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Considerations for Potential Changes to COVID-19 Vaccine Strain Composition

**Vaccines and Related Biological Products
Advisory Committee Meeting (1/26/2023)**

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Background

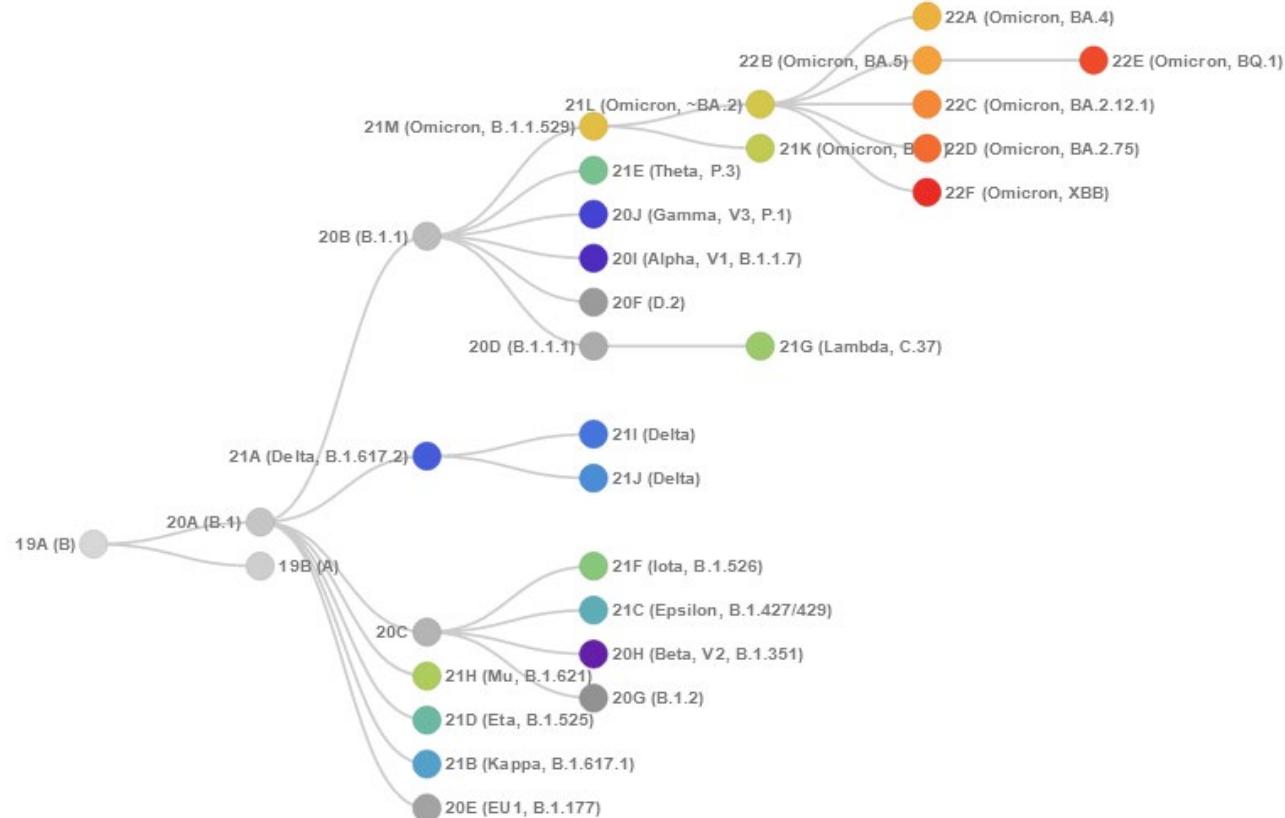
- At a previous meeting (April 6, 2022) of the Vaccines and Related Biological Products Advisory Committee (VRBPAC), the committee had an initial discussion about the process that would be used to update the strain composition of COVID-19 vaccines in the U.S. and considerations for use of additional booster doses; in a subsequent meeting (June 28, 2022), the committee discussed whether and how the SARS-CoV-2 strain composition of COVID-19 vaccines should be modified
- At the June 28, 2022 meeting, the VRBPAC voted in favor of inclusion of a SARS-CoV-2 Omicron component for COVID-19 booster vaccines in the U.S.
 - There was a general preference for a bivalent vaccine containing ancestral and Omicron strains
- On June 30, 2022, FDA notified vaccine manufacturers of their 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 18 years of age and older and 12 years of age and older, respectively on August 31, 2022
- No change in the strain composition of the primary series vaccines was recommended at that time

