show similar neutralizing antibody titers against the prototype and the delta virus across vaccine groups.

In the evaluable immunogenicity analysis of participants without evidence of prior infection, the GMT ratios for the 30 μg (N=178) and 60 μg (N=175) of bivalent vaccine BNT162b2 + BNT162b2 OMI (GMT 711 and 900, respectively) to the 30 μg (N=163) BNT162b2 prototype vaccine (GMT 456) were 1.56 (CI: 1.17, 2.08) and 1.97 (CI: 1.45, 2.68), respectively. The neutralizing antibody response to prototype virus are available from a sentinel group and show similar neutralizing antibody titers against the prototype and the delta virus across vaccine groups.

The data from these two studies suggest that an Omicron monovalent vaccine or Omicron plus ancestral bivalent vaccine as the 2nd booster vaccination (4th dose) improves the neutralizing antibody response to Omicron BA.1 compared to the prototype vaccine and does not negatively affect the neutralizing antibody response against the ancestral strain of virus against which the prototype vaccine was designed. There are also caveats to be noted relevant to the interpretation of these data that will be discussed at the advisory committee meeting.

3.6 Considerations for Primary Series Strain Composition

Available data indicate that currently authorized and approved COVID-19 vaccines based on the ancestral Wuhan strain (prototype vaccines) continue to provide protection against the most severe manifestations of COVID-19 caused by predominant SARS-CoV-2 variants. However, this protection is decreased compared to previously circulating variants, is subject to waning (in particular in populations at highest risk of severe COVID-19) and may be further impacted as newly emergent variants become predominant. Several lines of reasoning could potentially support a recommendation for moving toward primary series vaccination with an updated strain composition that is more closely matched with currently circulating variants; these include the prospect for improved vaccine effectiveness immediately after completion of the primary series (which would be limited to those individuals who have not already received a primary series) and the benefit of avoiding programmatic complexity that would accompany a different strain composition for booster doses than for primary series doses (in addition to the different presentations in use for various age groups).

On the other hand, clinical data are quite limited to inform the safety and effectiveness of modified COVID-19 vaccines for use in primary series regimens. Available data appear to indicate that monovalent vaccines (including one example of an Omicron monovalent vaccine) elicit a primary series neutralizing antibody response that is more narrowly directed against the specific vaccine antigen, and clinical data are not available to inform the breadth and robustness of the immune response elicited by primary vaccination with bivalent modified vaccines (e.g., ancestral plus Omicron). Thus, any recommendation at this time to transition to use of modified vaccines for primary vaccination would be based largely on extrapolation from data with booster doses administered to individuals who were primed with the ancestral antigen. In considering these and other factors, the WHO TAG-CO-VAC has recommended that prototype vaccines continue to be acceptable for primary vaccination (see [Section 3.3](#)).

4. Next Steps

As discussed in [Section 3.2](#), the April 6, 2022, VRBPAC agreed that the decisions on vaccine strain composition should be undertaken as a coordinated process led by FDA. This year is a

transitional year as we begin the process of strain selection for COVID-19 vaccines that more closely match the currently circulating virus variants. This VRBPAC meeting continues the FDA-led process of making data-driven decisions on vaccine strain composition for the 2022-2023 season, taking into account the VRBPAC input and global recommendations that WHO provided.

The April 6th VRBPAC noted that, in order to make a strain change decision, there should be evidence that current vaccine strain composition is not adequately effective against severe disease caused by circulating variants. In Sections [2.3](#) and [3.4](#) the current information on FDA-authorized and approved COVID-19 vaccine effectiveness and the state of SARS-CoV-2 VOC was discussed. Considering the current available data, FDA is requesting a VRBPAC discussion about whether a change is now necessary and what the optimal variant strain composition would be for the 2022-2023 season.

