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.

U.S. FOOD & DRUG ADMINISTRATION

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

Vaccines and Related Biological Products Advisory Committee Meeting (6/15/2023)

Jerry P Weir, PhD, Director
Division of Viral Products/OVRR/CBER/FDA

Background

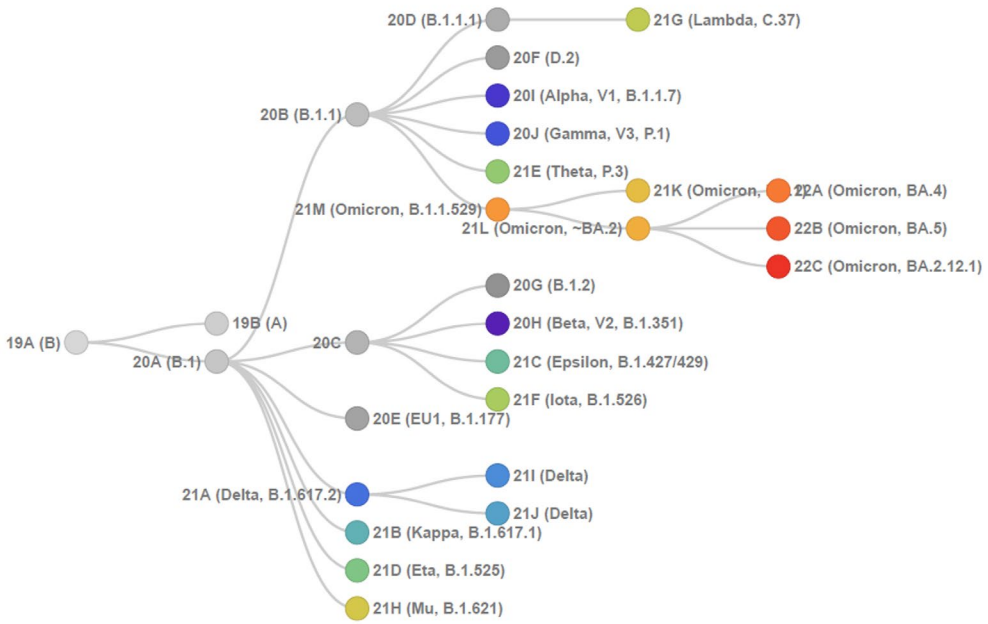
- The Vaccines and Related Biological Products Advisory Committee (VRBPAC) has previously convened three times to discuss the strain composition of COVID-19 vaccines in the U.S.
  - At the April 6, 2022 VRBPAC, the committee had an initial discussion about the framework for updating COVID-19 vaccine composition process
    - There was general agreement that COVID-19 vaccine strain composition decisions should be data driven and there should be evidence to indicate that a proposed modified vaccine composition would likely provide improved effectiveness compared to the current vaccine composition
  - At the June 28, 2022 VRBPAC, the committee discussed whether an updated COVID-19 strain composition was needed and voted to include a SARS-CoV-2 Omicron component for COVID-19 booster vaccines
    - There was a general preference for a bivalent vaccine containing ancestral and Omicron strains
  - At the January 26, 2023 VRBPAC, the committee had additional discussions about the approach to periodic updates of COVID-19 vaccine strain composition
    - There was agreement that 1) there should be a periodic assessment by FDA and VRBPAC to reassess current vaccines and decide if improvement is needed, 2) updating the strain composition of COVID-19 vaccines would likely be a continuous process, and 3) a late Spring/early Summer target for FDA/VRBPAC review and recommendation seemed reasonable and practical for delivery of an updated vaccine for a Fall vaccination campaign

