Vaccines and Related Biological Products Advisory Committee Meeting

Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please 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

COVID-19 Vaccine Strain Composition

Vaccines and Related Biological Products Advisory Committee Meeting (6/28/2022)

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

Introduction

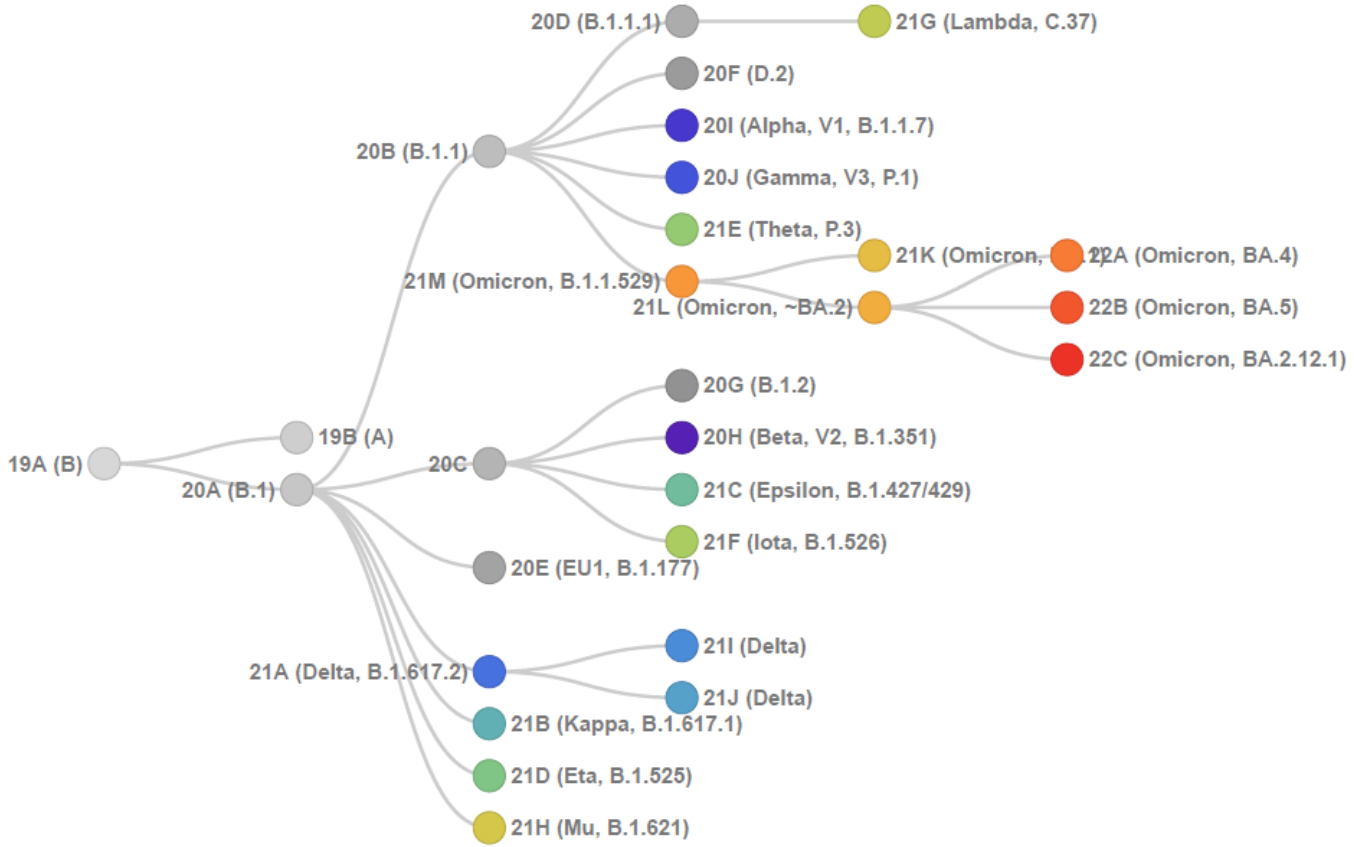
- At a previous meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) on April 6, 2022, the committee discussed the process that would be used to update the composition of COVID-19 vaccines in the U.S. and considerations for use of additional booster doses
- The April 6th discussion was not intended to make a specific recommendation for vaccine composition and there were no voting questions, but there was general agreement on several key points including:
  - Strain change 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
  - Decisions on COVID-19 strain composition should be a coordinated process led by FDA with VRBPAC input; the committee noted the challenges of global coordination, but there was general agreement that VRBPAC should consider any global strain composition recommendations
  - The expectation of the Committee was that the VRBPAC would meet again when additional data was available to consider whether and how the SARS-CoV-2 strain composition of COVID-19 vaccines in the U.S. should be modified

Considerations for Modifying the COVID-19 Strain Composition

- In considering a recommendation to modify the COVID-19 vaccine composition, several key questions will need to be addressed by the agency and the VRBPAC
  - 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?

