

**FDA Briefing Document
Vaccines and Related Biological Products Advisory Committee
Meeting June 5, 2024**

Selection of the 2024-2025 Formula for COVID-19 vaccines

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1 Meeting Objective

On June 5, 2024, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) will meet in open session to discuss and make recommendations on the selection of the 2024-2025 Formula for COVID-19 vaccines.

2 Background

2.1 Previous VRBPAC Discussions and Vaccine Composition Recommendations

VRBPAC has met multiple times since 2022 to discuss the selection of the Formula for COVID-19 vaccines. A bivalent COVID-19 vaccine containing the Original and Omicron BA.4/BA.5 components was recommended for COVID-19 vaccines (2022-2023 Formula). Following a discussion on the harmonization of strain composition and simplification of the immunization schedule for COVID-19 vaccines at the January 26, 2023 [VRBPAC meeting](#), a monovalent composition targeting the XBB.1.5 sublineage was recommended for COVID-19 vaccines (2023-2024 Formula), at the June 15, 2023 [VRBPAC meeting](#).

Based on the review of virus epidemiology data indicating recent dominance of the JN.1 sublineage, and data from post-monovalent XBB.1.5 human sera indicating a drop in neutralizing antibody responses against JN.1, the World Health Organization (WHO) Technical Advisory Group on COVID-19 Vaccine Composition recommended a [monovalent JN.1 lineage component](#) be included in the composition of COVID-19 vaccines (2024-2025 Formula). This recommendation was made on April 26, 2024, prior to the dominance of the KP.2 sublineage in the United States. Initial neutralization data of various vaccine candidates are now available for both the JN.1 and KP.2 sublineages and will be presented along with current SARS-CoV-2 epidemiologic data for VRBPAC's consideration.

2.2 FDA Approved and Authorized COVID-19 Vaccines

FDA has approved two COVID-19 vaccines for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. In addition, three vaccines are currently authorized by FDA for use in the U.S. under emergency use authorization (EUA).

2.2.1 Spikevax and Moderna COVID-19 Vaccine (2023-2024 formula)

Spikevax (COVID-19 Vaccine, mRNA) manufactured by Moderna is approved for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older. Spikevax contains nucleoside-modified messenger RNA (mRNA), encoding pre-fusion stabilized full-length Spike (S) protein of the Omicron sublineage XBB.1.5 SARS-CoV-2 strain, encapsulated in lipid particles. Moderna COVID-19 Vaccine (2023-2024 Formula), a formulation of the vaccine manufactured using the same process as Spikevax, is currently authorized under EUA for administration of a single-dose regimen to individuals 5 years of age and older, two-dose regimen in those individuals 6 months through 4 years of age previously not vaccinated with a COVID-19 vaccine, and a single-dose regimen to individuals 6 months through 4 years of age previously vaccinated with Moderna COVID-19 Vaccine. Individuals with certain kinds of immunocompromise 6 months through 11 years of age and older may be administered additional age-appropriate doses. For additional information on dosing and schedule, please refer to the Moderna COVID-19 Vaccine (2023-2024 Formula) [Fact Sheet](#). Safety and effectiveness data supporting [approval of Spikevax](#) and [authorization of Moderna COVID-19](#)

[Vaccine \(2023-2024 Formula\)](#) are detailed in the decision memoranda available on the [FDA Website](#)

2.2.2 Comirnaty, Pfizer-BioNTech COVID-19 Vaccine (2023-2024 formula)

Comirnaty (COVID-19 Vaccine, mRNA) manufactured by Pfizer for BioNTech, is approved for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older. Comirnaty contains a mRNA encoding the viral Spike (S) glycoprotein of the XBB.1.5 sublineage SARS-CoV-2 strain that is formulated in lipid particles. Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), a formulation of the vaccine manufactured using the same process as Comirnaty, is currently authorized under EUA for administration of a single-dose regimen to individuals 5 years of age and older, three-dose regimen in individuals 6 months through 4 years of age previously not vaccinated with a COVID-19 vaccine, two-dose regimen 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. Individuals with certain kinds of immunocompromise 6 months through 11 years of age may be administered additional age-appropriate doses. For additional information on dosing and schedule, please refer to the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) [Fact Sheet](#). Safety and effectiveness data supporting [approval of Comirnaty](#) and [authorization of the Pfizer-BioNTech COVID-19 Vaccine \(2023-2024 Formula\)](#) are detailed in the decision memoranda available on the [FDA website](#).