SARS-CoV-2 Virus Epidemiology Suggests Continued Evolution and Spread of Virus Variants

SARS-CoV-2 Variants Continue to Evolve



Phylogenetic relationship of SARS-CoV-2 variants

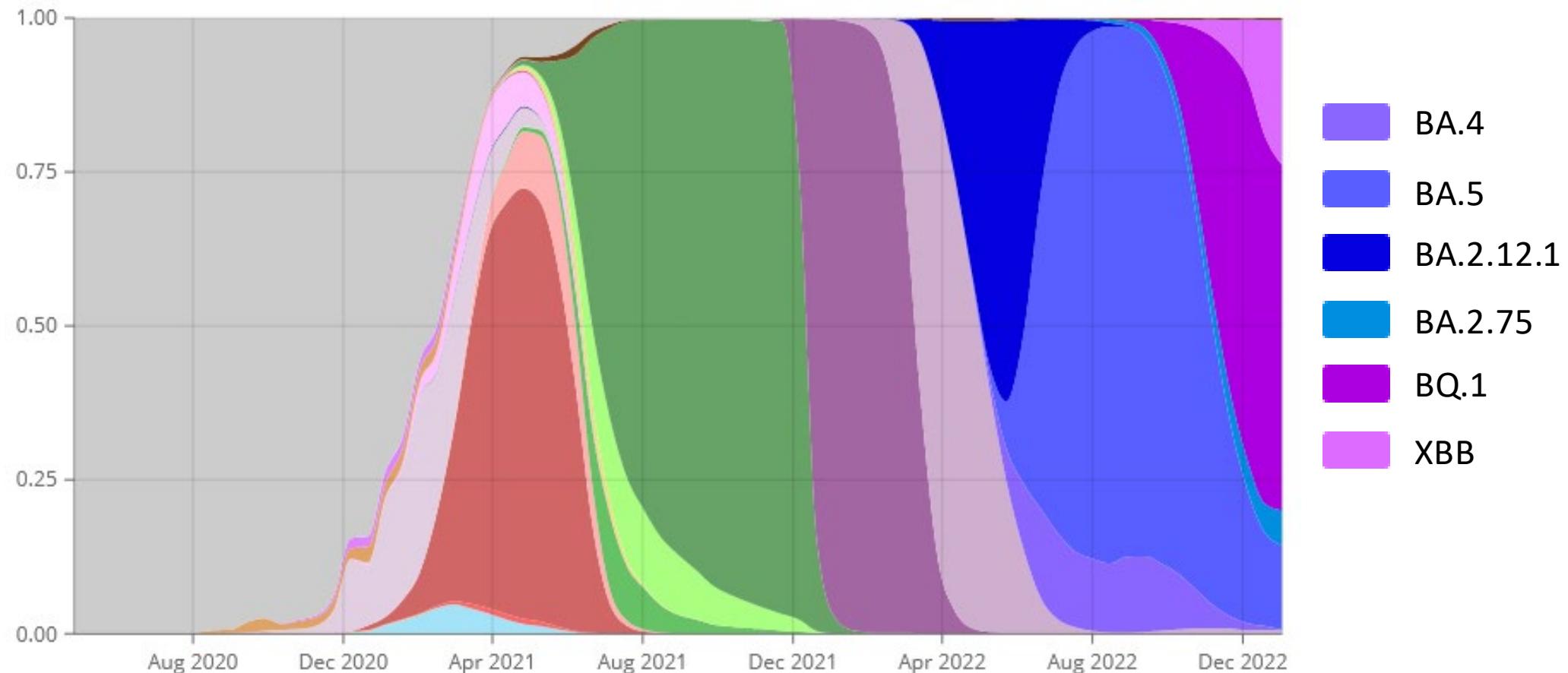


from <https://covariants.org/> using Nextstrain data (<https://nextstrain.org/>)