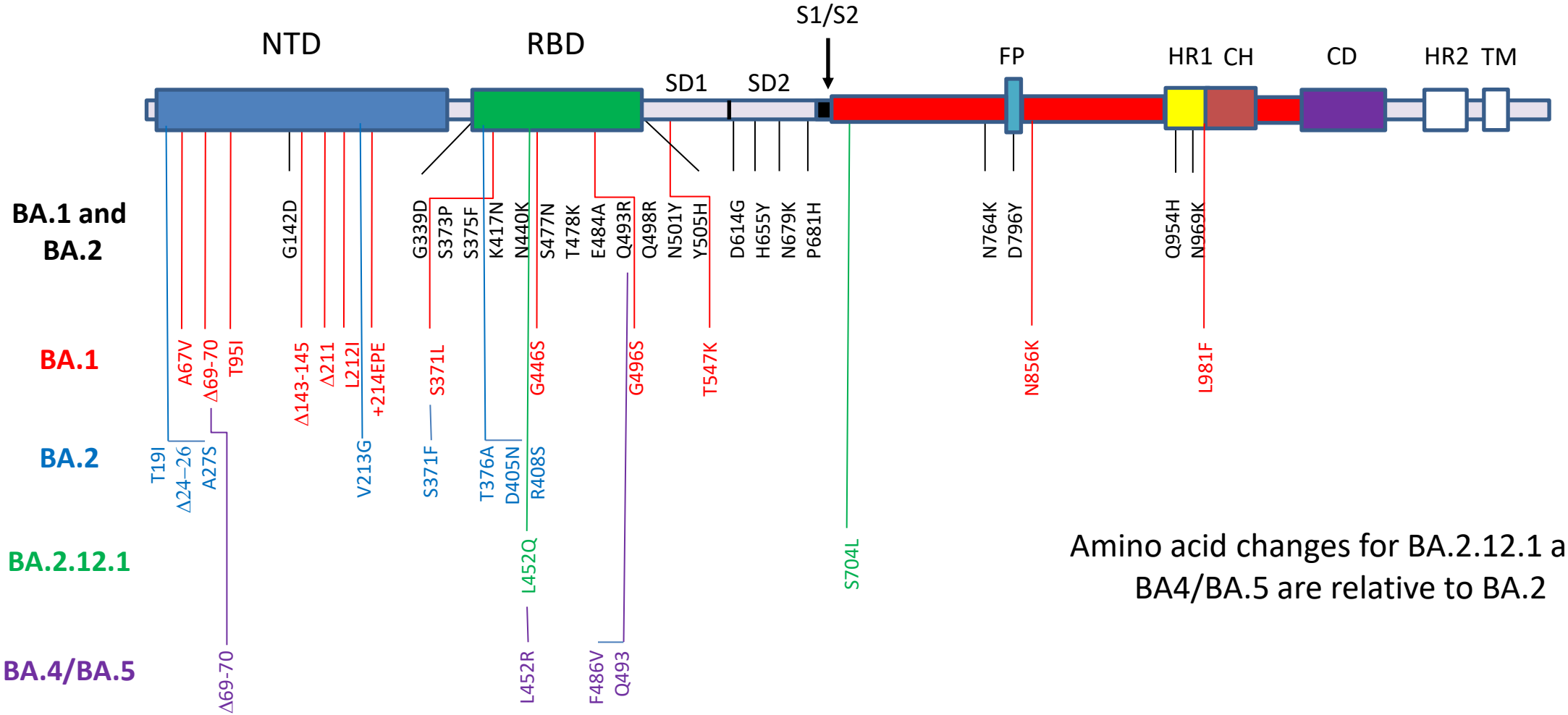
Are there SARS-CoV-2 virus variants circulating that are antigenically distinct from the strain included in current vaccines?

