Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

FDA Considerations and Recommendations for the 2025-2026 Formula of COVID-19 Vaccines in the United States

Vaccines and Related Biological Products Advisory Committee

May 22,2025

Jerry P Weir, PhD, Director

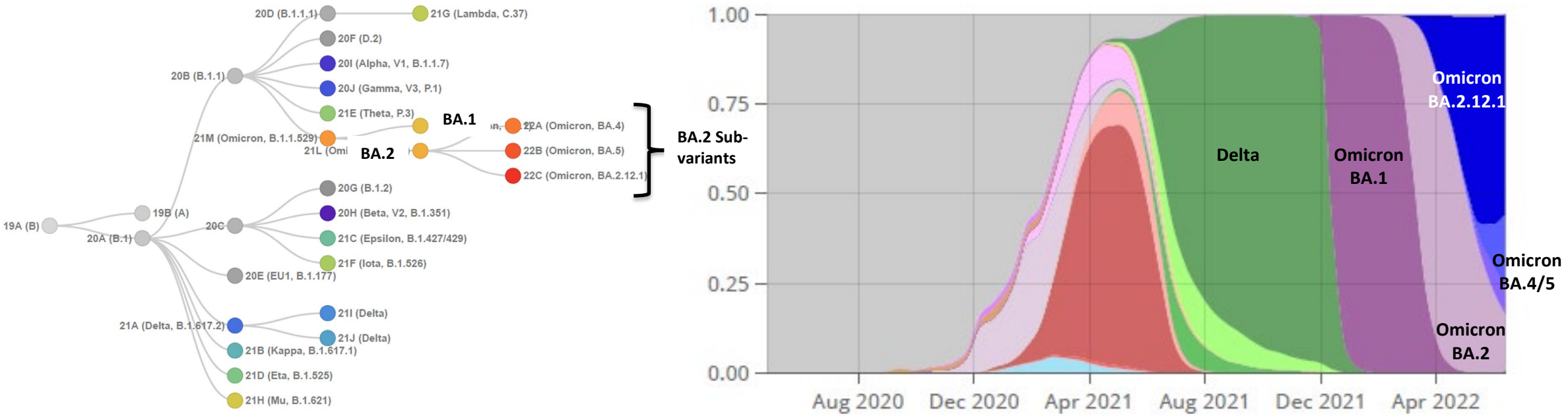
Division of Viral Products/OVRR/CBER/FDA

Background

- The Vaccines and Related Biological Products Advisory Committee (VRBPAC) has previously convened three times to discuss and recommend whether to update the antigenic composition of authorized/approved COVID-19 vaccines for the U.S.

COVID-19 Vaccine Composition Update – June 2022

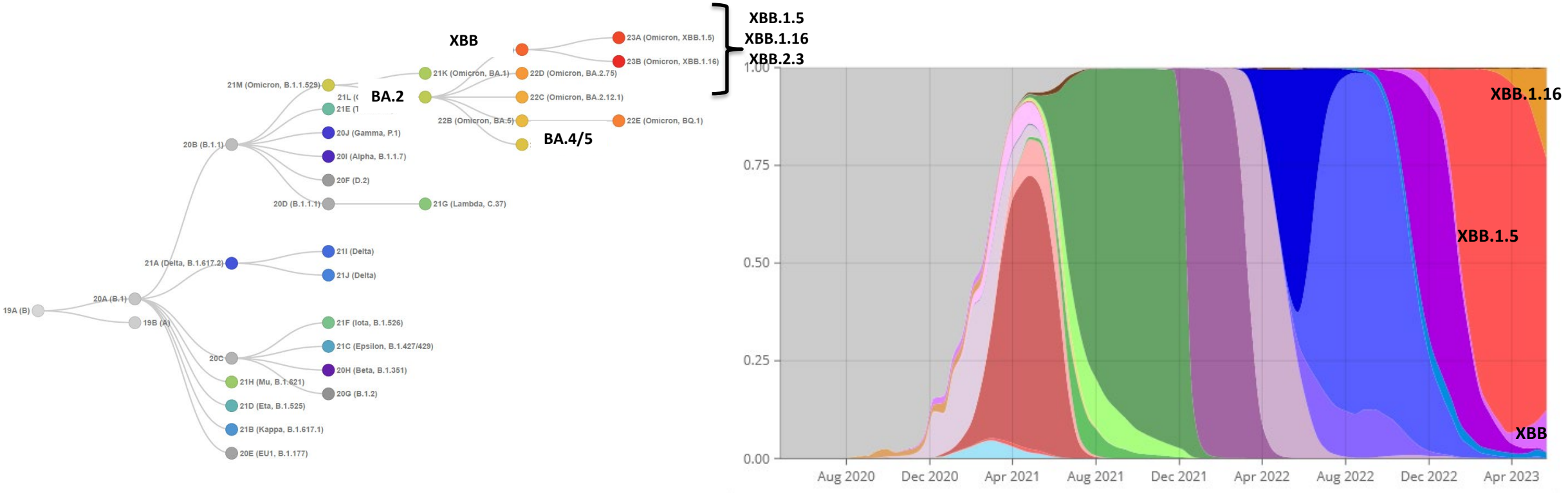
from https://covariants.org/ using Nextstrain data (https://nextstrain.org/