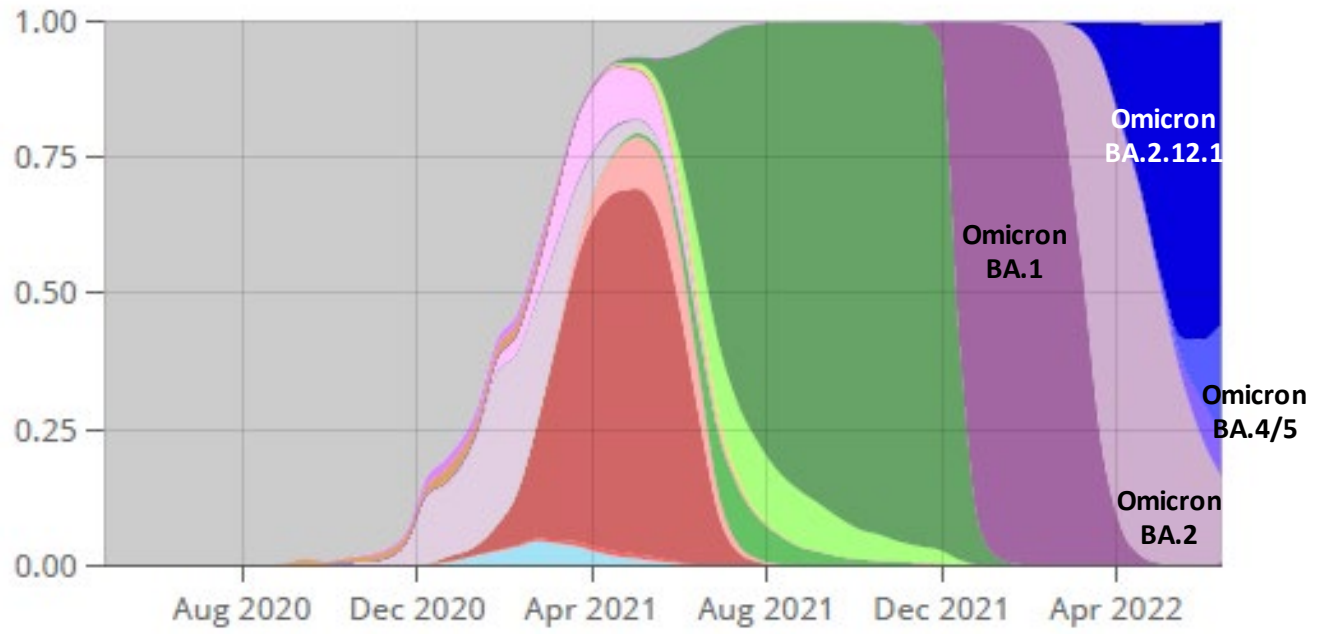
Previous Recommendation for COVID-19 Vaccine Strain Composition – 2022-2023

- VRBPAC met on June 26th 2022 to consider whether a change to the current COVID-19 vaccine strain composition was needed
- The committee voted to recommend inclusion of a SARS-CoV-2 Omicron component for COVID-19 booster vaccines in the United States
- The committee discussed the evidence supporting:
  - a monovalent (Omicron) or bivalent vaccine (prototype + Omicron)
  - the selection of a specific Omicron sub-lineage (e.g., BA.1 vs. BA.4/BA.5)
- On June 30, 2022, FDA notified vaccine manufacturers of FDA's recommendation to develop a bivalent vaccine (Ancestral plus Omicron BA.4/BA.5) as a booster dose to improve protection
  - The first bivalent vaccines from Moderna and Pfizer-BioNTech were authorized for use for individuals 18 years of age and older and 12 years of age and older, respectively on August 31, 2022