4.1 Options for Consideration in Recommending the Strain Composition of COVID-19 Vaccines

The current epidemiology of SARS-CoV-2, the evidence of waning immunity elicited by current COVID-19 vaccines, and the available immunogenicity data generated from a limited number of variant-specific vaccine candidates suggest that an updated vaccine composition may provide added benefit against currently circulating virus variants. This may be particularly important as the 2022-2023 winter season progresses and the risk of another major COVID-19 outbreak increases due to the combination of waning immunity, further evolution of variants, and increased indoor activity. Nevertheless, as noted above, uncertainties remain, and there are potential trade-offs associated with various options for modifying the composition of current vaccines. [Table 1](#) lists some of the possible options for consideration.

Table 1. Strain Recommendation Options

Number	Options	Pros	Cons
1	Make no recommendation	<ul style="list-style-type: none"> • Allows each manufacturer to pursue their own development options and work with the FDA to authorize/license based on current criteria and guidance • Maintains adequate supply of vaccine 	<ul style="list-style-type: none"> • Results in vaccines with different compositions that may be difficult to compare and may present public health authorities, healthcare providers, and patients with difficult decisions
2	Recommend that all vaccines used for both primary series and booster doses retain current composition (i.e., Wuhan Spike based)	<ul style="list-style-type: none"> • Maintains adequate supply of vaccine • Maximizes vaccine choices (i.e., types of vaccine platforms) • Likely maintains good effectiveness against severe disease • Simplifies studies of vaccine effectiveness and comparison to earlier efficacy studies 	<ul style="list-style-type: none"> • Composition of vaccine increasingly distant from circulating viruses leading to decreased effectiveness
3	Recommend that the composition of all vaccines used for booster doses be updated to contain an Omicron component that has been tested clinically (e.g., BA.1)	<ul style="list-style-type: none"> • Offers possibility of improved vaccine performance against currently circulating strains of virus for those already vaccinated • Retains primary vaccine composition that was evaluated in efficacy studies and is known to provide continued protection against severe disease • Resulting harmonization minimizes confusion associated with choice of different vaccine boosters 	<ul style="list-style-type: none"> • A BA.1 Omicron component for updated vaccines already somewhat outdated, although possibly better than Wuhan • Possibly eliminates some manufacturers from booster market who are unable to update their vaccines • May be confusing to implement if primary series vaccines and booster vaccines have different compositions • Use of updated vaccines as first booster doses would be based on extrapolation of data from studies of second booster doses and studies of other modified vaccine candidates as first booster doses • Could still have vaccines with different compositions unless the recommendation is specific (e.g., monovalent Omicron vaccine, bivalent Omicron/prototype vaccine) • Virus may continue to drift away from Omicron BA.1 component of vaccine

Number	Options	Pros	Cons
4	Recommend that the composition of all vaccines used for booster doses be updated to contain a more recent Omicron component (e.g., BA.2, BA.2.12.1, BA.4/ BA.5) without clinical evidence, based upon clinical data from studies with other candidate vaccines	<ul style="list-style-type: none"> • May be closer to what will be circulating in Fall/Winter of 2022 	<ul style="list-style-type: none"> • Multiple Omicron sub-variants continue to co-circulate • Selection of an Omicron sublineage other than BA.1 would rely on clinical data from studies with BA.1 component vaccines and other supportive data
5	Recommend that the composition of all COVID vaccines used for both primary series and booster doses be updated to contain an Omicron component (BA.1 OR BA.2, BA.2.12.1, BA.4/ BA.5)	<ul style="list-style-type: none"> • Eliminates confusion of having primary series vaccines and booster vaccines with different compositions 	<ul style="list-style-type: none"> • No data on effectiveness of a primary series vaccination with an Omicron containing vaccine • Some data suggest that Wuhan exposure (infection or vaccination) followed by Omicron exposure (infection) produces a broader antibody response than Omicron only exposure • May eliminate some manufacturers from the COVID vaccine market
6	Recommend that the composition of some vaccines used for booster doses be updated to contain something other than an Omicron component (e.g., Beta variant vaccine)	<ul style="list-style-type: none"> • Offers possibility of improved vaccine performance for some vaccines from manufacturers who have developed modified vaccine candidates directed at previous variants and who are unable to expediently produce a modified vaccine with an Omicron component • Provides additional vaccine booster choices 	<ul style="list-style-type: none"> • Results in booster vaccines with different compositions that may be difficult to compare and may present public health authorities, healthcare providers, and patients with difficult decisions • Inclusion of components directed at variants not currently circulating will be confusing for public • Such recommendations would likely have to be vaccine specific and probably beyond the scope of a VRBPAC discussion