- The Omicron variant had replaced previous SARS-CoV-2 viruses
- Manufacturers had produced and evaluated BA.1 vaccines in clinical trials
- BA.1 was no longer in circulation by June 2022 and was antigenically very distinct from BA.2-derived viruses
- VRBPAC recommended inclusion of a SARS-CoV-2 Omicron component for COVID-19 booster vaccines in the U.S.
  - FDA notified vaccine manufacturers of their recommendation to develop a bivalent (prototype plus Omicron BA.4/BA.5) COVID-19 vaccine

COVID-19 Vaccine Composition Update – June 2023

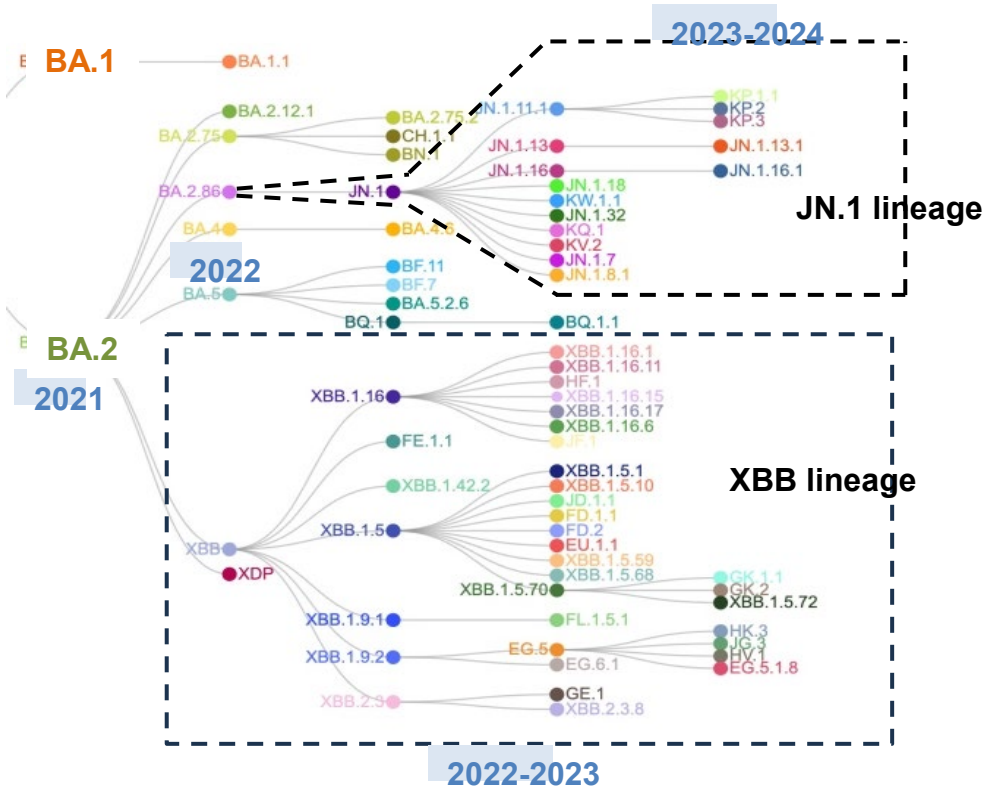
from https://covariants.org/ using Nextstrain data (https://nextstrain.org/