SARS-CoV-2 Variant Situation – June 2022

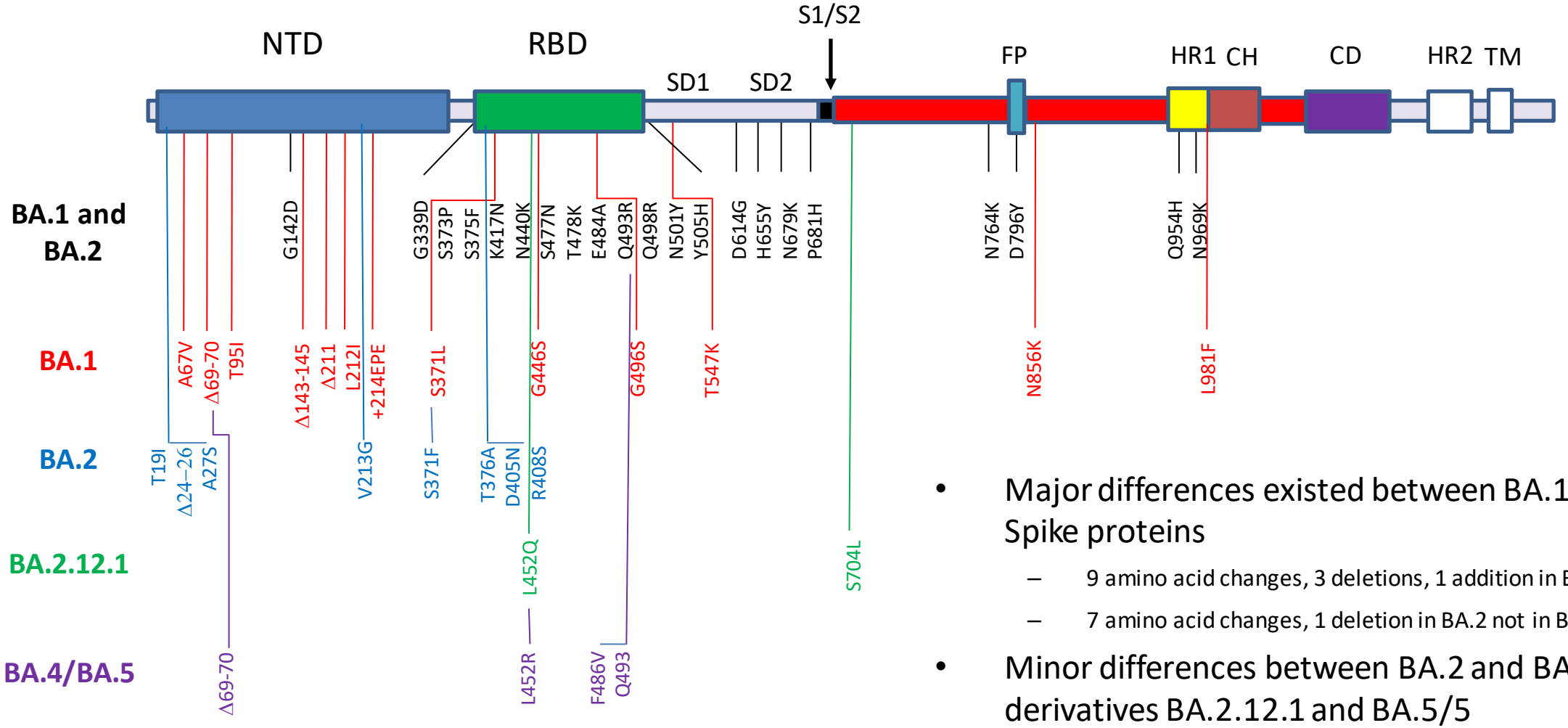
from https://covariants.org/ using Nextstrain data (https://nextstrain.org/)





- VRBPAC discussion concerned selection of Omicron sub-lineage variants BA.1 versus BA.4/5
- Manufacturers had produced and evaluated BA.1 vaccines in clinical trials and were prepared to supply a BA.1 containing vaccine for 2022-2023
- BA.1 was no longer in circulation by June 2022

Amino Acid Differences Between Omicron BA.1 and BA.4/BA.5 Spike Proteins



- Major differences existed between BA.1 and BA.2 Spike proteins
  - 9 amino acid changes, 3 deletions, 1 addition in BA.1 not in BA.2
  - 7 amino acid changes, 1 deletion in BA.2 not in BA.1
- Minor differences between BA.2 and BA.2 derivatives BA.2.12.1 and BA.5/5

Considerations for Modifying the COVID-19 Strain Composition for 2023-2024

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

Current Effectiveness of Authorized COVID-19 Vaccines and Need for a Periodic Strain Update

- Observational effectiveness data strongly suggested that updating the composition of the COVID-19 vaccines in 2022 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
- Nevertheless, there appears to be an inverse relationship between the time since vaccination and vaccine effectiveness, such that bivalent COVID-19 vaccine effectiveness against evolving Omicron sublineages appears to wane over time
- Data indicate that the bivalent COVID-19 vaccines elicit improved variant-specific neutralizing antibody titers, but the antibody titers decrease over time after vaccination and are substantially lower against more recent circulating strains of virus (e.g., XBB lineage viruses)
- Together, the available data suggest that an updated strain composition of COVID-19 vaccines to more closely match currently circulating XBB lineage viruses may be beneficial