5. Topics for VRBPAC Discussion

The June 28th VRBPAC meeting will consider the strain composition of COVID-19 vaccines for the U.S. The committee will be asked to discuss the available data on COVID-19 epidemiology,

current vaccine effectiveness, and clinical immunogenicity data for several candidate COVID-19 vaccines containing an Omicron component. Further, the committee will be asked to discuss whether a modified COVID-19 vaccine composition is needed and the various options to consider in recommending the strain composition of COVID-19 vaccines in the U.S.

For Discussion:

Please discuss the various considerations involved in updating the strain composition for COVID-19 vaccines in the U.S. Please provide input on the following and discuss whether any additional data are needed to facilitate a recommendation:

- Is a change to the current COVID-19 vaccine strain composition necessary at this time?
- Please discuss the evidence supporting:
 - 1) the selection of a specific Omicron sub-lineage (e.g., BA.1 vs. BA.4/BA.5)
 - 2) a monovalent (Omicron) or bivalent vaccine (prototype + Omicron)
 - 3) extrapolating the available clinical data for modified vaccines to different age ranges
- What additional data, if any, would be needed to recommend an updated composition of the primary series vaccine? If the booster vaccine composition changes, would continuing use of the prototype primary series vaccine this fall still be acceptable?

Voting Question:

Does the committee recommend inclusion of a SARS-CoV-2 Omicron component for COVID-19 booster vaccines in the United States?

6. References

- Andrews N, Stowe J, Kirsebom F, et al. NEJM 2022. DOI: 10.1056/NEJMoa2119451
- Arbel R, Sergienko R, Friger M, et al: BNT162b2 vaccine booster and mortality due to COVID-19. *N Engl J Med* 2021; 385:2413-2420. DOI: 10.1056/NEJMoa2115624.
- Bar-On YM, Goldberg Y, Mandel M, et al. Protection by 4th dose of BNT162b2 against Omicron in Israel. *medRxiv*, February 1, 2022; doi: <https://doi.org/10.1101/2022.02.01.22270232>. Preprint.
- Chemaitelly H, Hussein H, Ayoub H, et al. Duration of mRNA vaccine protection against SARS-CoV-2 Omicron BA.1 and BA.2 subvariants in Qatar. *medRxiv* 2022.03.13.22272308; doi: <https://doi.org/10.1101/2022.03.13.22272308> Preprint.
- Ferdinands JM, Rao S, Dixon BE, et al. Waning 2-Dose and 3-Dose Effectiveness of mRNA Vaccines Against COVID-19–Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Adults During Periods of Delta and Omicron Variant Predominance — VISION Network, 10 States, August 2021–January 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:255–263. DOI: <https://www.cdc.gov/mmwr/volumes/71/wr/mm7107e2.htm>
- Gazit S, Saciuk Y, Perez G, et al. Relative Effectiveness of Four Doses Compared to Three Dose of the BNT162b2 Vaccine in Israel. *medRxiv* 2022.03.24.22272835; doi: <https://doi.org/10.1101/2022.03.24.22272835>. Preprint.
- Hachmann NP, Miller J, Collier AY et al. Neutralization Escape by the SARS-CoV-2 Omicron Variants BA.2.12.1 and BA.4/BA.5 *medRxiv* 2022. DOI: <https://doi.org/10.1101/2022.05.16.22275151> Preprint.
- Iketani S, Liu L, Guo Y et al. Antibody evasion properties of SARS-CoV-2 Omicron sublineages. *Nature* 2022. DOI: 10.1038/s41586-022-04594-4.
- Korves C, Izurieta HS, Smith J, Zwain GM, Powell EI, Balajee A, Ryder K, Young-Xu Y. Relative effectiveness of booster vs. 2-dose mRNA Covid-19 vaccination in the Veterans Health Administration: Self-controlled risk interval analysis. *medRxiv* 2022.03.17.22272555; Preprint. DOI: <https://doi.org/10.1101/2022.03.17.22272555>
- Lusvarghi S, Pollett SD, Neerukonda SN et al. SARS-CoV-2 BA.1 variant is neutralized by vaccine booster-elicited serum but evades most convalescent serum and therapeutic antibodies. *Sci Transl Med* 2022. DOI: 10.1126/scitranslmed.abn8543.
- Mannar D, James W Saville JW, Zhu X et al. SARS-CoV-2 Omicron variant: Antibody evasion and cryo-EM structure of spike protein-ACE2 complex. *Science* 2022. DOI: 10.1126/science.abn7760.