2.2.3 Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 formula)

Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), which contains recombinant S protein of the SARS- CoV-2 XBB.1.5 sublineage strain and Matrix-M adjuvant, is authorized for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older. Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) is currently authorized under EUA for administration of a single-dose regimen at least 2 months after receipt of the last previous dose of COVID-19 vaccine to individuals 12 years of age and older previously vaccinated with any COVID-19 Vaccine. In individuals 12 years of age and older not previously vaccinated with any COVID-19 vaccine, Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) is currently authorized under EUA for administration as a two-dose regimen. Individuals with certain kinds of immunocompromise 12 years of age and older may be administered additional age-appropriate doses. For additional information on dosing and schedule, please refer to the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) [Fact Sheet](#). Safety and effectiveness data supporting [authorization for the Novavax COVID-19 Vaccine, Adjuvanted \(2023-2024 Formula\)](#) are detailed in the decision memoranda available on the [FDA website](#).

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

3.1 Current Effectiveness of Authorized COVID-19 Vaccines (2023-2024 Formula) and Need for a Selection of 2024-2025 Formula

Several observational studies ([DeCuir et al. 2024](#); [Joshi et al. 2024](#); [Link-Gelles et al. 2024](#)) have been conducted to evaluate the effectiveness of COVID-19 vaccines (2023-2024 Formula) that were introduced after emergence and global dominance of XBB sublineages. These studies indicate that updating COVID-19 vaccines to an XBB.1.5-based formula was associated

with positive health outcomes, including a reduction in hospitalization and urgent care utilization.

Since the introduction of COVID-19 vaccines (2023-2024 Formula) in fall 2023, SARS-CoV-2 has continued evolving into distinct sublineages by acquiring additional mutations (see section 3.2). Although real-world effectiveness studies suggest that currently approved/authorized COVID-19 vaccines (2023-2024 Formula) continue to provide protection against more currently circulating XBB sublineages, in prior years there appears to have been an inverse relationship between the time since vaccination and vaccine effectiveness, such that COVID-19 vaccine effectiveness against SARS-CoV-2 sublineages appears to wane over time ([Link-Gelles et al. 2023](#)) and that better matching of the vaccine to circulating strains is associated with improved neutralizing antibody titers ([Jiang et al. 2023](#)). Consistent with this observation, a decrease in effectiveness of COVID-19 vaccines (2023-2024 Formula) against COVID-19 caused by JN.1 lineage viruses has been reported ([Kirsebom et al. 2024](#); [Shrestha et al. 2024](#)).

Available data suggest that updating the current formula of COVID-19 vaccines to more closely match currently circulating JN.1 lineage viruses is warranted for the anticipated 2024–2025 respiratory virus season in the U.S.

3.2 Current Virus Surveillance

Since the emergence of the SARS-CoV-2 Omicron virus variant in late 2021, SARS-CoV-2 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 U.S., BA.5 sublineage dominated during much of fall 2022, while other Omicron sublineages, including BA.4 sublineage, co-circulated at lower frequencies. By winter 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 postvaccination and post-infection serum, but the BQ sublineages were rapidly replaced by the recombinant XBB virus and its sublineages by spring 2023, both in the U.S. and globally. 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 2023. The JN.1 variant, a descendant of the BA.2.86 lineage containing a new L455S mutation, was first detected in August 2023 and subsequently became the dominant subvariant by January 2024. JN.1 remained dominant during the remainder of winter and early spring 2024. However, in February 2024, the KP.2 subvariant containing two new mutations, i.e., F456L and R356T that appear to confer an advantage to the virus either in terms of fitness or escape from immunity, became noticeable. By late April 2024 KP.2 had become the dominant virus variant in the U.S. ([Figure 1](#), below).

SARS-CoV-2 evolution continues to be complex and remains unpredictable. There is no indication that SARS-CoV-2 evolution is slowing, though immunity appears to be mitigating severe clinical outcomes, particularly in younger populations. 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 critical importance of on-going global surveillance.