SARS-CoV-2 Variants Continue to Evolve and Spread



Proportion of SARS-CoV-2 Variants in the U.S. Over Time

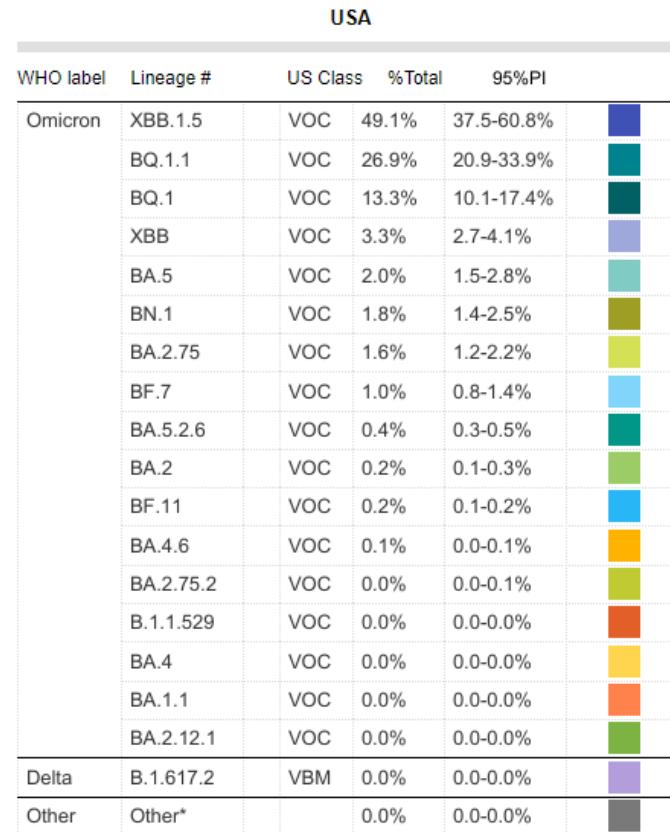


Proportion of total number of **sequences** (*not cases*), that fall into defined variant groups.
Last data point Jan 2-16, 2023. From <https://covariants.org/>

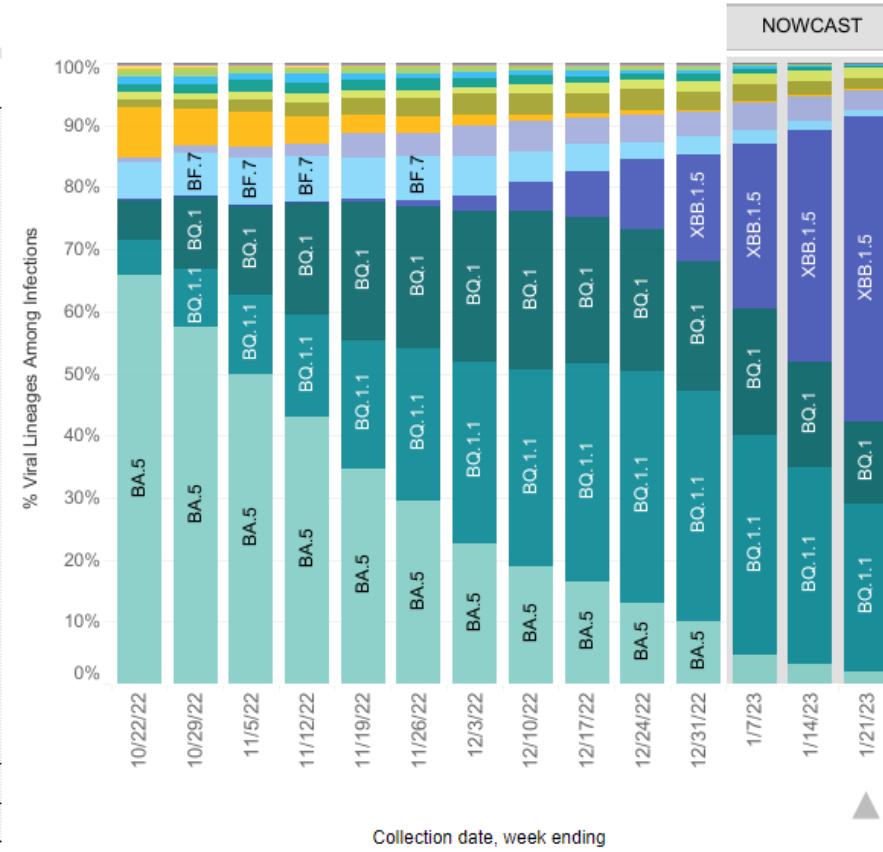
SARS-CoV-2 Variants Continue to Evolve and Spread (2)



