

**FDA Briefing Document**  
**Vaccines and Related Biological Products Advisory Committee Meeting**  
**June 15, 2023**

**Selection of Strain(s) to be Included in the Periodic Updated COVID-19 Vaccines  
for the 2023-2024 Vaccination Campaign**

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## **1 Meeting Objective**

On June 15, 2023, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) will meet in open session to discuss and make recommendations on the selection of strain(s) to be included in periodic updated COVID-19 vaccines for the 2023–2024 vaccination campaign.

## **2 Background**

### **2.1 Previous VRBPAC Discussions and Vaccine Composition Recommendations**

The VRBPAC met on [April 6](#) and [June 28](#), 2022, to discuss the framework for updating COVID-19 vaccine composition and the strain composition for the fall 2022 COVID-19 vaccines, respectively. Based on emerging clinical data, there was a preference for a bivalent vaccine booster that incorporated a component based on the Original SARS-CoV-2 strain and an Omicron variant component to provide greater breadth of immunity against SARS-CoV-2 variants including Omicron. Based on the totality of the evidence, on June 30, 2022, FDA notified COVID-19 vaccine manufacturers of its recommendation to develop a bivalent COVID-19 vaccine (containing Original and Omicron BA.4/BA.5 components), hereafter referred to as bivalent COVID-19 vaccines, as a booster dose to improve protection during the fall 2022 vaccination campaign.

At the January 26, 2023 [VRBPAC meeting](#), the committee discussed harmonization of the strain composition for primary series and booster doses, simplification of the immunization schedule, and an approach to periodic updates of COVID-19 vaccine strain composition. The committee unanimously voted in favor of harmonizing the COVID-19 vaccine strain composition for primary series and booster doses in the US to a single composition. The committee generally agreed that simplification of the immunization schedule was highly desirable and recommended that simplification be based on the best available evidence.

In March 2023, FDA notified COVID-19 vaccine manufacturers that they should plan to implement the proposals discussed at the January 26, 2023 VRBPAC and supported by the committee's vote and discussion. Specifically, FDA noted that the process of moving to a single vaccine strain composition, i.e., Original and Omicron BA.4/BA.5 for all mRNA-based COVID-19 vaccines, should also involve the consolidation of the different age group fact sheets for healthcare providers and for recipients and caregivers into a single fact sheet for healthcare providers and a single fact sheet for recipients and caregivers for each vaccine, and to simplify the vaccination regimens to the extent appropriate. Given the current state of naturally acquired, vaccine-induced, and hybrid (combined natural infection in the setting of at least one COVID-19 vaccination) immunity in the US population, FDA suggested for each of the authorized bivalent vaccines to move to a single dose for most individuals, with additional doses for the very young, those 65 years and older, and individuals with certain kinds of immunocompromise.

### **2.2 FDA Approved and Authorized COVID-19 Vaccines**

Two COVID-19 vaccines are currently FDA approved for active immunization to prevent COVID-19 caused by SARS-CoV-2; one for individuals 18 years of age and older, and the other for individuals 12 years of age and older. Three vaccines are currently authorized for use in the US under emergency use authorization (EUA).

### **2.2.1 Spikevax and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)**

Spikevax (COVID-19 Vaccine, mRNA) manufactured by Moderna, is approved for use as a two-dose primary series for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. Spikevax contains nucleoside-modified messenger RNA (mRNA) encoding the pre-fusion stabilized full-length Spike (S) protein of the original SARS-CoV-2 strain encapsulated in lipid particles. A bivalent formulation of the vaccine manufactured using the same process, Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), is currently authorized under EUA for administration of a single dose in individuals 6 years of age and older, two doses in those individuals 6 months through 5 years of age previously not vaccinated with a COVID-19 vaccine and a single dose in individuals 6 months through 5 years of age previously vaccinated with Moderna COVID-19 Vaccine. An additional (second) dose is authorized for individuals 65 years of age and older. Individuals with certain kinds of immunocompromise 6 months of age and older may be administered additional age-appropriate doses (section [2.3](#)). For additional information on dosing and schedule, please refer to the [Fact Sheet](#). Safety and effectiveness data supporting [approval of Spikevax](#) and [authorization of the Moderna COVID-19 Vaccine, Bivalent](#) are detailed in the decision memoranda available on the FDA website.