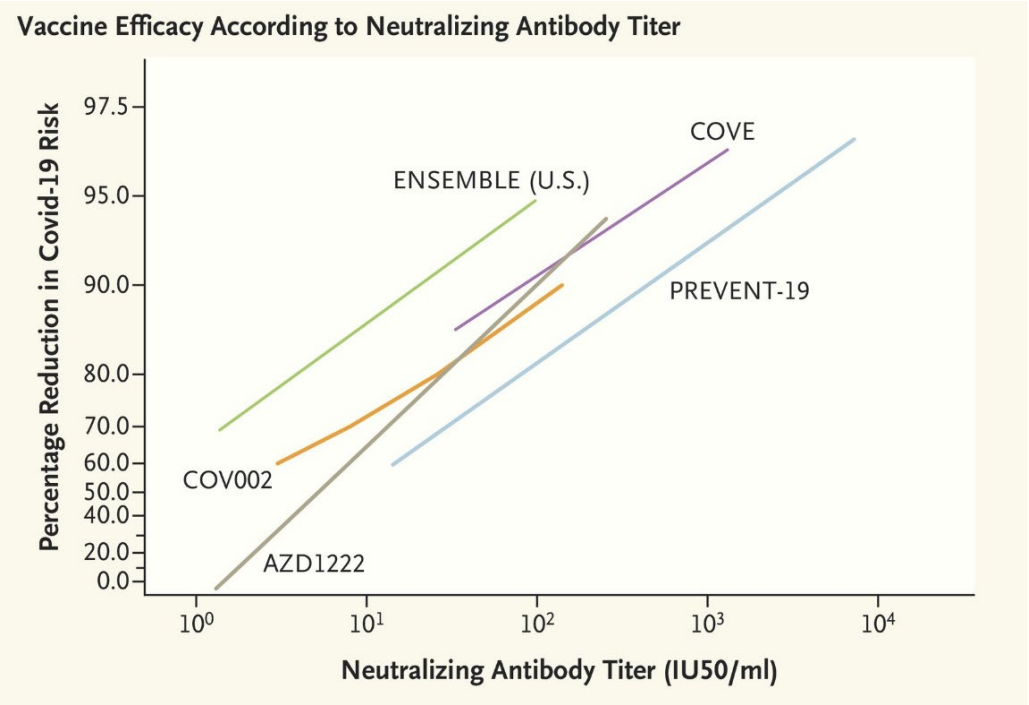
Summary of the Approach Used for the Vaccine Strain Composition Recommendation

- As proposed previously (January 2023 VRBPAC), the evidence used to determine the need for updating the strain composition of COVID-19 vaccines would ideally include multiple types and sources of data
- FDA reviewed various types of data as listed below and engaged with the key partners generating such data, including vaccine manufacturers and other US government agencies
  - Virus surveillance and genomic analyses to identify emerging new virus variants
  - Antigenic characterization of viruses to identify antigenically distinct variant viruses
  - Post-vaccination human serology studies to evaluate antibody responses generated by the current vaccines against more recently circulating virus variants (e.g., XBB-lineage viruses)
  - 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
- FDA reviewed the discussions and recommendations put forth by other regulatory groups and public health agencies
- FDA discussed manufacturing timelines with each of the manufacturers of authorized/approved COVID-19 vaccines to understand the impact of a strain composition recommendation on vaccine availability

