FDA Briefing Document
Vaccines and Related Biological Products Advisory Committee Meeting
May 22, 2025

Selection of the 2025-2026 Formula for COVID-19 Vaccines

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1 Meeting Objective

On May 22, 2025, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) will meet in open session to discuss and make recommendations on the selection of the 2025-2026 Formula for COVID-19 vaccines for use in the United States (U.S.).

2 Background

2.1 Previous VRBPAC Discussions and Vaccine Composition Recommendations

VRBPAC has met multiple times since 2022 to discuss and make recommendations on the selection of the strain compositions for COVID-19 vaccines. At the VRBPAC meeting on June 5, 2024, VRBPAC unanimously voted to recommend a monovalent JN.1-lineage vaccine composition for use in the U.S. beginning in the fall of 2024. On August 13, 2024, FDA further determined that the preferred JN.1-lineage for the COVID-19 vaccines (2024-2025 Formula) was the KP.2 strain, if feasible [for additional information, please see Updated COVID-19 Vaccines for Use in the United States Beginning in Fall 2024].

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 (2024-2025 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 SARS-CoV-2 Omicron variant KP.2, encapsulated in lipid particles. Moderna COVID-19 Vaccine (2024-2025 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 through 11 years of age, 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 (2024-2025 Formula) Fact Sheet. Safety and effectiveness data supporting approval of Spikevax and authorization of Moderna COVID-19 Vaccine (2024-2025 Formula) are detailed in the decision memoranda available on the FDA Website.

2.2.2 Comirnaty, Pfizer-BioNTech COVID-19 Vaccine (2024-2025 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 SARS-CoV-2 Omicron variant KP.2 that is formulated in lipid particles. Pfizer-BioNTech COVID-19 Vaccine (2024-2025 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 through 11 years of age, 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 regimen 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 (2024-2025 Formula) Fact Sheet. Safety and effectiveness data supporting approval of Comirnaty and authorization of Pfizer-BioNTech COVID-19 Vaccine (2024-2025 Formula) are detailed in the decision memoranda available on the FDA website.

2.2.3 Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula)

Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula), which contains recombinant S protein of the SARS- CoV-2 Omicron variant JN.1 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 (2024-2025 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 (2024-2025 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 (2024-2025 Formula) Fact Sheet. Safety and effectiveness data supporting authorization for the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 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 U.S.-Authorized/Approved COVID-19 Vaccines (2024-2025 Formula) and Need for a Selection of 2025-2026 Formula

An observational study (Link-Gelles, et al., 2025) conducted to evaluate the effectiveness of COVID-19 vaccines (2024-2025 Formula) introduced after emergence and global dominance of JN.1 sublineages indicates that updating COVID-19 vaccines to an JN.1 lineage-based formula (e.g., KP.2) was associated with positive health outcomes, including a reduction in hospitalization and urgent care utilization in adults of all ages. Vaccine effectiveness (VE) of COVID-19 vaccine (2024-2025 Formula) was 33% (95% CI: 28, 38) against COVID-19–associated emergency department or urgent care visits among adults aged ≥18 years and 45% (95% CI: 36, 53) – 46% (95% CI: 26, 60) against hospitalizations among immunocompetent adults aged ≥65 years, compared with individuals not receiving a COVID-19 vaccine (2024–2025 Formula) dose.

Since the introduction of COVID-19 vaccines (2024-2025 Formula) in fall 2024, SARS-CoV-2 has continued evolving incrementally (drift-like) into distinct sublineages by acquiring additional mutations (see section 3.2). Observational data from prior years indicates 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 (Ciesla, et al., 2023; Link-Gelles, et al., 2024) partly attributed to immune escape by emerging SARS-CoV-2 variants. Studies suggest better matching of the vaccine to circulating strains is associated with improved neutralizing antibody titers (Jiang, et al., 2023; Wang, et al., 2023; Springer, et al., 2023).

Preliminary data from several studies indicate a modest drop in neutralization titers against recently emerging JN.1 lineage subvariants (e.g., LP.8.1) in sera following immunization with the monovalent JN.1 COVID-19 vaccine (Chen, et al., 2025; Guo, et al., 2025; Li, et al., 2024; Liu, et al., 2024; Liu, et al., 2025; Mellis, et al., 2025; WHO, 2024; Zhang, et al., 2025) and indicating continued immune evasive evolution of variants. Updating the current formula of COVID-19 vaccines to more closely match currently circulating JN.1-lineage viruses (e.g., LP.8.1) may provide added benefit for the anticipated increase in virus spread during the 2025–2026 fall-winter 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., the BA.5 sublineage dominated during much of fall 2022, while other Omicron sublineages, including the 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 the late spring of 2024, the KP.2 subvariant containing two new mutations, i.e., F456L and R356T that appeared to confer an advantage to the virus either in terms of fitness or escape from immunity, became noticeable. By late May 2024, several additional JN.1-lineage variants, including KP.2 and KP.3, co-circulated in the U.S.