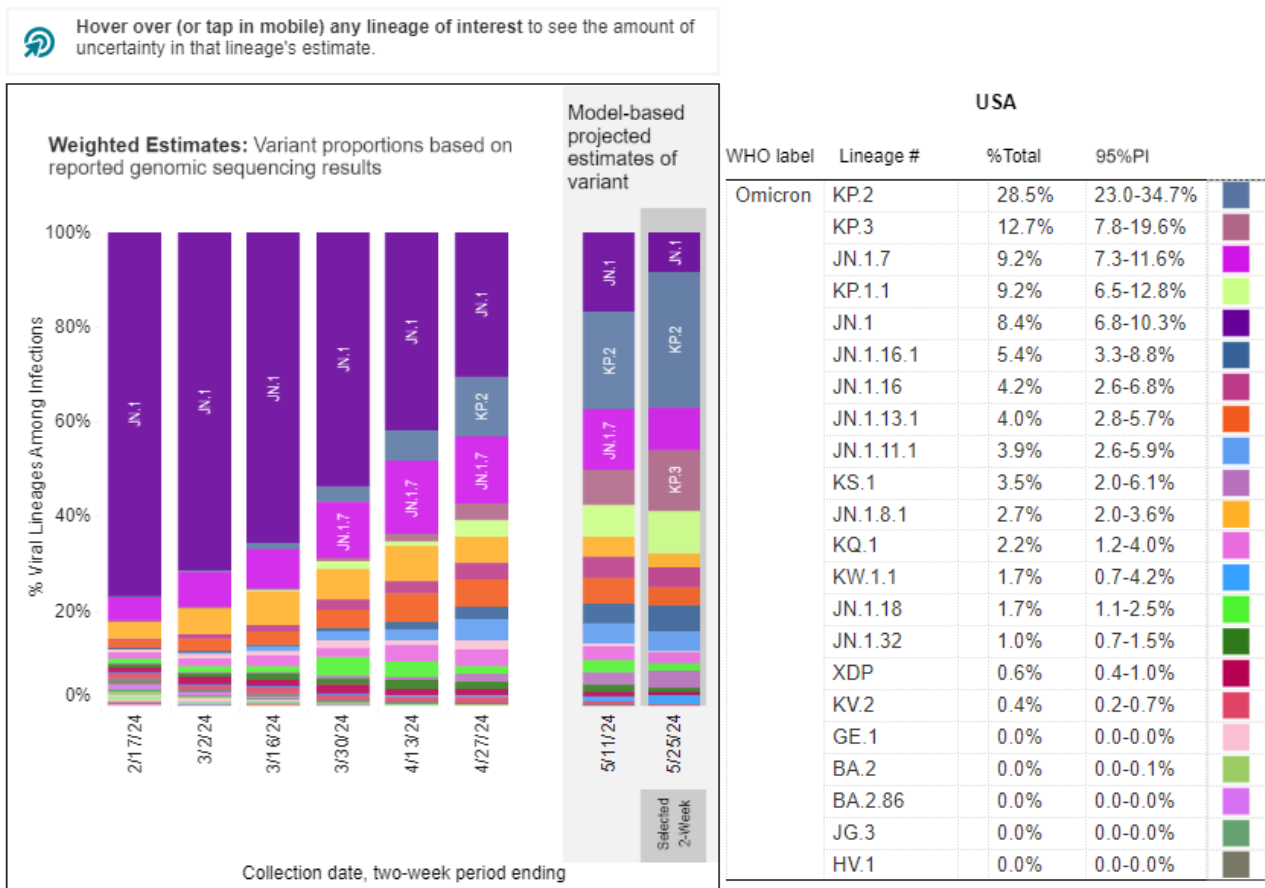
3.3 Antigenic Characterization of Current SARS-CoV-2 Variants

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.

During the period from February 4, 2024, to May 25, 2024, SARS-CoV-2 subvariants continued to evolve. At the beginning of this period, the JN.1 variant was dominant with small percentages of several other subvariants. However, as of May 25, 2024, the KP.2 subvariant became most prevalent (28.5%), followed by KP.3 (12.7%) and JN.1.7 (9.2%) ([Figure 1](#)).