Use of Virus Neutralization Data to Inform Vaccine Strain Selection

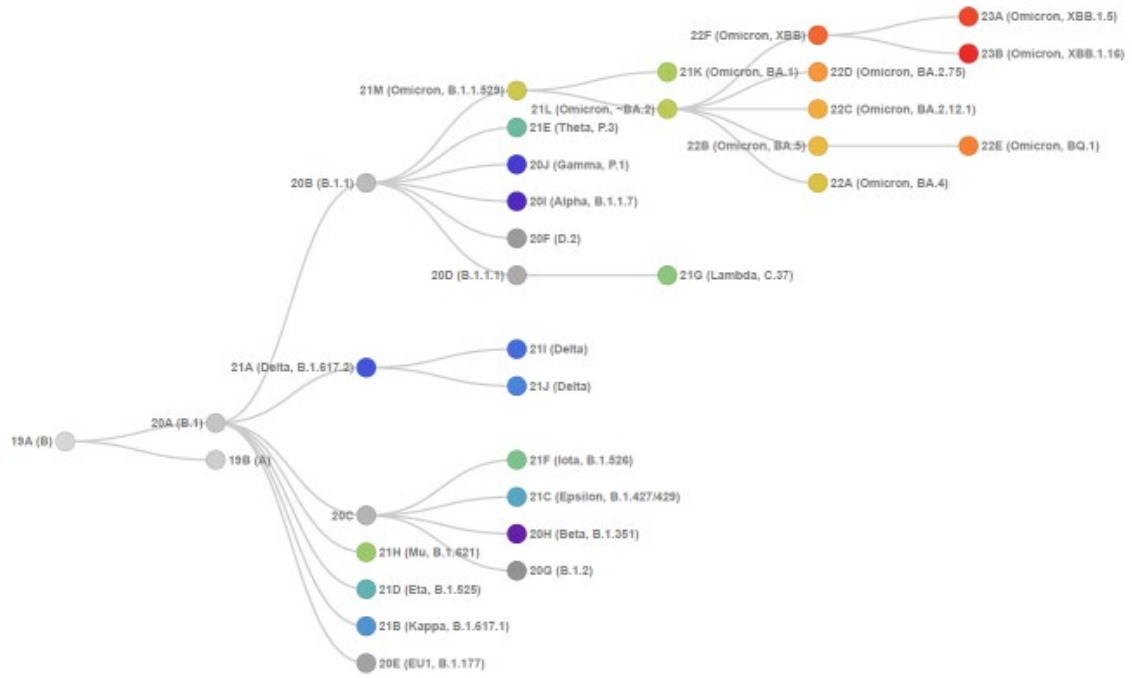
- Virus neutralization data are routinely used to establish antigenic relationships among contemporary viruses, evaluate antibody responses in post-vaccination studies, and evaluate candidate vaccines in pre-clinical studies
- Although other immune mechanisms are important for protection, and protective neutralization titers are unknown and likely vary among vaccine platforms and for different virus variants, neutralization has been shown to correlate with protection for all Spike based vaccines
  - Neutralization assays used by manufacturers of authorized/approved COVID-19 vaccines have been reviewed and evaluated by FDA

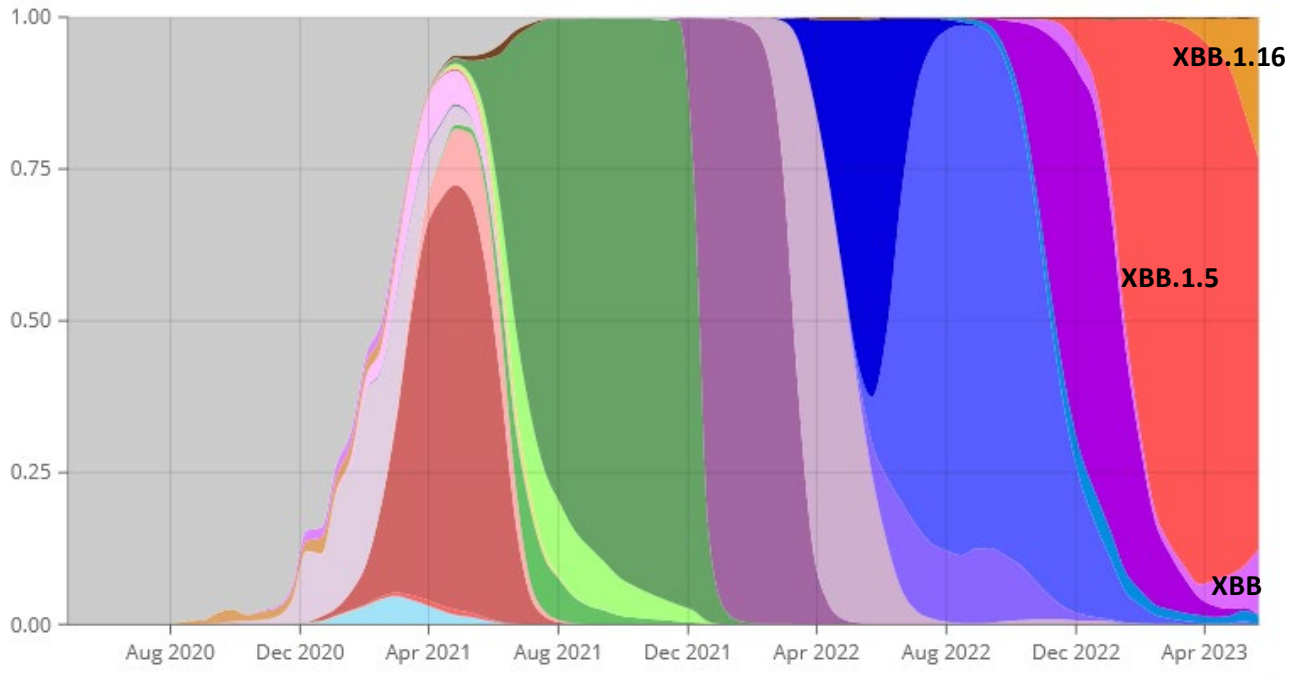
A Covid-19 Milestone Attained — A Correlate of Protection for Vaccines N Engl J Med 2022; 387:2203-2206
Peter B. Gilbert, Ph.D., Ruben O. Donis, Ph.D., Richard A. Koup, M.D., Youyi Fong, Ph.D., Stanley A. Plotkin, M.D., and Dean Follmann, Ph.D.