United States: 1/15/2023 – 1/21/2023 NOWCAST



United States: 10/16/2022 – 1/21/2023



<https://covid.cdc.gov/covid-data-tracker/#variant-proportions>



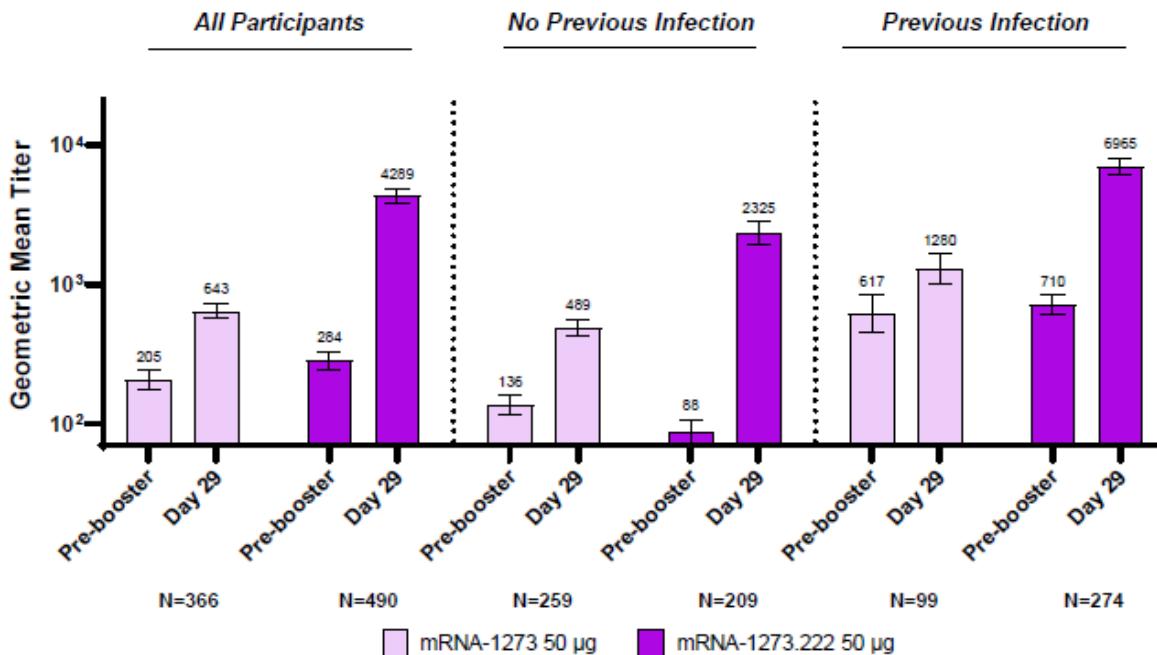
Immunogenicity Data Indicate that the Recommended Bivalent Booster Vaccines Elicit Improved Variant-Specific Neutralizing Antibody Titers

Updated COVID-19 Vaccines Elicit Improved Variant-Specific Neutralizing Antibody Titers