Figure 1. Recent antigenic evolution of SARS-CoV-2 in the United States

Weighted and Nowcast Estimates in United States for 2-Week Periods in 2/4/2024 – 5/25/2024 **Nowcast Estimates in United States for 5/12/2024 – 5/25/2024**



* Enumerated lineages and US VOC and lineages circulating above 1% nationally in at least one 2-week period. "Other" represent the aggregation of the lineages which are circulating <1% nationally during all 2-week periods displayed.

** These data include Nowcast estimates which are modeled projections that may differ from weighted estimates generated at later dates.

XDP was aggregated to JN.1.4 (same spike as JN.1 but recombinants are always difficult). While all lineages are tracked by CDC, those named lineages not enumerated in this graphic are aggregated with their parent lineages based on Pango lineage definitions. For a full list of the current Pango lineages see https://cov-lineages.org/lineage_list.html.

Source: Centers for Disease Control and Prevention. COVID Data Tracker. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2024, May 28. <https://covid.cdc.gov/covid-data-tracker/#variant-proportions>

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 that are reported against emerging variants are generally consistent across studies ([Branche et al. 2023](#); [Kurahde et al. 2023](#); [Qu et al. 2023](#); [Wang et al. 2023a](#); [Wang et al. 2023b](#); [Wang et al. 2023c](#); [Yue et al. 2023](#); [Zou et al. 2023](#)).

As noted above, the JN.1 virus variant that became dominant in North America and the rest of the world in late 2023 and early 2024 was in effect a global sweep, replacing the previous XBB lineage viruses that had dominated earlier in 2023. Although both XBB and JN.1 lineage viruses descended from earlier BA.2 derived viruses, the lineages evolved separately and are antigenically distinct. XBB was a recombinant of two BA.2 derived viruses, BA.2.10.1 and BA.2.75, with substantial Spike amino acid changes compared to the original BA.2 and included multiple amino acid mutations in the Spike receptor binding domain (RBD). The JN.1 variant is a descendant of the BA.2.86 lineage with a new L455S RBD mutation. Overall, BA.2.86 and the more recent related JN.1 lineage viruses contain over 30 Spike protein mutations in comparison with XBB lineage viruses, suggesting the potential for evasion of immunity elicited by prior infection and/or vaccination. JN.1 continued to evolve during spring 2024, giving rise to a group of JN.1 lineage subvariant viruses, many of which, such as KP.2, contain concerning new mutations in Spike RBD, most notably the so-called FLiRT mutations at F456L and R356T. While the landscape of JN.1-derived virus variants is quite diverse (Figure 1, above), currently the original JN.1 virus has almost disappeared. JN.1-derived variants containing F456L along with R346T (e.g., KP.2) and in some cases T572I (e.g., KP.3) are the fastest increasing viruses detected world-wide. Very early preliminary data from several laboratories indicate that these particular RBD mutations result in a further decrease in neutralizing antibody titers that were elicited by prior infection and/or vaccination.

In summary, the low neutralizing antibody titers to current JN.1 and KP.2 sublineages elicited by vaccination, infection, or hybrid immunity suggest that even individuals previously infected with an XBB-lineage virus and/or immunized with an XBB.1.5-based COVID-19 vaccine may be susceptible to infection with currently circulating JN.1 and KP.2 sublineages. That said, it is important to note that the degree of clinical illness following infection will likely 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 workshop entitled "[Global Perspectives on COVID-19 Vaccines Strain Update](#)" held February 26-27, 2024, 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. The conclusions of the meeting included: that use of prior knowledge on a specific product could be used for the approval of strain changes for currently authorized or approved COVID-19 vaccines; Spike antigen change procedures should take into consideration all available information and data

from studies; at the present time an updated vaccine composition for currently authorized or approved COVID-19 vaccines can be based on quality and non-clinical data; and that post-authorization commitments may be needed to gather data on vaccine effectiveness against severe outcomes as well as symptomatic disease. Immunogenicity data from clinical trials with updated vaccines are important to support future antigen change decisions. Additionally, it was noted that at the present time there are no apparent differences in SARS-CoV-2 circulation and transmission in the Northern and Southern Hemispheres.

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 April 26, 2024, 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 continues to circulate and evolve with important genetic and antigenic evolution of the Spike protein.
- The objective of an update to COVID-19 vaccine antigen composition is to enhance vaccine-induced immune responses to circulating SARS-CoV-2 variants.
- As the virus is expected to continue to evolve from JN.1, the TAG-CO-VAC advises the use of a **monovalent JN.1 lineage** as the antigen in future formulations of COVID-19 vaccines.