Evolution of SARS-CoV-2 Variants



Phylogenetic relationships SARS-CoV-2 clades – from https://covariants.org/ using Nextstrain data (https://nextstrain.org/

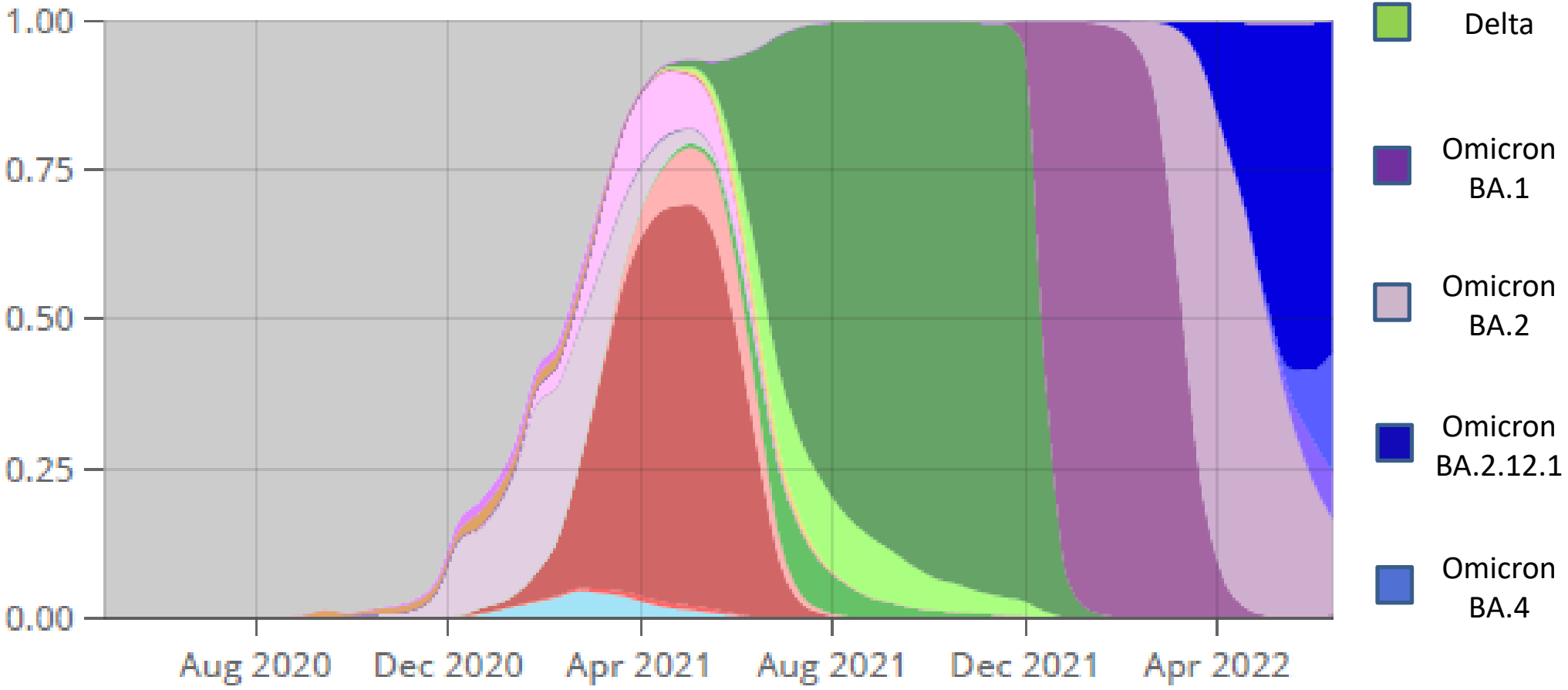
Amino Acid Changes in Omicron Spike Relative to the Spike of Prototype Vaccines



Amino acid changes for BA.2.12.1 and BA4/BA.5 are relative to BA.2

Have currently circulating SARS-CoV-2 virus variants become, or are they expected to become, dominant and displace earlier virus strains?

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



Proportion of total number of **sequences** (*not cases*), over time, that fall into defined variant groups. From https://covariants.org/

Is there evidence that current vaccines are less effective against new circulating virus variants than against previous strains of virus?

Effect of Mutations in Omicron S on Antibody Neutralization

- Numerous mutations in the Omicron Spike protein, relative to earlier SARS-CoV-2 viruses, include key mutations in the receptor-binding domain
- Several studies have documented the reduced neutralizing activity of approved or authorized therapeutic monoclonal antibodies against Omicron
- Various studies have documented reduced neutralizing activity of vaccinee sera against Omicron

Reduced Neutralization of Omicron Following Vaccination

- Neutralization titers in sera from 39 vaccinees (Pfizer) against D614G, Delta and Omicron (BA.1)
- Booster immunization improves the Omicron neutralizing activity