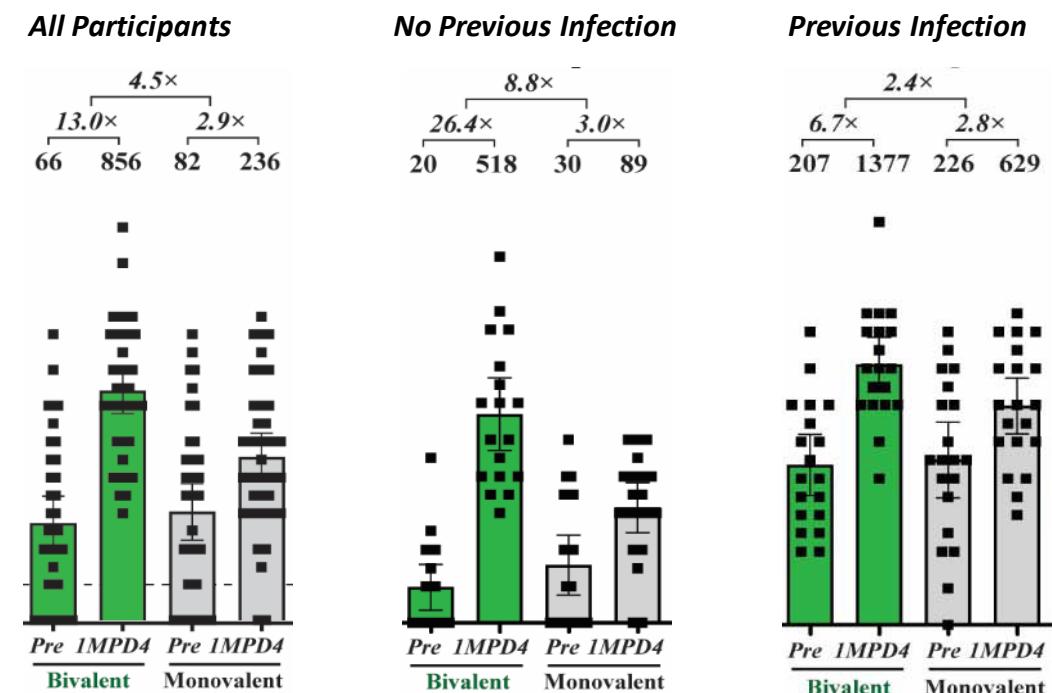


Omicron BA.4/BA.5 Neutralization – Data from vaccine manufacturers

Moderna BA.4/BA.5 Bivalent Vaccine



Pfizer BA.4/BA.5 Bivalent Vaccine



Safety and Immunogenicity of Omicron BA.4/BA.5 Bivalent Vaccine
medRxiv preprint doi: <https://doi.org/10.1101/2022.12.11.22283166>

Improved Neutralization of Omicron BA.4/5, BA.4.6, BA.2.75.2, BQ.1.1, and XBB.1 with Bivalent BA.4/5 Vaccine
medRxiv preprint doi: <https://doi.org/10.1101/2022.11.17.516898>

Updated COVID-19 Vaccines Elicit Improved Variant-Specific Neutralizing Antibody Titers (2)



- Results have recently been reported in several additional studies that describe the neutralizing antibody responses to the recommended bivalent booster vaccines containing an Omicron BA.4/BA.5 component
 - Interpretation of the data from these studies is complicated by several factors, including: limited number of subjects, differences in study populations, intervals between vaccination and sera collection, and the variability in the assays used and the status of assay qualification
 - The data have not been submitted to the FDA, and the FDA has not made any determination about the scientific or regulatory applicability
 - Nevertheless, the results from all of the currently reported studies trend in the same direction, i.e., improved variant-specific neutralization following administration of the bivalent BA.4/5 vaccine compared to a monovalent vaccine booster without an Omicron component
 - Davis-Gardner, ME et al. Neutralization against BA.2.75.2, BQ.1.1, and XBB from mRNA Bivalent Booster. *N Engl J Med* **388**;2 January 12, 2023.
 - Kurhade C et al. Low neutralization of SARS-CoV-2 Omicron BA.2.75.2, BQ.1.1 and XBB.1 by parental mRNA vaccine or a BA.5 bivalent booster. 2022. <https://doi.org/10.1038/s41591-022-02162-x>.
 - Collier, AY et al. Immunogenicity of the BA.5 Bivalent mRNA Vaccine Boosters. 2022. <https://doi.org/10.1101/2022.10.24.513619>
 - Wang Q et al. Antibody responses to Omicron BA.1 4/BA.5 bivalent mRNA vaccine booster shot. 2022. <https://doi.org/10.1101/2022.10.22.513349>



Observational Effectiveness Data Provide Real World Evidence that Supports the Use of the Recommended Bivalent Vaccine Booster

Updated COVID-19 Vaccines Provide Additional Protection Against Symptomatic Infection



- Results have recently been reported for several observational effectiveness studies of the recently recommended bivalent booster vaccines containing an Omicron/BA.4/BA.5 component
 - The studies differ in their design, and each has some limitations (typical for observational effectiveness studies)
 - Nevertheless, the results from all currently available effectiveness studies strongly suggest additional benefit of the recommended bivalent booster vaccines
 - Link-Gelles et al. Effectiveness of Bivalent mRNA Vaccines in Preventing Symptomatic SARS-CoV-2 Infection - Increasing Community Access to Testing Program, United States, September–November 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:1526–1530.
 - Tenforde et al. Early Estimates of Bivalent mRNA Vaccine Effectiveness in Preventing COVID-19–Associated Emergency Department or Urgent Care Encounters and Hospitalizations Among Immunocompetent Adults - VISION Network, Nine States, September–November 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:1616–1624.
 - Surie et al, Early Estimates of Bivalent mRNA Vaccine Effectiveness in Preventing COVID-19–Associated Hospitalization Among Immunocompetent Adults Aged \geq 65 Years — IVY Network, 18 States, September 8–November 30, 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:1625–1630.
 - Arbel, R et al. Effectiveness of the Bivalent mRNA Vaccine in Preventing Severe COVID-19 Outcomes: An Observational Cohort Study. *Lancet*. (preprint) 2023. <http://dx.doi.org/10.2139/ssrn.4314067>
 - Lin, D-Y et al. Effectiveness of Vaccination and Previous Infection Against Omicron Infection and Severe Outcomes in Children Under 12 Years of Age. 2023. <https://doi.org/10.1101/2023.01.18.23284739>