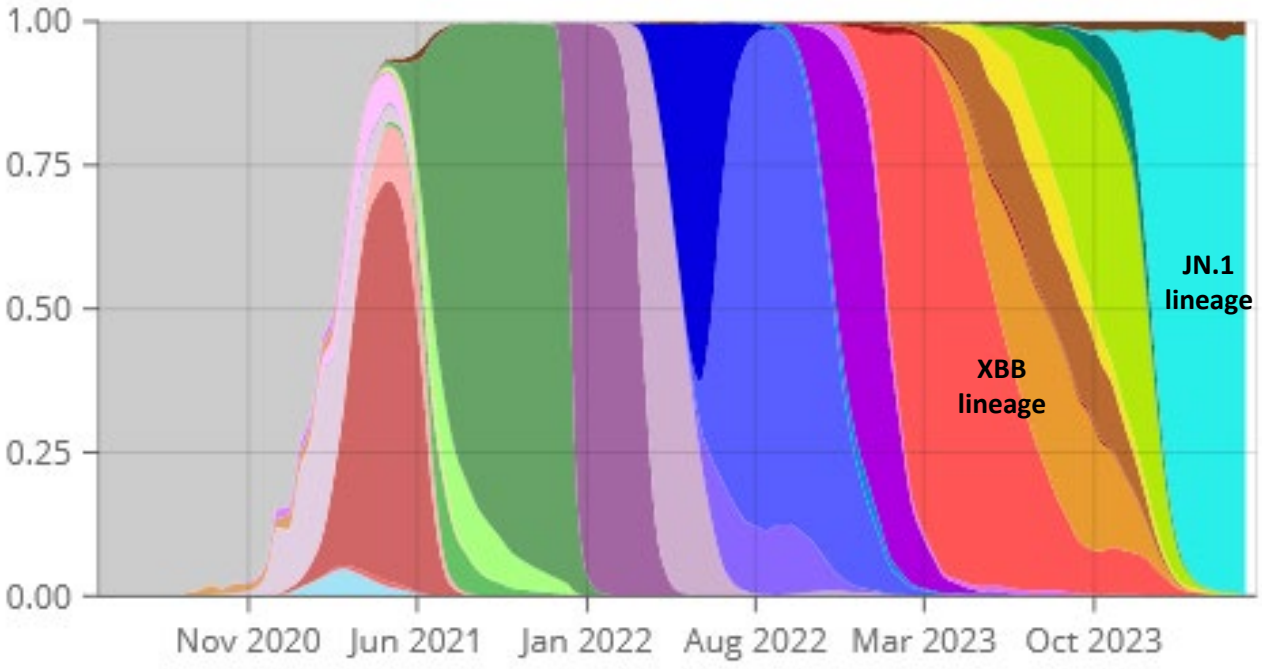


- XBB-lineage viruses had replaced previous BA.5-derived SARS-CoV-2 viruses and were antigenically distinct
- VRBPAC discussion concerned selection of XBB lineage variants, e.g., XBB.1.5, 1.16, 2.3
- VRBPAC recommended an update of the vaccine composition to a monovalent XBB-lineage for the United States
  - FDA notified manufacturers of their recommendation to develop a monovalent (XBB.1.5) COVID-19 vaccine

COVID-19 Vaccine Composition Update – June 2024

from https://covariants.org/ using Nextstrain data (https://nextstrain.org/





- JN.1-lineage viruses had replaced previous XBB-derived SARS-CoV-2 viruses
- The JN.1-lineage had already begun to diversify, e.g., KP.2, KP.3
- VRBPAC recommend an update of the vaccine composition to a JN.1-lineage for the United States
  - FDA notified manufacturers of their recommendation to develop a monovalent JN.1-lineage COVID-19 vaccine with the KP.2 strain, if feasible

Key Challenges for the COVID-19 Strain Composition Recommendation Process

- In contrast to influenza, and some other respiratory viruses, SARS-CoV-2 does not show a defined seasonality or periodicity
  - The timing for vaccine updating is not easily aligned with the emergence of virus variants
- SARS-CoV-2 continues to evolve and diversify in both stepwise (drift) and saltation (shift) patterns
  - At any given time, multiple variants may be co-circulating
  - Variants that become predominate are usually dominate for a relatively short period of time (months)
  - Evolution and diversity are driven both by virus fitness and escape from immunity, making it difficult to predict which variant will outcompete others to dominate the next variant wave
- At any given time, a relatively small amount of critical nonclinical and clinical data is available to make a composition recommendation
- Vaccine manufacturing technologies have different manufacturing considerations