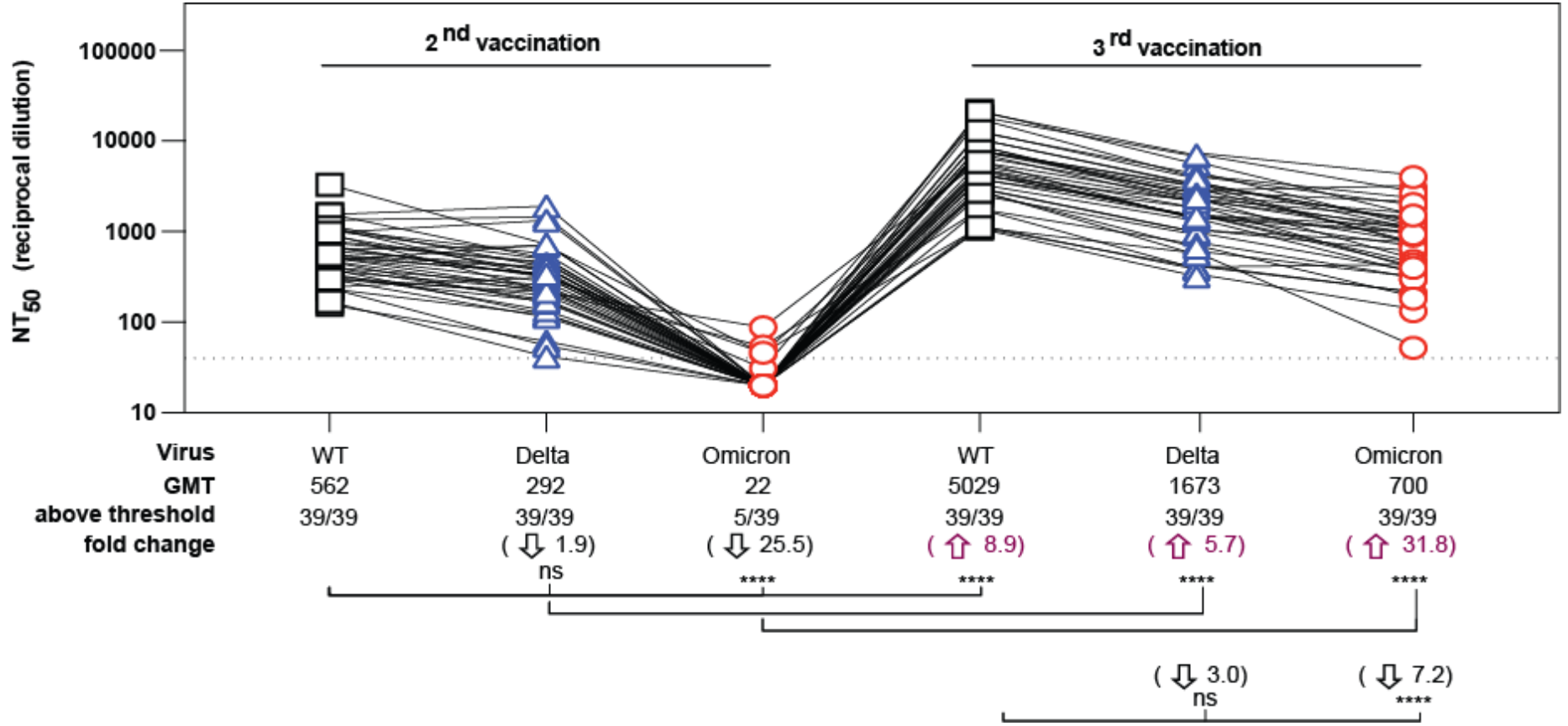
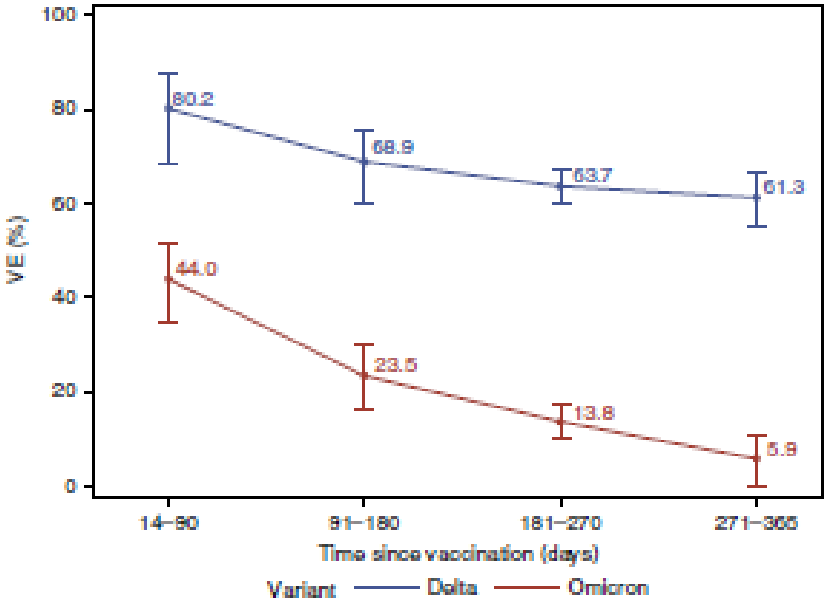