Summary of Key Data from Studies with Vaccines Containing an Omicron Component



- The preponderance of the data from vaccine manufacturers and independent researchers indicate an improved antibody response to SARS-CoV-2 Omicron variants following mRNA booster vaccination with the recommended bivalent vaccine containing an Omicron BA.4/BA.5 component
 - Similar results were reported previously for modified vaccine candidates containing an Omicron BA.1 component (discussed at the June 28 VRBPAC)
 - The BA.1-neutralizing antibody titers appeared to correlate with the quantity of the Omicron component in the vaccine, for both monovalent and bivalent formulations, suggesting further improvement in the variant-specific antibody response may be achievable
- Observational effectiveness data strongly suggest that bivalent booster immunization provides additional protection against symptomatic infection, emergency department/urgent care visits, and hospitalization
- The evidence that supports the use of a bivalent vaccine containing an Omicron component, together with recent pre-clinical data and clinical data with a bivalent vaccine used as a primary series in young children, suggest consideration of the same vaccine strain composition for primary and booster vaccinations

Approaches to Simplify the COVID-19 Vaccination Regimen, Possibly Leading to Improved Vaccine Coverage and Enhancing Public Health, Should be Considered

Simplification of the COVID-19 Vaccination Regimen May be Feasible



- Multiple COVID-19 vaccine compositions (e.g., different primary series and booster compositions) and immunization schedules complicate vaccine administration, communication, and uptake
- Simplification of the COVID-19 vaccination regimen would contribute to easier vaccine deployment, better communication and may improve vaccine coverage
- Significant simplification of the COVID-19 vaccination regimen could be effected by adopting:
 - The same COVID-19 vaccine composition for primary series and booster vaccination
 - A simplified immunization schedule that applies to all COVID-19 vaccines
 - The same vaccine strain composition for all Spike-based COVID-19 vaccines
 - Data driven vaccine composition recommendations would be made by the FDA after consultation with the VRBPAC

Recent Data Support an Alignment of COVID-19 Primary Series and Booster Vaccine Compositions



- At the present time, primary series vaccines remain monovalent (encoding or containing ancestral SARS-CoV-2 Spike protein), resulting in a complex vaccination program
- Moving to the same vaccine strain composition for all vaccine doses would simplify the COVID-19 vaccination regimen
 - Available immunogenicity and effectiveness data support the use of updated COVID-19 vaccines (bivalent ancestral and Omicron BA.4/BA.5) for booster vaccination
 - Recent pre-clinical and clinical data indicate that use of bivalent vaccines improves antibody responses against Omicron variants when used in naïve animals and as a primary series vaccine in young children, respectively
 - Scheaffer et al. 2022 (Preclinical studies with Moderna bivalent BA.4/BA.5 vaccine in naïve animals)
 - Muik et al. 2022 (Preclinical studies with Pfizer bivalent BA.4/BA.5 vaccine in naïve animals)
 - Moderna data from study of bivalent vaccine containing BA.1 used as a primary series vaccine in young children
 - A move to a single vaccine strain composition for primary and booster vaccination in the U.S. would align with a recent recommendation from the European Medicines Agency Emergency Task Force

A Simplified Immunization Schedule Could be Considered for Future Vaccination Campaigns



- An immunization schedule for future periodic COVID-19 vaccination campaigns would be simplified if a single dose of vaccine provided substantial additional protection for most individuals regardless of known vaccination status (e.g., no prior vaccination, primary series vaccination only, or primary series vaccination plus one or more booster vaccinations, etc.)
- At some stage of the pandemic such an assumption will be reasonable, and a single vaccine dose should suffice for most individuals due to pre-existing immunity acquired by prior infection, vaccination, or a combination of vaccination and prior infection
- A robust review of population level data should be capable of defining age groups that would have acquired pre-existing immunity
- Similarly, review of population level data should be able to define age groups that are effectively naïve due to lack of virus exposure and vaccination
 - For such individuals (e.g., young children without evidence of prior infection or vaccination), additional vaccine doses might be needed to establish protective immunity before periodic vaccination
- Risked based analysis should be able to identify other groups for whom an alternative immunization schedule might be needed (e.g., immunocompromised) and guide development of an appropriate strategy