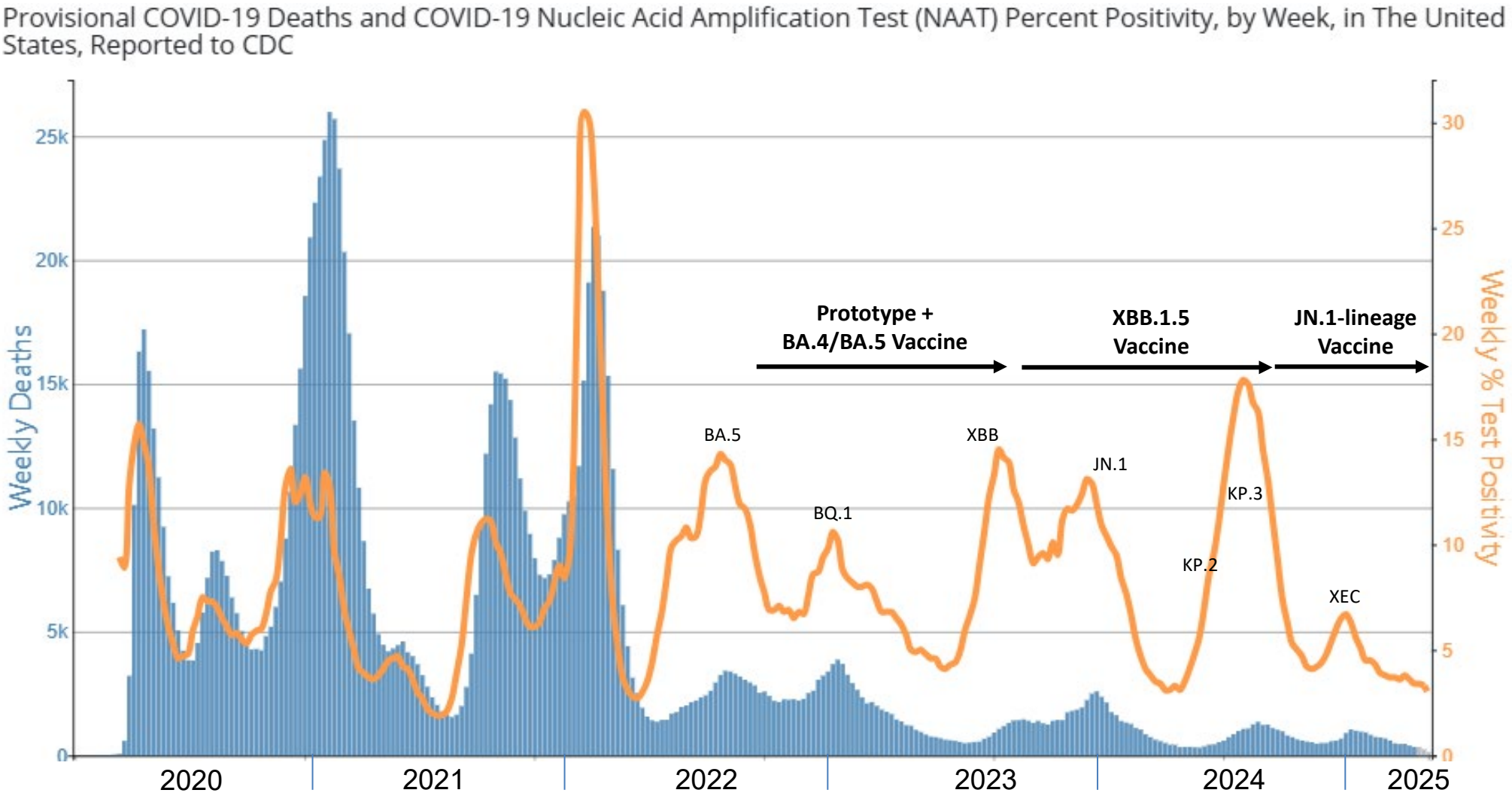
Major Considerations for Modifying the COVID-19 Strain Composition

- Key questions to be addressed by the agency and VRBPAC in considering whether to modify the COVID-19 vaccine composition include the following:
  - Have currently circulating SARS-CoV-2 virus variants become, or are they expected to become, dominant and displace earlier virus strains?
  - Are currently circulating SARS-CoV-2 virus variants antigenically distinct from current vaccines?
  - Is there evidence that current vaccines may be less effective against new circulating virus variants than against previous strains of the virus?
  - Is there evidence that a candidate vaccine with an updated composition will be more effective against new circulating virus variants and provide an improved clinical benefit?