Figure 1 – from Lusvarghi et al, 2022 ***Sci Transl Med* 14** eabn8543

Reduced Effectiveness of Current Vaccines Against Omicron Variants

- Currently available vaccines continue to be effective against severe disease outcomes caused by Omicron
  - Primary series VE against Omicron reduced; booster dose VE similar to that of previous variants
- Vaccine effectiveness against symptomatic COVID-19 due to Omicron is reduced

VE of 2 doses of Moderna against Omicron (red) and Delta (blue)



VE of 3 doses of Moderna against Omicron (red) and Delta (blue)

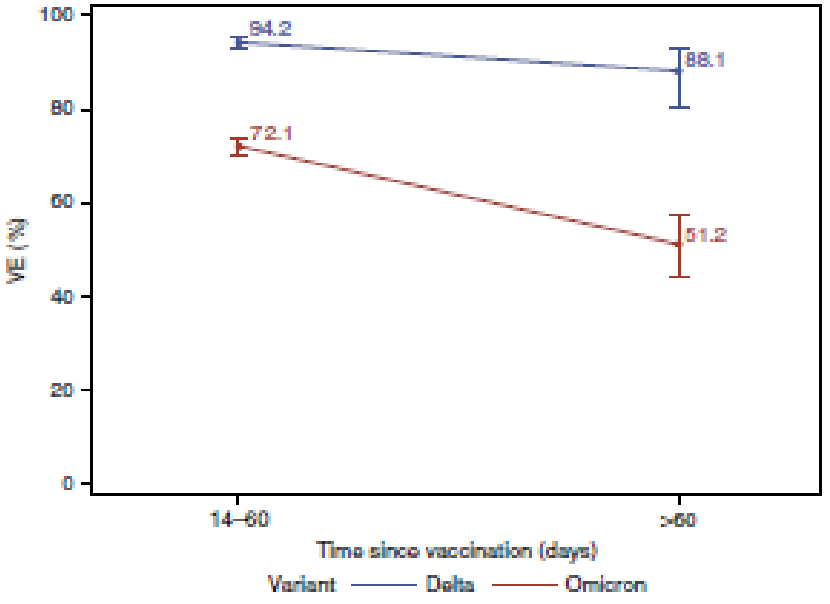


Figure 2 & 3 – from Tseng HF et al 2022 Nature Medicine 28:1063-1071

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?

Studies with Modified Vaccine Candidates

- Considering the current epidemiology of SARS-CoV-2, studies with candidate vaccines that include an Omicron component are relevant to inform a decision on vaccine strain composition
- Among COVID-19 vaccines currently authorized or approved for use in the US, clinical immunogenicity data for modified versions including an Omicron/BA.1 component are available for the Pfizer-BioNTech and Moderna COVID-19 vaccines
  - Available immunogenicity data are limited to neutralizing antibody responses, mainly following a 4th (second booster) dose
  - Data and analyses provided by the sponsors have not been independently verified
  - Much of the data are derived from assays that have not completed validation

Moderna COVID-19 Vaccine

- Analysis population: previously uninfected adults 18 years of age and older
- Vaccines evaluated:
  - mRNA-1273: monovalent, 50 µg mRNA encoding prototype S protein
  - mRNA-1273.214: bivalent, 25 µg each of mRNA encoding prototype or Omicron/BA.1 S protein

Neutralizing antibody GMT at 4 weeks after a 4th (2nd booster) dose

Neutralization Input Virus	mRNA 1273 GMT (95% CI) N=260	mRNA 1273.214 GMT (95% CI) N=334	GMT Ratio (95% CI) mRNA-1273.214/ mRNA-1273
Omicron/BA.1	1473 (1271, 1708)	2372 (2071, 2718)	1.75 (1.49, 2.04)
Ancestral (D614G)	5649 (5057, 6311)	5977 (5322, 6713)	1.22 (1.08, 1.37)

Pfizer-BioNTech COVID-19 Vaccine

- Analysis previously uninfected adults 18-55 years of age
- Vaccines evaluated:
  - BNT162b2: monovalent, 30 µg mRNA encoding prototype S protein
  - BNT162b2 OMI: monovalent, 30 µg mRNA encoding Omicron/BA.1 S protein