One Proposed Simplification of the COVID-19 Vaccination Regimen



- Additional data needed to pursue a simplified periodic vaccination strategy may include a better understanding of age-based rates of virus exposure and vaccination and identification of risk groups that would benefit from an alternative immunization strategy
- An example of a potential simplification vaccination strategy is shown below as a starting point for discussion:

General Population (age-based; one dose)*	Risk-based adjustments (dose(s) and schedule to be determined) **
Most adults	High-risk older adults
Older children and Adolescents	Persons with compromised immunity
Young children <i>who have been previously immunized</i>	Young children <i>who have <u>not</u> been previously immunized</i>

*Presumed to have had sufficient S protein exposures such that a single dose of COVID-19 vaccine induces or restores vaccine effectiveness

**Presumed to have insufficient preexisting immunity based on age and other risks (e.g., young children who have not been previously immunized, older adults who have higher-level risk for severe COVID-19 and death, and persons with compromised immunity); may require more than one dose of vaccine in each COVID-19 vaccination campaign, doses and schedule to be determined

Updating the SARS-CoV-2 Strain Composition of COVID-19 Vaccines Will be a Continuous Process

The Strain Composition of COVID-19 Vaccines May Need Periodic Updating



- Since broad spectrum, variant-proof vaccines do not yet exist, current Spike-based vaccines may need periodic updating to maintain effectiveness as SARS-CoV-2 continues to evolve
- A tentative framework for addressing future COVID-19 vaccine strain composition has been proposed (April 6 2022 VRBPAC)
- Manufacturers have requested additional details and clarity about the process for updating the strain composition of COVID-19 vaccines
 - Timing
 - Process and methodology for making a strain composition recommendation
 - Data package needed from manufacturers for authorization/licensure

Proposed Timing for COVID-19 Vaccine Strain Composition Review and Recommendation



- Practical considerations suggest a limit to how often vaccine composition changes can be implemented and include:
 - Manufacturing constraints
 - Availability of sufficient high-quality data on which to base a recommendation
- Based on the 2022 experience, a late Spring/early Summer (e.g., late May/early June) annual target for review, VRBPAC discussion, and recommendation seems reasonable and practical
 - Goal would be to reassess current vaccines and decide if improvement is needed and could offer benefit
- Emergence of a more pathogenic escape virus in the context of a public health emergency would prompt an ad hoc meeting of the VRBPAC, as has been done previously for emerging influenza viruses (e.g., H1N1pdm09)

