MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

SEPTEMBER 1, 2022
MEETING SUMMARY

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MEETING PURPOSE

The United States (US) Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC) convened a meeting of the Advisory Committee on Immunization Practices (ACIP) on September 1, 2022. The meeting took place remotely via Zoom, teleconference, and live webcast. This document provides a summary of the meeting, which focused on the epidemiology of COVID-19 and SARS-CoV-2 variants; immunology of SARS-CoV-2 variants; updates to COVID-19 vaccine effectiveness (VE) and vaccine safety; Moderna bivalent COVID-19 vaccine; Pfizer-BioNTech bivalent COVID-19 vaccine; Evidence to Recommendations (EtR) Framework assessment of bivalent COVID-19 booster doses; Clinical Considerations update; and votes on Moderna COVID-19 bivalent vaccine in individuals ≥18 years of age and Pfizer-BioNTech COVID-19 bivalent vaccine in individuals ≥12 years of age.

THURSDAY: SEPTEMBER 1, 2022

WELCOME AND INTRODUCTIONS

Call to Order/Roll Call

Dr. Grace Lee (ACIP Chair) called to order and presided over the September 1, 2022 ACIP meeting. She conducted a roll call, which established that a quorum was present. No conflicts of interest (COIs) were declared. A list of Members, *Ex Officios*, and Liaison Representatives is included in the appendixes at the end of this summary document.

CDC Announcements

Dr. Melinda Wharton (ACIP Executive Secretary, CDC) began by explaining that although this meeting originally was announced as a 2-day meeting with a 2-hour session the second day, ACIP did anticipate using that time as the committee was expected to complete its business during the first day. At the time the meeting was scheduled, it was unclear exactly when the Food and Drug Administration (FDA) would complete the regulatory action and it was anticipated that a 2-day meeting might be necessary. Given that the FDA was able to complete the regulatory actions, a 1-day ACIP meeting was expected to be sufficient.

Proceeding with meeting logistics, Dr. Wharton noted that copies of the slides for the day were available on the ACIP website and were made available through a ShareLink™ file for voting ACIP Voting Members, *Ex Officios*, and Liaisons. She indicated that the ACIP is at its heart a public body. Engagement with the public and transparency in the ACIP processes is vital to the committee's work. She indicated that there would be an oral public comment session prior to the vote at approximately 12:15 PM Eastern Time (ET). To create a fair and more efficient process for requesting to make an oral comment, people interested in making an oral comment are requested to submit a request online in advance of the meeting. Priority is given to these advanced requests, and if more people request to speak than can be accommodated, a blind lottery is conducted to determine who the speakers will be. Speakers selected in the lottery for this meeting were notified in advance of the meeting. Members of the public also can submit public comments through https://www.regulations.gov using Docket Number CDC-2022-0103. Information on the written public comment process, as well as information on how to make a comment, can be found on the ACIP meeting website.

As noted in the ACIP Policies and Procedures manual, ACIP members agree to forgo participation in certain activities related to vaccines during their tenure on the committee. For certain other interests that potentially enhance a member's expertise, CDC has issued limited COI waivers. Members who conduct vaccine clinical trials or serve on data safety monitoring boards (DSMBs) may present to the committee on matters related to those vaccines, but these members are prohibited from participating in committee votes on issues related to those vaccines. Regarding other vaccines of the concerned company, a member may participate in discussions with the provision that he or she abstains from all votes related to the vaccines of that company. ACIP members state any COIs at the beginning of each meeting.

FDA Announcements

Doran Fink, MD, PhD (CBER/FDA) reported that the reason this ACIP meeting was convened was because the previous day FDA, under its Emergency Use Authorization (EUA) authority, authorized 2 modified mRNA COVID-19 vaccines formulated to have bivalent strain compositions. The bivalent vaccine manufactured by Pfizer-BioNTech and has been authorized for use as a booster dose in individuals ≥12 years of age who are at least 2 months removed from completion of their COVID-19 vaccine primary series or at least 2 months removed from their most recent booster dose with a monovalent originally authorized COVID-19 vaccine. The bivalent vaccine manufactured by Moderna it is authorized for use in individuals ≥18 years of age who are at least 2 months removed from either completion of their primary series or their most recent booster dose with a monovalent originally authorized COVID-19 vaccine. Each of these bivalent vaccines contains a component for the original ancestral SARS-CoV-2 strain that was the basis for the originally authorized COVID-19 mRNA vaccines and a component for the Omicron BA.4 and BA.5 sub-lineages. These bivalent vaccines will replace the use of the original monovalent vaccines as booster doses in the populations who are eligible to receive them. Therefore, individuals ≥12 years of age who will be boosted with the Pfizer vaccine now will receive the bivalent vaccine. The original monovalent is no longer authorized for that population and likewise for Moderna for individuals ≥18 years of age.

FDA authorized these bivalent vaccines with the goal of improving the protection afforded by vaccine booster doses by having the vaccine strain composition more closely matched to the currently circulating SARS-CoV-2 strain, the vast majority of which in the US is now BA.5, and additionally by retaining the original strain component for which there is extensive experience in terms of these vaccines being safe and effective. In its authoritarian, FDA considered a totality of evidence that consisted primarily of an extrapolation approach based on data from clinical trials with similar bivalent vaccine formulations consisting of original the Omicron BA.1 sub-lineage components and extensive experience with the use of the original monovalent primary series and booster dose vaccines. All of these data represent data collected with human experience. Additionally, FDA considered supportive data from some animal studies that provided additional reassurance about the extrapolation approach. FDA encourages everyone who is eligible for these bivalent booster vaccines to get them to improve their protection against disease caused by SARS-CoV-2, including serious consequences of COVID-19 such as long COVID-19. FDA especially encourages individuals who have been waiting to get their booster dose who are far out from their last booster dose to take advantage of the authorizations of these bivalent vaccines heading into the Fall and Winter months for which modelling has predicted that COVID-19 disease activity will increase.

Discussion Summary

Dr. Wharton indicated that with FDA's regulatory action approving the updated bivalent booster the previous day, the ACIP has an opportunity to update and simplify its recommendations for vaccine use. The hope is that this is the start of moving toward with a more usual type of vaccine recommendations and process, as well as more normal cadence of ACIP meetings. While this will be a transition, it is an important move toward simpler recommendations and updated vaccines that are expected to provide protection. She expressed gratitude to the ACIP for their ongoing support.

Dr. Lee thanked Drs. Wharton and Fink for setting the stage for the day. The ACIP is hopeful that in moving into the next phase of the pandemic, they also can move into the next phase of the ACIP meeting schedule.

CORONAVIRUS DISEASE 2019 (COVID-19) VACCINES

Session Introduction

Dr. Matthew Daley (ACIP, WG Chair) provided the session introduction on behalf of the ACIP COVID-19 Vaccines Work Group (WG). He began with highlights of the global impact of the first year of COVID-19 vaccinations based on mathematical modelling of transmission and infection in 185 countries from December 2020 through December 2021.[1] Based on this modeling, COVID-19 vaccinations are estimated to have prevented between 13.7 to 15.9 million deaths globally. This represents an estimated 63% reduction in total COVID-19 deaths globally.

To provide an update on the use of the Novavax COVID-19 vaccine, Novavax is a protein subunit vaccine that has been authorized for emergency use. Novavax COVID-19 vaccine is now recommended as a 2-dose primary series for people ≥12 of age in the US. A total of 670,000 doses of this vaccine have been distributed across all US states and territories. A total of 3.2 million doses have been purchased by the US Government (USG). As of August 25, 2022, approximately 14,000 doses have been administered. This includes 2,591 individuals who have received the full 2-dose primary series.[2]

The ACIP COVID-19 Vaccines WG had a busy August. The WG reviewed extensive data regarding bivalent boosters and the broader context in which bivalent boosters are authorized. This included data from multiple clinical trials of bivalent boosters, including those with an Omicron component that have demonstrated safety and immunogenicity in more than 1700 adults both with and without prior SARS-CoV-2 infection. As referred to by Dr. Fink, this includes data from more than 1,400 individuals who received a bivalent vaccine with an Omicron component specifically. In addition, the WG reviewed antigenic cartography and the immunologic implications of SARS-CoV-2 variants, setting the context for bivalent vaccines. The WG also reviewed modelling data focused on pandemic outcomes in various scenarios, including the potential impact of new variants and varying vaccine/booster coverage. In addition, the WG reviewed extensive data regarding rare events of myocarditis after COVID-19 vaccination. The WG also reviewed the epidemiology of COVID-19 disease and variants, including currently dominant omicron BA 4/5 variant. Through all this, the WG has engaged in

[1] Watson, Barnsley, Toor et al. Lancet Infectious Diseases. 22:9(P1293-1302). https://doi.org/10.1016/S1473-3099(22)00320-6
[2] COVID Data Tracker: https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-people-additional-dose-totalpop Accessed 8/26/22

broad discussions regarding the use of bivalent boosters in people of all ages who are currently recommended to receive a booster.

Update on SARS-CoV-2 Variants and the Epidemiology of COVID-19Epidemiology of COVID-19 & COVID-19 Vaccine Coverage

CDR Heather Scobie, PhD, MPH (CDC/NCIRD) provided an update of the variants and epidemiology of COVID-19. The Omicron variant has 5 main sub-lineages numbered BA.1 through BA.5, which are further divided into hundreds of sub-lineages. Omicron has been shown to have increased transmissibility but decreased severity relative to previous lineages. Omicron has many mutations in the spike gene (S-gene) that are associative with lower VE, with reduced neutralization by sera from vaccinated or convalescent individuals. There also is a reduction in efficacy of some monoclonal antibody treatment.[3]

Based on trends in weighted variant proportion estimates and Nowcast data for the US from May 22, 2022 through August 27, 2022, Omicron sub-lineages have been over 99% predominant for many months. The BA.2 sub-lineage BA.2.12.1 sub-lineage have been displaced by the BA.4 and BA.5 sub-lineages. For the week ending August 27, 2022, BA.5 comprised 88.7% of sequences. BA.4.6 comprised 7.5% and BA.4 comprised 3.6%.[4] Based on the estimated numbers of reported COVID-19 cases by variants based on the variant proportion and scaled by the number of nucleic acid amplification tests (NAATs), including polymerase chain reaction (PCR) tests, the trends highlight that the more recent waves caused by the BA.4 Omicron sub-lineages and the BA.4 and BA.5 sub-lineages have been much smaller than the initial Omicron wave related to the BA.1 sub-lineages.[5] Looking at Nowcast estimates of variant proportions across the 10 HHS regions August 21–27, 2022, BA.5 represented the majority of circulating lineages in all regions during the most recent week.[6]

Looking at COVID-19 trends since the beginning of the pandemic, the number of cases associated with the Alpha variant was relatively small compared to the Delta and Omicron variants. Nationally reported cases started increasing in April, leveled off in June and July, and have been decreasing in August. There had been over 94 million reported COVID-19 cases in the US as of August 30, 2022.[7] Looking at the daily number of reported COVID-19 cases overlaid with a 7-day moving average of NAAT percent positivity, which is a marker of transmission intensity, the trends aligned remarkably well in late 2020 through early 2022. The trends become uncoupled starting in May, with numbers of reported COVID-19 cases leveling off while NAAT positively in late July increased to a high of 20% related to increased transmission, decreased provider-based testing, and increased at-home testing that is largely unreported. This resulted in an underestimation of reported cases. However, NAAT positivity in case counts have decreased during August, suggesting a decrease in overall transmission.[8]

[3] https://www.cdc.gov/coronavirus/2019-ncov/variants/omicron-variant.html; and https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/scientific-brief-omicron-variant.html
[4] https://covid.cdc.gov/covid-data-tracker/#variant-proportions Accessed August 26, 2022
[5] Data sources: https://covid.cdc.gov/covid-data-tracker/#variant-proportions and https://covid.cdc.gov/covid-datatracker/#trends_newtestresultsreported_7daytestingpositive_00
[6] https://covid.cdc.gov/covid-data-tracker/#variant-proportions Accessed August 26, 2022
[7] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#trends_dailycases Accessed August 31, 2022
[8] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#trends_newtestresultsreported_7daytestingpositive_00 Accessed August 31, 2022

In terms of weekly trends in the rates of COVID-19-associated hospitalizations by age group from COVID-NET, higher hospitalization rates always have occurred in the 65+ age group, followed by people 50–64 years of age and 18–49 years of age. Since April, hospitalization rates have increased more in the 65+ year age group compared to those among younger adults for whom there were not large increases in hospitalization rates.[9] Data from a *Morbidity and Mortality Weekly Report* (MMWR)[10] published the previous Friday showed that there has been a widening gap over time between hospitalization rates in older and younger adults and that age remains a strong risk factor for COVID-19 illness severity. Data from the same *MMWR* show that the median age of patients with COVID-19-associated hospitalization increased across the 3 periods, while the percentage of hospitalizations that were likely COVID-19-related decreased slightly between the Delta and Omicron periods. The percentage of cases with underlying conditions, immunosuppression, and residing in long-term care facilities (LTCF) increased, while outcomes related to clinical severity decreased. These trends were likely related to a combination of increasing vaccinations, waning immunity, changes in COVID-19 treatments, and differences in variant severity over time.

Looking at the 3-week moving average of age-adjusted rates of COVID-19-associated hospitalizations by race and ethnicity. Throughout the pandemic, American Indian and Alaskan Native (AI/AN), Black, and Hispanic persons have been disproportionately affected by COVID-19-associated hospitalizations compared with White and Asian Pacific Islander persons. The scale of these disparities has decreased after the Omicron surge, but hospitalization rates are still highest among AI/AN and Black persons.[11] In terms of COVID-19-related deaths, US trends in the daily number of provisional COVID-19 deaths have been reported to the National Vital Statistics System (NVSS) since the start of the pandemic. NVSS data come from death certificates and are generally considered to be more reliable than the death data reported through COVID-19 surveillance. There have been over 1,042,000 deaths due to COVID-19 reported cumulatively in the US as of August 27, 2022. Omicron has caused a sizable number of deaths despite decreased relative severity because of high case numbers.[12] Data on weekly trends in COVID-19-associate mortality rates from NVSS by age group[13] show that higher mortality rates are consistently observed in older age groups, most notably among those aged 75+ years, 65–74 years, and 50–64 years. Similar to hospitalizations, a recent increase has been observed in death rates for older ages, especially for adults ages 75+ years. Data on weekly trends in age-adjusted COVID-19-associated mortality rates from NVSS by race and ethnicity show that higher mortality rates have been observed throughout the pandemic among Black persons, AI/AN persons, and Hispanic persons compared with White persons. Since April, there has been less evidence of disparities in mortality rates by race and ethnicity, but mortality rates were low overall relative to earlier in the pandemic.

As of August 24, 2022 almost 224 million people in the US have been vaccinated with a primary series, which is 72% of people ≥5 years of age, while 49% people ≥5 years of age have received a first booster dose and 34% of people ≥50 years and older have received a second booster dose. Despite progress, there are still important differences in primary series vaccination coverage by age and booster dose coverage by race, ethnicity, and disability status.[14] Looking at adjusted rates of COVID-19 cases by vaccination status, case rates in people with a primary series increased during waves associated with Delta and Omicron

[9] Source: COVID-NET; https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html Accessed August 26, 2022
[10] Havers et al. MMWR 2022; 71(34);1085–1091. https://www.cdc.gov/mmwr/volumes/71/wr/mm7134a3.htm?s_cid=mm7134a3_w
[11] COVID-NET: https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network Accessed August 23, 2022
[12] https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm Accessed August 31, 2022
[13] https://data.cdc.gov/NCHS/Provisional-Weekly-Deaths-by-Region-Race-Age/tpcp-uiv5
[14] https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total Accessed August 24, 2022

variants. However, case rates for unvaccinated people have always exceeded those for vaccinated people. In July, unvaccinated people ages ≥5 years 2.4 times higher risk of testing positive for COVID-19 compared to people vaccinated with at least the primary series.[15] Regarding age-adjusted rates of COVID-19-associated hospitalizations by vaccination status and receipt of a booster dose, hospitalizations for COVID-19 have been consistently higher among unvaccinated than vaccinated people over time. In June, unvaccinated adults ages ≥18 years and older had 4.6 times higher risk of COVID-19 associated hospitalizations compared to those vaccinated with a primary series and at least 1 booster dose.[16] Looking at age-adjusted rates of COVID-19 associated deaths by vaccination status and receipt of booster doses, in July, unvaccinated people ages ≥5 years had 8 times the risk of dying from COVID-19 compared to people vaccinated with a primary series and at least 1 booster dose. This was a decrease from 20 times higher during January through March 2022. This analysis reported a decrease in the rate ratio from earlier in the year, possibly related to waning immunity and increased community transmission of the Omicron sub-lineages as well as other factors.[17]

In data from July 2022,[18] people ages 50 years and older with a second booster dose had 14 times lower risk of dying from COVID-19 compared to unvaccinated people the same age and 3 times lower risk of dying from COVID-19 than people of the same age with 1 booster dose. These data suggest that getting a second COVID-19 vaccine booster dose can enhance protection that might have decreased over time after received the last dose. Unvaccinated people are at much higher risk of severe COVID-19 illness than vaccinated people. Most (75%) vaccinated people who get severe COVID-19 illness have multiple risk factors including older age (most ≥65 years, but with risk increasing with age) and underlying medical conditions (immunosuppression, diabetes, chronic kidney disease, chronic lung disease, chronic cardiovascular disease, or chronic neurologic disease. Antiviral drugs can help reduce the risk of severe illness in people at higher risk.[19]

In summary, CDC continues to monitor emerging variants like the sub-lineages of Omicron, including their prevalence and impact on disease incidence, severity, and VE over time. Racial and ethnic minority groups have been disproportionately affected by COVID-19-associated hospitalization and mortality. These inequities have decreased over time, but have not been eliminated. Recent trends show evidence of increasing severe illness, including hospitalization and deaths in people of older age and people with underlying health conditions. Current vaccines offer protection against severe COVID-19 illness and death, so it is important to stay up-to-date (UTD) with vaccination, including receipt of all booster doses in eligible populations. Therapeutics and multiple prevention measures should be used to protect people at higher risk of severe COVID-19 illness regardless of vaccination status.

[15] https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status Accessed August 24, 2022
[16] https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination Accessed August 3, 2022
[17] https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status Accessed August 24, 2022
[18] https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccinbooine-status Accessed August 24, 2022
[19] Yek et al. MMWR 2022;71:19–25. https://www.cdc.gov/mmwr/volumes/71/wr/mm7101a4.htm; Taylor et al. MMWR 2022;71:466-473: http://dx.doi.org/10.15585/mmwr.mm7112e2 and unpublished COVID-NET data, as described here; Malden et al. MMWR 2022; 71(25);830-833: https://www.cdc.gov/mmwr/volumes/71/wr/mm7125e2.htm; Gold et al. MMWR 2022; 71(25);825-829: https://www.cdc.gov/mmwr/volumes/71/wr/mm7125e1.htm; Najjar-Debbiny et al. CID 2022;, ciac443, https://doi.org/10.1093/cid/ciac443; Dryden-Peterson et al. medRxiv 2022.06.14.22276393; https://doi.org/10.1101/2022.06.14.22276393

Discussion Summary

Dr. Poehling expressed appreciation for the data showing that the hospitalization rates are increasing, particularly for those over 65 years of age. It is commonly said that COVID-19 is more severe in adults than children, and she thought it was important to highlight that deaths and hospitalizations are more common in adults than children. However, children are hospitalized with COVID-19 all of the time. This is not a benign disease in children. She asked whether there are any data comparing baseline hospitalization rates across age groups.

Dr. Scobie indicated that during times of increased case incidence, hospitalization increases in all age groups. The trend she was talking about was that the relative increase is currently higher in older age groups. Taking them out, there are increases in all age groups.

Dr. Brooks emphasized the importance of framing the current situation on September 1, 2022. He was encouraged by the reduction in the disparities of African Americans and Alaskan Natives in terms of case rates, hospitalization rates, death rates. He believes a lot of this attributable to the efforts of the CDC and others to get out messaging that is targeted to these communities. Vaccination rates have leveled off in terms of disparities. The fact that the death rate is higher among the unvaccinated compared to those with the primary series and 1 or 2 booster underscores the importance of continuing to get boosted. Some of the population get COVID-19 vaccine weary and decide they are okay with the primary series and 1 booster.

Dr. Duchin (NACCHO) emphasized that these data clearly show the importance of booster doses in preventing severe disease, particularly among older adults and those with underlying health conditions. He requested additional information about how CDC is thinking about measuring the impact of post-acute sequelae or long COVID-19 and the potential benefit of vaccination in that context.

Dr. Scobie indicated that this is not assessed through ongoing surveillance because of the difficulty of reports in collecting the data systematically, but there are plans for ongoing repeated surveys that will be implemented to assess the importance of booster doses.

In terms of VE against long COVID-19, Dr. Link-Gelles indicated that the research generally has been mixed and inconclusive. However, there clearly is some benefit for prevention of initial infection, especially close to booster vaccination, and prevention of the severe disease that has been associated with a higher likelihood of long COVID-19. The lack of a standard definition globally, the inability to track patients longer-term, and the lack of diagnostic testing for long COVID-19 have complicated the ability to measure VE. However, this does remain a research priority. Perhaps during a future ACIP, a summary of the available information on this topic could be presented.

Dr. Sanchez asked whether it has been possible to analyze similar data in pregnant women to determine the effect of the primary series and boosting on COVID-19 hospitalization and mortality in that population.

Dr. Scobie indicated that this information may be available through COVID-NET, but she did not have that information. Information on pregnancy status was not collected as part of the vaccine impacts surveillance data she presented on the cases and deaths by vaccination status. Along with the request for a summary of long COVID-19 information, she could make a request for data on vaccine impacts on pregnant women from to colleges and the ACIP Secretariate.

Dr. Fleming-Dutra added that CDC is hoping to address questions about COVID-19 vaccine use in pregnant women in terms of effectiveness and their infants during a future ACIP meeting.