Neutralizing antibody GMT at 1 month after a 4th (2nd booster) dose

Neutralization Input Virus	BNT162b2 GMT (95% CI) N=141	BNT162b2 OMI GMT (95% CI) N=132	GMT Ratio (95% CI) BNT162b2 OMI/ BNT162b2
Omicron/BA.1	1100 (932, 1297)	1929 (1632, 2281)	1.75 (1.39, 2.22)
Ancestral (D614G)	12009 (10744, 13425)	11997 (10554, 13638)	Not Evaluated

Pfizer-BioNTech COVID-19 Vaccine (2)

- Analysis population: previously uninfected adults >55 years of age
- Vaccines evaluated:
  - BNT162b2: monovalent, 30 µg mRNA encoding prototype S protein
  - BNT162b2 OMI: monovalent, 30 µg or 60 µg mRNA encoding Omicron/BA.1 S protein
  - BNT162b2 + BNT162b2 OMI: bivalent, 30 µg (15 µg + 15 µg) or 60 µg (30 µg + 30 µg)

Omicron/BA.1-neutralizing antibody GMT at 1 month after a 4th (2nd booster) dose

Study Group	BNT162b2 30 µg N=163	BNT162b2 OMI 30 µg N=169	BNT162b2 OMI 60 µg N=174	BNT162b2 + BNT162b2 OMI 30 µg N=178	BNT162b2 + BNT162b2 OMI 60 µg N=175
GMT (95% CI)	456 (366, 568)	1015 (826, 1247)	1435 (1208, 1704)	711 (588, 859)	900 (726, 1116)
GMT Ratio (95% CI) vs. BNT162b2 30 µg	N/A	2.23 (1.65, 3.00)	3.15 (2.38, 4.16)	1.56 (1.17, 2.08)	1.97 (1.45, 2.68)

- In sentinel groups (N = 13-18), neutralizing antibody GMTs against the ancestral (D614G) strain were similar across modified vaccine candidates and compared to BNT162b2 prototype (30 µg) vaccine

Summary of Key Data from Studies with Vaccine Candidates Containing an Omicron Component

- Clinical immunogenicity data from candidate modified vaccines containing an Omicron/BA.1 component (mRNA vaccines from 2 manufacturers) indicate:
  - Improved (statistically superior) Omicron/BA.1-neutralizing antibody GMT compared to the prototype vaccine from each manufacturer, for all candidate vaccines tested (monovalent and bivalent)
  - The ancestral strain-neutralizing antibody response to the candidate modified vaccines did not appear to be decreased compared to the prototype vaccine
- In the one study that evaluated different doses of candidate modified vaccines, the Omicron/BA.1-neutralizing antibody titer appeared to correlate with the dose of Omicron component in the vaccine, for both monovalent and bivalent formulations
- Available data indicates the potential for improved vaccine effectiveness against the Omicron variant when an Omicron component is included in the vaccine

Limitations of the Studies with Vaccine Candidates Containing an Omicron Component

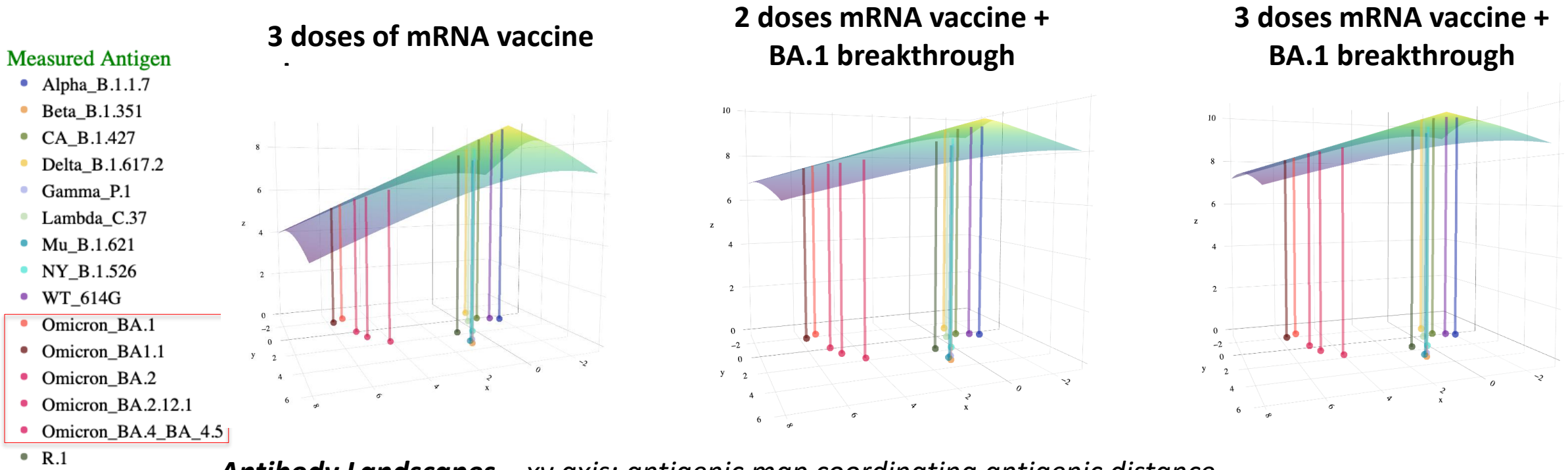
- Several important caveats to consider in evaluating the data:
  - A limited number of vaccine formulations can be evaluated in clinical trials making optimization of formulation (e.g., monovalent, multivalent, etc.) and dose difficult
  - Only neutralizing antibody is measured, and how relative differences in neutralizing antibody titer relate to clinical benefit is unknown
  - Available data are mainly limited to evaluation of a second booster dose; at this time, use of modified vaccines for a first booster dose or for primary series would need to rely on extrapolation (which may not be as reasonable for primary series in vaccine-naïve individuals)
  - All Omicron containing candidate vaccines evaluated to date have a BA.1 component and neutralizing antibody analysis has focused on the BA.1 virus sub-lineage (previous slides); evaluation of neutralizing antibody for other Omicron sub-lineages is ongoing
  - Data for the durability of the neutralizing antibody response is limited and only available for 1-month post-boost at the present time