Virus Surveillance and Genomic Analysis

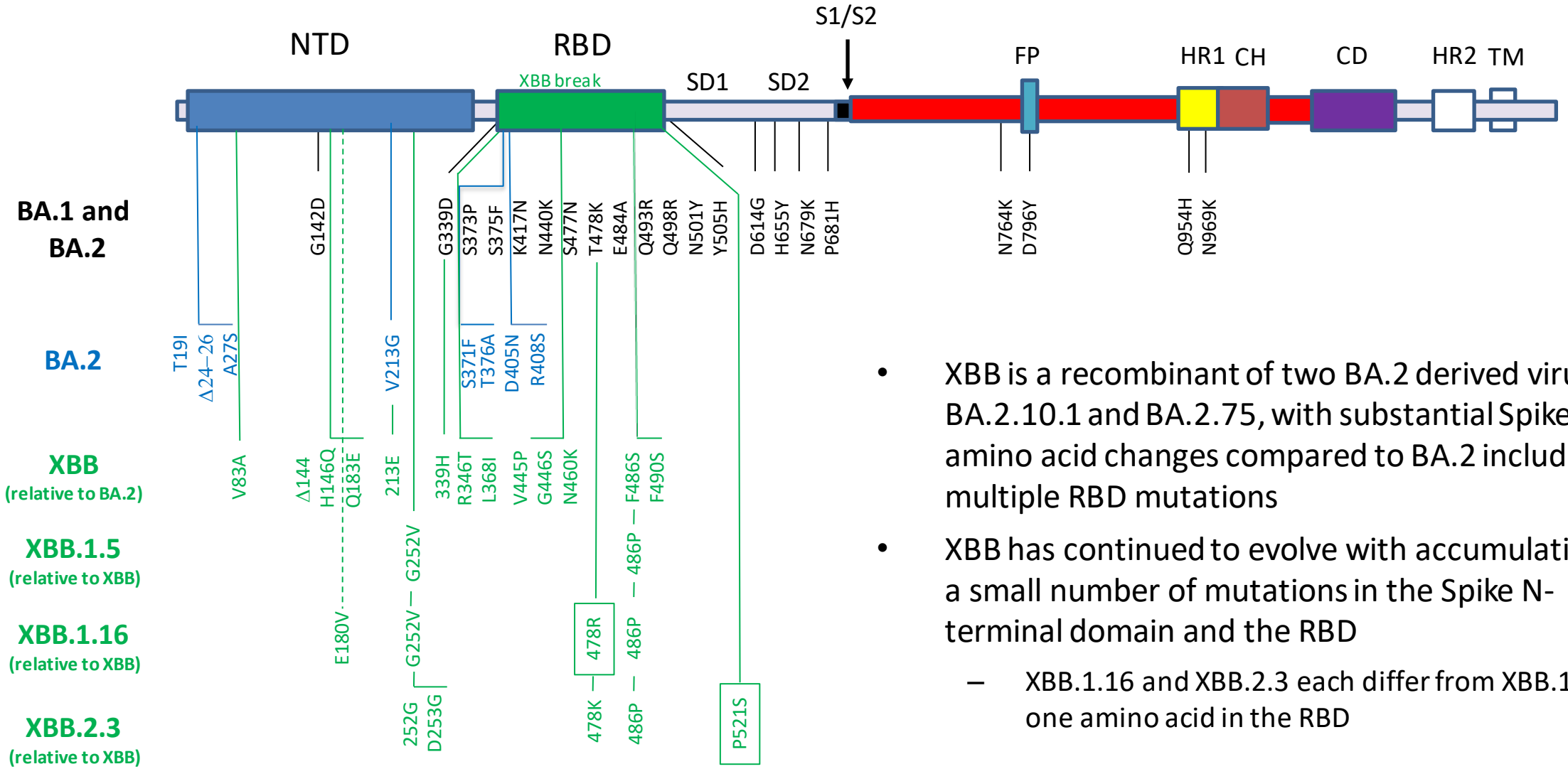
- Virus surveillance and genomic analyses are used to identify emerging new virus variants
- SARS-CoV-2 variants continue to evolve and spread; in June 2023, >95% of isolates are XBB sublineages