Dr. Lee emphasized that while the burden of severe disease and hospitalization is higher among older adults than children, it is important to keep in mind that COVID-19 is the fourth or fifth leading cause of death in children. She also asked whether there are any data comparing unvaccinated and potentially uninfected people in terms of severity during Omicron among those who were unvaccinated in Alpha or Delta, particularly in the context of the graphs Dr. Scobie showed on hospitalization rates. There is a perception that if the Omicron wave is less severe, it is not necessary to worry about it that much. The Omicron wave is occurring in a background of people who have had infection and vaccination, so the population is very different from an immune perspective than it was during the Alpha and Delta waves.

Dr. Scobie clarified that the results she showed were descriptive and did not adjust for the impacts of vaccination and would have to be interpreted in that light. While the particular study she described did not address Dr. Lee's point, she indicated that there are a number of publications that did that type of analysis and took into account immunity status that have shown that Omicron is less severe than previous variants. The issue is that there are so many more Omicron infections because of increased transmissibility. The reduced severity of Omicron is not something to take lightly because with a higher chance of getting the disease, there will continue a large number of hospitalizations and deaths.

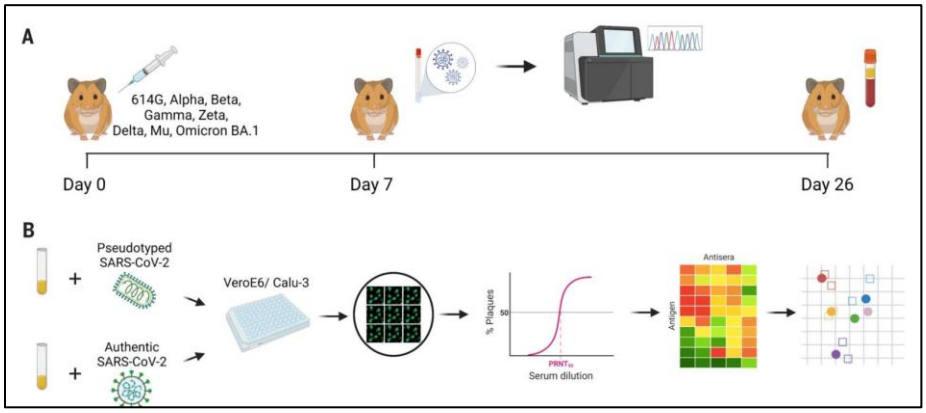
Looking at Slides 22 and 23, Dr. Sanchez observed that there are a lot of issues to address with respect to counseling patients about booster dosing in terms of the high seroprevalence among people who have had COVID-19 already. The data from June 2022 showing very high seroprevalence among the general population attests to the need for booster dosing and that they should be recommending it. There are a lot of questions about whether to get a booster now or wait until the Fall. The data suggest that even in an era of high natural infection, booster dosing presumably also has contributed to the decrease in hospitalization and mortality.

Immunology of SARS-CoV-2 Variants: Antigenic Cartography

Natalie J. Thornburg, PhD (CDC/NCIRD) provided an update on the immunology of Omicron variants, specifically focusing on the technique of antigenic cartography that laboratorians are using to estimate how different viruses are from each other, which can inform vaccine selection. Lineage numbers are not necessarily reflective of how different viruses are from ancestral viruses. The antigenic visualization method is used to determine how closely related different viruses are antigenically rather than in the genetic context. BA.5 is not necessarily more distant from the vaccine strain than BA.2 or BA.3 just because of the number. It is customary to look at virus lineages and viral variances in phylogenetic trees, which are generated according to genetic differences and not antigenic differences, which is not how the immune system sees viruses. The immune system sees viruses as shapes. Antibodies see the shape of a spike protein and not the linear sequence of nucleotides or amino acids. Antigenic cartography is a method to measure how different viruses might look to antibodies after vaccination or infections.

Antigenic cartography uses a matrix algorithm called a matrix completion-multiple dimensional scaling algorithm to generate a map. It originally was developed for H3N2 influenza viruses using hemagglutination inhibition (HAI) titers. Either 2- or 3-dimensional maps can be generated

using this method to see how closely related viruses are. This graphic provides an illustration of how antigenic cartography might be done:[20]



A matrix of viruses in sera is used to do neutralization assays and a checkerboard of the results is created from the neutralization assays. The method of cartography is not limited by the kind of sera or neutralization technique one is using. What is important in this method is that information is known about the material being used in the assay to know the history of the sera being used and the sequence of the virus being used. This is demonstrated in the above graphic in that this particular study inoculated hamsters with different viruses with known sequences and then collected serum at Day 7 and Day 26 from those hamsters that had antibodies raised against specific viruses. This showed that 2 different neutralization assays could be used due to virus neutralization assays, which are in the shell of a different virus with just the spike protein from SARS-CoV-2 with a known sequence or an authentic virus (a virus that has been isolated from a respiratory specimen from an infected person). Neutralization assays are then done to generate a matrix of neutralization titers, which is shown in the square with the red, yellow, and green boxes. For every individual virus, there is a neutralization titer against a specific serum that is used to create the map.

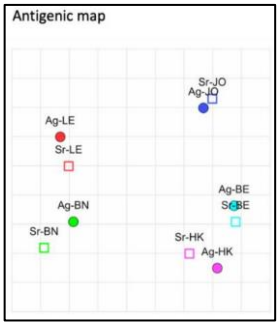
The titers generated from the neutralization assays of the different hamster serums can be used to create a distance map. In a lot of the maps that are being generated right now for coronaviruses, each square is a 2-fold difference change in neutralization titers. The distance table can be used to generate the antigenic map on which the viruses can be color coded. Most publications have been using empty squares for sera and filled circles as viruses to see how closely related they are as shown in these illustrations:

Map distances

	Sr-LE	Sr-BN	Sr-JO	Sr-BE	Sr-HK
Ag-LE	1.0	3.8	5.5	6.8	6.0
Ag-BN	1.9	1.4	6.4	5.7	4.2
Ag-JO	5.1	7.3	0.4	4.1	5.0
Ag-BE	5.9	6.8	3.7	0.6	2.3
Ag-HK	6.3	6.1	5.8	1.7	1.1

Table distances

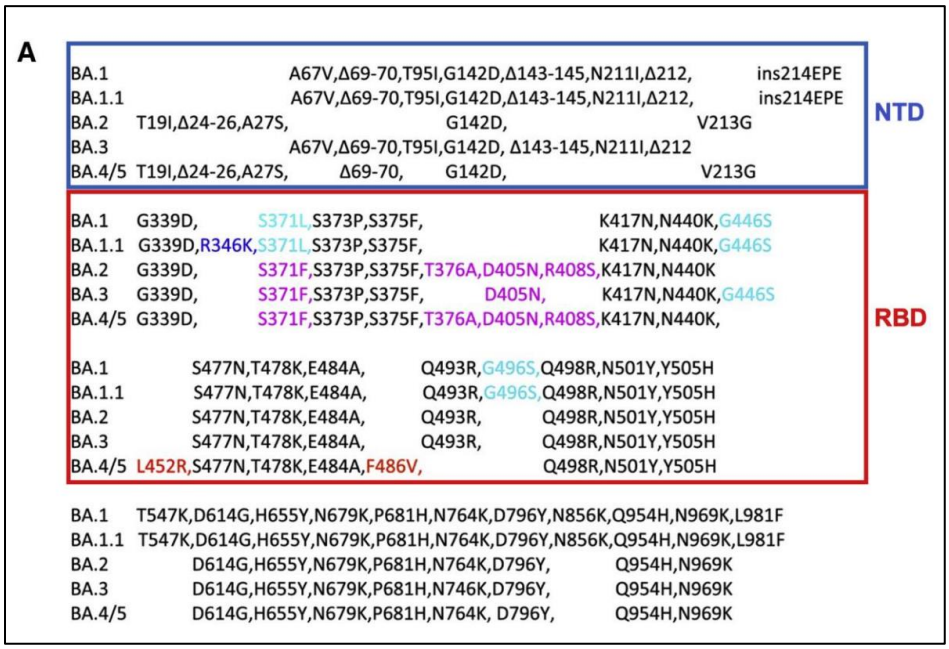
	Sr-LE	Sr-BN	Sr-JO	Sr-BE	Sr-HK
Ag-LE	0	5	6	>5	>5
Ag-BN	1	0	6	>5	3
Ag-JO	5	7	0	4	5
Ag-BE	6	7	3	0	2
Ag-HK	6	7	7	1	0



[20] Mykytn et al. Science immunology. 2022

There are advantages and disadvantages to this method. The advantages include that it is extremely easy to interpret because it is possible to look at the antigenic map above to see that in this case, antigen BE is pretty far from antigen LE, but BN and LE are pretty closely related. This method is fairly accurate and provides a really good overview rather than just looking at sequence alignments, which can be complex. This method also provides quantification and allows for predictions about how easily a virus might escape an antibody response. There are some drawbacks as well. This can be an over-simplification and there can be assay bias. For example, a map generated with pseudo virus neutralizations might look different than a map generated with authentic virus neutralization or animal sera versus human sera. There can be outlier effects, and there always is map uncertainty in that the dots are not actually as finite as they might not look in a map where there is some uncertainty.

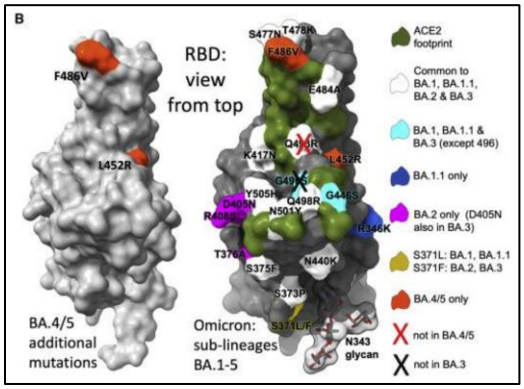
In terms of what is known about how antigenically similar Omicrons are from earlier viruses and how antigenically related they are to each other, this is a reminder of the Omicron lineages and sub-lineages in the amino acid variations that have been observed in the spike protein. This is not the full spike protein. It is just a few regions in some areas where there were adverse event variations between Omicron lineages:[21]



The end-terminal domain is shown in a blue square and the receptor-binding domain, which is where most of the potent neutralizing antibodies would be binding the receptor-binding domain and blocking ACE2 binding, is shown in the red square. The downstream of the receptor-binding domain is shown at the bottom.

[21] Tuekprakhon et al. Cell 2422-2433.e13. 2022

These are some of the amino acid differences projected onto the structure of the receptor-binding domain:[22]



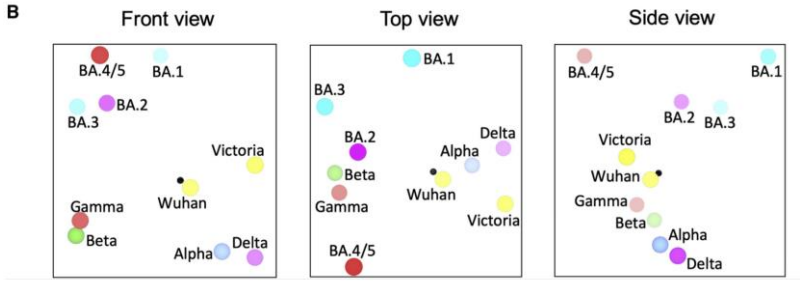
In the above illustration, the unique amino acids to BA.4/BA.5 are shown in B on the left in red. The different variant amino acids on the right are projected onto the ACE2 footprint where the spike receptor binding domain binds ACE2. There are some common to most of the Omicrons to BA.1, BA.2, BA.3, but not BA.4/BA.5 shown in white. Unique to BA.4/BA.5 is shown in red and unique to BA.2 is shown in magenta. It is pretty complex such that just looking at this, it would not necessarily be possible to say which one of these Omicrons is most different from ancestral virus or which is most likely to escape vaccine or neutralization.

Three antigenic maps from peer-reviewed publications include Omicron viruses, 2 of which are 2-dimensional and 1 of which is 3-dimensional. Only 2 of these maps include BA.4 and BA.5 type sequences. In this this one, investigators were able to look at the BA.1 and lineages of omicron but not BA.4 and BA.5 because this was submitted before the emergence and broad circulation of BA.4 and BA.5. This study used convalescent sera from unvaccinated persons to generate antigenic cartography for BA.1 and BA.2:[23]

The squares in the above maps are sera from convalescent patients and the circles are viruses. Red is Delta, light blue is ancestral viruses, green is Alpha, yellow is Beta, and Omicron viruses are light pink and dark pink off to the right. The takeaway from this is that Omicron viruses are more distantly related from ancestral viruses from the earlier variants and there is a more dramatic difference looking at individuals who had been vaccinated only as opposed to infected, using infected sera.

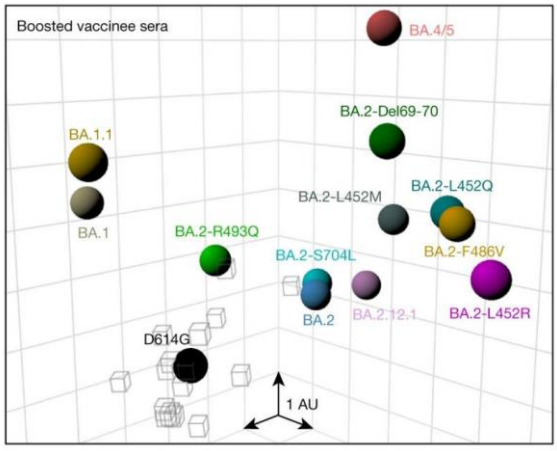
[22] Tuekprakhon et al. Cell 2422-2433.e13. 2022
[23] Van der Straten et al. Immunity 2022

In this study published in the summer[24] includes analyses of BA.4 and BA.5 and is a 3-dimensional map with the front, top, and side view views shown here:



While this is somewhat harder to look at and understand, this study also uses pseudovirus neutralization data. The investigators used serum from breakthrough BA.1 infections, so these participants had been vaccinated and then were infected with Omicron. They also had a panel of human monoclonal antibodies that they used to generate these maps. This map indicates that the omicron viruses cluster together, but consistent with the earlier study, cluster away from ancestral virus. They are quite antigenically distinct from the ancestral Wuhan virus. In this analysis, BA.4 and BA.5 are more distant to Wuhan than other Omicron viruses.

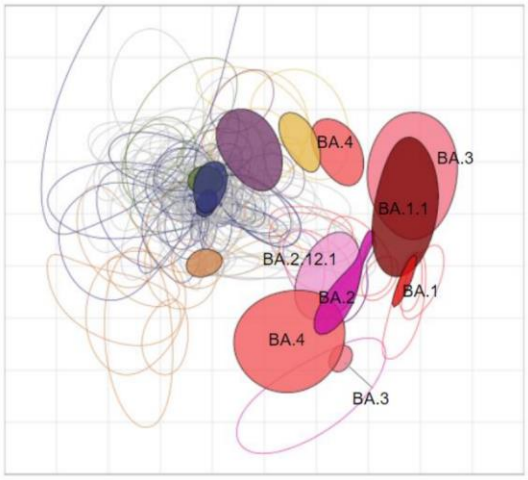
This is the last of the 3 published maps Dr. Thornburgh showed from a study[25] that used 21 known monoclonal antibodies, pseudovirus neutralization, and neutralization using post-third dose sera:



Each square in this one represents a 2-fold change in neutralization. This map is also 3-dimensional. It is shown here in 1 panel instead of 3 that the investigators generated by showing arrows on the bottom to identify which dimension is which. The black circle is ancestral virus strain D614G. BA.1 viruses at the top left are clustered somewhat away from BA.2 viruses toward the right in different colors of blue. There are a couple different variations of BA.2 lineage viruses. BA.4 and BA.5 viruses are toward the top right-hand corner. This map indicates that BA.4 and BA.5 might be most distantly antigenically related to ancestral virus compared to other Omicron lineage viruses.

[24] Tuekprakhon et al. Cell 2422-2433.e13. 2022
[25] Wang et al. Nature. 2022

Looking at these maps, it is easy to think of circles and squares as finite, but using bootstrapping, it is possible to see that there is overlap between Omicron lineages. Bootstrapping is a statistical method to estimate sampling distribution. There can be individual variation in the assays, viruses, and individual sera that are used. This map is from some aggregated data that was published in May 2022 that demonstrates that there is quite a bit of overlap in the antigenic maps between the Omicron viruses:[26]



The dark blue is ancestral and omicron viruses are showing in different shades of pink and red, and they cluster away from ancestral virus. There is some overlap, but using that aggregated data, either BA.1 or BA.4 viruses may be further away from ancestral viruses.

In conclusion, antigenic cartography is an analysis method to visually represent how antigenically related or distant viruses are to each other. They can be generated either in 2 or 3 dimensions, and the maps cluster Omicron variants away from ancestral and earlier virus variants. Initial examinations of Omicron lineages indicate that BA.4 and BA.5 viruses may be more antigenically distinct than BA.1 viruses. Notably, all of the published assays were done with pseudovirus neutralization. There are a number of studies underway that are using authentic viruses, so those data are expected to vary somewhat between different studies and between the serum panels that are being utilized.

Discussion Summary

Dr. Loehr commented that this was a very interesting way of representing the differences. He requested clarity on whether the distance Dr. Thornburgh was describing was basically how many antibodies were being generated from each individual variant so that the farther way, there are different antibody titers.

Dr. Thornburgh indicated that the distance is the change in neutralization titer between 2 different viruses. If 1 square is a 2-fold distance and the serum from a vaccinated person is measured against the vaccine strain and then one of the Omicrons, if it is 6-fold lower, it might be 3 squares separated.

[26] Aggregated Omicron neutralization data (last update 2022-05-26)

Dr. Duchin (NACCHO) noted that an article was published the previous day in the *New England Journal of Medicine* (*NEJM*) from Portugal that found that previous SARS-CoV-2 infection had a protective effect against BA.5 infection and they found that this protection was maximal for a previous infection with BA.1 or BA.2. He asked whether Dr. Thornburgh could comment on those findings in the human population in the context of the antigenic cartography work

Dr. Thornburgh responded that in terms of actual protection, data always trump any laboratory data being generated because it is real-world evidence of a protection rather than this very limited view of neutralization of viruses. This is a laboratory setting serum collection. There are limitations to this kind of analysis in terms of certainty. In the bootstrapped aggregated data, there was an overlap between Omicron. It is not terribly surprising that there is cross-protection between Omicrons. There are differences between omicrons, but there are not 50 differences. There are 3 amino acid changes or 10 amino acid changes. BA.2 is pretty similar to BA.4/5. It only has 3 differences in the spike protein, so with previous infection with BA.2, it does not surprise her that there is really good protection to BA.4/5. The same goes for BA.1. There are more changes when comparing BA.1 to BA.4 and BA.2 in comparison to BA.2 versus BA.4/5. The time since last infection matters as well because it is not just the sequence. It is waning of neutralizing antibody response in addition to the sequence of the virus to which one is being exposed.

Referring to Slide 7, the Van der Straten study, Dr. Sanchez observed that the more recent BA.4 and BA.5 variants were not included, but there was quite a distance of Omicron BA.1 from serum. This may explain some of the breakthrough infections.

Updates to COVID-19 VE During Omicron

LCDR Ruth Link-Gelles, PhD, MPH (CDC/NCIRD) provided updates on COVID-19 VE in the US during Omicron among children and adults organized by outcome and then by age within the outcomes of infection, emergency department/urgent care (ED/UC) visits, and hospitalizations. Starting with infections, the Increasing Community Access to Testing (ICATT) platform is national community-based drive-through testing data from pharmacies. This platform relies on self-reported vaccine history and uses a test-negative design in which the population is persons with at least 1 COVID-like symptom and a positive NAAT test and controls are symptomatic with a negative NAAT test. Models are adjusted for the variables of race, ethnicity, gender, patient state, site Census tract's Social Vulnerability Index (SVI), circulating cases of COVID-19 by zip code in the last 7 days, pharmacy partner, and test date. This analysis focused the BA.4/BA.5 predominant period during July 2, 2022 through August 20, 2022.[27]

Looking at relative VE for 3 versus 2 doses against symptomatic infection by age group, estimates for individual age groups are less important here than the overall trend, which is the same across age groups. There is less follow-up time for children 5–11 years of age due to the booster recommendation being more recent. However, the trend so far is the same as for older age groups. As a reminder, it has been observed previously that primary series VE against infection wanes to 0 within a few months, so these results should be taken in that context. In terms 3- versus 0-dose absolute VE against symptomatic infection and 4- versus 3-dose relative VE among adults 50–64 years of age, waning at or close to 0 VE is observed within a few

[27] CDC preliminary unpublished data. Prior infection excluded, other methods based on: Fleming-Dutra KE, Britton A, Shang N, et al. Association of Prior BNT162b2 COVID-19 Vaccination With Symptomatic SARS-CoV-2 Infection in Children and Adolescents During Omicron Predominance. JAMA. Published online May 13, 2022. doi:10.1001/jama.2022.7493

months of 3 doses as with younger age groups. There is potentially less waning of the fourth dose, although the follow-up time is limited given when the recommendation was made.