Additional Evidence to Support the Effectiveness of an Updated Vaccine Composition as a Booster

- Several studies have shown that vaccination followed by infection with a VOC leads to an enhanced and broadened antibody response to SARS-CoV-2 VOCs
- The results suggest that vaccination followed by booster vaccination with a VOC vaccine might also lead to a broadened antibody response
- The following selected examples are from recent published and from unpublished studies
  - Different methodologies, subject populations, and assays utilized
  - Assays are not validated nor standardized
  - The data have not been submitted to the FDA, and the FDA has not made any determination about its scientific or regulatory applicability

BA.1 infection after 2 vaccine doses elicits greater antibody breadth against Omicron variants

- BA.1 boosting by infection after 2 vaccine doses elicits greater breadth against Omicron variants than 3 vaccine doses
- Effect on breadth of BA.1 infection after 2 vaccine dose similar to that after 3 doses



Antibody Landscapes *– xy axis: antigenic map coordinating antigenic distance among the viruses; z axis: neutralizing antibody titer*

Unpublished data from IDCRP/USU EPICC and PASS studies, PIs: Pollett (HJF for IDCRP/USUHS) & Mitre (USUHS); Katzelnick (NIAID/NIH); Weiss lab (CBER/DVP)

Neutralizing Antibody Titers Against Omicron Sub-Variants following Vaccination and BA.1 or BA.2 Infection

- BA.1 or BA.2 infection after vaccination increases antibody titers against Omicron variants
- Titers against BA.2.12.1 and BA.4/BA.5 lower than titers against BA.1 or BA.2