### **2.2.2 Comirnaty, Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)**

Comirnaty (COVID-19 Vaccine, mRNA), manufactured by Pfizer for BioNTech, is approved for use as a two-dose primary series for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. Comirnaty contains a mRNA encoding the viral spike (S) glycoprotein of the original SARS-CoV-2 strain that is formulated in lipid particles. A bivalent formulation of the vaccine manufactured using the same process, Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), is currently authorized under EUA for administration of a single dose in individuals 5 years of age and older, three doses in individuals 6 months through 4 years of age previously not vaccinated with a COVID-19 vaccine, two doses if previously vaccinated with one dose of Pfizer-BioNTech COVID-19 Vaccine, or a single dose to individuals 6 months through 4 years of age previously vaccinated with two or three doses of Pfizer BioNTech COVID-19 Vaccine. An additional (second) dose is authorized for individuals 65 years of age and older. Individuals with certain kinds of immunocompromise 6 months of age and older may be administered additional age-appropriate doses (section [2.3](#)). For additional information on dosing and schedule, please refer to the [Fact Sheet](#). Safety and effectiveness data supporting [approval of Comirnaty](#) and [Pfizer-BioNTech COVID-19 Vaccine, Bivalent \(Original and Omicron BA.4/BA.5\)](#) are detailed in the decision memoranda available on the FDA website.

### **2.2.3 Novavax COVID-19 Vaccine, Adjuvanted**

Novavax COVID-19 Vaccine, Adjuvanted, which contains recombinant S protein of the SARS-CoV-2 original strain and Matrix-M adjuvant, is authorized for use as a two-dose primary series for active immunization to prevent COVID-19 in individuals 12 years of age and older, and as a first booster dose in the following individuals: Individuals 18 years and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate, and individuals 18 years of age and older who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted because they would otherwise not receive a booster dose of a COVID-19 vaccine. For additional information on dosing and schedule, please refer to the [Fact Sheet](#). Safety and

effectiveness data supporting authorization for the Novavax COVID-19 Vaccine, Adjuvanted are detailed in the decision memoranda available on the [FDA website](#).

### **2.3 Recent EUA Actions to Harmonize COVID-19 Vaccine Strain Composition and Simplify the Immunization Schedule**

Based on the discussions at the January 26, 2023, VRBPAC and the resulting FDA recommendations to the sponsors, (see section [2.1](#)), Moderna and Pfizer-BioNTech submitted requests to amend their EUAs to authorize a simplified vaccination schedule and use of their bivalent COVID-19 vaccines for all doses administered to individuals 6 months of age and older, including for an additional dose or doses for certain at-risk populations. For each vaccine, a single fact sheet for healthcare providers and a single fact sheet for recipients and caregivers were submitted in the EUA requests. EUA requests were supported by literature evidence that two or more exposures to the SARS-CoV-2 spike protein through vaccination and/or infection provide sufficient pre-existing immunity such that administration of a single dose of an authorized bivalent COVID-19 vaccine would likely induce or restore the expected protective immunity for a defined duration in immunocompetent individuals ([Carazo et al. 2022](#); [Carazo et al. 2023](#)). On April 18, 2023, the FDA authorized the use of the bivalent COVID-19 vaccines in all individuals 6 months of age and older allowing for use of a single dose in most adults and pediatric populations; two or three doses (based on the vaccine used) in the youngest pediatric populations, an additional dose for persons 65 years of age and older, and additional age-appropriate doses for persons with certain kinds of immunocompromise. The EUA actions on April 18, 2023, resulted in FDA no longer authorizing use of monovalent Moderna and Pfizer-BioNTech COVID-19 vaccines (containing the mRNA encoding spike protein of Original SARS-CoV-2 virus) and certain uses of the approved COVID-19 vaccines in the United States. For details, please refer to the FDA's webpage on [Emergency Use Authorization](#).

## **3 Considerations for a Periodic Updated Strain Composition of COVID-19 Vaccines**

### **3.1 Current Effectiveness of Authorized Bivalent COVID-19 Vaccines and Need for a Periodic Strain Update**

Following emergence of the Omicron variant and its sublineages (BA.4/BA.5 and related sublineages) in November 2021, and based on data suggesting improved protection against Omicron sublineages conferred by the bivalent vaccines compared to the monovalent vaccines, FDA, on August 31, 2022, authorized use of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for booster doses in individuals 18 or 12 years of age and older, respectively, and revised the scope of authorization for these manufacturers' monovalent vaccines to remove their use as a booster dose in those age groups for which a bivalent booster was authorized. Subsequently, FDA also authorized use of the respective bivalent vaccines for booster doses for younger age groups.