Proposed Process and Methodology for Making a Strain Composition Recommendation



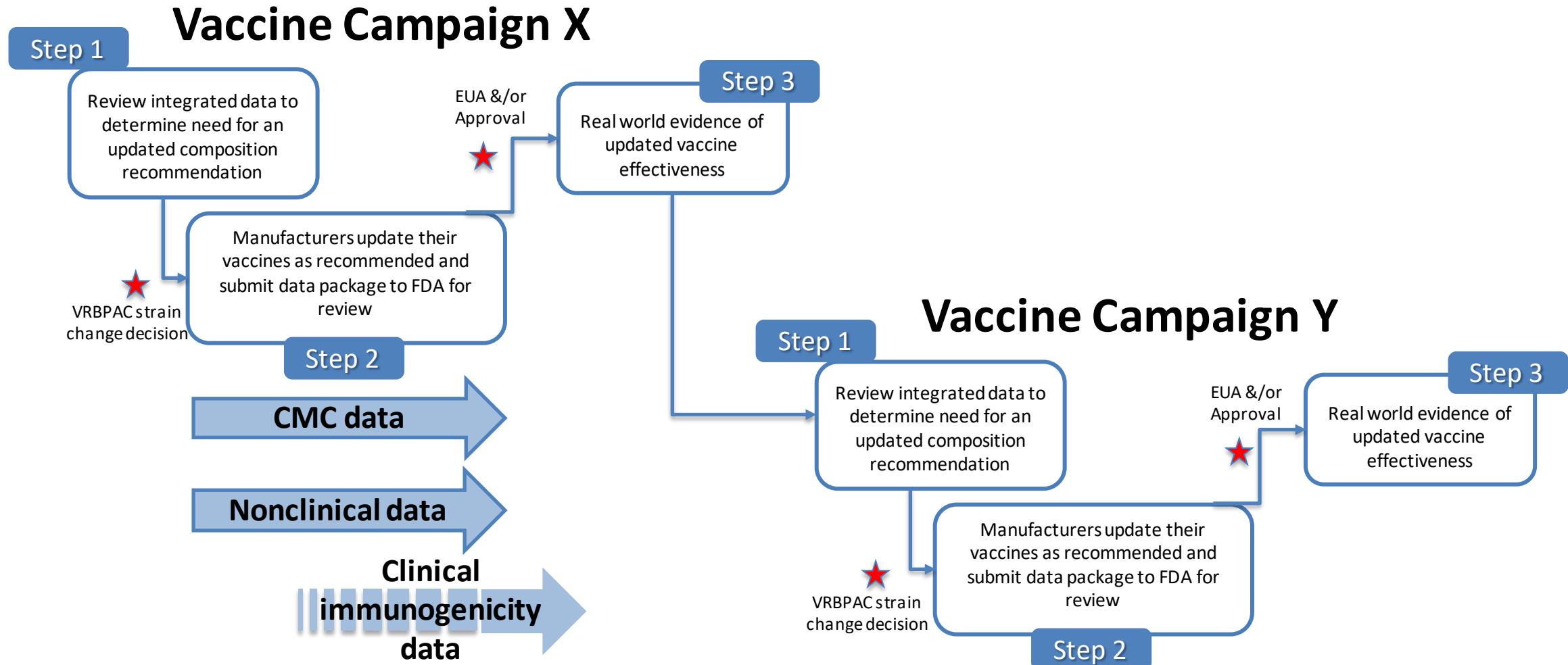
- The evidence used to determine the need for updating the strain composition of COVID-19 vaccines would ideally include multiple types and sources of data:
 - *Epidemiological and clinical surveillance* – to identify newly emerging and/or increasing COVID-19 outbreaks or epidemics, particularly those associated with increased transmissibility and/or clinical severity
 - *Virus surveillance and genomic analyses* – to identify emerging new virus variants
 - *Antigenic characterization of viruses* – to identify antigenically distinct variant viruses
 - *Integration of epidemiology, genomic analysis, and antigenic characterization* – to conduct antigenic mapping and fitness forecasting
 - *Post-vaccination human serology studies* – to evaluate the protective immunity offered by the current vaccines against antigenically distinct circulating virus variants
 - *Vaccine effectiveness studies* – to assess the effectiveness of current vaccines against co-circulating/emerging variants and to provide future guidance on the need for updated vaccines
- Generation of robust data for strain composition decision will require a coordinated effort of manufacturers, regulatory agencies, and other public health agencies

Proposed Data Package Needed from Manufacturers for Authorization/Licensure



- Each vaccine manufacturer would prepare a comprehensive data package for regulatory review of their updated COVID-19 vaccine that follows the most recent recommendation of the FDA and its Advisory Committee
- Submitted data would include:
 - Chemistry, manufacturing, and control data for the updated vaccine to ensure product quality and consistency
 - Pre-clinical data to support effectiveness of the updated vaccine
- The need for clinical data prior to authorization/approval would be based on several criteria, including experience of the manufacturer, the genetic and antigenic relatedness of the updated vaccine component to previous vaccines, and the prior demonstration of efficacy with the specific vaccine platform
- Clinical data post-authorization/approval will be crucial for ongoing evaluation of the vaccine composition process

Approach to updating vaccine composition: High-level overview of a continuous* iterative 3-step process



*at least annually

Voting Question for the Committee



Simplification of current COVID-19 vaccine use:

- *Vaccine composition:* Does the committee recommend harmonizing the vaccine strain composition of primary series and booster doses used in the U.S. to a single composition, e.g., the composition of all vaccines administered currently would be a bivalent vaccine (Original plus Omicron BA.4/BA.5)?

Discussion Topics for the Committee



Future periodic vaccination campaigns

Periodic update to COVID-19 vaccines:

- Vaccine composition: Please discuss and provide input on the consideration of periodic updates to COVID-19 vaccine strain composition, including to the currently authorized or approved vaccines to be available for use in the U.S. in the fall of 2023.

Discussion Topics for the Committee (2)

Future periodic vaccination campaigns

Simplification of COVID-19 vaccine use:

- Immunization schedule: Please discuss and provide input on simplifying the immunization schedule to authorize or approve:
 - A) one dose for most adults, adolescents, older children, and for young children who were previously immunized;
 - B) additional dose(s) for:
 - i) high-risk older adults and persons with compromised immunity;
 - ii) young children who have not been previously immunized



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