By late summer 2024, the JN.1-derived variant KP.3.1.1 had become the dominant variant in the U.S. but was beginning to be replaced by the XEC variant virus, a recombinant between KS.1.1 and KP.3.3, both of which were also JN.1-lineage viruses (Li, et al., 2024). XEC had 7 amino acid changes relative to JN.1. By the beginning of 2025, the XEC variant was the dominant circulating variant but was beginning to be replaced by another JN.1-derived virus variant, LP.8.1. Variant LP.8.1, which is now the dominant circulating virus variant, has 9 Spike amino acid substitutions relative to its progenitor JN.1 and 8 amino acid differences compared with XEC.

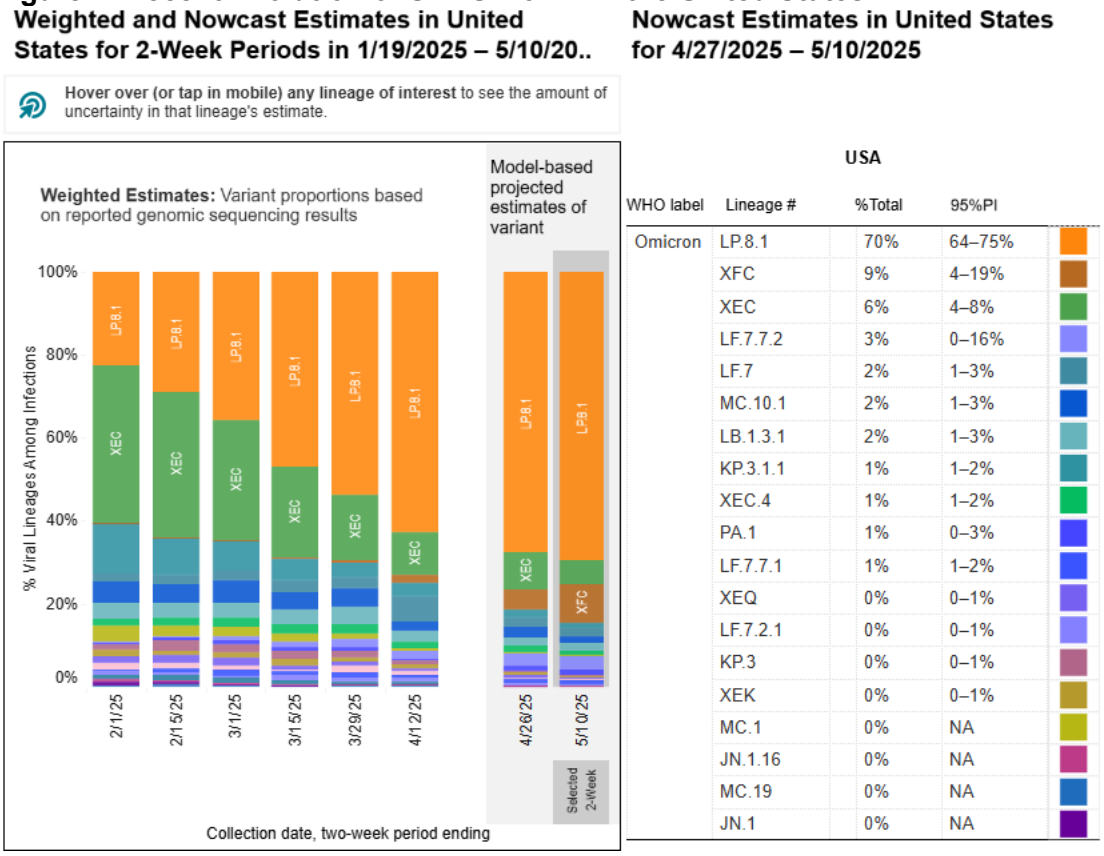
Although all SARS-CoV-2 variants circulating in humans for over the last year have derived from the JN.1 variant, there has been continued evolution and diversification from the original JN.1 virus, with many of these JN.1-derived variants having amino acid changes in the Spike protein at epitopes targeted by neutralizing antibodies. SARS-CoV-2 evolution continues to be complex and remains unpredictable. 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 ongoing global surveillance.

3.2.1 Antigenic Characterization of Current SARS-CoV-2 Variants

As immunity increases globally from vaccinations and/or infections, natural selection of immune escape variants may play 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 January 2025 to May 2025, SARS-CoV-2 subvariants continued to evolve. As noted above, at the beginning of this period, the XEC and KP.3.1.1 variants were dominant with small percentages of several other subvariants. However, by March 2025, the LP.8.1 subvariant became most prevalent and continues to be the dominant variant into May 2025 (Figure 1).

