



## MEMORANDUM

TO: File

FROM: Peter Marks, MD, PhD, Acting Director, Office of Vaccines Research and Review (OVRR), Center for Biologics Evaluation and Research (CBER)

DATE: June 30, 2022

RE: Fall 2022 COVID-19 Vaccine Strain Composition Selection Recommendation

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The purpose of this memorandum is to document considerations behind the Food and Drug Administration's (FDA, the Agency, or we) recommendation to vaccine manufacturers seeking to update their COVID-19 vaccine that they should develop a bivalent prototype + Omicron BA.4/5 spike protein COVID-19 vaccine for use as a booster dose in potentially eligible populations during a possible fall 2022 vaccination campaign. Specifically, this memorandum delineates information relevant to the advice that we have provided to the manufacturers.

### I. Background

The response to the ongoing COVID-19 pandemic has been complicated by the rapid evolution of the virus. The current circulating SARS-CoV-2 virus variants are antigenically distinct from the strain included in current authorized and approved vaccines. As a result, available FDA-approved and -authorized COVID-19 vaccines are less effective against currently circulating virus variants than against previously circulating strains of virus. It is our expectation that candidate vaccines with an updated strain composition that is more closely matched to currently circulating virus can be manufactured according to requirements for quality and consistency and in sufficient quantity to meet public health needs to be used as booster doses in the United States (U.S.) this fall. Additionally, candidate vaccines with such an updated strain composition may be more effective against circulating and potentially emerging virus variants and consequently may have a more favorable benefit-risk balance than currently available COVID-19 vaccines.<sup>1</sup>

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<sup>1</sup> For more information see FDA's Briefing document for the June 28, 2022 Vaccines and Related Biological Products Advisory (VRBPAC) meeting, available at <https://www.fda.gov/media/159452/download>.

### A. *SARS-CoV-2 Variants of Concern (VOC)*

Since the original Omicron variant (designated as the BA.1 variant) spread rapidly around the world, the virus has 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 to early May, Omicron BA.2.12.1 began rapidly spreading and became the dominant strain in the U.S. for a time. Most 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 as of June 25, 2022, when combined constitute the majority of the circulating SARS-CoV-2 virus in the U.S..

Compared to the prototype strain spike (S) antigen used in currently available COVID-19 vaccines (referred to here as prototype 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. The large number of mutations is of particular concern, including the 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.<sup>2</sup> 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.<sup>3</sup> 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

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<sup>2</sup> See 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; 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; 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; 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.

<sup>3</sup> See 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; 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.

other VOCs.<sup>4</sup> 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).<sup>5</sup> 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. 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. It should be noted that the S protein amino acid sequences of BA.4 and BA.5 used for vaccine production are identical and can be considered together.

#### *B. World Health Organization (WHO) Recommendations for COVID-19 Vaccine Strain Composition*

The WHO Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC) issued an updated interim statement on June 17, 2022.<sup>6</sup> The key recommendations in the recent interim statement stated:

- 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.

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<sup>4</sup> See 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.

<sup>5</sup> See Covariants website: <https://covariants.org/>.

<sup>6</sup> See WHO's Interim statement on the composition of current COVID-19 vaccines, dated June 17, 2022, available at <https://www.who.int/news/item/17-06-2022-interim-statement-on--the-composition-of-current-COVID-19-vaccines>.



- 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 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.

*C. The June 28, 2022 VRBPAC Meeting*

On June 28<sup>th</sup>, 2022, a meeting of the Vaccines and Related Biological Products Advisory (VRBPAC) convened in an open session to discuss whether and how the SARS-CoV-2 strain composition of COVID-19 vaccines should be modified. The committee heard presentations on: the current epidemiology of the COVID-19 Pandemic and SARS-CoV-2 variants (H Scobie, CDC); COVID-19 vaccine effectiveness (R Link-Gelles, CDC); modeling future epidemiology of the COVID-19 pandemic (J T Lessler, University of North Carolina); vaccine manufacturer presentations on clinical data regarding variant vaccines (ModernaTX, Pfizer, Inc., Novavax Inc.); considerations for vaccine strain composition from the WHO TAG-Co-VAC (K Subbarao, WHO Collaborating Center for Reference and Research on Influenza, Melbourne, Australia); and the FDA perspective on the considerations for strain composition modifications of COVID-19 vaccines.<sup>7</sup>

After these presentations and the committee discussion, the VRBPAC voted 19-2 in favor of the inclusion of a SARS-CoV-2 Omicron component for COVID-19 booster vaccines in the U.S. Although there was not a vote on the topic, there was general preference among committee

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<sup>7</sup> See FDA's website for background materials on the June 28, 2022 VRBPAC meeting, available at <https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-june-28-2022-meeting-announcement>.



members for a bivalent vaccine with an ancestral strain and an Omicron strain. Specifically, there seemed to be a preference for vaccine coverage of Omicron sublineages BA.4 and BA.5.