Moving to ED/UC visits, VISION is a multi-state network of electronic health records (EHRs) Like ICATT, it uses a test-negative design with cases having COVID-like illness (CLI) and a positive PCR and controls having CLI with a negative PCR. VE is adjusted by propensity to be vaccinated weights, calendar time, region, local virus circulation, and age. Vaccination is determined via EHRs and state and city registries. Regarding VE during Omicron mid-December through mid-Jul 2022 for children 5–11 years of age and adolescents 12–15 years of age by time since last dose, similar patterns are seen across age groups with VE of 2 doses against ED/UC visits waning substantially. In adolescents 12–15 years of age, there is a nice bump in VE with a third dose. However, there were not enough children 5–11 years of age with booster doses to provide an estimate in that age group.[28] Looking at adult VE during the BA.2 and BA.4/BA.5 periods, similar patterns are observed in the 2 time periods with waning by time since the most recent dose. During the BA.4 and BA.5 period when more data were available on the fourth dose, it appears that the fourth dose wanes somewhat more slowly compared to 2 and 3 doses.[29]

Looking at a new VE platform that has not been shared previously with the ACIP, COSMOS is an opt-in database of more than 162 million patient records drawn from healthcare organizations using the Epic EHR platform. Like other the platforms presented, this is a test-negative design focused on Omicron BA.2 and BA.4 and BA.5 periods among children and adolescents 5–15 years of age. Cases were symptomatic with a positive SARS-CoV-2 test within 14 days before or 3 days after the encounter, and controls were symptomatic with a negative SARS-CoV-2 test14 days before or 3 days after the encounter. There were not enough vaccinated hospitalized children to assess VE for hospitalizations, so this analysis focuses on ED and UC visits only. Similar patterns were seen with this platform as were seen in VISION, with waning of 2 and 3 doses among children 5–11 years of age and adolescents 12–15 years of age. There were wide confidence intervals, especially around the third dose.[30]

VISION results for mRNA VE for hospitalizations among immunocompetent adults ≥18 years of age by number of doses and time since last dose receipt between late March and late July 2022, VE against hospitalization continues to be higher and more sustained over time versus less severe outcomes. Estimates were not included for the 14 to 149 days after the second dose due to small numbers of people recently finishing their primary series during the summer. VE during BA.4 and BA.5 was generally similar to VE during BA.2 predominance. So far, the fourth dose shown appears to be waning somewhat more slowly compared to the third dose, although, the confidence intervals are too wide to be conclusive.[31]

Data were assessed from CDC's Influenza and Other Viruses in the Acutely Ill (IVY) platform from the December 2021 through July 2022 Omicron period among adults ≥18 years of age who were hospitalized at 21 medical centers in 18 states. Cases have CLI illness and a positive PCR or antigen test and controls have CLI and a negative PCR. Looking at VE among immunocompetent adults during Omicron predominance, the fourth dose is estimated only among adults s ≥50 years of age. As with VISION, waning was seen of the second and third

[28] CDC, preliminary unpublished
[29] BA.2/BA.2.12.1 estimates: Link-Gelles et al. *MMWR*: https://www.cdc.gov/mmwr/volumes/71/wr/mm7129e1.htm; BA.4/BA.5 estimates: CDC, preliminary unpublished data.
[30] CDC, preliminary unpublished data
[31] BA.2/BA.2.12.1 estimates: Link-Gelles et al. MMWR: https://www.cdc.gov/mmwr/volumes/71/wr/mm7129e1.htm; BA.4/BA.5 estimates: CDC, preliminary unpublished data

doses, though there was more sustained VE against infection. There was not enough statistical power to estimate VE in the IVY Network of 2 or 4 doses, but 3-dose VE had evidence of waning.

To summarize, VE against severe disease continues to be higher and more sustained over time than VE against infection. VE during BA.4 and BA.5 predominance was generally comparable to VE during BA.2 predominance. A third dose provided significant additional protection against infection and severe disease in all ages. While the third dose did wane, especially against infection, it appears to have waned slightly more slowly compared to the second dose, with similar patterns seen across age groups. Fourth-dose coverage was too low to draw conclusions, but additional benefits were demonstrated against all outcomes with slower waning apparent—especially against hospitalization.

Discussion Summary

Dr. Long requested clarification regarding whether it was that VE against BA.4 and BA.5 hospitalization was equal to and had the same decay as it did against earlier, suggesting that there would be no seeming advantage of the bivalent vaccine against Omicron BA.4 and BA.5 in the short-run and that VE in the long-run against hospitalization is unknown.

Dr. Link-Gelles clarified that these data all were from the monovalent vaccines. No data were provided for bivalent vaccines. Slide 14 is hospitalization data among immunocompetent adults for monovalent vaccine only with currently used vaccines. For BA.2 and BA.4/BA.5, the patterns are generally the same. She cautioned against interpreting lower VE during BA.4/BA.5 using these data because of the wide confidence intervals. But the same general pattern is seen in that there is some indication of waning of the third dose and the fourth dose seems to bump back up, perhaps even a little higher than the initial third dose. These are much higher VEs and more sustained effectiveness for hospitalization than what was seen for infection, but it is an indication that the bivalent vaccine should provide at least similar or better protection against Omicron since it will be a better match.

Dr. Poehling said the way she was interpreting these data was that the primary series wanes a lot, and it is the third and fourth booster doses that provide important protection against severe disease, even when using the monovalent vaccine.

Dr. Link-Gelles confirmed that interpretation. A pattern has been seen for every variant so far that the primary series provides some protection, but it is relatively limited and wanes quickly and the third dose is key for having more sustained protection. Early indications are that the fourth dose likewise provides additional benefit in those for whom it is recommended.

Dr. Long asked how confident Dr. Link-Gelles was about that last statement. Looking at the data, the studies and average times since the fourth dose were 27 days, 38 days, and 84 days or 90 days before significant waning was seen. Considering the small number of subjects and the wide confidence intervals, she asked Dr. Link-Gelles to tell her statistically whether she was confident about the last statement—not about what everything else has shown, but what this 4-dose to boosters has shown that there is slower waning.

Dr. Link-Gelles emphasized that the issue is there was relatively limited follow-up time after the fourth dose because of when it was recommended. The number of cases who have been hospitalized after receipt of a fourth dose are fairly low, so she did not think that they could conclude that there is or is not waning of a fourth dose. The basic indication is that a little extra

protection is provided after a fourth versus a third dose. Certainly, there is extra protection after a distant third dose. Compared to the individuals who got 3 doses more than 120 days ago, there is a definite benefit of the fourth dose. But she thinks it is way too early to conclude one way or the other about waning of a fourth dose.

COVID-19 Vaccine Safety Update: Primary Series in Young Children and Booster Doses in Older Children and Adults

Tom Shimabukuro, MD, MPH, MBA (CDC/NCEZID) provided an update vaccine safety, with a focus on CDC vaccine safety monitoring systems, the safety of primary series mRNA COVID-19 vaccination in children ages 6 months–5 years, and the safety of mRNA COVID-19 booster vaccinations in people ≥5 years of age. As a reminder, one of the systems CDC uses is the Vaccine Adverse Event Reporting System (VAERS).[32] VAERS is the nation's spontaneous reporting or passive surveillance system that is comanaged by CDC and FDA. VAERS accepts reports from everyone regardless of the plausibility of the vaccine causing the event or the clinical seriousness of the event. Key strengths of VAERS are that it can rapidly detect potential safety problems and can detect rare adverse events (AE). The key limitation is that as typical with passive surveillance, cause and effect generally cannot be determined from VAERS data alone. v-safe[SM] is a voluntary CDC smartphone-based monitoring program for COVID-19 vaccine safety.[33] It uses text messaging and web surveys to check in with vaccine recipients after vaccination. It solicits participant reports on local injection site reactions, systemic reactions, and health impacts. Parents can register and complete surveys on behalf of their child. The Vaccine Safety Datalink (VSD) is CDC's EHR-based system for surveillance and research. It is a collaborative project between CDC and 9 integrated healthcare organizations. Rapid Cycle Analysis (RCA) is done in the VSD, which is near real-time sequential monitoring. The aims are to monitor the safety of COVID-19 vaccines weekly using prespecified outcomes of interest and to describe uptake of COVID-19 vaccines over time in the VSD population.

The first part of this presentation focused on the safety of primary series vaccination in children 6 months–5 years of age. Looking at US reports to VAERS after the primary series of Pfizer vaccine among children 6 months–4 years and of Moderna vaccines among children 6 months–5 years of age, over 890,000 doses of Pfizer vaccine and over 664,000 doses of Moderna vaccine had been administered during the analysis period. There were 496 reports after receipt of Pfizer vaccine and 521 reports after Moderna vaccine. The key takeaway is that 98% of these reports for both Pfizer and Moderna were classified as non-serious and there were no reports of myocarditis for either of these vaccines. The most frequent Medical Dictionary for Regulatory Activities (MedDRA) preferred terms[34] in VAERS reports following the primary series of Pfizer and Moderna vaccines were very similar and primarily systemic reactions.

In terms of v-safe[SM] enrollment among children following Pfizer and Moderna vaccination, about 890,000 primary series of Pfizer vaccine have been administered to children 6 month through ≤4 years of age and about 664,000 children 6 months through ≤5 years of age have received the primary series of Moderna. Enrollment in v-safe[SM] includes 14,725 children following Moderna vaccination and 8,541 children following Pfizer vaccine. In terms of health impacts reported in children aged 6 months to ≤2 years of in the 0 to 7 days following vaccination by dose, injection site reactions and systemic reactions are commonly reported for both Moderna and Pfizer vaccines. The reactogenicity profiles for Dose 1 are quite similar for Moderna and

[32] http://vaers.hhs.gov
[33] https://vsafe.cdc.gov
[34] https://www.meddra.org/how-to-use/basics/hierarchy

Pfizer vaccines. For Dose 2, there is higher reporting for injection site reactions, systemic reactions, and health impacts for Moderna that is not seen for Pfizer, for which there might be slightly lower reporting for Dose 2. Dose 3 data are not yet available for Pfizer, but this information will be available in the future as more time elapses. The patterns are similar for children 3–5 years of age, with injection and systemic reactions being fairly commonly reported after both vaccines. The Dose 1 reactogenicity profile for Moderna and Pfizer look quite similar, with some higher reporting for reactogenicity following Moderna but not for Pfizer.

Moving onto VSD data, these are the VSD COVID-19 vaccine RCA pre-specified surveillance outcomes and the settings in which they are monitored:

Prespecified outcomes	Settings
Acute disseminated encephalomyelitis	Emergency dept, Inpatient
Acute myocardial infarction – **First ever in EHR in ICD-10 era**	Emergency dept, Inpatient
Acute respiratory distress syndrome	Emergency dept, Inpatient
Anaphylaxis – **First in 7 days in EHR in ICD-10 era**	Emergency dept, Inpatient
Appendicitis	Emergency dept, Inpatient
Bell's palsy – **First ever in EHR in ICD-10 era**	Emergency dept, Inpatient, Outpatient
Cerebral venous sinus thrombosis	Emergency dept, Inpatient
Disseminated intravascular coagulation	Emergency dept, Inpatient
Encephalitis / myelitis / encephalomyelitis	Emergency dept, Inpatient
Guillain-Barré syndrome	Emergency dept, Inpatient
Immune thrombocytopenia	Emergency dept, Inpatient, Outpatient
Kawasaki disease	Emergency dept, Inpatient
Multisystem inflammatory syndrome in children/adults (MIS-C/MIS-A)	Emergency dept, Inpatient
Myocarditis / pericarditis – **First in 60 days in EHR in ICD-10 era**	Emergency dept, Inpatient
Narcolepsy / cataplexy	Emergency dept, Inpatient, Outpatient
Pulmonary embolism – **First ever in EHR in ICD-10 era**	Emergency dept, Inpatient
Seizures (including 0-7 days for youngest ages)	Emergency dept, Inpatient
Stroke, hemorrhagic	Emergency dept, Inpatient
Stroke, ischemic	Emergency dept, Inpatient
Thrombosis with thrombocytopenia syndrome – **First ever in EHR in ICD-10 era**	Emergency dept, Inpatient
Thrombotic thrombocytopenic purpura	Emergency dept, Inpatient
Transverse myelitis	Emergency dept, Inpatient
Venous thromboembolism – **First ever in EHR in ICD-10 era**	Emergency dept, Inpatient, Outpatient

Based on the analysis period through August 13, 2022 about 50,000 Pfizer primary series doses and about 52,000 Moderna doses have been administered, so just over 100,000 total primary series mRNA COVID-19 vaccinations in the age groups 6 months–4 years (Pfizer-BioNTech) and 6 months–5 years (Moderna). To date, there have been no statistical signals detected for any prespecified surveillance outcomes for either mRNA COVID-19 vaccine.

In summary of primary series vaccination in children ages 6 months–5 years of age, the initial safety findings of both mRNA COVID-19 vaccines are consistent with those observed in the clinical trials. Systemic and local reactions are commonly reported AEs. Vaccination errors also are being reported to VAERS. There have been no unexpected safety findings to date and there is no evidence of an increased risk for myocarditis following mRNA COVID-19 vaccination in children 6 months–5 years of age.

Moving to COVID-19 vaccine safety of booster doses 6 months–5 years of age, based on reports to VAERS following first and second mRNA COVID-19 booster vaccinations for all mRNA vaccines combined, a substantial number of first booster doses and a decent number of second booster doses have been administered. A smaller number of first booster doses have been administered for children 5–11 years of age. Regarding the most frequent MedDRA preferred terms in reports to VAERS following the first booster dose in children ages 5–11 years, the top 10 clinical outcomes are mainly systemic and local reactions. Among children ≥12 years of age, proportionately in these older age groups, there are not that many error reports than seen with the younger age groups. Many of the serious reports likely represent COVID-19

disease or signs and symptoms associated with COVID-19 disease. Vaccine breakthrough infection was reported in 618 out of 7,217 serious reports. Following the second booster dose in persons ≥50 years of age, there was a similar pattern of COVID-19 breakthrough disease and signs and symptoms likely associated with COVID-19 disease commonly reported for serious reports.

VAERS reporting rates of verified myocarditis per million mRNA COVID-19 first and second booster vaccinations in the 0–7 days post-vaccination, males 12–29 years of age had elevated reporting rates for myocarditis compared to background rates. This was not seen for males in ≥30 years of age or in any of the age groups for the females. There have not been any elevated reporting rates for males or females for second booster dose in individuals ≥50 years of age. This table compares VAERS reporting rates of verified myocarditis per 1 million mRNA COVID-19 vaccinations of Pfizer-BioNTech and Moderna combined in Days 0–7 post-vaccination:

	Dose 2 (primary series)		1st booster dose	
Age group	**Male**	**Female**	**Male**	**Female**
5–11 years	2.5	0.7	0.0	0.0
12–15 years	47.1	4.2	12.9	0.7
16–17 years	78.7	7.4	21.6	0.0
18–24 years	39.3	3.9	13.1	0.6
25–29 years	15.3	3.5	4.4	2.2
30–39 years	7.8	1.0	1.9	0.9
40–49 years	3.3	1.6	0.2	0.6
50–64 years	0.7	0.5	0.4	0.1
65+ years	0.3	0.5	0.7	0.2

The trend here is that the reporting rates for myocarditis per million doses administered in the Days 0–7 post-vaccination are consistently higher following Dose 2 compared to the first booster dose. They exceed background rates in the age groups of males 5–49 years of age and females from 12–29 years of age. A general trend here is that reporting rates for myocarditis appear to be higher for Dose 2 compared to the first booster dose. The caveat is that this is based on spontaneous reporting and is subject to reporting biases.

Looking at data on reactions and health impact events reported by v-safe[SM] participants 5–11 years of age at least once in Days 0–7after homologous Pfizer vaccination by dose, the take-home message is that reported reactogenicity (e.g., injection site, health impacts) tends to be fairly similar for booster doses compared to Dose 2 for Pfizer in this age group. Among adolescents 12–17 years of age, there are more self-reported local and systemic reactogenicity and health impacts are similar as in the younger children. Booster dose reactogenicity appears to be fairly similar to Dose 2 reactogenicity in this age group for Pfizer vaccination. Looking at v-safe[SM] participants ≥18 years of age, both Moderna and Pfizer are included because Moderna is available in this age group. For Moderna, there may be slightly more reporting of reactogenic events. The trend here is that the booster dose reactogenicity appears to be slightly lower than Dose 2 reactogenicity, but may be somewhat higher than Dose 1. Reported reactogenicity

following Moderna may be slightly higher than for Pfizer, but the same general pattern is observed for Pfizer as observed for Moderna. Booster dose reactogenicity may be slightly lower reporting for booster doses compared to Dose 2. In terms of individuals ≥50 years of age, second booster dose data were available. There was higher self-reported reactogenicity for Moderna compared to Pfizer. Dose 2 had the highest reported reactogenicity. For both vaccines there was a trend of decreasing reported reactogenicity for the first booster dose and the second booster dose after Dose 2 with a primary series.

In terms of safety in the VSD, about 94,000 booster doses have been administered among children 5–11 years of age, about 265,000 in adolescents 12–16 years of age, and about 2.2 million Moderna dose one booster doses and about 2.8 first booster doses for Pfizer among persons ≥18 years of age. In children 5–11 years of age for the first booster dose, there have been no statistical signals for any prespecified surveillance outcomes. In the 1–21-day risk interval after the first booster in people ≥12 years of age, there was a statistical signal for myocarditis and pericarditis in the combined Pfizer/Moderna grouping. These are individuals who received the Pfizer primary series and Pfizer first booster plus those who received the Moderna primary series and Moderna first booster. There were no signals for any other pre-specified outcomes.

A more detailed analysis was performed to assess the signal for myocarditis and pericarditis during the 0–7-day risk interval post-vaccine versus the comparison interval 22–42 days post-vaccination with the first booster. Among persons 12–15 and 16–17 years of age from Pfizer data, for males 12–15 years of age, there was a statistically significant elevated adjusted rate ratio of 18.5 (1.85 – 551.84). That translates into 61.7 (20.0 – 143.9) excess cases per million doses administered in the 0–7-day risk interval compared to the 22–42-day post-vaccination control comparison interval. For persons 16–17 years of age, the adjusted rate ratio was not estimable because there was an 8 to 0 split between the intervals, but it was statistically significant because the lower bound of the confidence interval was 2.03. For person 18–39 years of age for the combined doses and males with a primary series of Pfizer and a Pfizer booster, elevated adjusted rate ratios were observed that were statistically significant.

Regarding VSD incidence rates of verified myocarditis/pericarditis in the 0–7 days after Pfizer-BioNTech vaccination in people 5–39 years of age following Dose 2 and the first booster dose, Most Dose 2 incidence rates were higher than the first booster dose incidence rate. However, the case counts were small case counts and the confidence intervals were wide, so there was not much statistical difference. However, there were exceptions. In persons 16–17 years of age for males and females, a higher incidence rate was seem following the first booster Dose 2 for males at 188 compared to 137 and for females at 36.4 compared to 9.3. However, the counts were relatively small and the confidence intervals were wide. Those estimates of the incidence rates were not statistically different. Regarding the Moderna incidence rates, data were available for persons 18–29 and 30–39 years of age, the incidence rates were higher for males than for females.

In summary of mRNA COVID-19 vaccine safety of booster doses in people ≥5 years of age, the safety findings were generally consistent with those observed for primary series vaccination. The evidence suggests an increased risk for myocarditis following the first booster dose. However, myocarditis is a rare event following mRNA COVID-19 booster vaccine. CDC has verified 131 myocarditis case reports to VAERS in people ≥5 years of age after 123 million mRNA COVID-19 booster vaccinations. The risk is primarily observed in adolescent and young adult males. There has been no statistical signal for myocarditis to date in children 5–11 years

of age following the first booster dose. In VAERS data, the reporting rates of myocarditis are lower following the first booster dose versus Dose 2 of the primary series. As a reminder, the reporting rates are higher for Dose two compared to Dose 1 of the primary series. In VSD analyses, myocarditis and pericarditis incidence following the first booster dose and Dose 2 of the primary series were similar, though case counts were small and confidence intervals around point estimates were wide.

CDC monitors the following pregnancy and reproductive health outcomes/topics in multiple systems including v-safe[SM], the v-safe[SM] pregnancy registry, VSD, VAERS, and the Clinical Immunization Safety Assessment Project (CISA):

- Miscarriage
- Stillbirth
- Preterm birth
- Birth defects
- Pregnancy complications
- Pregnancy outcomes
- Infant outcomes
- Neonatal outcomes
- Maternal adverse events and maternal conditions
- Menstrual irregularities
- Post-menopausal bleeding
- Safety of booster doses
- SARS-CoV-2 infection after vaccination
- Co-administration with other vaccines (e.g., influenza)

For the outcomes studied, there have been no concerning findings for pregnancy and reproductive health outcomes following COVID-19 vaccination. Data on COVID-19 vaccine safety during pregnancy and reproductive health outcomes following vaccination will be presented during a future ACIP meeting.

Discussion Summary

Dr. Long asked whether there is any information on the interval between first and second dose in those who got myocarditis or did not and/or any information on the interval between Dose 2 and the booster in the populations assessed and those who had myocarditis or not. This is so much more common after the second dose, perhaps there is some kind of existing underlying issue that predisposes certain people to myopericarditis. There generally is a longer interval between Dose 2 and the first booster, so it would be interesting to know by interval who had myopericarditis and whether the duration of the interval had any effect. Noting that about 50% of people in this age range had natural COVID-19 infection, with or with or without vaccine on board, she wondered whether there is any information on whether people who got myocarditis at the booster stage had a recent natural COVID-19 infection.

Dr. Shimabukuro indicated that in the VSD, there was little variability in the interval between first and second doses. Because the schedule was followed closely, there is not enough variability there to draw any conclusions. There also is little variability in the interval between Dose 2 and the first booster dose. The case counts from myocarditis are still small, so there is not enough information on intervals to draw any firm conclusions about that at this time. The best data come from Canada where, because of differences in the recommendations in the provinces, there is substantial variability between the first and second doses of the primary series. Canada has data showing that the longer the interval between the doses, the lower the risk for myocarditis. While there is some evidence that extending the interval may reduce the risk of myocarditis, there is not enough variability in the US for a pretty rare outcome to be able to draw any

conclusions. However, it is worth looking into further. In terms of whether people who got myocarditis at the booster stage previously had natural COVID-19 infection, not every infection is captured in EHRs. Therefore, they do not always know for certain whether cases may have been infected. There are not sufficient data now to draw any conclusions about whether having natural infection and then receiving a booster may put people at higher risk for myocarditis than those who have not had natural infection who get a booster.