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



Source: Centers for Disease Control and Prevention. COVID Data Tracker. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2025, May 14. https://covid.cdc.gov/covid-data-tracker/#variant-proportions
** These data include Nowcast estimates which are modeled projections that may differ from weighted estimates generated at later dates.
# Enumerated lineages and US VOC and lineages circulating above 1% nationally in at least one 2-week period. "Other" represents the aggregation of the lineages which are circulating <1% nationally during all 2-week periods displayed. 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 described in more detail here: https://cov-lineages.org/lineage_list.html.

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 (Chen, et al., 2025; Guo, et al., 2025; Li, et al., 2024; Liu, et al., 2024; Liu, et al., 2025; Mellis, et al., 2025; WHO, 2024; Zhang, et al., 2025).

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 with the original BA.2 and included multiple amino acid mutations in the Spike RBD. The JN.1 variant was a descendant of the BA.2.86 lineage with a notable new L455S RBD mutation. Overall, the JN.1-lineage viruses contain over 30 Spike protein mutations in comparison with the earlier XBB-lineage viruses. This suggested the potential for evasion of immunity elicited by prior infection and/or vaccination and prompted the recommended vaccine strain composition update in 2024 to a JN.1-lineage virus.

As noted above, JN.1 continued to evolve during 2024 and into 2025, giving rise to a diverse group of JN.1-lineage subvariant viruses, many of which contain concerning amino acid mutations in the Spike N-terminal domain (NTD) and RBD that have the potential to affect neutralization by antibodies elicited by prior infection and/or vaccination. For example, the LP.8.1 variant that is now dominant has a deletion in the NTD (S31 del) that was not present in JN.1 and several key RBD differences compared with JN.1 (R346T, V445R, F456L, and Q493E). Preliminary data from several laboratories indicate that these particular Spike mutations result in modest decrease in neutralizing antibody titers that were elicited by prior infection and/or vaccination with older strains of JN.1-lineage viruses (Chen, et al., 2025; Guo, et al., 2025; Li, et al., 2024; Liu, et al., 2024; Liu, et al., 2025; Mellis, et al., 2025; WHO, 2024; Zhang, et al., 2025). That said, it is important to note that the relationship between a decrease in neutralization titers and clinical outcome is incompletely understood.

3.3 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 vaccines. Nevertheless, global public health agencies and vaccine regulators have had ongoing discussions throughout the year to address the issue of periodically updating COVID-19 vaccines in an effort to align the criteria for selection and the recommendations for updating COVID-19 vaccines, when possible.

The World Health Organization (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 proposed modifications to COVID-19 vaccine antigen composition. Recently, the TAG-CO-VAC advised that a monovalent JN.1 or KP.2 vaccines remain as appropriate vaccine antigen, while a monovalent LP.8.1 is a suitable alternative vaccine antigen (Ref: https://www.who.int/news/item/15-05-2025-statement-on-the-antigen-composition-of-covid-19-vaccines) to be included in the composition of COVID-19 vaccines (2025-2026 Formula).

4 Options for Selection of Strains for Updated COVID-19 Vaccines for the 2025-2026 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 for use in the U.S. The relevant data reviewed would ideally include multiple types and sources of data. In preparation for the May 2025 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 XEC virus was predominant earlier this year, but more recently other subvariants (e.g., LP.8.1) have become predominant.
- **Antigenic characterization of viruses to identify antigenically distinct variant viruses**. As described in section 3.3, recent SARS-CoV-2 subvariants such as LP.8.1 have additional amino acid changes relative to previously circulating SARS-CoV-2 JN.1-like variants, suggesting continued evolution and increasing antigenic drift 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 JN.1 sublineage virus variants**. Since COVID-19 vaccine manufacturers are best positioned to generate the robust data needed from postvaccination human serology studies, FDA conducts 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 these 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 responses) 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 these 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 an updated COVID-19 vaccine formula. 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 manufacturers of U.S.-authorized/approved COVID-19 vaccines have been evaluating candidate vaccines “at risk” in preparation for a strain change in an anticipated 2025-2026 Formula, in the event that such a change is recommended. In general, the manufacturers have indicated a

shorter timeline is needed for mRNA vaccine strain 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, while current circulating SARS-CoV-2 variants have derived from the JN.1 variant that appeared in late 2023, the JN.1 virus lineage continues to evolve. The LP.8.1 subvariant has now become the predominant circulating strain, but other virus subvariants including LF.7 and XFG have also been increasingly detected in recent weeks. Because of the continuing antigenic drift between JN.1 and KP.2, that were used in the 2024-2025 vaccine, and the currently circulating subvariants, a review and discussion regarding the need for a strain composition update for COVID-19 vaccines is warranted.

5 VRBPAC Meeting Topics

On May 22, 2025, VRBPAC will meet in open session to discuss and make recommendations on the selection of the 2025-2026 Formula for COVID-19 vaccines for use in the U.S. 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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