Vaccine Strain Composition Recommendation Process

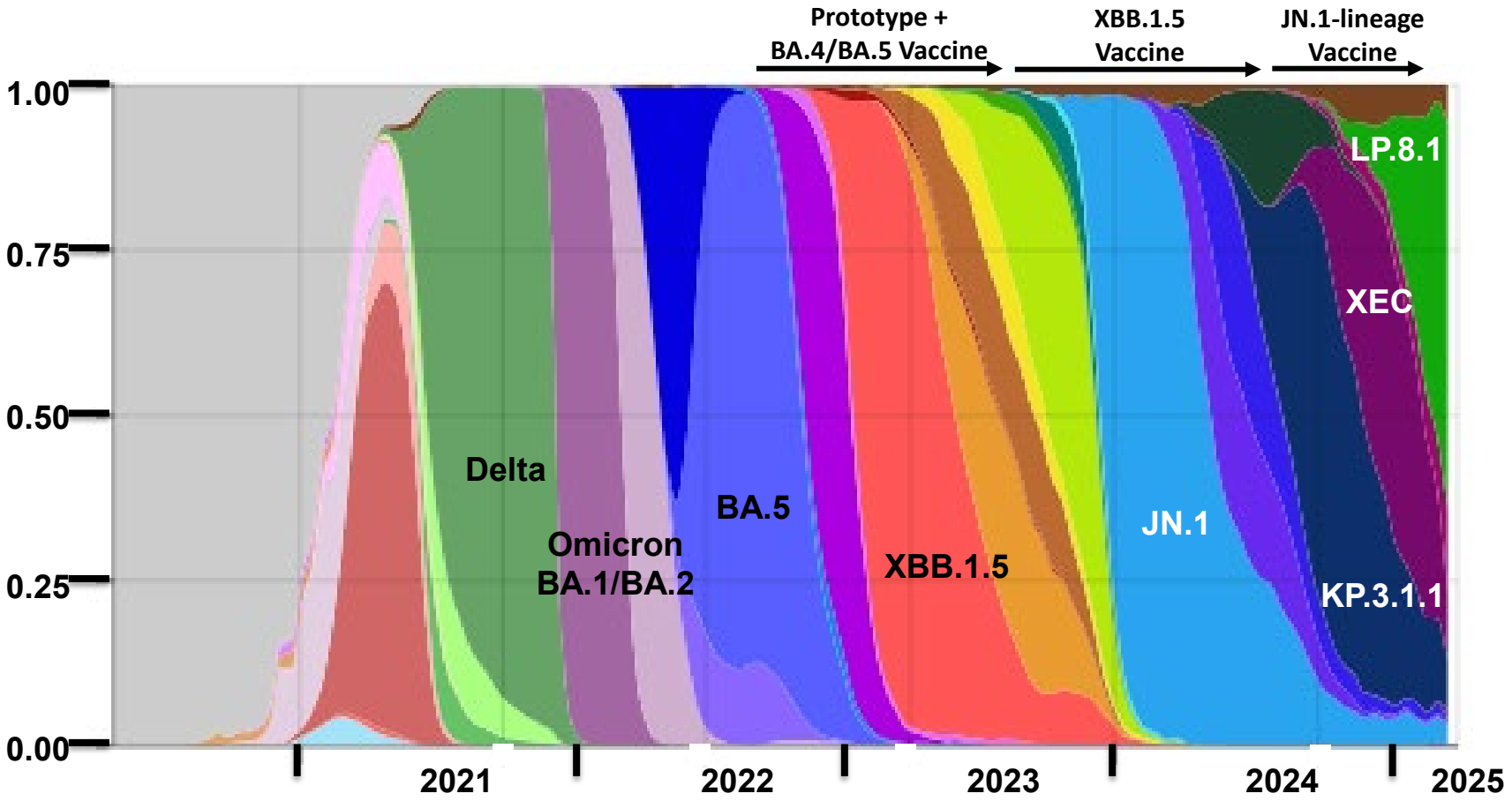
- To address the key issues necessary for considering a modification of the COVID-19 strain composition, FDA reviews multiple types of data (listed below) and engages with the key partners generating such data, including vaccine manufacturers and other government agencies
  - Virus surveillance and genomic analyses to identify emerging new virus variants
  - Antigenic characterization of viruses to identify antigenically distinct variant viruses
  - Effectiveness data for current vaccines
  - Postvaccination human serology studies to evaluate antibody responses generated by the current vaccines against more recently circulating virus variants
  - Available post-infection human serology studies to evaluate antibody responses generated by recently circulating virus variants
  - 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
- FDA reviews the discussions and recommendations put forth by other regulatory groups and public health agencies
- FDA discusses manufacturing timelines with each of the manufacturers of U.S.-authorized/approved COVID-19 vaccines to understand the impact of a strain composition recommendation on vaccine availability

Vaccine Strain Composition Recommendations are Impacted by Rapid Virus Evolution and Lack of Virus Seasonality



SARS-CoV-2 Continues to Evolve and Diversify

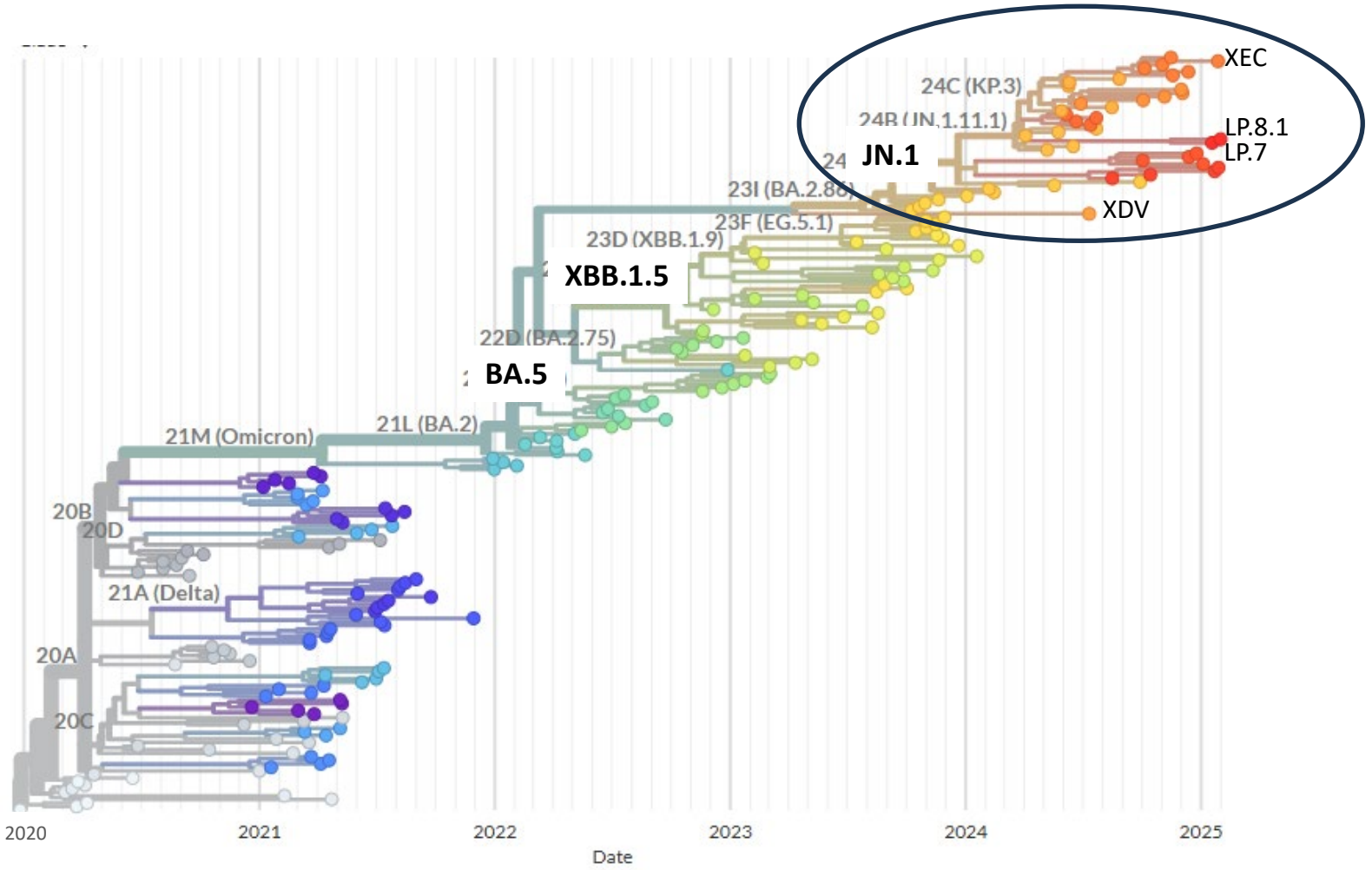
- XBB-lineage viruses were displaced by BA.2.86/JN.1-lineage viruses in a global sweep in early 2024