Dr. Klein added that the myocarditis/pericarditis case definition for the VSD excludes individuals who had AIDS or COVID-19 infection 60 days prior to myocarditis.

Dr. Poehling recalled that before the approval in this age group, there was a lot of discussion about the concern that the vials look very similar. She encouraged manufacturers to move forward to develop more distinct vials to reduce the likelihood of vaccine errors.

Dr. Daley asked Dr. Shimabukuro to put the vaccines errors in VAERS in the context of other vaccines in terms of whether this is partially a function of the new vaccine or it reflects different doses in different ages, and whether he knew about SAEs among those who experienced vaccine administration errors.

Dr. Shimabukuro indicated that there is evidence that when a new vaccine comes to market or there is a new recommendation for an age group, there are increases in reports of errors to VAERS during the initial uptake period while providers are getting use to the products. That tends to decrease over time, so this may be the reason for the current errors being reported. The problem also may be magnified by recommendations coming rapid fire, and then perhaps the issues regarding packaging. The overwhelming majority of these error reports do not report an adverse health event. When there are AEs associated with these error reports, they tend to be similar to what is seen in general. Looking at the data, there were no SAEs associated with one of the error reports among the younger children. For children 5–11 years of age, 4 of the events were classified as serious. Although they met the regulatory definition of serious, they did not appear to be clinically serious. The one concern might be that if a child gets an adult dose of an mRNA vaccine whether that will put them at increased risk for myocarditis. However, they have not seen a case of this occurring.

Public Comment

The floor was opened for public comment during the September 1, 2022 ACIP meeting at 12:20 PM ET. All speakers submitted a request in advance of the meeting and the final list of public commenters was determined via a lottery. Everyone was reminded that the ACIP appreciates diverse viewpoints that are respectful in nature and issue-focused. The comments made during the meeting are included in this document. Members of the public also were invited to submit written public comments to ACIP through the Federal eRulemaking Portal under Docket No. CDC-2022-00103. Visit http://www.regulations.gov for access to the docket or to submit comments or read background documents and comments received.

Elizabeth Fashing
Parent of Two Children

My name is Elizabeth Fashing. I am a parent to 1 children, one 9 and one just recently turned 5. I am asking our committee today to please not delay consideration of the booster availability to children under 12. Our whole family did get COVID-19 this past April, and 3 of us were fully vaccinated, but unfortunately my 4-year-old had to suffer the consequences of getting COVID

without the benefit of vaccine protection and he was the sickest among us. He had gastrointestinal issues and a high fever for a week, and I do not think that it was fair for him to have to suffer from this disease without the benefit of vaccine protection because of the delay in approving the vaccine for the under 5 population. And he is just now going to be fully vaccinated in about a week, because we just started the Pfizer series on him a couple of months ago as soon as it became available to his age group. I'm not a medical professional. I'm not a research scientist. I understand that there are special liability issues and considerations for studying medications in young children, but those cautions cannot be to the detriment of getting children access to life-saving vaccines. There is going to be another pandemic, and it could very well be more deadly to children, and we cannot delay them care due to over-cautions. So, I would like to ask that the administration of medical and vaccine trials be revamped to ensure that our most vulnerable are included from the beginning in trials. Thank you.

Dorit Reiss, JD
Professor of Law
University of California
Hastings College of the Law

My name is Dorit Reiss. I am a Professor of Law at the University of California Hastings College of the Law. Thank you again for the opportunity to comment and for your thorough, careful work. I have 4 points to make. First, I'm concerned about the process for bringing the BA.5/BA.5 boosters forward. FDA's VRBPAC committee comes with very little data, and no human trials, and has not been reconvened, and there is still no direct human data. I think something like this needs more transparency to open deliberation, and I am grateful to ACIP for giving such a thorough deliberation of the data and knowing where it stands, but it would have been nice to have it earlier. I realize we have no other mitigation measures in place, that hundreds are dying every day, and there is real pressure to act, and it's exactly at this time that expert agencies need to act to maintain confidence and cutting costs does not help. If lack of transparency decreases usage, where is the benefit? I also understand that ACIP needs to respond to what it has for a suggested recommendation, help with clarity, and to address all ages, which is good, but the process is concerning. Second, I've heard from colleagues in the medical field that there is substantial confusion as to when people should give boosters, including the new boosters, after a recent infection. Guidance from ACIP on the timing of boosters after reinfection would be really, really helpful in relation to the new one. Third, I want to remind everyone that Dr. Shimabukuro set out for us in detail the vaccines we currently use in the United States. Though Pfizer, Moderna, and Novavax have an extremely strong safety record, they're not risk-free. But, the risks are small and, by and large, those thinking to deter others from vaccinating have to resort to misleading tactics like misrepresenting VAERS reports, misrepresenting non-casual reports from the trial data, and attributing death and harm to vaccine with no evidence or against the evidence. We could wish the vaccines were more effective against infection, but they're safe and they prevent hospitalization and death as again described here. The extent of misinformation contained about the vaccine led to many unnecessary deaths and harm and is built on a tower of lies. And finally, I would like to ask again that the hardworking and dedicated ACIP staff put up the topic for an emergency meeting when you announce the emergency meeting. I think it will help people decide whether to request to comment and help them tailor comments before the meeting and not in align, like September emergency meeting. Aligning boosters would not be that much additional work. I know the staff has worked really hard over the last few years.

Patricia Neuenschwander, MSN, RN, CPCP
Self

I've been a nurse for over 28 years and have given public comment several times to this committee, but this one takes the cake. Let me start with the absurdity that you are asking for public comments before you present the data being used to evaluate the safety or efficacy of these products. The fact that this committee is meeting today to consider recommending products that have not gone through any human trials, you have gone from junk science to no science. The FDA granted Emergency Use Authorization yesterday without convening with the VRBPAC committee to provide any expert opinion. It's absurd! Are you really going to use data extrapolated from different, unnamed experimental products or mouse studies to recommend these products to millions of Americans? You consider this rigorous science? Absurd! The study using the extrapolated Pfizer product, not the product you're here for today, had 600 adults age 55 or older, yet authorization is given for 12-year-olds and older? Absurd! After 1 month—1 month using a rapidly waning product, the immune response of the participants who receive a new bivalent vaccine were [unclear]. What immune response data? No data on better protection from infection, transmission, hospitalization, or death? Just better antibody production? Which I will remind the committee has not been shown in randomized clinical studies to mean better protection. It's absurd! The FDA says the safety data accumulated from the other experimental products is relevant to these products because, "they are manufactured using the same process." So, any product that uses the same manufacturing process is deemed automatically safe? Absurd! Use of these products will require unvaccinated people to take 2 doses of the old vaccine with the original strain that's been long gone before being eligible to take the new boosters. It's absurd! The FDA says the booster you receive does not need to be from the same manufacturer as your primary vaccination or previous booster. Where is the clinical trial? It's absurd! Providers should offer all vaccines for which a person is eligible for with this experimental product without any clinical trials? Absurd! If recommended, the new booster, by the way, fourth or fifth dose if you're keeping score, with no long-term safety will be the CDC's definition of up-to-date. This will impact millions of people's abilities to maintain employment, attend school, go to college, or participate in any activity that has the requirement of being "fully vaccinated!" It's absurd! You have the opportunity to do the ethical, morally right thing today. Help your providers blindly trust you. The data is not there, and you know it. Do not return us to unethical human experimentation. Put an end to this absurdity and require rigorous, large-scale clinical trials before you put your name on these products. Or you can choose to look the other way and potentially put millions of people in grave danger of harm. Please do your job.

Mary Mahoney
Advocate for Older Adults

Good afternoon. My name is Mary Mahoney and I am speaking on behalf of myself and my family. I want to start by thanking this committee for your ongoing commitment to ensuring Americans have access to safe and effective protections against this devastating virus. As COVID-19 continues to evolve, I am encouraged to see how the science continues to evolve along with it. When the vaccines were initially approved and made available, each member of my family was eager to receive our dose. The vaccine has provided us with the protection we were desperately needing in order to return to so many meaningful aspects of our lives that had been on hold such as going to school, attending church, and being around the older adults that we love. When the booster shots were approved or recommended, we were just as eager to follow the guidance of this committee and our physicians in adding as much needed layers of protection. We now find ourselves once again looking to this advisory committee and the CDC for clear and straightforward guidance on who should receive the newly approved bivalent

booster doses and when. As my children head back to school, and we are all heading back into another flu and pneumonia season, we are eager to gain access to the best protection available to us to ensure a strong immunity as possible against COVID-19. I urge this committee to provide clear guidance on this, on the use of the new bivalent booster shots and that every eligible American understands how and when to take this next step in protecting ourselves and our families. Thank you for your time.

Meghan Rapp
Self

Good afternoon. My name is Megan Rapp. I speak today to enthusiastically endorse boosters as a tool in preventing the spread of COVID and protecting against severe disease. I'd like to thank you for the work you are doing to make bivalent boosters available to people 12-plus. I also speak today on behalf of my 1 1/2-year-old daughter, Caroline, because Caroline is really too little to speak, though she can say "all done." She is also too little to follow the CDC's guidance on personal responsibility around COVID mitigation, such as assessing risk, wearing a mask, getting therapeutics, or accessing boosters. I speak today to call on you and other federal agencies like the FDA to immediately do everything in your power to stop leaving children like Caroline behind with regards to COVID. Let's speak to the issue of vaccine uptake for under 5. Parents like me were told under 5 vaccines would be coming in February, then March, then April, etc. I kept asking CDC and FDA leadership, "When would my daughter be able to get a COVID vaccine, too?" "Soon," you said. Children are vulnerable and this takes more time. I wonder why, for the most vulnerable, the agencies tasked with keeping my child safe instead allowed delays which left her more vulnerable and for longer. While we waited for that under 5 vaccine rollout for Caroline, she and every single other toddler in her class got COVID. This artificially-created delay in taking more time for young children's boosters will have the same impact. Kids will get COVID. Parents will decide that kids don't need the booster since they just had COVID. Children get left behind on the next variant booster when the new strain crops up and the loop continues. Have we learned nothing from the primary vaccine rollout for children? Delays don't magically increase vaccine update. I speak to urge you to create a plan for authorizing bivalent boosters for kids under 12 now, based on the same criteria for adults, similar to the way the annual flu vaccines are authorized. If you have legitimate reasons not to do this, we parents deserve to know. I deserve to know if Caroline will finally be able to go to a Christmas service this year or meet Santa in person. Please do better for Caroline and children who can't assess personal risk and who are too little to wear a mask. Take decisive actions now to bring timelines together. Young children need access to boosters in order to be, as Caroline would say, "all done" with COVID, too. Thank you.

Julie Boom, MD
Texas Children's Hospital
Baylor College of Medicine

Thank you. The last two and a half years have been a sobering reminder of the discomfort and devastation that infectious diseases can cause in our lives. Despite the relentless work of the medical and scientific communities to develop SARS COVID vaccines, we have lost over 1,040,000 lives to COVID-19. In addition, over 200,000 US children have lost 1 or both parents to COVID-19. Gratefully, COVID-19 vaccines have dramatically decreased hospitalization rates and deaths since their implementation. Despite strong vaccine effectiveness and outstanding uptake by persons over 65 years of age, COVID-19 vaccine uptake has been suboptimal, especially amongst children. From a recent summary of CDC data shared by the American Academy of Pediatrics, 60% of teens 12 and older have received 2 doses of COVID-19 vaccine

doses, while only 30% of children 5 to 11 years of age have received 2 doses. Sadly only 7% of children 6 months to 5 years have received 1 or more COVID-19 vaccines. Even though children have experienced much lower hospitalization and death rates compared to adults, over 1,700 children have died from COVID-19 since the beginning of the pandemic. As you examine the evidence to recommend bivalent COVID-19 boosters for persons 12 years and up, I urge you to consider one of the most important factors contributing to low vaccine uptake—vaccine hesitancy. Unfortunately, vaccine hesitancy is not only impacting COVID-19 vaccine, but also routine childhood vaccines. As evidenced by wastewater surveillance, polio myelitis has found its way back into United States and has caused a preventable case of paralysis in an unvaccinated adult in New York. Even though many thought a series pandemic would diminish anti-vaccine sentiment, the opposite has occurred. Espousing personal liberty and individualism, many have spread information on social media preying on worried parents, many who are just trying to do the best thing for their child. Beyond Polio, we are now faced with the spread of monkeypox. Sadly, the first US death from monkeypox occurred in my County, Harris County. At Texas Children's Hospital, we are again working quickly and diligently to partner with our local and state health departments to ensure we can assist with vaccination of persons at risk or who have been exposed to monkeypox. As a general pediatrician with 27 years of experience and Director of the Immunization Project at Texas Children's Hospital, I know that vaccines are the best way to protect persons from contagious diseases. We must do everything we can to eliminate vaccine-preventable diseases in our communities and globally, which includes not only recommending and administering vaccines, but clearly communicating vaccine safety and benefit information and to address misinformation and hesitancy. I urge you to give these factors your every consideration today. Thank you.

Katherine Falk
Parent and Vaccine Advocate
Oakland, California

I want to again thank the committee for all their work. I've commented before. We are in our third year with this pandemic, and while I'm excited about a new and hopefully better booster, I'm also somewhat trepidatious—not about any risk from the vaccine itself. I'll be getting it along with my whole family as soon as we can, but about the public reception and willingness to take advantage of it. In Alameda County where I live, 90.4% of us got 1 shot, 83.3% got 2, but only 56.4% got a booster. This is all ages. Combine this with the lack of real push for mask wearing anymore, and no wonder this season could have been referred to as hot zone summer. We need better communication and clear messaging from our public officials and the CDC, and for the booster, carefully managed expectations. The other thing I want to bring up is VAERS, because I'm seeing it brought up a lot online. Anti-vaxxers are hard at work as usual doing their utmost worst to scare people into skipping boosters for themselves and their children, and they are using VAERS as one of their tools. I've started describing VAERS to people as a tip line. I think that's a good analogy since a tip line is an important part of any law enforcement or public safety system, even if some of the tips themselves are not helpful or even accurate. But I think the VAERS website could use some refreshing and the communication about what it is and isn't needs to be clear and reiterated at every level. Thank you.

Abraham Alahmad, PhD
Associate Professor in Pharmacology
Texas Tech University Health Sciences Center

Good afternoon. My name is Abraham Alahmad. I'm an Associate Professor in Pharmacology Texas Tech University Health Sciences Center. First, I would like to thank the committee and staff for outstanding effort to put forth in this meeting and the past and during this pandemic, ensuring that lifesaving vaccines are recommended in a transparent manner to the public. My only comment and concern today that I share with the committee is the rather confusing information about booster and vaccination rate among children below the age of 12, which had been lagging in uptake as we're heading to the full winter season and time of the year. In the past year, have been shortly worsening when it comes to the most cases, hospitalizations, and deaths. These vaccines are very safe. They still hold on against Omicron variant. They have been quite a [unclear] here based on the number of COVID-19 admissions that appeared in the panhandle. This is possibly even more accented in rural areas. I have witnessed here [unclear]. To give you numbers, we only have yet to reach 50% of the population in the panhandle who have received 2 doses. We only have 20% with 1 booster dose. But [unclear] when it comes to cases, stressed healthcare system, [unclear] in the pandemic. It is unlikely due to vaccine shortages. In fact [inaudible] have been very successful in [unclear]. If the committee and CDC can improve the communication outreach to the public with clear, accessible information across the board, but also [unclear] behind vaccination rates,
as the vaccine [unclear] have been very successful in seeing that and [unclear] this preparation it will be clearly appreciated. Thank you.

Booster Doses of Moderna COVID-19 Vaccines in Adults, Adolescents, & Children

Jacqueline Miller, MD (Moderna) presented data on Omicron booster-containing doses of Moderna COVID-19 vaccines in adults, adolescents, and children. For the Fall US booster campaign, Moderna is producing a 50 µg bivalent vaccine containing 25 µg of mRNA encoding the original strain by protein sequence and 25 µg encoding the sequence for the spike protein of BA.4/BA.5. The indication is for a single 50 µg booster administered at least 2 months after either completion of the primary series or receipt of a booster dose of any authorized or approved monovalent COVID-19 vaccine.

Although mRNA-1273 protects against variants of concern, especially in the case of severe disease, the purpose of adding mRNA encoding variant sequences[35, 36] to the booster doses is to improve the immunogenicity against Omicron lineages, which have remained dominant for the past 8 months; induce a broader cross-neutralization response to other potential variants of concern; and extend the duration of protection. Data consistently show the ability of these bivalent variant vaccines to address these goals.

As the virus has continued to evolve, Moderna has evaluated 3 monovalent and 4 bivalent vaccine candidates designed to address variants of concern. More than 7,000 adults have received a booster dose of one of these vaccine candidates. Critical data are primarily available for the Beta (mRNA-1273.211) and Omicron BA.1 (mRNA-1273.214) vaccines. The BA.4/BA.5 bivalent (mRNA-1273.222) vaccine was in a clinical trial that completed enrollment the previous week. Data are anticipated to be available at the end of the year.

[35] FDA Briefing Document for June 26, 2022 VRBPAC Meeting
[36] WHO Interim Statement on the Composition of Current COVID-19 Vaccines (June 17, 2022)

To review the available clinical data for the bivalent SARS-CoV-2 vaccines targeting variants of concern, currently available clinical data includes safety, immunogenicity, and 6-month antibodies persistence data from 300 participants who received the Beta-containing bivalent vaccines. Median follow up in these subjects was 245 days after the third dose booster. After the fourth dose, safety and immunogenicity data are available in 437 participants who received the Omicron BA.1-containing vaccine who were followed for a median of 43 days. These clinical data form the basis of Moderna's submission for bivalent boosters. There were also pending data from the 512 participants who were recently vaccinated with the Omicron BA.4/BA.5-containing vaccine. This trial completed enrollments the previous week and the data are expected later this year.[37]

The demographic data from the study of the BA.1 bivalent vaccine were compared to the mRNA-1273 fourth dose control group. Third doses in these groups were given approximately 8 months after completion of the primary series and the fourth dose was administered approximately 4.5 months after the third. About one quarter of the participants had evidence of prior SARS-CoV-2 infection at the pre-booster time point. Comparing the fourth dose BA.1 Omicron-containing bivalent booster to post-dose 2 with mRNA-1273 post-dose 3 mRNA-1273, the solicited local adverse reactions included injection site pain, erythema, swelling, and axillary swelling and tenderness. The reported rates after Dose 2, 3, and 4 were at least similar or lower than mRNA-1273 second and third doses in the bivalent Omicron BA.1-containing fourth dose vaccine. Importantly, there were no Grade 4 events reported after the BA.1 booster.

Looking at the same 3 groups in terms of the systemic solicited symptoms, both the frequency and severity of the solicited systemic reactions were observed to be lower after a bivalent fourth dose booster and after mRNA-1273 administered as a second or third dose. Once again, no Grade 4 reactions were reported after the BA.1-containing booster. In terms unsolicited AEs that were reported within 28 days after vaccination, rates of each category of AE were similar between the mRNA-1273 and BA.1 bivalent vaccine group. Among the 3 SAEs reported, cases of prostate cancer and traumatic fracture were reported in the BA.1 group and a single case of spinal osteoarthritis was reported in the mRNA-1273 group. None of these SAEs were considered by the investigators to be vaccine-related, and there were no cases of myo- or pericarditis reported in either group.

Regarding the immunogenicity analyses that were used in this study to infer effectiveness, the primary objectives of the study were to demonstrate the superiority of the BA.1-containing vaccine over mRNA-1273 in terms of neutralizing antibody responses to BA.1 and to demonstrate the non-inferiority of the bivalent vaccine to mRNA-1273 in terms of the original strain neutralizing antibody titers. For the BA.1 superiority hypotheses, there were 2 criteria to assess success. The first was that the BA.1 GMT ratio had to have a 97.5% confidence interval lower bound which exceeded 1.0. The actual ratio was 1.75 with a lower bound of 1.49, so this criterion was met. The second criterion was that the lower bound of the 97.5 confidence interval around the group difference seroresponse rate would exceed minus 10%. This was also met with a point estimate of 1.5% and a lower bound of minus 1.1%. In terms of the non-inferiority hypotheses to the immune responses against the original strain, the lower bound of the 97.5% confidence interval had to be greater than 0.67. This was met with a point estimate of 1.22 and a lower bound of 1.08. For the group difference in seroresponse rate, the lower bound had to be

[37] Chalkias et al. Research Square 2022, doi: 10.21203/rs.3.rs-1555201/v1; in press *Nat Med*; Chalkias et al. medRxiv 2022, doi: 10.1101/2022.06.24.22276703; in press *New Engl J Med*

greater than -10%. This was also met as the response rate in both groups for 100%. Therefore, the study met the primary objective to demonstrate superiority in terms of BA.1 antibody titers and non-inferiority in terms of original strain neutralizing antibody titers.

Importantly, the primary hypotheses were evaluated in subjects who had no evidence of prior infection. It is known that, at this moment in time, many vaccinated individuals have experienced SARS-CoV-2 infection. They comprised about a quarter of the participants in this particular study. In terms of the GMTs and the fold rises to BA.1 in all participants, regardless of previous SARS-CoV-2 infection, both the mRNA-1273 groups and the Omicron BA.1-containing bivalent vaccine, even the subjects with evidence of prior infection were observed to have substantially higher pre-vaccination titers derived benefits from the BA.1 bivalent vaccine, with a 4-fold rise in post-vaccination titers to Omicron BA.1. This exceeds the 2.5-fold rise observed in the mRNA-1273 group and led to a GMC ratio of 1.9 and a lower bound of the 95% confidence interval of 1.50.