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

Virus Characterization – Key Amino Acid Changes in XBB Lineage Spike Proteins



- XBB is a recombinant of two BA.2 derived viruses, BA.2.10.1 and BA.2.75, with substantial Spike amino acid changes compared to BA.2 including multiple RBD mutations
- XBB has continued to evolve with accumulation of a small number of mutations in the Spike N-terminal domain and the RBD
  - XBB.1.16 and XBB.2.3 each differ from XBB.1.5 by one amino acid in the RBD

Virus Characterization – XBB Lineage SARS-CoV-2 Viruses

- Genomic analysis suggests a close relationship among XBB lineage viruses
- Antigenic characterization of circulating XBB lineage viruses is limited to a few recent studies, but also suggests antigenic similarity among XBB lineage viruses
  - In one study, sera from XBB.1 infected hamsters (mono-specific) neutralized XBB.1, XBB.1.5, and XBB.1.16 pseudoviruses to a similar extent, but poorly neutralized pseudoviruses expressing earlier spike proteins (e.g., BA.5) – Yamasoba D et al., Lancet Infect Dis 2023
  - Several studies, including those presented at this VRBPAC by manufacturers of authorized/approved COVID-19 vaccines, show substantial decreases in neutralizing antibody response against XBB subvariants
  - Data from pre-clinical studies with XBB.1.5 and XBB.1.16 candidate vaccines, conducted by the manufacturers of authorized/approved COVID-19 vaccines, indicate substantial cross-neutralization between XBB.1.5 and XBB.1.16; cross-neutralization also observed against XBB.2.3 (more limited data)
  - Preliminary data from a clinical study with one XBB.1.5 candidate vaccine also indicate substantial cross-neutralization between XBB.1.5 and XBB.1.16

Post-Vaccination Human Serology Studies

- Post-vaccination human serology studies are used to evaluate antibody responses generated by the current vaccines against more recently circulating virus variants (e.g., XBB-lineage viruses)
  - COVID-19 vaccine manufacturers are well positioned to generate the robust data needed from post-vaccination human serology studies
  - Sera are available only from recipients of current vaccines or infected individuals (i.e., no exposure to an XBB vaccine; limited exposure to XBB-lineage virus)
  - Neutralization titers measured against new variants (e.g., XBB.1.5, XBB.1.16, etc.) can only indirectly suggest similarities or differences between the variants.
- Data, presented at this VRBPAC by the manufacturers of authorized/approved COVID-19 vaccines, indicate that recent virus variants, particularly XBB descendent lineage viruses, are especially resistant to neutralization by antibodies elicited by prior vaccination and/or infection
- Similar results showing substantial reductions in neutralizing antibody titers against XBB-lineage viruses in recipients of current vaccines have been reported in other studies
  - Branche AR et al., CID 2023. NIH COVAIL Clinical trial.