- Pulliam JRC, van Schalkwyk C, Govender N et al. Increased risk of SARS-CoV-2 reinfection associated with emergence of Omicron in South Africa. *Science* 2022. DOI: 10.1126/science.abn4947.
- Qu P, Faraone J, Evans JP et al. Neutralization of the SARS-CoV-2 Omicron BA.4/5 and BA.2.12.1 Subvariants. *N Engl J Med* 2022. DOI: 10.1056/NEJMc2206725.
- Richardson SI, Madzorera VS, Spencer H et al. SARS-CoV-2 Omicron triggers cross-reactive neutralization and Fc effector functions in previously vaccinated, but not unvaccinated, individuals. *Cell Host Microbe* 2022. DOI: 10.1016/j.chom.2022.03.029.
- Stowe J, Andrews N, Kirsebom F et al. Effectiveness of COVID-19 vaccines against Omicron and Delta hospitalisation: test negative case-control study. Preprint. <https://khub.net/documents/135939561/430986542/Effectiveness+of+COVID-19+vaccines+against+Omicron+and+Delta+hospitalisation+-+test+negative+case-control+study.pdf/d0e803c0-3dd2-0c1b-03b8-0a12fd211980>
- Taylor CA, Whitaker M, Anglin O, et al. COVID-19–Associated Hospitalizations Among Adults During SARS-CoV-2 Delta and Omicron Variant Predominance, by Race/Ethnicity and Vaccination Status — COVID-NET, 14 States, July 2021–January 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:466–473. DOI: <https://www.cdc.gov/mmwr/volumes/71/wr/mm7112e2.htm>.
- Tenforde MW, Patel MM, Gaglani M, et al. Effectiveness of a Third Dose of Pfizer-BioNTech and Moderna Vaccines in Preventing COVID-19 Hospitalization Among Immunocompetent and Immunocompromised Adults — United States, August–December 2021. *MMWR Morb Mortal Wkly Rep* 2022; 71:118–124. DOI: <https://www.cdc.gov/mmwr/volumes/71/wr/mm7104a2.htm>.
- Tseng HF, Ackerson BK, Luo Y, et al. Accepted, *Nature Medicine*. Effectiveness of mRNA-1273 against SARS-CoV-2 Omicron and Delta variants. *Nature Medicine*, 2022. <https://doi.org/10.1038/s41591-022-01753-y>.
- Zhou T, Wang L, Misasi J et al. Structural basis for potent antibody neutralization of SARS-CoV-2 variants including B.1.1.529. *Science* 2022. DOI: 10.1126/science.abn8897.