Subsequent to the authorizations of the bivalent mRNA COVID-19 vaccines as boosters in children and adults, observational data indicated that the bivalent COVID-19 vaccines provided improved protection from COVID-19 caused by sublineages of Omicron including the BA.4/BA.5 sublineage, compared to the original vaccines. ([Andeweg et al. 2022](#); [Babouee Flury et al. 2022](#); [Bates et al. 2022](#); [Chin et al. 2022](#); [Hansen et al. 2023](#); [Tenforde et al. 2022](#); [Arbel et al. 2023](#)). Overall, these data strongly suggested that updating the composition of the COVID-19 vaccines from the original monovalent to a bivalent containing Original and Omicron BA.4/BA.5 components offered benefit in protection from COVID-19 disease caused by Omicron sublineages.

SARS-CoV-2 continues to evolve into distinct sublineages by acquiring additional mutations (see section 3.2). Although real-world effectiveness studies suggest that the current bivalent vaccines continue to provide protection against other circulating sublineages of Omicron, including the XBB–XBB.1.5 ([Lin et al. 2023](#); [Link-Gelles et al. 2023](#)), there appears to be an inverse relationship between the time since vaccination and vaccine effectiveness, such that bivalent COVID-19 vaccine effectiveness against Omicron sublineages appears to wane over time ([Link-Gelles 2023](#)). Additionally, studies indicate that neutralizing antibody titers induced by the current bivalent COVID-19 vaccines against XBB-XBB1.5-related sublineages are lower relative to neutralizing antibody titers induced against the matched BA.4/BA.5 sublineage ([Jiang et al. 2023](#)). These data suggest that an updated strain composition of COVID-19 vaccines to more closely match currently circulating Omicron sublineages is warranted for the 2023–2024 vaccination campaign.

### 3.2 Current Virus Surveillance

Since deployment of the bivalent COVID-19 vaccines in September 2022, the SARS-CoV-2 Omicron variant has continued evolving into distinct sublineages with additional mutations in the spike gene, as well as elsewhere in the genome. This has led to successive waves of many Omicron sublineages across the globe. In the US, BA.5 sublineage dominated during much of fall 2022, while other Omicron sublineages, including BA.4 sublineage, co-circulated at lower frequencies. Because BA.5 and BA.4 sublineages share the same spike mutations, the global dominance of BA.5 indicates that mutations in non-spike genes contributed to its fitness advantage. BA.5 sublineages, like the earlier BA.1 Omicron sublineages, were much less susceptible to neutralization by post-vaccination (with Original strain vaccines) and post-infection sera compared to the pre-Omicron variants.

By winter of 2022, BQ sublineages diverged from BA.5 by acquiring additional mutations in the spike receptor binding domain (RBD), resulting in K444T, N460K, and R346T (BQ.1.1) substitutions. These changes conferred additional immune escape from post-vaccination and post-infection serum, but the BQ sublineages were rapidly replaced by XBB sublineages by spring 2023, both in the US and globally. The XBB parent lineage is a recombinant of BA.2.10.1 and BA.2.75 sublineages, thus highlighting the relevance of recombination as an important mechanism of generating new variants. Recombination can happen during virus replication when a cell is infected by more than one variant.

XBB sublineages have continued to emerge with accumulations of a small number of mutations in the spike N-terminal domain and the RBD. The XBB.1.5 sublineage spread globally in the first quarter of 2023, reaching dominance in North America, as well as other parts of the world by April. Compared to the parental XBB lineage virus, XBB.1.5 has G252V and S486P spike substitutions. These changes may confer additional growth advantage, likely due in part to increased affinity to the ACE2 receptor conferred by the S486P change ([Yue et al. 2023](#)). Two additional Omicron sublineages, XBB.1.9 and XBB.1.16, have co-circulated with XBB.1.5. The XBB.1.9 variant has the same spike as XBB.1.5 but has a mutation in the Orf9b gene that may alter virus-host interactions to increase viral fitness ([Jiang et al. 2020](#); [Gao et al. 2021](#)). Orf9b mutations have emerged in other sublineages, including XBB.1.16. From February to April the XBB.1.16 sublineages surged in India, quickly dominating other variants. Compared to XBB, XBB.1.16 has E180V, G252V, K478R, and S486P spike substitutions. XBB.1.16 is reported to have a higher reproductive number compared to XBB.1 and XBB.1.5, and the proportion of XBB.1.16 viruses is rising rapidly in many other countries, including the US. Preliminary reports indicate no further immune evasion from these new substitutions in the XBB.1.16 spike compared to XBB.1.5 ([Yamasoba et al. 2023](#); [Wang Q et al. 2023a](#)). Overall, XBB sublineages