from https://covariants.org/ using Nextstrain data (https://nextstrain.org/

JN.1 Evolution has Resulted in a Very High Level of Virus Diversity

- The total number of Spike amino acid substitutions among JN.1-lineage viruses is low compared with the number of differences between JN.1 and previous lineages (e.g., XBB, BA.5)
- However, individual substitutions have been associated with escape from neutralizing antibodies elicited by prior infection and/or vaccination, but the clinical impact is difficult to ascertain



adapted from https://nextstrain.org/ncov/open/reference

SARS-CoV-2 Variants – Current Proportions

Variants – U.S.
4/27-5/10/25

Lineage #	%Total	95%PI
LP.8.1	70%	64–75%
XFC	9%	4–19%
XEC	6%	4–8%
LF.7.7.2	3%	0–16%
LF.7	2%	1–3%
MC.10.1	2%	1–3%
LB.1.3.1	2%	1–3%
KP.3.1.1	1%	1–2%
XEC.4	1%	1–2%
PA.1	1%	0–3%
LF.7.7.1	1%	1–2%
XEQ	0%	0–1%
LF.7.2.1	0%	0–1%
KP.3	0%	0–1%
XEK	0%	0–1%

CDC COVID Data Tracker: Variant Proportions

Variants – Global
3/31-4/27/25

- Among 6,893 sequenced samples from 41 countries, proportions of the top 10 sub-lineages were:
  - LP.8.1.1 (25%)
  - XEC (8%)
  - LP.8.1 (7%)
  - NB.1.8.1 (5%)
  - LF.7.2.1 (4%)
  - XEC.4 (3%)
  - LF.7 (2%)
  - LP.8.1.6 (2%)
  - MC.21.1 (2%)
  - LF.7.9 (2%)
- Total proportion of **LF.7** and all its sub-lineages was **12%**.
- Total proportion of **LP.8.1** and all its sub-lineages was **38%**.

Global data provided by CDC;
Data Source: GISAID and NCBI GenBank

- LP.8.1 and sublineages are dominant in the U.S. and globally, but may be leveling off in U.S.
- LF.7 and sublineages make up a significant proportion of virus variants globally, although low in number in the U.S.
- XFC, which is increasing in proportion in the U.S., is a recombinant between LF.7 and LP.8.1.1.
- Amino acid changes in the NTD of most recent JN.1-lineage viruses have a new glycosylation site -ΔS31 (LP.8.1) or T22N, (LF.7 and XFC)
- Recent JN.-1 lineage viruses have additional shared substitutions that have been independently selected
- Some non-JN.1 lineage viruses have been reported but are very low in number (e.g., BA.3.2)

Current Effectiveness of Authorized COVID-19 Vaccines

- Data presented at this VRBPAC (CDC and TAG-CO-VAC presentations) indicate that updating COVID-19 vaccines to a JN.1-lineage composition in 2024 was associated with positive outcomes relative to pre-existing immunity, including a reduction in hospitalization and urgent care utilization