Additionally, the TAG-CO-VAC noted that given the limitations of the evidence upon which the recommendations above are derived and the anticipated continued evolution of the virus, the TAG-CO-VAC strongly encourages generation of data on immune responses and clinical endpoints (i.e., vaccine effectiveness) on the performance of all currently approved COVID-19 vaccines against emerging SARS-CoV-2 variants, and candidate vaccines with an updated antigen over time.

The TAG-CO-VAC recommendation for a monovalent JN.1 lineage vaccine was made at a time when JN.1 was almost completely dominant and before JN.1 lineage-derived virus variants with FLiRT mutations, such as KP.2, became dominant in the U.S. This change in epidemiology warrants consideration.

4 Options for Selection of Strains for Updated COVID-19 Vaccines for the 2024-2025 Vaccination Campaign

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

In previous discussions with 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 2024 VRBPAC discussion, FDA reviewed various types of data as listed below, engaged with the key partners generating such data, including vaccine manufacturers and other U.S. 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 JN.1 virus was predominant earlier this year, but more recently the KP.2 subvariant with two notable additional amino acid mutations became predominant.
- **Antigenic characterization of viruses to identify antigenically distinct variant viruses.** As described in section [3.3](#), SARS-CoV-2 subvariants JN.1 and KP.2 have additional amino acid changes relative to previously circulating SARS-CoV-2 variants, suggesting continued evolution and increasing immunological distance from the components of currently authorized or approved COVID-19 vaccines.
- **Postvaccination human serology studies to evaluate antibody responses generated by the current vaccines against more recently circulating virus variants such as JN.1 lineage and KP.2 subvariant 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 U.S.-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 meeting by the vaccine manufacturers.
- **Nonclinical 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.** Nonclinical immunogenicity data (e.g., neutralizing antibody) can provide an indication of how well antibodies to Spike of one strain will cross-neutralize other variant strains of SARS-CoV-2 and thus help inform formula selection in combination with other data. As with human serology studies, COVID-19 vaccine manufacturers are also able to generate nonclinical immunogenicity studies with new candidate vaccines and each of the manufacturers of U.S.-authorized/approved COVID-19 vaccines have produced candidate vaccines at risk and evaluated them in nonclinical studies. These data will be presented at the VRBPAC meeting by the vaccine manufacturers.

4.2 Manufacturing Considerations

Recommendations for updating the antigenic composition of COVID-19 vaccines must consider the time needed for manufacturers to implement and deliver an updated COVID-19 vaccine. The timelines likely differ for different manufacturing technologies and are also affected by manufacturing experience and the availability and capacity of manufacturing facilities. All three vaccine manufacturers have been evaluating candidate vaccines “at risk” in preparation for an antigenic change in an anticipated 2024-2025 Formula in the event that such a change was recommended. In general, the manufacturers have indicated a shorter timeline is needed for mRNA vaccine antigenic composition changes compared with that needed for protein subunit vaccines.

4.3 Summary of Considerations for Selection of Strain(s) for inclusion in 2024-2025 COVID-19 Vaccines

As noted in section [3.2](#), although JN.1 sublineages were predominant through spring 2024 in the U.S., the KP.2 subvariant has now become the predominant circulating strain. Because the antigenic distance between JN.1 and JN.1-derived subvariants such as KP.2 subvariants is not far, it is possible that vaccines developed against JN.1 may adequately protect against KP.2. However, further SARS-CoV-2 evolution may lead to further divergence from JN.1, and

consideration may need to be given to the selection of the subvariant that is currently predominant to assure the best possible match as the virus further evolves.

5 VRBPAC Meeting Topics

On June 5, 2024, VRBPAC will meet in open session to discuss and make recommendations on the selection of the 2024-2025 Formula for COVID-19 vaccines. The committee will be asked to discuss available evidence on recent and currently circulating SARS-CoV-2 variants, including data from virus surveillance and genomic analyses, antigenic characterization analyses, vaccine effectiveness and clinical immunogenicity studies of current U.S.-authorized/approved COVID-19 vaccines and nonclinical immunogenicity studies of candidate vaccines expressing or containing updated Spike antigens.

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