In terms of improved antibody titers the Omicron sublineages, the major objective is developing the bivalent vaccines. Regarding the antibody titers to BA.1 and the original strain, stratified by age group 18 to <65 years and greater than or equal to ≥65 years of age, post-vaccination, the BA.1 bivalent vaccine was consistently immunogenic to both the original and BA.1 strain in subjects ≥65 years of age who are at increased risk for the severe complications of COVID-19. The observed antibody titers against the BA.1 variant of concern were higher with the bivalent vaccines compared to mRNA-1273, regardless of age stratum. Antibody titers to the original and BA.1 strain also were analyzed in subjects stratified by age. With both strains evaluated, the BA.1 bivalent vaccine was consistently immunogenic across age groups. The induction of cross-protection to other Omicron sublineages was another major objective for the development of the bivalent booster vaccine.

The ability of antibody titers induced by BA.1 bivalent vaccine and mRNA-1273 to cross-neutralize BA.4/BA.5 was analyzed, stratified by evidence of prior infection. Both vaccines demonstrated an increase in GMT to BA.4/BA.5, which showed evidence of cross-neutralization. The higher antibody titers induced with a BA.1 booster offers a reason to anticipate that the BA.4/BA.5 bivalent vaccine will lead to improved antibody titers. The antibody titers also were stratified to BA.4/BA.5 by evidence of prior infection and age group. As observed with the BA.1 antibodies, the bivalent vaccine consistently induced numerically higher titers against BA.4/BA.5 across age strata, which indicates that those adults ≥65 years of age will also benefit from cross-protection conferred by the bivalent vaccine. Bivalent vaccines also were also developed to induce better cross-protection to strains which are not included in the vaccine. Looking at antibody titers and relative GMC ratios in terms of binding antibodies for the BA.1 bivalent vaccine compared to mRNA-1273 at 28 days post-vaccination, for all variants studies (Alpha, Beta, Delta, and Gamma), binding antibody titers were significantly higher with the BA.1 bivalent vaccine as compared to mRNA-1273. Recognizing that neutralizing antibody data also are important with this vaccine, Moderna is in the process of generating those data and will share them when available.

Data also were analyzed with respect to antibody persistence, which is another important consideration for the bivalent vaccine. Data from the individuals who received the Beta-containing variant vaccines were compared to mRNA-1273 comparing a third dose to a third dose at Day 29 and then Day 181 or 6 months after vaccination. For the original strains with D614G and the Beta, Omicron, and Delta variants, the GMT ratio for the Beta strain was consistently higher than 1.0. Importantly, the GMC ratios increased even further to the original

strains, Beta and Omicron BA.1, at 6 months after vaccination, which suggests that the bivalent boosters may improve longer term cross-neutralizing antibody durability.

Moving to specific data which have been generated with the BA.4/BA.5 bivalent vaccine, Dr. Miller presented the non-clinical data in mice that supported Moderna's EUA submissions.[38] The BA.4/5 bivalent vaccine was evaluated in a murine animal model expressing a human ACE2 receptor. These mice previously were primed with mRNA-1273 and then were boosted approximately 31 weeks later with the BA.4/BA.5-containing bivalent vaccine, BA.1 bivalent vaccine, and mRNA 1273 with a sham vaccination. The two bivalent vaccines both induced statistically significantly higher antibody titers against the Omicron sublineages as compared to mRNA-1273. These mice were then challenged with 10^4 platforming units of a BA.5 strain 4 weeks after the booster dose was given. As Moderna has consistently observed, results from its murine challenge studies correlated with observations in human clinical trials. These data are supportive of the immunogenicity of the BA.4/BA.5-containing bivalent vaccine.

Moderna is generating data with booster doses in the pediatric population. Its submissions of booster data generated in children 12–17 and 6–11 years of age are currently ongoing to the FDA. The original pediatric studies were extended to evaluate booster studies of mRNA-1273 in these populations. Similar to adults where the booster is administered at half the dose of the primary series, adolescents received a booster of 50 μg after a 100 μg primary series. Children 6–11 years of age received a 25 μg booster after a primary series of 50 μg. Moderna expects to complete these submissions by mid-September. In the youngest age stratum of children 6 months–5 years of age, Moderna is evaluating a primary series with a bivalent BA.1-containing vaccines and booster doses with both mRNA-1273 and the BA.1 bivalent vaccine. Results from this trial should be available by the end of the year. They also are exploring ways to evaluate primary series and boosters with the BA.4/BA.5 vaccine.

In summary, the bivalent booster vaccines have been generally well-tolerated in individuals ≥18 years of age. Local and systemic reactogenicity are generally similar to or lower than that observed with Dose 2 and Dose 3 of mRNA-1273. No new safety concerns have been observed in Moderna's booster vaccine studies. The prespecified immunogenicity objectives, which align with FDA guidance for the licensure of bivalent booster vaccines, were met for superiority to BA.1 and non-inferiority to the original strain. There were significantly higher antibody titers to BA.4/BA.5 with the BA.1 bivalent vaccine, and binding antibody titers were also higher than mRNA-1273 against more distant variants of concerns. Higher immune responses also were observed in individuals ≥65 years of age who are at the highest risk for the complications of severe COVID-19 disease. Moderna's Beta-containing bivalent vaccines demonstrated improved durability of neutralizing antibodies compared to mRNA-1273 at 6 months after vaccination. Preclinical data for the BA.4/BA.5-containing bivalent vaccine in mice is supportive of VE. This is being verified in an ongoing clinical trial. The bivalent BA.4/BA.5 vaccine will be presented in a 2.5 mL vial. It is intended to have a 0.5 mL administration for adults ≥18 years of age. As Moderna is reducing the number of doses in the multi-dose vial, they are working toward the future looking for single syringe presentation.

[38] Scheaffer et al, manuscript under preparation

Discussion Summary

Dr. Brook noted that in the presentation, Dr. Miller showed viral particles in the respiratory, upper respiratory, and lungs of the mice. In the clinical studies for the other age groups and with no booster, he asked whether they measured viral particles in the respiratory tract and if this was going to be considered a correlate of VE in adults.

Dr. Miller indicated that the investigators conduct challenge studies in the mouse model prior to initiating the first clinical trials with mRNA-1273 and saw evidence that the vaccine is capable of inducing antibodies that can neutralize virus and protect against infection in the various areas of the respiratory tract. Ultimately, the best data come from human clinical trials. As they switched from the BA.1 variant vaccine that Moderna initially prepared to discuss at the VRBPAC meeting in June over the summer to the BA.4/BA.5-containing vaccine, they have been able to manufacture doses and conduct the clinical trials in the mice more quickly than they have been able to execute the human clinical trial. Data further supporting the BA.4/BA.5 will come from the clinical trial for which enrollment just completed, which they will present later this year. The Beta-containing variants and the BA.1-containing variant vaccines both performed in a similar way, demonstrating superior antibody titers to the variant of concern as compared to mRNA-1273 and noninferiority to the original strain. Moderna believes that the consistency of the clinical results are the basis on which they are licensing or authorizing the vaccine.

Dr. Edwards, Moderna, added that he has led the research for SARS-CoV-2 vaccines for the last 2.5 years. In terms of the animal studies performed over the course of the development of the original vaccine and in the evaluation of the bivalent vaccines is what was represented as a common measurement that Moderna performs in animal studies. That includes mouse, hamster, and non-human primate (NHP) studies. It is a good measurement to indicate the level of protection that is provided for the different vaccine regimens. Unfortunately, it is not something that can be performed clinically due to constraints around certain types of sampling that they could perform within clinical studies. That is why they have relied on either efficacy measurements or post-clinical observations in order to establish efficacy.

Dr. Cineas asked whether there are data on breakthrough clinical cases in the BA.1 group versus mRNA-1273 or whether there has not been enough follow-up time for those data.

Dr. Miller indicated that they do not yet have those data for the BA.4/BA.5-containing vaccine. Because they have the median of 43 days of follow-up after BA.1, they do have those data. There are disease incidence rates in the mRNA-1273 groups versus the BA.1-containing vaccine groups that were followed and compared. They were followed both for subjects with no evidence of prior infection and subjects with evidence of prior infection. In the BA.1 bivalent group, the incidence rate was 2.5%. In the mRNA-1273 group, the rate was 2.4%.

Referring to Slide 18, Ms. Bahta recalled that Dr. Miller mentioned “significantly higher. To her, it appeared that the confidence intervals were overlapping.

Dr. Miller indicated that the GMRs were shown in the top bar immediately below the name of the variant of concern (VOC), followed by a 95% confidence interval. Those 95% confidence intervals are all above the value of 1.0. These are the between group comparisons that were performed in an exploratory fashion to look at comparisons between groups. They do need to be interpreted conservatively because the multiplicity adjustments are made for the primary endpoints of the trial. Moderna feels that these data are indicative that they may expect to see

higher neutralizing antibody titers as they have seen for the Beta-containing vaccine at 28 days after vaccination and higher GMRs and tighter confidence intervals after 6 months.

Dr. Sanchez emphasized that these vaccines are needed to cover other barriers. Referring to Slide 25, he asked whether the studies planned in children 6 months–5 years of age also will be with the BA.1 vaccine.

Dr. Miller confirmed that those studies are also with the BA.1 vaccine, but they also have been requested to conduct clinical trial work with the BA.4/BA.5 vaccine. They are currently in the process of figuring out the best way to do that in the pediatric population. The strategy all along has been to generate data as quickly as possible to enable implementation of a vaccination program before the Fall/Winter cold and influenza season by bracketing investigations of the bivalent vaccine in adults, particularly in the oldest adults ≥65, and then in the youngest children 6 months–5 years of age to provide a view of the antibody titers at both of the extremes of age. Moderna is extending the Kaiser effectiveness study that they have talked about a number of times with ACIP to look at the BA.4/B.5. That protocol is being extended down to 6 months of age into booster doses for the pediatric population. That may be the best evidence with which they will be able to demonstrate in the future.

Dr. Sanchez expressed concern about the data presented in humans on the BA.1 vaccine. While it certainly looks very promising and he understood the constant shift of variants, the studies with BA.4/BA.5 are ongoing in humans. He wondered whether that was premature.

Dr. Miller reiterated that the clinical data Moderna prepared for the Fall campaign was assuming predominance of the BA.1 strain for Omicron. That is why they have analyze the BA.4/BA.5 neutralizing capability of the BA.1 vaccine, because the 2 Omicron sublineages are obviously related. There is about a 4-mutation difference between them as opposed to about a 35-mutation difference between the original strain and the BA.1 Omicron vaccine. They will continue to generate the BA.4/BA.5-containing data. Moderna anticipates that just as the Beta-containing variants and the BA.1-containing various bivalent data were consistent with each other, both in terms of safety and the patterns of immunogenicity, there will be improved immunogenicity to VOCs both for the sequence in the vaccine but also across other variants of concern as compared to the original strain. In the safety data and the reducing reactogenicity profile that they see after subsequent doses have been consistent between both of the bivalent formulations study. She thinks continuing to study BA.4/BA.5 is the best they can do to be able to be ready for the Fall cold and winter influenza season with a vaccine that best matches the current circulating strain. The data look excellent for the BA.1 variant.

Dr. Poehling observed that in clinical studies, the longest follow-up at 245 days would be with the Beta variant bivalent vaccine. One of the major questions regards the extent to which waning is seen. She asked whether clinical data are available on the waning with the Beta variant over the 245 days.

Dr. Miller said the reason Moderna has data from the Beta variants is because the Beta variant emerged in Fall of 2020, so they have had longer to follow those subjects than with the BA.1-containing variant, which emerged around Thanksgiving of 2021. In all cases, the antibody titers with the Beta bivalent-containing vaccine are numerically higher than what is seen with an mRNA-1273 vaccine. The distance between the 2 actually increases at the 6-month time point and Moderna believes that there is a biologic basis for this. That is actually why they advocated fairly strongly for the bivalent composition. When the mRNA in a bivalent formulation is delivered to the cell, the mRNA for the original strain spike sequence and for whatever bivalent-

containing sequences are delivered to the cell, which means that the ribosomes are translating in the same cell strands of both the original and the variant of concerns, these amino acid chains still naturally assemble into trimers. Moderna has been working with the University of Washington and has been able to demonstrate in a publication that they are in the process of submitting, that heterotrimers are actually formed. What that means is that unlike with the original 1273 where the original 3-spike sequence is the only one available, they have sequences from both the original strain and the variant of concerns. This actually leads to more open confirmation and exposure of additional antigens. They believe that t is exposure to those additional antigens that leads to the improved antibody persistence, not only against the variant of concern but against the original strain and other variants as well.

Dr. Kotton noted that about the 3% of the US population is estimated to be immunocompromised. She asked whether they were included in any of these cohorts and if there are further data or plans for studying that population, which has been exceptionally vulnerable to COVID-19.

Dr. Miller reported that they have conducted a separate Moderna-sponsored clinical trial in patients with solid organ transplants and also supported a collaborator in a clinical trial investigating booster doses in patients with solid tumors and hematologic cancers. In both cases, they have been able to observe that the vaccine is immunogenic and lead to additional immune responses. In the cancer population, they studied 3 doses. In the transplant population, they studied up to 4 doses. Those data are actually going to form part of the basis of Moderna's supplemental BLA (sBLA) for booster dose full licensure as opposed to EUA authorization. They are actively working on that submission now in order by the end of the year to prepare for the 2023 season.

Dr. Kotton indicated that having access to those data would help to better inform patients as to what the best plan would be for them.

Dr. Miller indicated that the data in cancer patients already has been published and they will share that publication with the committee. The data from the solid organ transplant patients also can be shared with the committee.

Ms. McNally indicated that as the Consumer Representative for ACIP, she wanted to try to distill down an issue for the public in terms of the extent, if any, to which Moderna's research and development process differed in the creation of the bivalent vaccine from the original vaccine.

Dr. Miller indicated that the original vaccine was part of a clinical development program that included the Phase 1, 2, and 3 clinical trials. Moderna views the bivalent vaccines as extensions of the SARS-CoV-2 virus much like the influenza vaccine is changed every year as the influenza virus evolves. Instead of a full efficacy trial each year as is done with influenza vaccines, they are measuring immune responses and inferring effectiveness, because they have observed that immune responses correlate with protection against disease. Those are data that Moderna has published in conjunction with the NIH recently in *Science*. Moving forward, as they have done with influenza vaccines, they will continue to evaluate the clinical data, compare those immune responses, and show the consistency to the original clinical trial.

Dr. Loehr recognized that these are animal studies for the BA.4/BA.5 variants and agreed that in the future, there are likely to be more variants that should be treated in the same way as influenza variants if there is evidence that the pattern seems to flow smoothly and new variants

can be used every year. After thinking about it, he was comfortable even though there are only animal data and there are no human data supporting the BA.4/BA.5 variants booster.

Dr. Duchin, NACCHO, recalled Dr. Miller stating that the mouse study data accurately predicted what is known now through human data for the mRNA-1273 variant and requested that she say more about that to help people understand the relevance of the mouse data and how it is has been a useful and accurate predictor of what is seen in humans.

Dr. Miller said the value of this particular murine model is that the animals express the human ACE2 receptor. The reason that is important is that the ACE2 receptor in humans is actually the port of entry into human cells by this virus. By using an animal that is expressing that same protein, it is possible to see the impact of the biology the vaccine has on the animal that would be susceptible to infection in the same way a human would be.

Dr. Edwards, Moderna, added that Moderna has 2.5 years of experience with these animal models and how they do correlate to human immune responses. They have seen very good correlation between effective doses and effective bivalent vaccines between mice, NHP, and humans to this point. One particularly relevant point is that in these animal studies, they measure the impact of variants on neutralizing titers. F-or example, a BA.1 neutralizing titer in a mouse vaccinated with 1273 is many-fold reduced versus the original strain. They see the same thing recapitulated when assessing human sera. Both from an immunogenicity standpoint and an impact of variants standpoint, these animal models have translated very well.

Dr. Sanchez asked about studies in pregnancy and, to get an idea of how the vaccine is formulated, whether the 2 different mRNA strains are encoding the different spike protein and it is just 1 strand that codes both and if the ultimate protein crosses the placenta.

Dr. Miller reported that Moderna is conducting a safety follow-up study in pregnant women. There is a registry in which the study is currently ongoing through which approximately 800 pregnancies overall will be examined. In terms of the regarding mRNA sequences, there are 2 distinct mRNA sequences. The first sequence is the original sequence that was in mRNA-1273. It encodes for the full-length spike protein from the original Wuhan strain. The second sequence includes the sequence from a BA.4/BA.5. It is important to note that the spike protein sequence is identical from BA.4/BA.5, which is why if is referred to it as a BA.4/5 sequence. Those 2 are individual sequences on lipid nanoparticles. More than 1 lipid nanoparticle is able to enter the cell, which is how both mRNA sequences are able to be translated inside the same cell. In terms of transfer across the placenta, Moderna has conducted developmental and reproductive toxicology studies with mRNA-1273 as well as other vaccines in its pipeline and they do not see that the pregnancy or fetus is impacted by vaccination.

Dr. Edwards, Moderna, added that the mRNAs that are included are co-formulated in the same lipid nanoparticles and then delivered to the same cells. Further, they also introduced to both mRNAs the 2 proline mutations that stabilize the conformation of the spike protein into the prefusion conformation. In terms of pregnancy, they have evidence from animal studies that there is placental transfer of both IgG and to a limited degree IgA. That also includes maternal transfer via breast milk. In terms of the protein that is generated by the mRNA and whether that crosses the placenta, Moderna has done developmental and reproductive toxicity studies.

Dr. Miller added that this protein has been engineered to be cell surface expressed, so it is not a protein that is secreted in the same way that a subunit protein might be injected and flowing freely. It is mRNA that is entering the cells, and then the protein itself is cell surface expressed. It is not secreted protein.

Referring to Slide 7, Dr. Lee noted that the interval between the third and the fourth dose looks like the average is 4.5 months, but the lower range is around 3 months. The lower bound of approval is 2 months from the last prior dose or the last dose and he wondered whether there are any safety data for that 2- to 3-month window.

Dr. Miller indicated that Moderna is generating data with respect to the 2-month window in collaboration with the National Institutes of Health (NIH). The data available now comes from previous collaborations with the NIH in the 3-month window. The 2-month window was requested of them based on the desire to make boosters available prior to potential increases in infection rates.

Doran Fink, FDA, confirmed that this was correct. There are no clinical trial data or significant real-world data with a booster dose at a 2-month interval. However, there are data with booster dose intervals ranging from 3 through 6, 7, and 8 months or longer for vaccine reactogenicity that do not seem to show a difference in the level of reactogenicity compared to the interval. One specific concern about the interval is the risk of vaccine-associated myocarditis that has been observed most prominently following the second primary series dose and also a first booster dose in certain populations. They do not have data one way or another that would suggest that a risk of myocarditis would be higher or lower following an interval of 2 months as opposed to 3 months. Frankly, any clinical trials of the size that FDA is able to look at for considering the authorization of these booster doses would not be adequately powered to look at the myocarditis anyway. They do have experience, as the committee knows, with the risk of myocarditis relative to the primary series interval between first and second doses. Those data indicate that the risk when the primary series doses are separated by at least 2 months appears to be lower than when the primary series doses are administered closer together and there is no further reduced risk with interval longer than 2 months. Based on the totality of evidence that FDA has, and also considering the timeliness of making this booster dose available to individuals who may have received their last vaccination more recently, those considerations underlie FDA's decision to authorize these bivalent boosters with a minimum interval of at least 2 months. He stressed that FDA understands that most people who would be eligible for these second boosters will have received their last COVID-19 vaccination well beyond 2 months previously. Therefore, there is a relatively small fraction of individuals who might be considering getting one of these bivalent boosters at an interval of close to 2 months.

Dr. Lee recalled that a question was raised during the last ACIP meeting and earlier in this meeting regarding the VAERS AE reporting regarding potential administration errors and the concern that the committee has had with regard to labeling. She requested further information about single dose syringes in terms of whether there are any plans to modify or make the labeling clearer to minimize the risk of administration errors going forward.

Dr. Miller indicated that it is the intent to get to product-specific presentation for each individual presentation.

Dr. Mustafa, Moderna, added that it is in Moderna's forecast to move to a specific presentation by age. As they move out of the pandemic configuration, they have this as part of their long-range strategic planning for having specific use presentations.

Dr. Lee emphasized that it would be helpful for ACIP to hear a clear plan from both manufacturers regarding the timing for when changes would occur to the labeling. There are many administration errors that seem disproportionate to what has been seen with other vaccines or with the adult vaccines. She feels strongly that anything that can be done to support implementation by providers, public health, and pharmacists would be extremely helpful in the delivery of these vaccines and getting them to the children who need them.

Pfizer-BioNTech COVID-19 Omicron-Modified Bivalent Vaccine

Kena Swanson, PhD (Pfizer) presented immunogenicity and safety data today for Pfizer-BioNTech's bivalent Omicron-modified variant vaccine. She emphasized that throughout the pandemic, SARS-CoV-2 variant epidemiology has been rapidly changing. In particular, there has been the emergence of the more antigenically distinct Omicron variants of concerns with demonstrated increased transmissibility and evidence for partial immune escape. With that in mind, the focus of this discussion was on the bivalent vaccines that include an Omicron BA.4/BA.5 component to address COVID-19 due not only to the Omicron sublineages, but also due to potential subsequent variants of concern.

Over the past 2-plus years, Pfizer-BioNTech has gained substantial clinical experience with variant modifying vaccines across different age groups. This was first evaluated early in the pandemic when the Beta variant of concern was of particular interest when it initially emerged. Pfizer-BioNTech evaluated a monovalent form of the Beta variant-modified vaccine in individuals 18–55 years of age, both as a primary series and as a third and fourth dose booster. More recently, they have subsequently evaluated the Omicron BA.1 variant-modified vaccine both as a monovalent formulation in adults 18–55 years of age as primary series and fourth dose booster and a bivalent formulation in adults ≥55 years of age. Pfizer also has an ongoing study of the bivalent BA.1 vaccine in adults 18–55 years of age. Throughout the clinical evaluation of each of these vaccines, the pre-clinical data also generated with these same formulations have reliably predicted responses in humans. That is across the Omicron BA.1 both monovalent and bivalent data. In terms of the focus of the day's discussion being Omicron BA.4/BA.5 bivalent vaccine, Pfizer has an ongoing clinical study evaluating this vaccine in individuals 12–55 years of age and >55 years of age. Dr. Swanson described some of the pre-clinical data that has shown some evidence which it is anticipated will be translated to observations in humans as in the prior pre-clinical evaluation of variant-modified vaccines.