- Data presented by manufacturers of U.S.-authorized/approved COVID-19 vaccines indicate that vaccines with updated JN.1-lineage monovalent formulations elicited stronger neutralizing antibody responses against JN.1 and JN.1-descendent viruses than previous XBB.1.5 vaccines

- Previous studies have found that vaccine effectiveness appears to decrease as time since vaccination increases, often as new SARS-CoV-2 variants emerge

Postvaccination Human Serology Studies

- Postvaccination human serology studies are used to evaluate antibody responses generated by the current JN.1-lineage vaccines against more recently circulating virus variants
  - Postvaccination sera are available from recipients of current monovalent JN.1 vaccines, but not from proposed candidate vaccines
  - Neutralization titers measured against new variants (e.g., LP.8.1, LF.7) can reveal immune evasion of these variants compared with the vaccine strain, but only indirectly suggest similarities or differences among the new variants

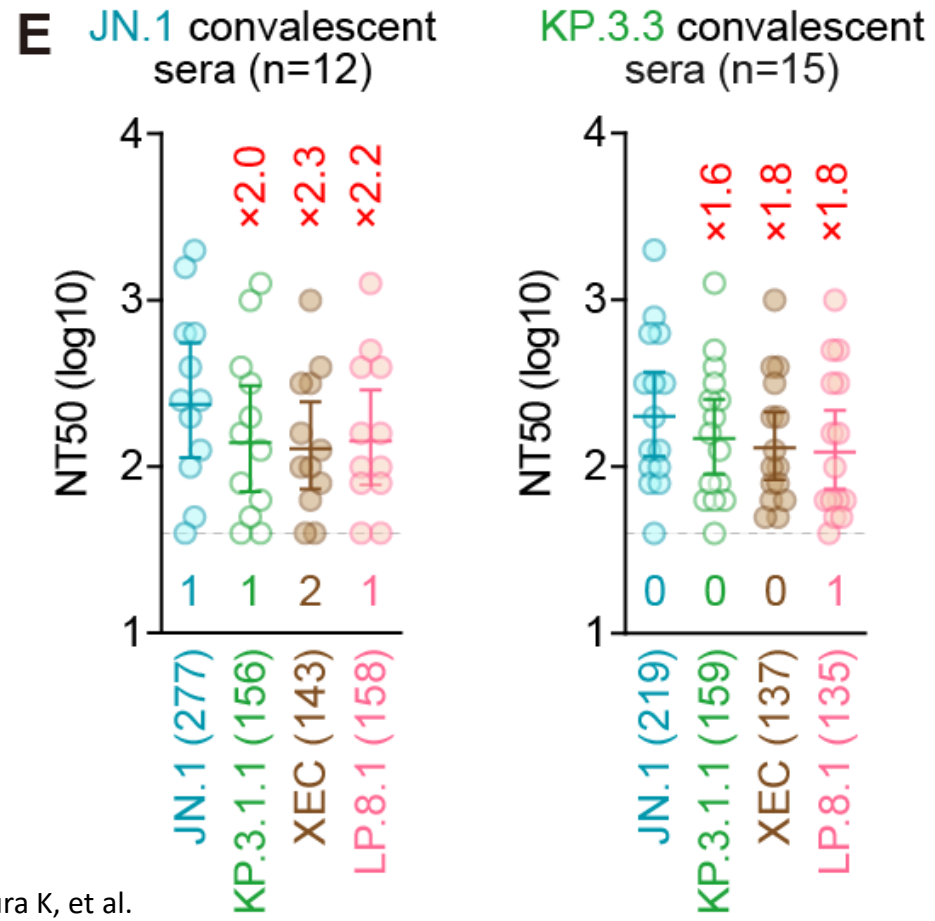
- Data presented at this VRBPAC by the manufacturers of U.S-authorized/approved COVID-19 vaccines, as well as from other studies, indicate that recent virus variants are modestly more immune evasive to antibodies elicited by prior JN.1-lineage vaccination

Nonclinical Immunogenicity Studies With New Candidate Vaccines

- Nonclinical immunogenicity studies are used to evaluate immune responses generated by new candidate vaccines (e.g., expressing or containing updated variant Spike components) against antigenically distinct circulating virus variants
- Data from such nonclinical immunogenicity studies (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 strain selection in combination with other data
- Studies are dependent on COVID-19 vaccine manufacturers producing candidate vaccines at risk and conducting studies to generate the data for evaluation
- Study designs are heterogeneous and do not fully recapitulate human exposure
- Data presented at this VRBPAC by the manufacturers of U.S.-authorized/approved COVID-19 vaccines indicate that candidate vaccines with updated JN.1-lineage monovalent formulations elicit somewhat stronger neutralizing antibody responses against more recently circulating JN.1-descendent viruses

Post-Infection Human Serology Studies

- Post-infection human serology studies also provide additional information to evaluate antibody responses generated by a previously circulating virus variant against more recently circulating virus variants
- Such studies are limited in number, employ different assays for analysis, and usually have small numbers of sera available that are from subjects with very heterogeneous exposure histories
- The available data indicate that neutralizing antibody titers elicited by JN.1 infection are modestly reduced against the more recent circulating strains of JN.1-lineage viruses (e.g., LP.8.1) relative to JN.1