accounted for >95% of the circulating virus variants in the US by early June 2023; at this time, other minor circulating variants worldwide include XBB.1.9, XBB.2.3, and EG.1 in Europe, XBB.1.22 in Africa, and XBC.1.6 (Deltacron recombinant) in Oceania. The XBB.2.3 sublineage is present in several parts of the world and appears to be increasing in proportion in India where XBB.1.16 has dominated. Compared to the parental XBB, XBB.2.3 has G184V, D253G, F486P, and P521S spike substitutions. It also lacks the T478R substitution present in XBB.1.16. and shares the T478K substitution with XBB.1.5.

SARS-CoV-2 evolution is complex and remains unpredictable. There is no indication that SARS-CoV-2 evolution is slowing down, though immunity appears to be mitigating severe clinical outcomes. Intrinsic viral factors, including mutation rate and recombination potential, generate possibilities for increased transmissibility and adaptation to the host. At the same time, host immune responses and other factors contribute to selection of variants. Generation of immune escape variants may be further facilitated by chronic infections in immunocompromised hosts or potentially by waning of immunity in immunocompetent hosts. Thus far, the impressive plasticity, especially in spike, suggests that the virus can continue evolving by both incremental (drift-like) and saltatory (shift-like) modes, underscoring the importance of on-going global surveillance.

### 3.3 Antigenic Characterization of Current SARS-CoV-2 Variants

As immunity increases globally from vaccinations and/or infections, natural selection of immune escape variants appears to be playing an increasing role in SARS-CoV-2 evolution. Many mutations have emerged in the receptor binding domain of spike, which is the main target of antibodies that neutralize the virus. Neutralizing antibody titers correlate with protection and help guide decisions about variants for vaccine updates ([Khoury et al. 2021](#); [Gilbert et al. 2022](#); [Khoury et al. 2023](#)). Other components of the immune system also contribute to protection and selection of escape variants. Because prior antigenic exposures from vaccines and infections can influence vaccine responses and clinical outcomes, they are important considerations when making decisions about vaccine composition.

The bivalent vaccines, which contain a half-dose each of the original and BA.4/5 spike mRNAs, have been reported to induce either similar or modestly higher (~1.3-5.8 fold) neutralizing antibody titers against the BA.4/5 sublineages than the original monovalent booster vaccines ([Kurahde et al. 2023](#); [Davis-Gardner et al. 2023](#); [Collier et al. 2023](#); [Branche et al. 2023](#); [Wang W et al. 2023](#); [Zou et al 2023](#)). However, a direct comparison of titers elicited by the monovalent and bivalent booster vaccines is confounded by non-contemporaneous sample collections, use of different assays among studies, and heterogeneous immune histories among the study participants within and among studies. Nonetheless, monovalent and bivalent boosters consistently elicit much higher titers against the original strain than the BA.4/5 sublineages, possibly due to recall of memory B cells from prior doses of the original vaccine ([Röltgen et al. 2022](#); [Cao et al. 2022](#); [Park et al. 2022](#); [Carreño et al. 2023](#); [Alsoussi et al. 2023](#); [Wang Q et al. 2023a](#)). This apparent immune imprinting towards previously encountered antigens may involve preferential expansion of antibodies to epitopes shared between the antigens. An Omicron infection after vaccination can also boost responses to the original or an earlier variant ([Cao et al. 2022](#); [Park et al. 2022](#); [Reynolds et al. 2022](#)). However, a second Omicron exposure from infection has been shown to boost responses to the new antigen and may overcome potential negative effects of immune imprinting ([Yisimayi et al. 2023](#)).