In terms of immunogenicity data with Pfizer-BioNTech Omicron BA.1-containing variant vaccines, C4591031 Substudy D included approximately 1,420 participants 18–55 years of age in which a primary titer series of the monovalent Omicron BA.1-containing vaccine was evaluated at a 30 µg dose level. These participants had no evidence of prior SARS-CoV-2 infection. Looking at serum neutralizing titers 1 month after the second dose of a primary series of the monovalent Omicron BA.1 vaccine compared to the USA Washington 2020 and Delta strains, a very Omicron-specific neutralizing response was observed with a monovalent Omicron BA.1 vaccine in naïve individuals. Looking at pre-clinical data, the same monovalent Omicron BA.1-containing vaccine was evaluated at the same dose regimen at Day 0 and Day 21 in naïve mice. This was at a dose level of 0.5 µg. Again, there was a very Omicron-specific response. In addition, neutralization was evaluated against not only the reference strain, but

also Beta and Delta. The original ancestral strain spike combined with the Omicron BA.1 spike elicits a more balanced immune response across the different variants of concerns, including the reference strain in this preclinical study. This provides some evidence to support that bivalent vaccine will provide a better and broader immune response compared to a monovalent approach in a naïve background.

Study C4591031 Substudy E evaluated the bivalent Omicron BA.1-containing vaccine among approximately 1920 participants >55 years of age who received either the bivalent Omicron BA.1-containing vaccine administered as a 30 µg fourth dose or the or the prototype vaccine administered as a 30 µg fourth dose. Dose 4 was administered at a median of 6.3 months from Dose 3. One goal was to understand the Omicron BA.1 neutralizing antibody response as part of the evaluation of the superiority criteria that needed to be met in order to demonstrate a substantial improvement in the Omicron BA.1 neutralizing response with the bivalent vaccine compared to the prototype. In order to meet superiority criteria, the GMR of the neutralizing response in the bivalent vaccine had to be >1.0 to meet simple superiority criteria for the lower bound of the 95% confidence interval. Superiority was met with a lower bound of 1.17 and a GMR of 1.56. Looking at the Omicron BA.1 neutralization response but instead of GMR now evaluating seroresponse rate, the seroresponse noninferiority criterion that needed to be met was a lower bound of the 95% confidence interval for the percentage difference in response rates between the bivalent vaccine group and the prototype vaccine group being > -5. The lower bound of the confidence intervals for the bivalent vaccine was > -5, which had a lower bound of 4.0. Therefore, noninferiority was met for the seroresponse rates.

Now looking at before vaccination and 1-month post-dose, a substantial increase was observed in Omicron BA.1 neutralization activity in the bivalent vaccine-containing group compared to the prototype. The geometric mean fold rise (GMFR) from before vaccination and 1-month post-fourth dose was 9.12 for the bivalent vaccine compared to 5.8 for the prototype. Moving beyond the Omicron BA.1 neutralizing response also was important in the bivalent composition, which also includes the original ancestral sites to demonstrate noninferiority of the reference strain neutralizing response, used a validated SARS-CoV-2 neutralization assay. In this case for noninferiority criteria, the lower bound the 95% confidence intervals GMR between the bivalent and the prototype vaccine was required to be >0.67. The GMR was 0.99 with a lower bound of 0.82, so the noninferiority criterion was met.

To summarize the safety data, the reactogenicity profile of the bivalent Omicron BA.1-containing vaccines given as a fourth dose was compared to the prototype vaccine given as a fourth dose in this same study in participants >55 years of age. The reactogenicity profile was very similar between the variant-modified vaccine compared to the prototype vaccine. There also are data showing similar trends in the original data variants modified vaccine studies and with the monovalent Omicron BA.1-containing vaccines. Over time, there has been the emergence of the BA.4 variant and now the dominance of the BA.5 variant. These 2 sublineages include the same spike antigen. The neutralization activity was evaluated with the prototype vaccine group preceding the fourth dose and the Omicron BA.1-containing vaccines at the fourth dose, which showed a nice increase in the Omicron neutralizing response. In this subset analysis, neutralization of BA.4/5 was observed. However, this was reduced compared to the BA.1 variant, which was why Pfizer subsequently went on to evaluate a BA.4/BA.5-containing bivalent vaccine. Looking at the booster settings of the Omicron BA.1 monovalent and bivalent vaccines in mice that have received 2 prior doses of the original BNT162 V2 vaccines, similar trends were observed. There were improved Omicron neutralizing responses in the Omicron-containing vaccine groups and reduced neutralization activity against the BA.4/BA.5 variants. This is a nice translation of preclinical to clinical data.

In terms of the BA.4/BA.5 monovalent and bivalent vaccine compositions that were evaluated as a booster dose, again looking at a third dose in mice that previously received 2 doses of the BNT162b2 vaccine, the neutralization data were 7 days post-third dose. This analysis evaluated neutralization activity against the ancestral strain, which in this case was Wuhan 21, compared to the Omicron sublineages BA.1, BA.2, BA.2.12.1, and BA.4/BA.55. The key takeaway for this analysis was that there was a more balanced immune response against the Omicron sublineages with the 4/5 containing vaccines, including substantial increases in the matched strains of BA.4/BA.5 compared to the Omicron BA.1 monovalent and the prototype vaccine. Following this initial evaluation in mice, a follow-on study was performed to confirm these results. This confirmatory study showed that Omicron BA.4/BA.5 monovalent and bivalent boosters in mice substantially increased Omicron neutralization responses to all omicron variants, including BA.4/BA.5.

To summarize the Omicron BA.4/BA.5-modified variant vaccine, Pfizer-BioNTech has shown that the reactogenicity profile of the various vaccines that have been evaluated clinically (Beta, Omicron BA.1) are similar overall to the prototype BNT162b2 vaccine. Alpha and Delta also were evaluated in prior clinical studies. In each of these studies, the reactogenicity profile has been similar to the prototype vaccine, BNT162b2. The evaluation of the Omicron BA.1-containing vaccines, both monovalent and bivalent, demonstrated superiority for the Omicron BA.1 GMR, non-inferiority for the seroresponse, and non-inferiority for the reference strain GMR. Across the evaluation of variant-modified vaccines to date, pre-clinical immunogenicity data have reliably predicted observations in humans. Including the latest Omicron BA.4/BA.5 modified variant of vaccine booster in mice improved neutralizing responses across Omicron sublineages. Collectively, similar trends are anticipated in the ongoing BA.4/BA.5 bivalent clinical study. An EUA has been granted for use of the bivalent Omicron BA.4/BA.5 variant-modified vaccine at the 30 µg dose level as a booster dose for eligible populations ≥12 years of age. There will be further clinical evaluation of a BA.4/BA.5 bivalent vaccine in pediatric populations.

Discussion Summary

Ms. McNally said that as the ACIP's Consumer Representative, she wanted to ask Dr. Swanson the same question shed asked Dr. Miller regarding the extent to which Pfizer's research and development process differed in the creation of this vaccine from the original vaccine.

Dr. Swanson responded that it is important to note that from the first modified vaccine that Pfizer evaluated, the Beta monovalent, through the current Omicron BA.4/BA.5, the only change has been in the variant-specific sequence changes in the mRNA itself. All of the processes for making the mRNA drug substance and formulating it into the lipid nanoparticle follow the exact process as has been used throughout generation of the COVID-19 vaccine, the BNT162b2.

Dr. Poehling asked whether Pfizer has any long-term data among its variant studies in humans on what is known about the persistence or the waning of the immune response.

Dr. Swanson indicated that Pfizer has on-going follow-up to assess the duration of the antibody response in their clinical studies. They are still following out to a later time point of 6 months and beyond. The data they currently have available on persistence would be in a subset of participants who received 3 doses of the BNT162b2 prototype vaccine. They evaluated activity against the reference strains and the Omicron BA.1 variant of concern at the time. This was before BA.4/BA.5 emerged. Similar antibody decay rates are seen between the reference strain

and Omicron BA.1 at least out to 5 months after Dose 3. Pfizer is continuing to follow the overall kinetics with more subjects and more time.

Dr. Kotton asked what work is underway for immunocompromised patients and what information might inform decision-making for this vulnerable population.

Dr. Swanson indicated that Pfizer is conducting a study on immune compromised individuals. To date, the enrollment rate has not been as expected. While vaccination in this population is generally recommended, there are no data at this point specific to that study in the immunocompromised group.

Dr. Kitchin added that with broad recommendations in most countries for immunocompromised persons to be vaccinated in the face of the threat of SARS-CoV-2, it still has been difficult to enroll individuals into clinical trials. Therefore, they do not have data yet in that population. They do not currently have any ongoing studies of administration of the bivalent BA.4/BA.5 vaccine in immunocompromised individuals.

Dr. Kotton emphasized that this makes it challenging for ACIP to think about how to best couch its recommendations, so she encouraged studies in this highly vulnerable population.

Dr. Sanchez said his comments would be similar for Pfizer as for Moderna in terms of the packaging of this vaccine and studies on pregnancy. Referring to Slide 17, he asked about the monovalent versus bivalent presentation of the variant vaccine in terms of immunogenicity, potentially generating lower antibody neutralization titers, and the potential for more rapid decay.

Dr. Swanson indicated that in the clinical study among individuals >55 years of age, monovalent Omicron BA.1 versus bivalent Omicron BA.1 was evaluated. There was a trend for slightly higher Omicron BA.1 neutralizing responses in the monovalent vaccine group compared to the bivalent group. While she did not think it could be speculated as to whether that difference was clinically meaningful, similar trends are being seen preclinically, with slightly higher strain matched responses with monovalent versus bivalent presentation with the BA.1-containing and the BA.4/5-containing vaccines. She referred back to the primary series immunogenicity data that showed clear benefit of having that bivalent composition. The goal is to ensure that they are solving for the current circulating variants, but also anticipating potential future variants by applying that bivalent approach. In term of whether there is a statistically significant decrease in titers when the monovalent and BA.4/5 are combined, Dr. Swanson said did not think so and recalled that the confidence intervals were overlapping. In terms of pregnancy, they have an ongoing study within pregnant women. They have run into similar challenges with enrollment, given that the vaccine was made available for this group.

Dr. Kitchin added that the data analyses are still ongoing in the study conducted in pregnant women, which is following the pregnant women and their infants. That study originated with the original vaccine, but Pfizer will be generating data from that study despite the difficulties in enrollment.

Dr. Daley asked what Pfizer's specific plans are concerning presentation of any pediatric products to minimize dose administration errors and what the timeline would be for those plans.

Dr. Swanson recalled that there also was a similar question regarding the current rollout of the BA.4/BA.5 for persons ≥12 years of age and older.

Referring to Slide 38 from the back-up slides, Dr. Levine indicated that the bivalent Omicron-containing vaccine will retain the gray cap as per the original vaccine. The reason for this is that the Omicron-containing bivalent vaccine is essentially the same drug product and contains the same formulation as the original vaccine, albeit it contains the different strain much like the influenza vaccine. The gray cap is a visual indication that the product is the same dose, requires the same storage conditions, and has the same handling requirements as the original cap presentation. There is differentiation between the original primary series vaccine for the original vaccine and the BA-4/BA.5-containing bivalent vaccines through the label.

Dr. Lee pointed out that when they get to the Clinical Considerations, it would be clearer why they were asking these questions. The dilution/no dilution, colors of the cap, accuracy of expiration data, et cetera have be somewhat overwhelming. It was not clear whether the µg dosing was 30/30 or 15/15 for the Omicron components. Having the information on dosing would be incredibly helpful.

Dr. Kitchin or Levine indicated that the labeling on expiration date has been changed. While this has been flagged as a potential mislabeling, that was not the case. Pfizer was labeling the product conservatively with the information that was available at the time to try and make sure that they have the product available to patients as soon as possible. And as soon as they got the information to update the label and the approval that allowed for that update, that was done so as quickly as possible.

Dr. Deeks (NACI) noted that with respect to the various studies, it looked like the monovalent Beta and Omicron went down to age 18 and the bivalent studies went to >55 years of age and requested clarification on whether the bivalent BA.4/BA.5 had not been studied in anyone 12–17 years of age as the age group for whom there is an authorization.

Referring to Slide 4, Dr. Swanson indicated that it was correct that the bivalent Omicron BA.1 data presented during this session and that are currently available are in individuals >55 years of age. Within that same study, they have enrolled and will be generating additional data on participants 18–55 years of age with the BA.1 bivalent-containing vaccine. For the BA.4/5, they have stratified the clinical studies to ensure they have a sufficient numbers of individuals 12–17 years of age, 18–55 years of age, and those >55 years of age for receiving the BA.4/5 bivalent as a fourth dose booster.

Dr. Anderson (PIDS) expressed gratitude to both manufacturers for what sounded like efforts to move clinical trials of the bivalent vaccine into children of all ages, the data from which everyone anxiously awaits.

Dr. Long emphasized that there are not many data upon which to make confident decisions. For the bivalent BA.4/5 vaccine, there are no human antibody data even over a very short period of time. While they had heard that many doses have been purported to lengthen the antibody response, they had not seen sufficient data on adding something new such as BA.4/5 and in whom this vaccine might be used. She asked for clarification about whether they were seeing all of the human clinical data on BA.4/5.

Dr. Swanson indicated that they have extensive data on the prototype vaccine for which they have seen very consistent responses through the third dose against both the ancestral strain and different variants of concern, including Omicron. The BA.4/5 bivalent study is ongoing, so they do not yet have specific clinical data for that bivalent vaccine composition. However, the

Omicron lineage has been the most antigenically distance variant of concern to date for SARS-CoV-2 throughout the SARS-CoV-2 pandemic. When a much more antigenically distinct spike is combined with the original ancestral spike, the more distant there is in the following of the diversity of antigen-specific memory B cells over time. The anticipation would be that combining something so distant would result in some chance of improving upon not only memory B cells recognizing epitopes that are shared between the ancestral and the BA.4/5, but also potentially specific to BA.4/5—so a broadening of the protective immunity. They will generate the data. That is within the realm across different disease areas, including influenza, where that could be an anticipation in the data that they will see. They have seen in the preclinical studies a maturation of the neutralizing antibody response. In terms of the initial data with a third dose booster of the BA.4/5, the data they had to include in this presentation were 7 days post-Dose 3. They also have gone on to look at 1 month with the BA.1-containing bivalent vaccine and are now generating data for the BA.4/5 bivalent. They do see nice continual increases in the neutralizing antibody response against either the BA.1 or BA.4/5 over time, so she thinks there is some opportunity that that they may see some expansion in the breadth of protection.

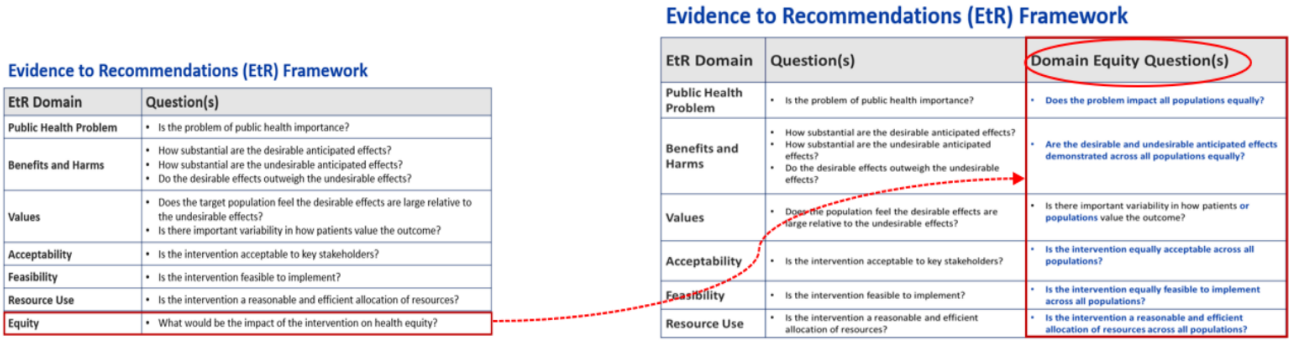
Dr. Long asked whether there was anticipation of when they would be asking for authorization for boosters of the bivalent in children 5–11 years of age.

Dr. Gruber indicated that Pfizer anticipates providing data from the existing study, the BNT162b2 booster data in children 5–11 years of age, about cross-reactive immune response against BA.1 and BA.4/5 and anticipate that they would file for submission sometime in the first part of October. As Dr. Swanson said, they are working with their FDA partners to identify the best way to move forward into the younger age groups with appropriate trials and getting data as quickly as possible so that they could further extend the potential for the bivalent BA.4/5 and original containing vaccines as soon as possible.

EtR Framework: Bivalent COVID-19 Vaccine Booster Doses

Sara Oliver, MD, MSPH (CDC/NCIRD) provided updates to the EtR Framework on bivalent COVID-19 vaccine booster doses. As a reminder, the EtR Framework is a structure for describing the totality of the information considered in moving from evidence to ACIP recommendations. While they have walked through numerous EtRs to date, it has been difficult to answer a single question to highlight the impact of the intervention on health equity. For the last several months, a subset of the COVID-19 ACIP WG engaged in a critical review of the Equity Domain and gathered extensive input and feedback through consultation with health equity experts and other partners, such as the National Medical Association (NMA) and the Office of Minority Health and Health Equity (OMHHE). Throughout this process, it has become clear that consideration of equity is integral to every aspect of the production, study, authorization, and recommendation of COVID-19 vaccines. The need for a systematic reliable, and action-oriented review of evidence toward enhanced equity also was made clear, but structural problems require structural solutions. The adjustment of the structure is required for meaningful change, and an adjustment of the EtR framework to enable systematic, reliable review of evidence toward actionable recommendations to enhance equity may help facilitate meaningful change. Therefore, at least for this presentation, the WG proposed a change to the equity domain. Now as a consideration across each other EtR domain, the WG recommends the systematic, reliable inclusion of data to speak to the equity considerations in each domain to demonstrate the data and encourage actions needed to enhance equity as relevant to each domain.

Therefore, for this presentation, the voting question on equity was removed and attention to equity was enhanced across all of the other domains as shown here:



Evidence to Recommendations (EtR) Framework

EtR Domain	Question(s)
Public Health Problem	• Is the problem of public health importance?
Benefits and Harms	• How substantial are the desirable anticipated effects? • How substantial are the undesirable anticipated effects? • Do the desirable effects outweigh the undesirable effects?
Values	• Does the target population feel the desirable effects are large relative to the undesirable effects? • Is there important variability in how patients value the outcome?
Acceptability	• Is the intervention acceptable to key stakeholders?
Feasibility	• Is the intervention feasible to implement?
Resource Use	• Is the intervention a reasonable and efficient allocation of resources?
Equity	• What would be the impact of the intervention on health equity?

Evidence to Recommendations (EtR) Framework

EtR Domain	Question(s)	Domain Equity Question(s)
Public Health Problem	• Is the problem of public health importance?	• Does the problem impact all populations equally?
Benefits and Harms	• How substantial are the desirable anticipated effects? • How substantial are the undesirable anticipated effects? • Do the desirable effects outweigh the undesirable effects?	• Are the desirable and undesirable anticipated effects demonstrated across all populations equally?
Values	• Does the population feel the desirable effects are large relative to the undesirable effects?	• Is there important variability in how patients or populations value the outcome?
Acceptability	• Is the intervention acceptable to key stakeholders?	• Is the intervention equally acceptable across all populations?
Feasibility	• Is the intervention feasible to implement?	• Is the intervention equally feasible to implement across all populations?
Resource Use	• Is the intervention a reasonable and efficient allocation of resources?	• Is the intervention a reasonable and efficient allocation of resources across all populations?

This will be an iterative process that will require feedback from ACIP and others and the process will continue for future EtRs.

Given that EUAs were issued for the bivalent Pfizer vaccine in those ≥12 years of age and the bivalent Moderna vaccine for those ≥18 years of age and there would be votes for these specific vaccines and age groups, the question for this EtR Framework analysis was, "Does ACIP support the use of updated (bivalent) COVID-19 vaccine booster doses for those individual in age groups already currently recommended to receive a COVID-19 vaccine booster?" The current recommendations are that people 5–49 years of age are recommended for 3 doses and those ≥50 years of age are recommended for 4 doses. The overall future proposed recommendation would for individuals recommended for a primary series and a bivalent booster dose, regardless of the previous booster doses given. Age and vaccines for this will be as authorized by FDA and recommended by ACIP and CDC. This is not necessarily the recommendation for this meeting, but is where it is envisioned that the future of the program would be going. While they would hear from Dr. Hill later in the day regarding the details for the schedule, Dr. Oliver wanted to orient everyone to the broader discussion they hoped to have during this session.