Chen L, Kaku Y, Okumura K, et al.
Virological characteristics of the SARS-CoV-2 LP.8.1 variant.
Lancet Infect Dis. 2025;25(4):e193

Global Alignment of COVID-19 Strain Composition Recommendations

- There are many challenges for global coordination of the COVID-19 vaccine strain composition
- Nevertheless, global public health agencies and vaccine regulators meet throughout the year in an effort to align the criteria used and the vaccine strain composition recommendations when possible
  - The WHO Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC) issued a statement on May 15, 2025, on the antigen composition of COVID-19 vaccines (update presented at this VRBPAC)
    - “advises manufacturers that monovalent JN.1 or KP.2 vaccines remain appropriate vaccine antigens; monovalent LP.8.1 is a suitable alternative vaccine antigen.”
    - “vaccination should not be delayed in anticipation of access to vaccines with an updated composition.”
  - The European Medicines Agency (EMA) issued a statement on May 17, 2025, providing a recommendation to update the antigenic composition of authorized COVID-19 vaccines for 2025-2026
    - "Adapting vaccines to target the LP.8.1 variant of the JN.1 family of Omicron subvariants is preferentially recommended to ensure cross-reactivity against current dominant and emerging strains. Vaccine compositions targeting other JN.1 descendants could be considered if there is adequate justification.”
    - “Vaccines targeting JN.1 or KP.2 strains could still be considered for the vaccination campaigns in 2025 until updated LP.8.1 vaccines become available.”
  - Recommendations are similar; minor differences in wording reflect the different constituencies represented by the various agencies

Summary-1

- SARS-CoV-2 continuous to evolve without a well-defined seasonality, complicating the vaccine composition process for regulators and manufacturers
- The SARS-CoV-2 JN.1 virus variant that emerged in late 2023/early 2024 replaced previous XBB-lineage viruses in a global sweep and the overwhelming majority of viruses detected since that time have been derived from JN.1
- SARS-CoV-2 JN.1 has continued to evolve genetically and antigenically over this time, resulting in a very high level of virus diversity
- The number of amino acid substitutions in the Spike glycoprotein among JN.1-lineage viruses is lower than the number of differences between JN.1 and previous lineages (e.g., XBB, BA.5), but some substitutions are known to contribute to immune evasion
- As JN.1-lineage viruses continue to diversify, the number of Spike amino acid substitutions in JN.1-lineage viruses in 2025 (e.g., LP.8, LF.7) has increased compared with the number of substitutions in JN.1-lineage viruses in 2024 (e.g., KP.2, KP.3) and many substitutions are in the NTD and RBD regions that may reduce virus neutralization

Summary – 2

- The accumulated clinical and nonclinical data suggest that recent JN.1-lineage viruses may be modestly more resistant to neutralization by antibody elicited by prior infection and/or vaccination
- Many of these JN.1-descendent variants have shared mutations
- While virus neutralization has been shown to correlate with protection for all Spike-based vaccines, the clinical impact of a reduction in neutralization titer of this magnitude is difficult to ascertain
- Vaccine manufacturers have continued evaluating updated candidate vaccines at risk in 2025 to generate data to inform a composition recommendation and in preparation for implementation of an updated composition recommendation if needed
- Vaccine platforms have unique manufacturing issues, and the manufacturing timelines can be impacted by the final choice of antigen
- The totality of available evidence indicates that a monovalent JN.1-lineage vaccine is warranted for COVID-19 vaccines (2025-2026 Formula) to be used in the U.S., but the continued evolution and diversity of JN.1-lineage viruses complicates the specific strain selection decision

Future Directions for the COVID-19 Vaccine Composition Process

- Updating the SARS-CoV-2 strain composition of COVID-19 vaccines is a continuous process
- Many challenges for composition recommendation remain
  - SARS-CoV-2 continues to evolve without a well-defined seasonality and in an unpredictable manner
  - An informed vaccine composition recommendation depends upon a variety of types of data, much of which is limited and often not available at the time when composition recommendations are under consideration, including:
    - Declining virus surveillance data
    - Limited availability of candidate vaccines from manufacturers
    - Imperfect nonclinical models that characterize antigenic differences among virus variants and reflect the complex immune histories in the human population
    - A limited amount and variety of clinical data from persons with different combinations of vaccinations and infection exposures

Voting Question for the Committee

1. For the 2025-2026 Formula of COVID-19 vaccines in the U.S., does the committee recommend a monovalent JN.1-lineage vaccine composition?

Please vote “Yes” or “No” or “Abstain”

Discussion Topic for the Committee

- Based on the evidence presented, please discuss considerations for the selection of JN.1 and/or a specific JN.1-lineage strain for COVID-19 vaccines (2025-2026 Formula) to be used in the U.S.


FDA
U.S. FOOD & DRUG
ADMINISTRATION