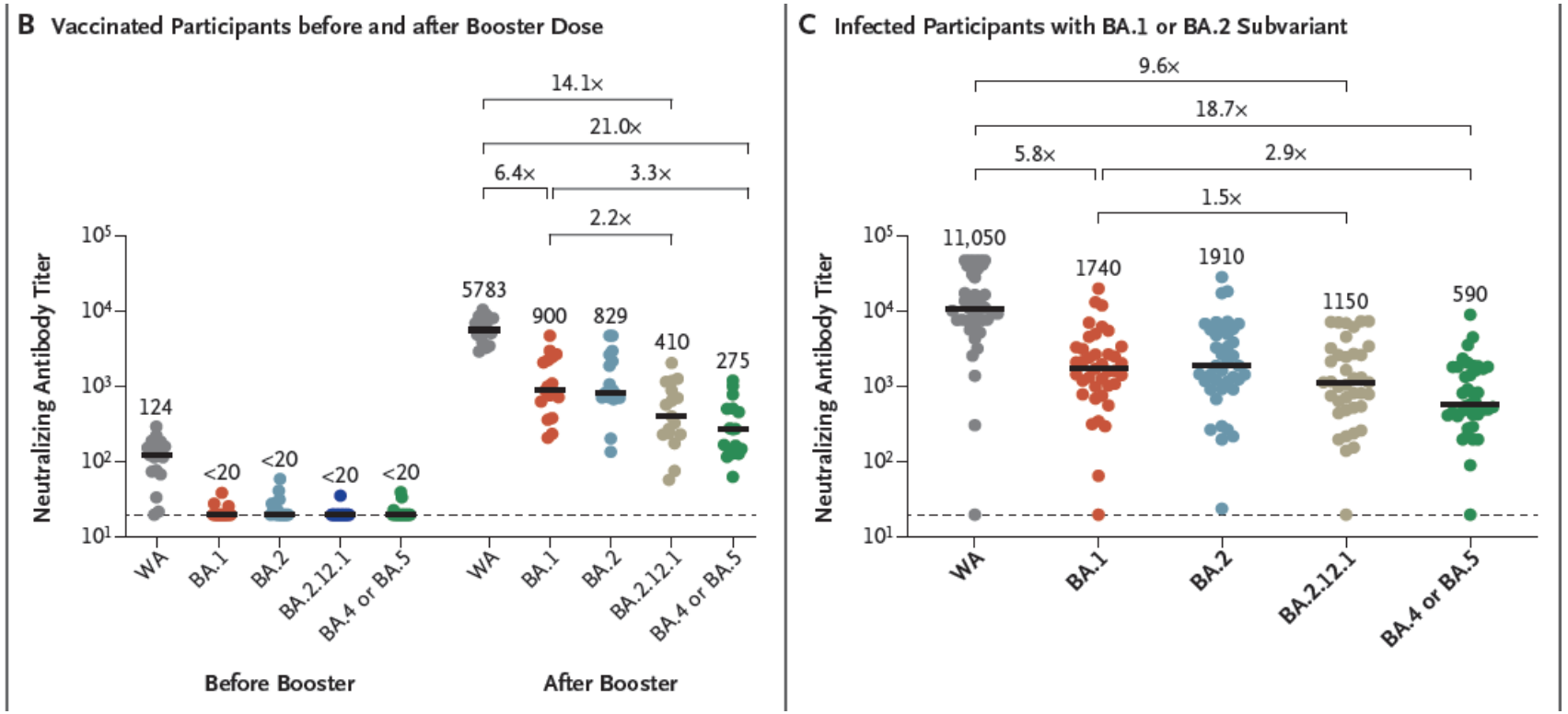


Figure 1B & 1C – from Hachmann NP et al 2022 N Engl J Med DOI: 10.1056/NEJMc2206576

Summary

- Currently circulating SARS-CoV-2 viruses are antigenically distinct from strains that circulated early in the pandemic and on which current COVID-19 vaccines are based
- The SARS-CoV-2 Omicron variant has become dominant globally, poses a higher risk of re-infection than previous virus strains, and continues to evolve into sub-lineages that are also antigenically distinct
- By several measures, including escape from antibody neutralization and protection against infection, the current vaccines appear less effective against Omicron variants than against previous strains of virus
- The available data indicate that an Omicron booster vaccination will increase and broaden the antibody response to SARS-CoV-2 Omicron viruses

Conclusions and Future Directions

- The preponderance of the data indicate an improved antibody response to SARS-CoV-2 Omicron variants and the potential for improved vaccine effectiveness when an Omicron component is included in a vaccine booster
- Many challenges and uncertainties remain
  - Vaccine formulation decisions (e.g., dose, monovalent vs multivalent, etc.) will be important for antibody response to modified booster vaccines
  - Vaccine effectiveness studies will be crucial in determining if higher and broader antibody titers to VOCs translate into clinical benefit
  - The protective antibody titers for highly transmissible viruses such as recent Omicron sub-lineages may be different than for previous strains
  - Modification of the COVID-19 vaccine composition will include programmatic and operational challenges
- The strain composition process for COVID-19 vaccines will benefit from further refinement
  - Improved coordination and consensus regarding the types of data needed for strain composition decisions and where and how such data is generated

Discussion Questions for the Committee

Please discuss the various considerations involved in updating the strain composition for COVID-19 vaccines in the U.S. Please provide input on the following and discuss whether any additional data are needed to facilitate a recommendation:

- Is a change to the current COVID-19 vaccine strain composition necessary at this time?
- Please discuss the evidence supporting:
    1) the selection of a specific Omicron sub-lineage (e.g., BA.1 vs. BA.4/BA.5)
    2) a monovalent (Omicron) or bivalent vaccine (prototype + Omicron)
    3) extrapolating the available clinical data for modified vaccines to different age ranges
- What additional data, if any, would be needed to recommend an updated composition of the primary series vaccine? If the booster vaccine composition changes, would continuing use of the prototype primary series vaccine this fall still be acceptable?

Voting Question for the Committee

- Does the committee recommend inclusion of a SARS-CoV-2 Omicron component for COVID-19 booster vaccines in the United States?


FDA
U.S. FOOD & DRUG
ADMINISTRATION