## **II. Discussion**

Several key issues will need to be addressed for any recommendation to modify the composition of COVID-19 vaccines. These issues include the current epidemiology of circulating virus variants, the antigenic relatedness of currently circulating virus variants to the strain included in current vaccines composition, whether there is evidence that current vaccines are less effective against new circulating virus variants than against previous strains of virus, and whether there is data that indicates a candidate vaccine with an updated strain composition will be more effective against new circulating virus variants and provide an improved clinical benefit. The FDA has reviewed a variety of data relevant to each of these issues that informed our advice to vaccine manufacturers seeking to update their COVID-19 vaccine composition for a potential fall 2022 booster vaccination campaign.

As noted above, epidemiological data indicates that the SARS-CoV-2 Omicron variant has become dominant globally. The Omicron VOC poses a higher risk of re-infection than previous virus strains and has further evolved into sub-lineages that are also antigenically distinct but much more closely related to each other than to previous circulating variants. Because of their antigenic relatedness, these sub-lineages are not classified as separate VOCs. Virus surveillance data indicates that almost all SARS-CoV-2 viruses in the world are currently descended from the Omicron variant lineage, and there is no evidence to suggest that earlier strains of virus such as the original prototype strain represented in current vaccines, nor the previously identified VOC (Alpha, Beta, Gamma and Delta), are in existence. Modeling data such as that presented in the April 6<sup>th</sup> VRBPAC and phylogenetic analysis strongly suggest that future strains of virus will evolve from the Omicron VOC. As of June 25, 2022, the Omicron sublineages BA.4 and BA.5 constitute the majority of circulating Omicron sublineages in the U.S.

As noted in the Agency's VRBPAC briefing document,<sup>8</sup> the current authorized and approved COVID-19 vaccines in the U.S. are based on the original prototype strain, and the recent and current circulating SARS-CoV-2 variants harbor mutations in the S protein that confer at least partial antigenic escape from vaccine-elicited immunity. Results from observational studies that have investigated the effectiveness of primary vaccination with authorized and approved

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<sup>8</sup> See Briefing document, available at <https://www.fda.gov/media/159452/download>.



vaccines have shown decreased effectiveness against certain variants (notably Omicron, for which neutralizing antibody titers are decreased compared with the prototype strain) and waning effectiveness over time.<sup>9</sup> Although first booster doses have restored waning vaccine effectiveness (VE), including against severe disease and hospitalization associated with Omicron,<sup>10</sup> 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<sup>11</sup> and lower effectiveness among the immunocompromised.<sup>12</sup> Taken together the data suggest that current COVID-19 vaccines are less effective against new circulating virus variants than against previous strains of virus.

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

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<sup>9</sup> See 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>; Andrews N, Stowe J, Kirsebom F, et al. NEJM 2022. DOI: 10.1056/NEJMoa2119451; 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>.

<sup>10</sup> See Tseng, et al, *ibid*; Andrews, et al, *ibid*; Taylor et al, *ibid*; 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>.

<sup>11</sup> See Tseng, et al, *ibid*; 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>; ; 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>; 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.

<sup>12</sup> See 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>.





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.<sup>13</sup> The evaluation of modified vaccines for the purpose of vaccine strain composition decisions will need to rely on comparative immunogenicity data due to the time constraints involved in vaccine manufacturing and clinical efficacy evaluation. Toward that end, several manufacturers have prepared modified vaccine candidates for immunogenicity evaluation in clinical trials. Among COVID-19 vaccines currently authorized or approved for use in the U.S., clinical immunogenicity data for modified versions including an Omicron (BA.1) component are available for the Pfizer-BioNTech and Moderna COVID-19 vaccines.

A superior Omicron (BA.1) neutralizing antibody response was elicited to a candidate bivalent vaccine from Moderna containing 25 µg each of mRNA encoding prototype and Omicron (BA.1 sub-lineage) S protein compared to the response elicited by the approved Moderna booster vaccine (50 µg mRNA encoding prototype S protein). In addition, the neutralizing antibody response to the ancestral SARS-CoV-2 strain elicited by both vaccine boosters was similar.