The continued diversification of the Omicron variant has resulted in successive waves of lineages/sublineages, often with decreased susceptibility to neutralization. Despite use of different neutralization assays involving different cohorts with heterogeneous immune histories,

the neutralization titer trends against the emerging variants are consistent ([Yue et al. 2023](#); [Wang Q et al. 2023a](#); [Kurahde et al. 2023](#); [Branche et al. 2023](#); [Wang W et al. 2023](#); [Zou et al 2023](#); [Wang Q et al. 2023b](#); [Qu et al. 2023](#)). Neutralizing antibody titers elicited by the bivalent vaccines or monovalent vaccines plus an Omicron infection (hybrid immunity) were generally lower (~4-fold) against BQ sublineages than against the BA.4/5 sublineages. Neutralizing antibody titers were further diminished (~ 2-fold) against the parental XBB lineage virus compared to the BQ variant, and ~ 8-fold diminished compared to the BA.4/5 sublineages. Titers dropped further (~2-fold) against the XBB.1.5 sublineages compared to the parental XBB lineage virus and further yet (~16-fold) compared to the BA.4/5 sublineages. Preliminary data indicate that neutralization titers elicited by the bivalent vaccines or monovalent vaccines plus an Omicron infection were similar against XBB.1.5 and XBB.1.16 ([Yamasoba et al. 2023](#)). The relatively low neutralizing titer against the XBB-lineage variants in those who had received the bivalent vaccine has also been associated with faster waning of titers to XBB.1.5 ([Lasrado et al. 2023](#)).

Antigenic cartography is a visualization tool that uses antibody titers from convalescent sera following primary infections by a single virus variant or post-vaccination sera from infection-naïve individuals to create a 2-dimensional map that displays the antigenic relatedness among variants ([Smith et al. 2004](#)). Variants are positioned on the map according to antigenic distances that are determined by the fold differences in antibody titers compared to a reference variant. The precision of the location of a given variant on the map depends on the number of serum samples used for that variant; fewer number of samples for a given variant reduce the certainty of the position of that variant on the map. In maps of SARS-CoV-2 variants, pre-Omicron variants form a cluster that is antigenically distant from Omicron variants ([Wilks et al. 2022](#); [Mykytyn et al. 2022](#); [van der Straten et al. 2022](#); [Wang W et al. 2022](#)). Omicron lineages form a separate broader cluster in which several Omicron lineages are antigenically distinct from each other, indicating diversification among the Omicron lineages. At this time most individuals have had more than one antigenic exposure from infection, vaccination or both; therefore, future antigenic maps may depend on primary infection sera generated in animals, as is done using ferret sera to generate influenza antigenic maps.

Antibody landscapes are often used to visualize recognition of variants by complex sera elicited by exposures to multiple different antigens from vaccination, infection, or hybrid immunity ([Fonville et al. 2014](#)). Antibody titers corresponding to variants are fitted into a continuous surface or landscape in the z dimension above the 2-dimensional antigenic map. Elevations in the landscape indicate high titers to variants in that region of the antigenic map. Dips in the landscape, as seen for lineages in the Omicron cluster, identify immunologically vulnerable regions of the antigenic space containing lineages that are not well covered by sera ([Wang W et al. 2022](#); [Branche et al. 2022](#)). Landscapes may be used to infer titers against new variants in an antigenic map without direct titer measurements.

In summary, the low neutralizing antibody titers to current XBB sublineages elicited by vaccination, infection, or hybrid immunity indicate that those who have not had an infection with an XBB-lineage virus are probably susceptible to infection with the current XBB.1.5 and closely related XBB.1.16 sublineages. However, the degree of clinical illness will vary depending on age, co-morbidities, immune profiles, and other host factors.

### **3.4 Global Alignment of COVID-19 Strain Composition**

The continued evolution of SARS-CoV-2, the unpredictable emergence and spread of virus variants, and the diversity of vaccine manufacturers and complexities in vaccine supply present challenges for a globally coordinated recommendation for periodically updating COVID-19

vaccine composition. Nevertheless, global public health agencies and vaccine regulators have had ongoing discussions throughout the year to address the issue of changes to vaccine strain composition in an effort to align the criteria for vaccine strain selection and vaccine composition recommendations when possible.