Pre-Clinical Immunogenicity Studies With New Candidate Vaccines

- Pre-clinical 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
- 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
  - Studies are dependent on COVID-19 vaccine manufacturers producing candidate vaccines at risk and conducting studies to generate the data for evaluation
- Data, presented at this VRBPAC by the manufacturers of authorized/approved COVID-19 vaccines, indicate that updated XBB monovalent formulations of candidate vaccines elicit stronger neutralizing antibody responses against XBB descendent lineage viruses than current bivalent vaccines (Original plus BA.4/5)

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 18, 2023, on the antigen composition of COVID-19 vaccines (update presented at this VRBPAC)
    - "One approach recommended by TAG-CO-VAC is the use of a monovalent XBB.1 descendent lineage"
  - The International Coalition of Medicines Regulatory Authorities (ICMRA), an informal group of international regulatory authorities, met on May 8, 2023, to discuss the antigen content of COVID-19 vaccines
    - "XBB is considered an adequate candidate for vaccine's composition update"
  - The European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency (EMA) issued a statement on June 7, 2023, on updating COVID-19 vaccines composition for new SARS-CoV-2 virus variants
    - "a monovalent vaccine composition is suitable to ensure adequate immunogenicity against circulating SARS-CoV-2 in both primed and naïve individuals"; "the inclusion of a strain belonging to the XBB family of Omicron subvariants is adequate to ensure cross-reactivity against current dominant and emerging strains"

Future Directions

- Updating the SARS-CoV-2 strain composition of COVID-19 vaccines will be a continuous process
- Many challenges and uncertainties remain, including among others:
  - Improving durability of protection
  - Understanding how differences in neutralization titer relate to clinical outcomes
- Improved coordination, possibly including additional resources, is needed to generate quality data needed for strain composition decisions; examples of critical data include:
  - Timely production of mono-specific animal sera (e.g., hamster sera) for determining antigenic relationships among contemporary circulating viruses using standardized neutralization assays
  - Additional sources of human sera from recipients of current vaccines to evaluate the need for an updated vaccine composition
  - Additional sources of human sera from individuals infected with contemporary circulating viruses to qualify/standardize assays
  - An independent and reliable risk assessment of circulating virus variants to focus resources and better predict the need for an updated vaccine composition

Summary

- By several measures, including escape from antibody neutralization and waning protection, current COVID-19 vaccines appear less effective against currently circulating variants (e.g., XBB-lineage viruses) than against previous strains of virus
- Manufacturers of authorized/approved COVID-19 vaccines have been evaluating updated candidate vaccines “at risk” and are prepared to provide an updated vaccine for 2023-2024
  - Manufacturing timelines may be impacted by the final choice of vaccine antigen

Summary – 2

- Pre-clinical data from three different vaccine manufacturers indicate that updated XBB monovalent formulations elicit stronger neutralizing antibody responses against XBB descendent lineage viruses than current bivalent vaccines
  - Available data strongly suggest that inclusion of an antigen from early strains of SARS-CoV-2 (e.g., Wuhan) in an updated vaccine formulation is unlikely to enhance the response to current variants
- Preliminary data from a clinical study with one XBB.1.5 candidate vaccine also indicate improved neutralizing antibody responses against XBB descendent lineage viruses
- The totality of available evidence suggests that a monovalent XBB-lineage vaccine is warranted for the 2023–2024 vaccination campaign

Voting Question for the Committee

1. For the 2023-2024 Formula of COVID-19 vaccines in the U.S., does the committee recommend a periodic update of the current vaccine composition to a monovalent XBB-lineage?

Please vote "Yes" or "No" or "Abstain"

Discussion Topic for the Committee

- Based on the evidence and other considerations presented, please discuss the selection of a specific XBB lineage (e.g., XBB.1.5 or XBB.1.16 or XBB.2.3) for inclusion in the 2023-2024 Formula of COVID-19 vaccines in the U.S.


FDA
U.S. FOOD & DRUG
ADMINISTRATION