Pfizer-BioNTech has studied two Omicron-containing candidate vaccines, a monovalent version and a bivalent version. In one study, a superior Omicron (BA.1) neutralizing antibody response was elicited to a candidate monovalent vaccine containing 30 µg of mRNA encoding Omicron (BA.1 sub-lineage) S protein compared to the response elicited by the authorized Pfizer-BioNTech booster vaccine (30 µg mRNA encoding prototype S protein). In a second study, bivalent candidate vaccines containing mRNA encoding prototype and Omicron (BA.1 sub-lineage) S protein at 2 different doses and monovalent vaccines containing mRNA encoding Omicron at 2 doses were compared to the authorized Pfizer-BioNTech booster vaccine. All tested candidate vaccines containing an Omicron component elicited a superior Omicron (BA.1) neutralizing antibody response.

The results from these 3 studies indicate that an improved Omicron antibody response results from inclusion of the Omicron component in the vaccine. While all tested vaccines included a BA.1 Omicron strain, the data suggests that candidate vaccines containing other Omicron sub-lineages (BA.2, BA.4/BA.5) would be similarly immunogenic and provide improved neutralizing

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<sup>13</sup> See FDA's Guidance for Industry, entitled "Emergency Use Authorization for Vaccines to Prevent COVID-19," available at <https://www.fda.gov/media/142749/download>.

antibody responses to Omicron sub-lineage viruses because of the relatedness of S protein among the various Omicron sub-lineages.

In addition to clinical immunogenicity data from candidate vaccines containing an Omicron component, additional data relevant to the potential effectiveness of an updated vaccine composition as a booster was reviewed. Several studies have shown that vaccination followed by infection with a VOC leads to an enhanced and broadened antibody response to SARS-CoV-2 VOCs. While infection is different from vaccination, the results from such studies suggest that vaccination with a current vaccine followed by booster vaccination with a VOC vaccine might also lead to a broadened antibody response. The WHO-TAG-Co-VAC presented several examples of such data in their June 11<sup>th</sup> interim statement. Those examples, as well as more recent data, including unpublished studies that reported the improved neutralizing antibody responses to multiple Omicron sub-lineages following Omicron BA.4 or BA.5 infection, support the conclusion that an Omicron S protein exposure, either through vaccination or infection, increases and broadens the neutralizing antibody response to more recently circulating strains of virus.

Taken together, the data indicate that a modified booster vaccine composition is now warranted. Note that at this time we are not advising manufacturers to change the primary vaccination series, as right now there are inadequate clinical data to make such a recommendation.

The preponderance of evidence indicate that an improved antibody response to SARS-CoV-2 Omicron variants results from inclusion of an Omicron component and suggests the potential for improved vaccine effectiveness for a modified booster formulation. In considering the recommended Omicron strain to be included in a modified vaccine formulation, it is appropriate to be guided by current epidemiological data as well as the breadth of protection that a modified vaccine might offer. The subvariants BA.4 and BA.5 are now dominant in the United States, and BA.1 is no longer circulating. Preliminary laboratory and epidemiologic evidence indicate that vaccines with a BA.1 spike may not be as effective against the BA.4 and BA.5 variants. As there is evidence for an increased breath of cross-reactive neutralizing antibodies elicited by modified vaccines containing an Omicron component, we expect that variants with a BA.4/5 component will provide a cross-reactive neutralizing antibody response that will more likely match the variant strains that may evolve to circulate during fall 2022 and after.

Toward this end, FDA has recommended that vaccine manufacturers considering updating their vaccines for a potential fall 2022 booster campaign add a BA.4/5 component. In addition, because the currently authorized and approved COVID-19 vaccines provide protection against COVID-19, we are recommending that vaccine manufacturers maintain a component of the





prototype strain. Should we receive requests to authorize modified COVID-19 vaccines, in evaluating such requests we expect that it will be appropriate to consider that available clinical immunogenicity data from clinical studies of vaccines containing Omicron BA.1 components, among other data potentially applicable to the safety and effectiveness of modified vaccines.

### **III. Conclusion**

For the reasons noted above, to optimize protection during a potential fall 2022 booster vaccination campaign, FDA is recommending that vaccine manufacturers develop a bivalent (prototype + Omicron BA.4/5 S protein) COVID-19 vaccine for use as a booster dose. Specifically, FDA is requesting that vaccine manufacturers expediently conduct clinical studies in relevant populations (inclusive of different age groups and vaccination history) to generate clinical safety and immunogenicity data with a bivalent (prototype + Omicron BA.4/5 S protein) booster composition of its authorized COVID-19 vaccines. The Agency considers the current year to be transitional, and data becoming available from clinical studies over the coming months may inform any future recommendation for primary series strain composition.