The International Coalition of Medicines Regulatory Authorities (ICMRA) is an informal group of international regulatory authorities that promotes collaboration and communication to address common challenges. At an [ICMRA COVID-19 Omicron variant workshop](#) on May 8, 2023, FDA and other regulators met to discuss global regulatory alignment to adapt COVID-19 vaccines to emerging SARS-CoV-2 variants and to discuss the preferred strain composition for future vaccine updates. There was general agreement among the participants that while vaccines based on the original virus strain can still be protective against severe disease, protection wanes with time and is reduced against subsequent waves of variant viruses. Both real world evidence and immunogenicity data suggest that a vaccine composition that more closely matches circulating virus strains can significantly improve vaccine-induced immunogenicity and protection. Further, based on the global dominance of the XBB descendent lineages, in conjunction with the high level of baseline immunity to the ancestral virus strain, regulators concluded that a monovalent XBB vaccine would be an adequate candidate for a COVID-19 vaccine composition update and would likely increase the chances of matching more closely virus variants in the immediate future. While the group acknowledged the need for flexibility in terms of vaccine strain updates in different regions of the world, there was a consensus that global coordination of changes in vaccine composition is critical to ensure transparency of public health decisions on vaccination policies and implementation.

The 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 variants of concern (VOCs) on the performance of COVID-19 vaccines and to provide recommendations to WHO on COVID-19 vaccine strain composition. On May 18, 2023, the TAG-CO-VAC issued a [statement](#) on the antigen composition of COVID-19 vaccines, summarizing the data reviewed by the group on the antigenicity and cross-protection following infection and/or vaccination in the context of currently circulating XBB viruses. Some of the major recommendations in this most recent statement are as follows:

- SARS-CoV-2 XBB.1 descendent lineages currently predominate globally, and the current trajectory of virus evolution indicates that XBB will likely be the progenitor of SARS-CoV-2 variants in the near future
- XBB descendent lineages are highly immune evasive
- To improve protection, particularly against symptomatic disease, COVID-19 vaccines should induce antibodies that neutralize XBB descendent lineage viruses
- One recommended approach is the use of a monovalent XBB.1 descendent virus such as XBB.1.5
- Future formulations of COVID-19 vaccines should move away from inclusion of the index virus (i.e. Wuhan strain)

The TAG-CO-VAC statement strongly encouraged the generation of additional clinical immunogenicity and effectiveness data in humans receiving updated COVID-19 vaccines and stressed the importance for multilateral organizations, governments, and manufacturers to continue collaborations.

Overall, there is convergence of opinion regarding an updated strain composition at this time and on the value of global coordination, when possible, with the aim of improving vaccine performance and vaccine availability.

## 4 Options for Selection of Strains for Updated COVID-19 Vaccines for the 2023-2024 Vaccination Campaign

### 4.1 Summary of the Approach and the Data Reviewed for the Vaccine Strain Composition Recommendation

In previous discussions with the VRBPAC, FDA described the proposed evidentiary basis that would be used to determine the need for updating the strain composition of COVID-19 vaccines. The relevant data reviewed would ideally include multiple types and sources of data. In preparation for the June 2023 VRBPAC discussion, FDA reviewed various types of data as listed below, engaged with the key partners generating such data, including vaccine manufacturers and other US government agencies, and reviewed the discussions and recommendations put forth by other regulatory groups and public health agencies as noted above.

- **Virus surveillance and genomic analyses to identify emerging new virus variants.** As described in section [3.2](#), SARS-CoV-2 XBB-lineage viruses currently predominate in the US and globally.
- **Antigenic characterization of viruses to identify antigenically distinct variant viruses.** As described in section [3.3](#), SARS-CoV-2 XBB-lineage viruses have numerous amino acid changes relative to previously circulating viruses and the strains used in the authorized bivalent vaccines, suggesting continued evolution and increasing immunological distance from the Omicron BA.4/BA.5 component of current authorized COVID-19 mRNA vaccines.
- **Post-vaccination human serology studies to evaluate antibody responses generated by the current vaccines against more recently circulating virus variants such as BQ- and XBB-lineage viruses.** Since COVID-19 vaccine manufacturers are best positioned to generate the robust data needed from post-vaccination human serology studies, FDA set up informal technical working group meetings with each of the manufacturers of currently authorized/approved COVID-19 vaccines to share and discuss findings from human serology studies of their current vaccines against current circulating viruses. These data will be presented at the VRBPAC by the vaccine manufacturers.
- **Pre-clinical immunogenicity studies to evaluate immune responses generated by new candidate vaccines (e.g., expressing or containing updated variant spike components) against antigenically distinct circulating virus variants.** Pre-clinical immunogenicity data (neutralizing antibody) can provide an indication of how well antibodies to the spike of one strain will cross-neutralize other variant strains of SARS-CoV-2 and thus help inform strain selection in combination with other data. As with human serology studies, COVID-19 vaccine manufacturers are also able to generate pre-clinical immunogenicity studies with new candidate vaccines and each of the manufacturers of authorized/approved COVID-19 vaccines has produced several candidate vaccines at risk and evaluated them in pre-clinical studies. These data will be presented at the VRBPAC by the vaccine manufacturers.