Beginning with the first EtR domain of the Public Health problem, over 94 million COVID-19 cases had been reported to CDC through August 29, 2022.[39] Hospitalization rates peaked for all age groups during last winter's Omicron wave. Since April 2022, hospitalization rates in older age groups have increased relative to the other age groups.[40] In June, unvaccinated adults had 4.6 times higher COVID-associated hospitalization rates compared to those who were vaccinated with at least 1 booster.[41] Also in June, unvaccinated people ≥5 years of age had 8 times higher COVID-associated death rates compared to those with at least 1 booster dose.[42] In June 2022, people ≥50 years of age with 2 booster doses had a 14 times lower risk of dying from COVID-19 compared to unvaccinated individuals and a 3 times lower risk of dying from COVID-19 than people with 1 booster dose.[43]

[39] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#trends_dailycases Accessed August 30, 2022
[40] COVID-NET; https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html Accessed August 26, 2022
[41] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination Accessed August 3, 2022
[42] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status Accessed August 24, 2022
[43] https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccinbooine-status Accessed August 24, 2022

Moving to vaccination data and trends in the cumulative percentage of the US population vaccinated with a primary series by age group, persons ≥65 years of age had the highest coverage at 92%. Coverage decreased as age decreased, with the lowest coverage among children 5–11 years at 3%. Individuals 6–5 years of age are also recommended to receive a vaccine but were not included in these data. In terms of coverage for first booster doses by age group, the highest coverage was among those ≥65 years of age at 65% and the lowest coverage was among children 5–11 years of age at 13%. Looking at trends in coverage for second booster doses by age group, the highest coverage was among persons ≥65 years of age, but only 41% overall had completed a second booster.[44]

In terms of the equity question for this domain regarding whether the problem impacts all populations equally, the case rate was higher among the large metro classification and the death rate was higher in the rural population in the recent Omicron surge.[45] Looking at weekly cases by race and ethnicity throughout the pandemic, cases have been higher among racial and ethnic minority populations.[46] In terms of COVID-19 hospitalizations by race and ethnicity, hospitalizations were higher among racial and ethnic minority populations, although this was more pronounced earlier in the pandemic.[47] For COVID-19-associated deaths, mortality rates have been higher throughout the pandemic among racial and ethnic minority populations and were more pronounced earlier in the pandemic. Recent mortality rates show less evidence of these disparities.[48]

In summary of the public health domain, over 94 million COVID-19 cases have been reported in the US as of August 2022. Since April 2022, hospitalization rates in older age groups have increased relative to other age groups. In addition, during Omicron predominance in June 2022, unvaccinated adults ≥18 years of age 4.6 times higher hospitalization rates compared with those who received at least 1 booster, and unvaccinated individuals ≥5 years of age and older had an 8t times higher death rate. Vaccination rates are much higher among older adults relative to other ages groups. People of racial and ethnic minority groups have been disproportionately burdened by COVID-19 illness, hospitalization, and death. Therefore, the WG felt that COVID-19 is of public health importance—especially among populations recommended to receive a booster.

Turning to the domain of benefits and harms and beginning with a summary of the available clinical trial data, there are data from the Moderna bivalent booster clinical trial with BA.1 and Pfizer BioNTech bivalent booster clinical trial data with BA.1 (–BNT162b2+BNT162b2 Omi: 30 µg bivalent: 15 µg ancestral + 15 µg BA.1). There are no international data yet available for bivalent boosters and there are no clinical trial data for bivalent boosters with BA.4/5 available to date.

[44] CDC Immunization Data Lake. Accessed 8/22/22; First and second boosters do not include Texas for all ages or Idaho for ages <18

[45] CDC COVID Data Tracker. Trends in COVID-19 Cases and Deaths in the United States, by County-level Population Factors. https://covid.cdc.gov/covid-data-tracker/#pop-factors_7daynewcases Accessed August 25, 2022

[46] CDC COVID Data Tracker. COVID-19 Weekly Cases and Deaths per 100,000 Population by Age, Race/Ethnicity, and Sex. https://covid.cdc.gov/covid-data-tracker/#demographicsovertime Accessed August 25, 2022

47 CDC COVID Data Tracker. COVID-NET Laboratory-confirmed COVID-19 hospitalizations. https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network Accessed August 25, 2022

[48] Source: https://data.cdc.gov/NCHS/Provisional-Weekly-Deaths-by-Region-Race-Age/tpcp-uiv5 (National Vital Statistics System provisional death certificate data)

In the Moderna Phase 2/3 trial, persons were given a 50 µg bivalent boost of mRNA-1273.214 that included 25 µg of the ancestral Wuhan-Hu-1 strain and 25 µg of the Omicron B.1.1.529 spike as a second booster vaccine (P205 Part G) compared to 50 µg mRNA-1273 (ancestral) as a second booster vaccine (P205 Part F). The trial participants were adults ≥18 years of age. A total of 437 participants received a bivalent booster and 377 received an mRNA-1273 ancestral booster. The dosing interval from the first booster to the bivalent booster was 136 days and from first booster to second ancestral booster was 134 days. The median follow up was 43 to 57 days. Immunogenicity was assessed by the antibody response on Day 29 after the study vaccination. Based on the GMRs, comparing the antibody response in participants that received the bivalent booster to those who received the monovalent ancestral vaccine, the bivalent vaccine met superiority criteria for both Omicron and ancestral SARS-CoV-2 antibodies. The superiority criteria also were met in participants with or without evidence of infection on Day 29, with the highest GMTs observed in those with prior infection.[49]

Local reactogenicity with the Moderna bivalent booster (mRNA-1273.214) as a 4th dose was similar to the second and third doses of the ancestral Moderna vaccine. The most commonly reported Grade 3 local reaction was redness. Systemic adverse reactions with the bivalent vaccine were lower than systemic reactions from second and third doses and the ancestral vaccine, and the most commonly reported systemic adverse reaction was fatigue. No Grade 4 events were reported in the trial. There were no SAEs assessed as related to the vaccine. There were 2 participants who experienced 2 SAEs, a prostate cancer diagnosis and a traumatic fracture, within 28 days of the booster dose. There were no deaths or adverse events of special interest (AESI), including myocarditis or pericarditis. In the bivalent booster group, all severe events included reactogenicity events (fatigue, chills, arthralgia, headache) and 1 patient reported lymphadenopathy (axillary/cervical).

Moving to the Pfizer BioNTech bivalent booster clinical trial with BA.1 (C4591031), individuals received a fourth dose of a 30 µg bivalent vaccine comprised of BNT162b2 ancestral and BNT162b2 Omi BA.1 and were compared to those who received a fourth dose of 30 µg of the BNT162b2 ancestral monovalent vaccine. The study evaluated safety and immunogenicity among participants ≥55 years of age. A total of 305 participants received the bivalent Omicron vaccine BNT162b2 Omi (BA.1) and 305 received monovalent BNT162b2 ancestral vaccine. The dosing interval from the first booster to the second booster was 6.3 months and the median follow-up was 1.7 to 1.8 months. Immunogenicity was assessed by the antibody response 1 month after the study vaccination. Based on the GMRs, comparing the antibody response in participants who received the bivalent booster to those who received the monovalent ancestral vaccine, the bivalent vaccine met superiority criteria for Omicron antibodies and non-inferiority criteria for ancestral SARS-CoV-2 antibodies.

In participant ≥55 years of age, local and systemic reactogenicity with the Pfizer bivalent vaccine were similar to the prototype vaccine. Fever >38.9 °C to 40.0 °C was reported by 4 participants in the vaccine group. No fevers >40.0 °C were reported. For persons 18–55 years of age, monovalent Omicron-modified vaccine (30 µg dose) showed similar reaction as prototype vaccine. No bivalent reactogenicity data were available in this age group. No AEs were assessed as related to the vaccine. There were no life-threatening AEs or deaths reported by participants. There were no cases of anaphylaxis, hypersensitivity, myocarditis, pericarditis, appendicitis, or other AESIs. In the bivalent booster group, all severe events included reactogenicity events such as fatigue, chills, arthralgia, and headache. Some mild to moderate events of lymphadenopathy also were reported.

[49] https://www.medrxiv.org/content/10.1101/2022.06.24.22276703v1.full.pdf

To summarize the clinical trial data, a bivalent booster dose of both Moderna and Pfizer COVID-19 vaccines increased the immune response in those who had completed a primary series and a previous booster. Compared with ancestral booster dose, the bivalent booster doses demonstrated a superior response to Omicron and either a superior or non-inferior response to the ancestral strain. The bivalent booster doses had a similar reactogenicity profile to the primary series and to an ancestral booster dose. It should be noted that the data from the clinical trials are limited in size, age, and bivalent booster type.

In terms of other considerations, the risk of myocarditis following a bivalent booster dose is unknown. There are limited data from second booster doses of the current COVID-19 vaccines as its recommended only for adults ≥50 years of age. Therefore, Dr. Oliver reviewed the risk of myocarditis following a second dose in the primary series and the first booster dose by age group and sex. She showed the tables shared earlier by Dr. Shimabukuro earlier of the VAERS reporting rates of verified myocarditis per 1 million mRNA COVID-19 vaccinations (Pfizer-BioNTech and Moderna combined) for Days 0–7 post-vaccination; VSD incidence rates of verified myocarditis/pericarditis in the 0–7 days after Pfizer-BioNTech vaccination in people ages 12–39 years for Dose 2 and a first booster dose and the same data following a primary series and booster dose after Moderna vaccination; and the myocarditis/pericarditis crude reporting rates per million doses administered following COVID-19 mRNA vaccines from the Ontario, Canada[50] surveillance data showing that across all ages, the rates of myocarditis were lower after a booster dose than after Dose 2 of the primary series. Based on CDC enhanced surveillance for myocarditis outcomes following mRNA COVID-19 vaccination in VAERS case reports among individuals 5–29 years of age at least 90 days after the myocarditis diagnosis,[51] most patients who were reached reported no impact on their quality of life and most did not report missing school or work. Among the 226 patients whose providers completed the follow-up surveys, most HCP (80.1%) indicated that patients were fully recovered or probably fully recovered.

In summary of myocarditis and pericarditis, the risk of myocarditis has been identified after COVID-19 vaccine. This risk is rare and primarily observed in adolescent and young adult males. Among the VAERS data, the reporting rates of myocarditis are lower after a booster dose compared to the primary series. Among VSD data, the incidence following Dose 2 of a primary series and a booster dose are similar, but the case counts are small. Surveillance data from Canada indicate that the risk of myocarditis or pericarditis following the first booster dose appears lower than the risk following the second dose of the primary series. This was observed for both Pfizer and Moderna products across all age groups.[52] Most individuals with myocarditis and pericarditis had fully recovered at follow-up. Based on data from pre-Omicron estimates, the risk of adverse cardiac outcomes were 1.8 to 5.6 times higher after SARS-CoV-2 infection than after mRNA COVID-19 vaccination among males 12–17 years of age.[53] An interval of 8 weeks between vaccine doses may further lower the myocarditis risk.

[50] https://www.publichealthontario.ca/-/media/Documents/nCoV/epi/covid-19-aefi-report.pdf?sc_lang=en
[51] As previously presented to ACIP: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-06-22-23/03-COVID-Shimabukuro-508.pdf
[52] Public Health Agency of Canada. NACI: Recommendations on the use of bivalent Omicron-containing mRNA COVID-19 vaccines. Sept 1, 2022
[53] DOI: http://dx.doi.org/10.15585/mmwr.mm7114e1

As a reminder, VaST closely reviews data from US safety monitoring systems and other sources. Through August 2022, VaST held 64 teleconference meetings. This is their interpretation of the safety data, with a special focus on myocarditis. They felt that for v-safe[SM], the reactions and health impacts were not higher after a booster dose than after a primary series Dose 2. For VAERS, there were no additional concerns and myocarditis reporting rates were lower after a booster dose than a primary series. For VSD, there were few myocarditis or pericarditis cases after a booster dose, and the risk estimates were imprecise. The risk after booster doses appeared similar compared to the risk after the primary series Dose 2. VaST also reviewed additional vaccination data in pregnancy, for which no safety concerns were identified from any of the systems that have data on primary series and the first booster dose. VaST will continue to closely review the safety data, including data after a bivalent vaccine booster once these are available.

To better understand the impact of a fall booster rollout, data were reviewed from projects in the COVID-19 Scenario Modelling Hub, which is a multi-team effort aimed at creating and modelling planned scenarios for the mid- to long-term COVID-19 situation. There are typically 5 to 10 submissions per scenario round at the national level, and results are ensembled and summarized by the Hub. Rounds 14 and 15 were planning scenarios projecting COVID-19 burdens through mid-2023 under different booster policies. In Round 14, the VE with the bivalent boosters was assumed to be 80% against symptomatic disease with non-immune escape strains. The scenario included a targeted booster campaign in persons ≥50 years of age versus influenza vaccine-like uptake in person ≥18 years of age. The model also looked at no variant versus a Fall "variant X" with 40% immune escape and 20% increased severity. Round 15 was a rapid round aimed to update Round 14 and consider booster dose time. The same VE and variant assumptions were used as in Round 14 but the scenario assumed booster recommendations with influenza-like uptake in persons ≥18 years of age starting in September 2022 versus starting in November 2022.[54]

The Round 14 national ensemble projection intervals showed that regardless of the presence of a new variant, influenza vaccine-like uptake in individuals ≥18 years of age would lead to over a 20% reduction in hospitalizations and over a 15% reduction in deaths versus a recommendation for individuals ≥50 years of age.[55] The Round 15 national projection intervals showed that absent a new variant, boosters to individuals ≥18 years of age in September could prevent over 100,000 more hospitalizations[56] and nearly 10,000 more deaths[57] compared to a booster rollout in November.

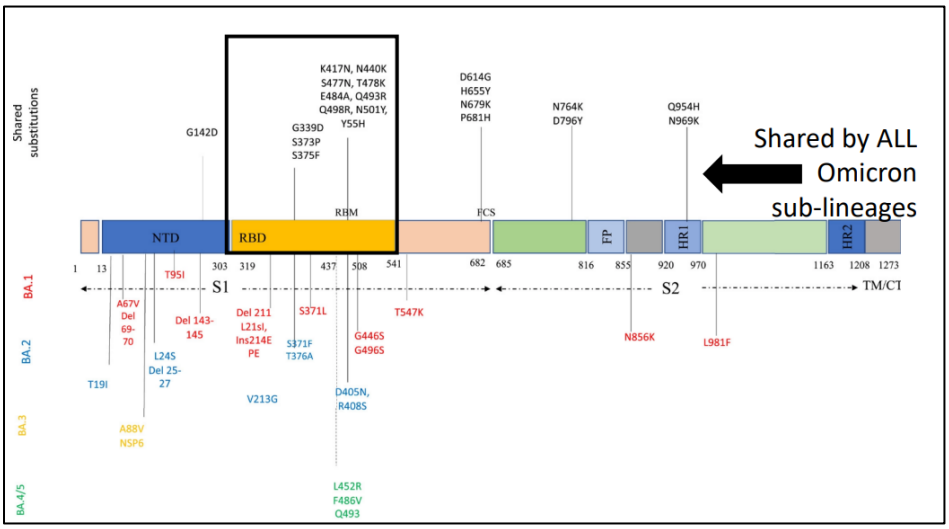
Immune tolerance and concerns for COVID-19 vaccine booster doses have been discussed before. As a reminder, immune tolerance is the concern that giving additional doses of COVID-19 vaccine would lead to lower antibody levels or a failure to restore antibody levels to what was seen after a previous dose or T-cell exhaustion. However, data have not been seen at this point to suggest that this is occurring. Bivalent vaccine is able to improve vaccine titers in individuals without prior infection and also provided a robust boost in antibody titers for individuals with prior infection. High antibody titers were seen for bivalent vaccine prior to SARS-CoV. High antibody titers seen for this bivalent vaccine plus prior infection could lead to slower waning and prolonged protection against COVID-19 and severe disease.[58]

[54] https://data.cdc.gov/Flu-Vaccinations/Influenza-Vaccination-Coverage-for-All-Ages-6-Mont/vh
[55] https://covid19scenariomodelinghub.org/
[56] 95% Confidence Interval: 21,000-251,000
[57] 95% Confidence Interval: 500-19,000
[58] Chalkia et al, medRxiv 2022, doi 10.1101/2022.06.24.22276703; In press *New Engl J Med*

Imprinting previously also was discussed previously. Imprinting, sometimes known as the "original antigenic sin" is the concern that the initial exposure to one virus strain primes B-cell memory and limits the development of memory B-cells and neutralizing antibodies against new strains. However, data suggest an improved diverse response attained with bivalent vaccines. Antibody titers to all SARS-CoV-2 variants tested were higher with the bivalent vaccine compared to the monovalent ancestral vaccine.[59]

Earlier in the day, they heard from Dr. Thornburg about antigenic cartography or ways to map out the antibody responses. Antigenic cartography uses 2D and 3D maps to visualize how closely related the antibody responses are for different viruses. Antibody landscapes are another form of cartography that evaluate the diversity of the immune response. A flat landscape is better as it indicates that the response to all viruses or variants are similar. When the sheet of paper or the landscape is sloped, it means that the responses were very skewed to one particular variant. A study done by the NIH looked at antibody responses on Day 15 after giving a variety of vaccines, including several different bivalent vaccines. For the Day 15 antibody response, and especially for those with a history of prior infection, the bivalent vaccines with a prototype + Omicron composition provided the most robust response that was diverse and similar across the different variants.[60]

In terms of Omicron itself and the differences between BA.1 and BA.4/5, the clinical data from the bivalent vaccines are obtained primarily using BA.1. Compared to the ancestral virus, which was circulating in early 2020 and is what is currently in the monovalent vaccines, all Omicron sub-lineages have shared mutations highlighted in this graphic by the black arrow:



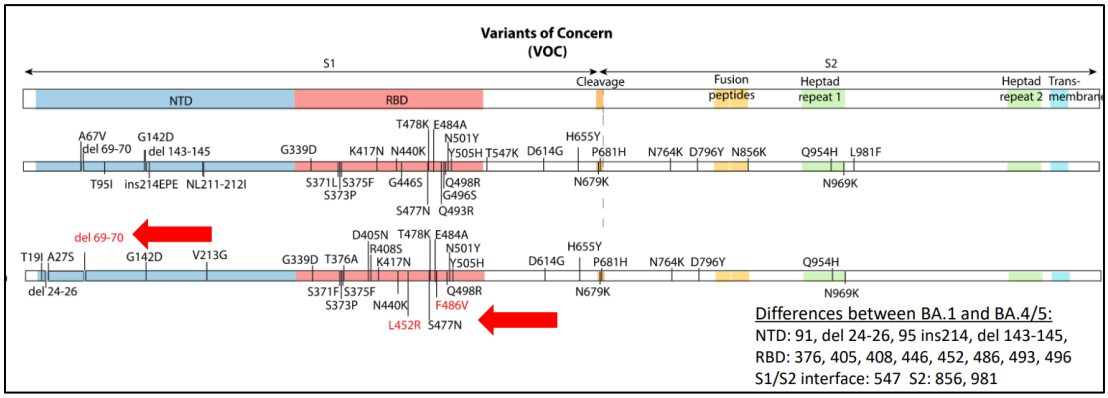
Many of these mutations are in the receptor binding domain highlighted in the box with RBD. The receptor binding domain, as the name implies, is the primary binding site for antibodies. These mutations contribute to decreased neutralization and increased transmissibility for the omicron sub-lineages. Any vaccine that uses any Omicron subvariant would include all of these mutations.[61]

[59] https://www.biorxiv.org/content/10.1101/2022.02.03.479037v1.full.pdf; and https://assets.researchsquare.com/files/rs-1555201/v1_covered.pdf?c=1650045900

[60] https://www.medrxiv.org/content/10.1101/2022.07.12.22277336v1.full.pdf

[61] Evolution of the SARS-CoV-2 omicron variants BA.1 to BA.5: Implications for immune escape and transmission – Shrestha Reviews in Medical Virology - Wiley Online Library

Regarding the differences between BA.1 and BA.4/BA.5 specifically, the reason there are 2 numbers is that because BA.4 and BA.5 are 2 different Omicron sub-lineages, but the spike protein for each, which is the focus of the vaccine, is identical. When talking about what is in the vaccine, the spike protein is for both BA.4 and BA.5, but it is still just a single sequence, not 2 different ones. Looking at this graphic, the bar at the top is for BA.1 and the bar at the bottom is BA.4/BA.5:



The numbers and letters seen are areas where they different from the main virus of comparison. The text on the bottom right lists all of the differences between BA.4 and BA.5. The figure highlights where several of these are with the red arrows. There are differences overall, but they fundamentally are not a completely new or different virus. They actually share most of the same genetic code except the highlighted red differences.[62]

The world is in a different position now than in 2020 or 2021. Especially with the recent Omicron surges for the past year, many people also have had a SARS-CoV-2 infection. This impacted the antigenic landscapes and raises the consideration of COVID-19 vaccination with and without prior SARS-CoV-2 infection. The study from Qatar looking at VE with 2 or 3 doses of mRNA vaccines with or without prior infection showed that individuals who had 3 doses of vaccine and a prior infection were the most protected, with a VE of nearly 80%. The effectiveness of prior infection alone was around 50%.[63] The risk of reinfection fundamentally changed during the Omicron surge as well. Another study looked at EHRs in the US and assessed the risk of reinfection through the calendar months. As the US went into the Omicron surge, the risk of reinfection increased significantly.[64]

Given that the discussion for this meeting was focused primarily on bivalent mRNA vaccines and ACIP was being asked to consider the broader program as well, Dr. Oliver provided information on non-mRNA boosters. At this time, the published data are limited. The study looked at a handful of individuals who received a Novavax primary series and a booster compared to those who received original monovalent mRNA vaccines. Although no data were available to compare what this would look like with the updated bivalent vaccines, the responses overall were fairly similar to what was seen with the monovalent mRNA vaccines. Notably, this was only with 4 or 5 individuals in the Novavax group.[65] Another RTC assessed third dose boosters given 10–12 weeks after an initial course of the Pfizer-BioNTech COVID-19

[62] SARS-CoV-2 variants ~ ViralZone (expasy.org)
[63] Altarawneh HN, Chemaitelly M, Ayoub HH, et.al. Effects of Previous Infection and Vaccination on Symptomatic Omicron Infections. N Engl J Med 2022; 387:21-34
[64] Individuals with recent prior SARS-CoV-2 infection are at reduced risk of Omicron infection and associated hospitalization (medrxiv.org)
[65] DOI: 10.1126/science.abq020

primary series. All booster doses resulted in an increase in anti-spike IgG concentration, but the third dose of the mRNA vaccines resulted in GMCs that were about 3 times higher than those observed in the Novavax booster recipients. All boosters in the study showed acceptable side effect profiles.[66]

In terms of the equity question for this domain pertaining to whether the desirable and undesirable anticipated effects are demonstrated across all populations equally, this language was very specifically chosen to assess the following:

Are the desirable and undesirable anticipated effects demonstrated across all populations? • Were persons of all races and ethnicities included in clinical trials or observations? • Do the demographics of study populations reflect demographics of the US population? • Are there specific population groups for which the burden of the public health problem or benefit of the intervention is of particular concern? – If so, are these population groups represented in clinical trials or observations?	Are the desirable and undesirable effects equally demonstrated across all populations? • Were desirable and undesirable effects examined by population group? • Are there any desirable or undesirable effects which appear more frequently in one or more population groups?