### 4.2 Manufacturing Considerations

Recommendations for updating the strain composition of COVID-19 vaccines must consider the time needed for manufacturers to implement and deliver a new updated COVID-19 vaccine. The timelines likely differ for different types of vaccines and are also affected by manufacturing

experience and the availability and capacity of manufacturing facilities. At the January 26, 2023, VRBPAC, each of the manufacturers of the currently US-authorized/approved COVID-19 vaccines were asked to present their views and plans for an annual COVID-19 vaccine update and their capacity to deliver a periodic updated vaccine for fall 2023. The three vaccine manufacturers stated that they planned to evaluate candidate vaccines “at risk” and that they were prepared to provide a periodic updated vaccine for a fall 2023-2024 vaccination campaign in the event development of such a vaccine was recommended. In general, the manufacturers indicated a shorter timeline was needed for an mRNA vaccine periodic update compared to that needed for a protein subunit vaccine periodic update. However, regular interactions between the manufacturers and FDA/CBER in the informal technical working group meetings, coupled with evaluation of candidate vaccines made “at risk”, has mitigated some of the timeline differential between the two vaccine platforms. The appropriate timing for periodic updates of COVID-19 vaccine strain composition will be re-evaluated in the future as needed.

#### **4.3 Summary of Considerations for Selection of Strain(s) for inclusion in 2023-2024 COVID-19 Vaccines**

As noted in section [3.2](#), XBB sublineages accounted for >95% of the circulating virus variants in the US by early June 2023. While XBB.1.5 continues to decline to just over 50% of presumed circulating virus in the US, XBB.1.16 is on the rise and XBB.2.3 is slowly increasing in proportion. The current trajectory of virus evolution suggests that XBB.1.16 could be dominant by fall 2023 but that XBB.2.3 and other XBB sublineages could also continue to increase in proportion as the virus evolves. Spike proteins of XBB.1.16, XBB.1.5 and XBB.2.3 are similar with few amino acid differences (refer to section [3.2](#)), and available studies suggest little to no further immune evasion from these new substitutions in the XBB.1.16 spike compared to XBB.1.5 ([Yamasoba et al. 2023](#); [Wang Q et al. 2023a](#)).

The totality of available evidence suggests that a monovalent XBB-lineage vaccine is warranted for the 2023–2024 vaccination campaign. Current sublineages under consideration include XBB.1.5, XBB.1.16, or XBB.2.3. Preliminary data from animal studies assessing cross-reactivity of XBB.1.5-induced immune responses (neutralizing antibodies) to XBB.2.3 and cross-reactivity of XBB.1.16-induced immune responses (neutralizing antibodies) to XBB.2.3 to inform these decisions, will be presented at VRBPAC. Other factors to inform decision making to be discussed at the VRBPAC meeting include virus surveillance and genomic analyses, antigenic characterization of viruses, human serology studies from current vaccines, and manufacturing timelines.

### **5 VRBPAC Meeting Topics**

The June 15<sup>th</sup> VRBPAC meeting will consider the strain composition of COVID-19 vaccines for the US. The committee will be asked to discuss the available data on the circulation of SARS-CoV-2 virus variants, current vaccine effectiveness and clinical immunogenicity data of current vaccines against recently circulating viruses, the antigenic characterization of circulating virus variants, and pre-clinical immunogenicity data generated by new candidate vaccines expressing or containing updated spike components. The committee will be asked to discuss and make recommendations on the selection of strain(s) to be included in periodic updated COVID-19 vaccines for the 2023-2024 vaccination campaign.

## 6 References

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