For all future EtRs, the WG commits to evaluating the benefit-risk data through this lens as well. The demographic make-up of the Moderna clinical trial for the bivalent vaccines consisted of a smaller percentage of Hispanic and Latino participants than make up the US Census data. Likewise, the trial was comprised of a larger proportion of White participants within the US population.[67] Similarly, the Pfizer trial had less racial and ethnic diversity than the US population. Additionally, because the trial was conducted in persons >55 years of age, the median age of the trial participants was much higher than what is seen in the US population.

In terms of the results by race and ethnicity, the Moderna vaccine bivalent vaccine demonstrated that Omicron BA.1 and original strain neutralizing antibodies after the fourth dose were comparable across racial groups. In the Pfizer BioNTech trial, subgroups of participants >55 years of age in the safety population generally had similar AE profiles from study vaccination to 1 month post-dose across various vaccine groups when evaluated by subgroups of sex, race, and ethnicity. Overall, there were no meaningful differences between the subgroups for the Omicron variant or the original strain. However, it should be noted that in both trials the subgroups of race and ethnicity included a limited number of participants, so the results should be interpreted with caution.

To summarize the data available overall to inform the recommendations in terms of the benefits and harms, there is experience from using the COVID-19 vaccine mRNA platforms for nearly 2 years and over 600 million doses in the US alone. There are extensive VE studies as well as robust post-authorization safety data across multiple platforms. Clinical human data from bivalent COVID-19 vaccines are available in over 1,700 persons. This includes data on bivalent vaccines with both Beta and Omicron variants from manufacturers and NIH studies. Over 1,400 individuals received a bivalent vaccine with the Omicron component specifically. While there are subtle differences in mutations between the BA.1 and BA.4/BA.5 spike protein sequences, it is not anticipated that any differences would be seen in the safety or reactogenicity of the vaccines based on these limited mutations. The overall composition of the vaccine as well as the total antigenic load are the same as the current booster doses. Data from the antigenic cartography and antibody studies and modeling data also were reviewed.

[66] DOI: https://doi.org/10.1016/S0140-6736(21)02717-3
[67] https://www.medrxiv.org/content/10.1101/2022.06.24.22276703v1.full.pdf; US Census Bureau QuickFacts: United States

In terms of what is known, COVID-19 vaccines have a high degree of safety. Rare events of myocarditis have been seen after the mRNA vaccines in post-authorization studies, and cases of myocarditis have been attributed to the vaccine in the Novavax clinical trials. COVID-19 vaccines also provide high levels of protection against severe disease. Initially, the COVID-19 vaccines also provided high levels of protection against infection and transmission. However, as the virus evolved, more rapid waning of protection was noted against asymptomatic and milder disease. COVID-19 booster doses further increase protection against severe disease. Bivalent COVID-19 vaccines expand the immune response after vaccination. Vaccines that contain Omicron will improve the antibody response to Omicron. Bivalent vaccines appear to provide a more diverse response overall, which may improve the immune response to future variants as well.

However, it also is important to acknowledge what is not known. The rates of myocarditis after bivalent COVID-19 vaccines are not known. It is unlikely that the inclusion of Omicron would increase myocarditis rates. Age and sex of the individual are likely contributing factors to development of myocarditis after vaccine. The interval since the previous dose and total dose may be related. However, it is unlikely that the inclusion of Omicron would have an impact. The incremental increase in VE is unknown. Antibody titers to currently circulating variants were higher after bivalent booster dose than with the current monovalent booster. However, most of the data to inform recommendations were from that BA.1 bivalent vaccine. The incremental benefit of going from BA.1 to BA.4/BA.5 are unknown. The duration of protection for these vaccines also is unknown. However, antibody titers after bivalent vaccine and prior infection were robust. This combination of prior infection and the bivalent vaccine may prolong the duration of protection, which could decrease the need for frequent boosters. However, as with all vaccines, the duration of protection may vary by age and immune status.

To summarize the balance of benefits and risks for these bivalent vaccines, Moderna and Pfizer BioNTech bivalent vaccines increase the immune response for those who have completed a primary series and a previous booster. Similar reactogenicity profiles were seen with the primary series and ancestral booster dose. Myocarditis risk following a bivalent booster dose is unknown, but is anticipated to have a similar risk to what is seen after monovalent vaccine booster doses. Modelling projects that more hospitalizations and deaths would be averted when booster doses are recommended broadly for persons ≥18 years of age compared to only persons ≥50 years of age and when the booster campaign would begin in September compared to November. The benefits and harms for the US population are best assessed when clinical trial and study populations are optimally representative of the US population. The WG felt that the substantial desirable anticipated effects were moderate, the undesirable anticipated effects were small, and the balance favors the intervention.

Moving to the values domain, survey data from an online survey conducted in partnership with the CDC and the University of Iowa[68] conducted recently over the month of August showed that 72% of eligible respondents said that they definitely or probably would get an updated booster that protects against Omicron. Among people who said that they were unsure about getting a booster, people felt that they have enough protection from their prior dose or that the booster may not be effective. When asked why people would get a booster, preventing them from spreading to others and preventing severe disease were the most common responses. Moving into the Fall, implementation of a COVID-19 booster program will overlap with the influenza vaccination season as well. When survey recipients were asked if they would be willing to get

[68] CDC and University of Iowa/RAND survey, August 2022, unpublished

an influenza shot and the updated COVID-19 at the same time, 63% of individuals were extremely or somewhat willing to receive them together.

Regarding the equity question for this domain regarding whether there is important variability in how patients or populations value the outcome, booster uptake has remained relatively steady, with those groups with higher initial vaccine uptake also more likely to have received their booster dose. This means that older adults, college graduates, and those with higher incomes remain the most likely to be both vaccinated with a primary series and booster.[69] There is notable difference in the vaccinated versus the vaccinated with the primary series versus boosted status among adults of Hispanic or Latino ethnicity. Despite a high vaccine uptake, around a third of the adults who say that they have completed a primary series have not yet received a first booster. In terms of why people have not received a booster, shown by race and ethnicity, a higher proportion of vaccinated adults without a booster of Hispanic ethnicity felt that they have enough protection from prior infection or may have had side effects from previous doses or could be worried about missing work from the symptoms post-vaccine.

In summary of the value domain, 72% survey respondents reported that they were likely to receive an updated booster, with the prevention of spread to others (46.2%) and a change in case severity (38%) appearing to lead as the main reasons why they would want to get an updated booster. Nearly two-thirds of adults were willing to receive a COVID-19 vaccine and an influenza shot at the same time. However, receipt of a booster to date demonstrates persistent vaccine inequity. Adults of older age, those with college degrees, and those with higher incomes remain most likely to be vaccinated with a primary series and booster. Notably, about a third of adults of Hispanic or Latino ethnicity have not yet received a booster despite completion of a primary series. The WG felt that the target population felt that the desirable effects were moderate relative to undesirable effects. However, there is probably important uncertainty or variability.

The domain of acceptability can be considered through the lens of acceptability of the COVID-19 vaccination program overall. Over 800 million doses have been delivered to date. Over 90% of the population has received at least 1 dose and over 223 million individuals have completed a primary series. There is a broad network of COVID-19 vaccine providers, including critical pharmacy providers, federal partners, and jurisdictional providers.[70] For the equity question for this domain regarding whether the intervention is equally acceptable across all populations, Asian, American Indian, and Alaskan Native, Native Hawaiian, or other Pacific Islander populations have the highest percentage among those who are fully vaccinated or have completed a primary series, whereas the Black populations have the lowest vaccination to date. As it pertains to booster vaccination trends by race and ethnicity, multi-racial and Asian populations have the highest percent among those who received their first booster dose, and second booster dose receipt is higher again among multi-racial populations relative to other racial and ethnic groups.[71] There also have been disparities by population for those who have completed a primary series by county and urbanicity, with those enlarged metropolitan areas having a higher vaccination rate than those in rural populations.[72] Vaccination rates vary by

[69] The survey was conducted July 7 – 17, 2022, online and by telephone among a nationally representative sample of 1,847 U.S. adults. KFF COVID-19 Vaccine Monitor: July 2022. https://www.kff.org/coronavirus-covid-19/poll-finding/kff-covid-19-vaccine-monitor-july-2022/ Accessed August 9, 2022

[70] Source: Data pulled from CDC COVID Data Tracker as of 08/17/22 1200

[71] CDC COVID Data Tracker. Trends in Demographic Characteristics of People Receiving COVID-19 Vaccinations in the United States. https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends Accessed August 31, 2022

[72] CDC COVID Data Tracker. COVID-19 Vaccination Equity. https://covid.cdc.gov/covid-data-tracker/#vaccination-equity Accessed August 31, 2022

race, ethnicity, and disability status.[73] As shown before, a provider's recommendation remains very important to COVID-19 vaccine acceptance. This importance appears highest among individuals who are over 65 years of age, Black, retired or with incomes under $30,000. This indicates that the potential for healthcare providers to increase the acceptability of these bivalent vaccines through communications with their providers.

To summarize acceptability, over 800 million does doses of COVID-19 vaccines have been delivered across a wide network of vaccine providers. However, significant disparities and completion of the primary series and receipt of booster doses still persist by race and ethnicity, urbanicity, and differences in abilities including vision, hearing, mobility, and cognition. However, it is important to note that the detection of the disparities does not necessarily explain the disparities. Differences in acceptability can be what contributes to the disparities, but through listening sessions when revising the equity domain, they heard caution against explaining all disparities as vaccine hesitancy or low acceptability when other drivers also may be present. Differences in access may contribute to these disparities as many others may as well. Identifying and understanding these and other drivers in equity is a critical step toward closing these equity gaps and there is further work to do here. In the meantime, healthcare provider recommendations are important and continue to appear to increase the acceptability of COVID-19 vaccination, particularly among adults who are Black, over the age of 65, retired, and of lower income. The WG felt that the vaccine is probably acceptable to key stakeholders.

Moving to feasibility, looking at trends in completed primary series and first boosters for persons 5–11 years of age, 12–17 years of age, 18–49 years of age, for most individuals ages 5–49 years of age, it has been 6 months or more since their last COVID-19 vaccine dose. While many persons 50–64 years of age and ≥65 years of age have received a second booster in the past 6 months, comparatively few have received a dose in the past 8 weeks. Overall, the numbers have declined with each of the booster recommendations. In September, based on the total number of persons eligible, which includes those who have completed a primary series but not received a COVID-19 vaccine in the past 2 months consistent with the language in the EUA is almost 210 million individuals. The number ineligible, which would be those who had a vaccine dose in the past 2 months, is less than 5 million.[74]

Overall, the US Government has purchased approximately 171 million bivalent mRNA vaccine booster doses for the Fall and beyond, with the options to purchase additional doses as needed. Based on this, there will be a sufficient and finite supply of these vaccines. Limited supply settings are not anticipated overall. However, jurisdictions have been given considerations for selecting sites to receive the initial doses based on ability to rapidly use the vaccine. These considerations were in the Operational Planning Guide[75] provided to jurisdictions, including location and access to a range of populations to ensure equitable distributions; ability the reach those at highest risk of COVID-19; ability to handle the large product shipments; and ability to administer the vaccines. Overall, the bivalent vaccines have the same storage and handling parameters as the monovalent vaccines that they are used to handling. However, both manufacturers' bivalent vaccines will have gray label borders but different injection volumes. The monovalent and bivalent labels for the Pfizer vaccine have identical cap and label colors.

[73] CDC COVID Data Tracker. COVID-19 Vaccination among People with Disabilities. https://covid.cdc.gov/covid-data-tracker/#vaccinations-disability-status Accessed August 25, 2022

[74] Source: CDC IZDL; Accessed 8/22/22; First boosters does not include Texas for all ages or Idaho for ages <18

[75] CDC Fall Vaccination Operational Planning Guide – Information for the Fall Vaccine Campaign, Including Upcoming Bivalent COVID-19 Vaccine Booster Doses. https://www.cdc.gov/vaccines/covid-19/downloads/CDC-Fall-Vaccination-Operational-Planning-Guide.pdf Accessed August 19, 2022

For Moderna, the bivalent vaccine will be distinct from the adult monovalent dose but may look similar to the product for ages 6–11 years.

In terms of the equity question for this domain regarding whether it is feasible to implement across all populations, the WG looked at data from the CDC COVID Data Tacker[76] demonstrating persistent racial and ethnic disparities and receipt of the first booster among those who are eligible. The WG previously reviewed the survey data demonstrating that about a third of adults of Hispanic or Latino ethnicity have completed a primary series but not received a booster. Based on the Data Tracker, persons ≥12 years of age who are eligible for a first booster, over half of those of Hispanic or Latino ethnicity had not received it. In fact, more than half of eligible populations among American Indian, Alaskan Native, Black, Native Hawaiian, and Pacific Island populations also have not received their first booster.

In summary, use of the bivalent COVID-19 vaccines appears feasible but with some important limitations. Over 200 million people will be eligible for these bivalent vaccines. Most are at least 6 months out from their last COVID-19 vaccine does. CDC has provided an Operational Planning Guide for jurisdictions preparation, and there will be a sufficient but finite supply of these bivalent vaccines. Some aspects of these vaccines will be easy for implementation, but vials and labeling may require additional education. Importantly, significant racial and ethnic disparities persist in receipt of a booster, suggesting that the intervention may not be equally feasible to implement across all populations. The WG felt that the updated bivalent vaccines are probably feasible to implement.

Regarding the domain of resource use, a study by Abhishek Pandey et al[77] evaluated COVID-19 attributable disease and direct medical costs that could be averted by a booster program under 2 potential scenarios. Looking at coverage similar to influenza vaccination rates and what would result if broader coverage of 80% was achieved, this study estimated that an early Fall booster vaccination program that reaches coverage similar to the 2020-2021 influenza season could prevent up to approximately $62 billion in direct medical costs, which would further increase with broader coverage of the vaccines. This is not yet published in a peer-reviewed publication or a model that CDC has conducted, but it includes data of possible estimates of a cost-benefit scenario using their model estimates.

Then for the equity question for this domain regarding whether the intervention is a reasonable and efficient allocation of resources across all population, cost-effectiveness data are not yet available for most demographic subgroups. However, 1 study[78] was available for older adults that looked at the cost-effectiveness of the first booster dose of the Pfizer BioNTech vaccine administered 6 months after the second dose among adults ≥65 years of age from a healthcare system perspective. Compared to a 2-dose primary series but without a booster, the booster strategy in 100,000 older adults resulted in a net monetary benefit of over $3 million and a gain of 3.7 quality adjusted life years over 180 days. Noting that the cost-effectiveness of the boosters is highly sensitive to the population incidence of COVID-19 and the VE, the study estimated that offering COVID-19 boosters to adults ≥65 years of age in the US was likely to be cost effective.

[76] CDC COVID Data Tracker. Demographic Characteristics of People Receiving COVID-19 Vaccinations in the United States. https://covid.cdc.gov/covid-data-tracker/#vaccination-demographic Accessed August 27, 2022

[77] Abhishek Pandey et al., "How Many Lives Could a Fall COVID-19 Booster Campaign Save in the United States?," To the Point (blog), Commonwealth Fund, July 26, 2022. https://doi.org/10.26099/rc8x-dx51

[78] https://doi.org/10.1016/j.ijid.2022.03.029

To summarize the domain of resource use, a fall vaccination campaign that expands eligibility for boosters and moves more aggressively to reach people could avert a surge of hospitalizations and deaths that would result in substantial savings and direct medical costs. The WG felt that the bivalent vaccines probably were a reasonable and efficient allocation of resources.

The current Moderna vaccine includes 50µg of the ancestral strain. For the current monovalent Pfizer vaccine, there are 30µg of the ancestral strain. The updated bivalent Moderna vaccine contains 25µg of the ancestral strain and 25µg of the spike protein from Omicron BA.4/BA.5. The updated Pfizer bivalent vaccine contains 15µg of ancestral and 15µg of BA.4/BA.5. Overall, the bivalent vaccines have the same total antigen amount as the monovalent vaccines, but with the additional Omicron composition.

To summarize, the data presented in EtR show that the current monovalent COVID-19 vaccines have dramatically reduced COVID-19 hospitalizations and deaths. However, as the virus has evolved, there have been declines in neutralizing antibodies and VE, and there has been more rapid waning from the vaccines. Inclusion of a second SARS-CoV-2 variant in the vaccine broadens the antibody response. Omicron-specific bivalent vaccines were studied in over 1,400 individuals. Omicron-specific bivalent vaccine resulted in higher antibody titers for Omicron variants, higher titers for other SARS-CoV-2 variants, and titers that were as high or higher for ancestral SARS-CoV-2. Broad uptake of the COVID-19 vaccine booster doses early this Fall could prevent over 100,000 hospitalizations compared to a later or more limited rollout and may even save billions of dollars of direct medical costs.

COVID-19 Pre-Exposure Prophylaxis Guidance

Evelyn Twentyman, MD, MPH (CDC/NCIRD) reviewed COVID-19 pre-exposure prophylaxis (PrEP) guidance, pointing out that this simplification of recommendations is a great opportunity to look closely at the spectrum of resources available to protect people with moderate to severe immunocompromise. Therefore, in addition to the potential new recommendation to receive an updated bivalent booster, Dr. Twentyman reviewed existing recommendations for PrEP, which can be used in complement COVID-19 vaccines to protect the immunocompromised population. PrEP refers to a medication that is given before exposure to an infectious disease to protect an individual against that disease. The PrEP, Evusheld™, is recommended for those ≥12 years of age who weigh at least 40 kilograms or 88 pounds with moderate to severe immunocompromise due to a medical condition or receipt of certain immunosuppressing treatments. Examples of such medical conditions or treatments are included in the Evusheld™ EUA Fact Sheets on CDC's website[79] and are similar to those previously leading to eligibility for multiple boosters. Evusheld™ is also recommended to be given to those who are unable to receive COVID-19 vaccines due to a history of severe adverse reaction to a COVID-19 vaccine or one of its components.

Tixagevimab/Cilgavimab (Evusheld™) is a combination of 2 long-acting human monoclonal antibodies derived from B-cells donated by convalescent patients after SARS-CoV-2 infection. The FDA issued an EUA for use of Evusheld™ for PrEP in December 2021, revised the EUA to increase the dose to 300 mg of each monoclonal antibody in February of 2022, and revised the Fact Sheet for Healthcare Providers[80] to recommend Evusheld™ be administered every 6 months in June 2022. Evusheld™ must be prescribed by a healthcare provider. Doses can be

[79] Evusheld Healthcare Providers FS 06292022 (fda.gov); Image: ASPR Webinar: What is Evusheld? https://aspr.hhs.gov/COVID-19/Therapeutics/Products/Evusheld/Pages/default.aspx
[80] https://www.fda.gov/media/154701/download

found through the US Government Therapeutic Locator Tool on the Administration for Strategic Preparedness & Response's (ASPR's) website.[81] As of August, there is also a new ordering pathway available through the HHS Health Partner Order Portal (HPOP)[82] such that in addition to the larger orders available through the HPOP distribution process, providers who are not participating in that process can now order up to 3 doses through the Small Volume Orders portal.[83]

Use of Evusheld™ is evidence-based. In an RCT,[84] Evusheld™ had efficacy for the prevention of COVID-19. In multiple other studies,[85] including real-world data, Evusheld™ was observed to have efficacy against severe COVID-19 outcomes including during this period of Omicron variant predominance. Additionally, in vitro studies show that Evusheld™ is predicted to work against BA.4/BA.5. Despite the protection that Evusheld™ can provide, most people who are immunocompromised in the US have not actually received Evusheld™. Among the almost 7 million individuals with immunocompromise, only about 5% have actually received doses of Evusheld™. This is not an issue of supply. Current Evusheld™ supply far exceeds demand. More than 390,000 doses are already distributed and available for use today.[86] Evusheld™ is distributed by the USG at no cost to participants, although some locations of administration may have an associated administration fee.

In terms of how use of monoclonal antibodies for PrEP can complement receipt of COVID-19 vaccines for optimal protection of those with immunocompromise, after any dose of COVID-19 vaccine, an individual should wait 2 weeks before receiving Evusheld™. After Evusheld™ receipt, there is no minimum interval to the next COVID-19 vaccine either within a primary series or if receiving a booster dose. Evusheld™ is recommended to be administered every 6 months and individuals should consult with their physician for a prescription. CDC is in the process of updating several webpages to make this information more widely available. Updated content for healthcare providers will include descriptions of patient eligibility and detailed Evusheld™ administration guidance, as well as those links to options for ordering Evusheld™. Updated content for the general public will include additional information about how to know if someone is eligible for Evusheld™, as well as the dose finder mentioned earlier. Updated language within the Interim Clinical Considerations for use of authorized and approved COVID-19 vaccines will clearly describe how use of Evusheld™ complements COVID-19 vaccination to optimally protect people with moderate to severe immunocompromise.

Interim Clinical Considerations for COVID-19 Vaccines: Bivalent Boosters

Dr. Elisha Hall (CDC/NCIRD) presented anticipated updates to the Interim Clinical Considerations for COVID-19 vaccine bivalent booster doses, contingent on a recommendation for these vaccines. August 31, 2022, Moderna and Pfizer bivalent vaccines were authorized. The Moderna bivalent vaccine was authorized for use in people ≥18 years of age and the Pfizer bivalent vaccine was authorized for use in people ≥12 years of age. These vaccines were

[81] https://covid-19-therapeutics-locator-dhhs.hub.arcgis.com/
[82] https://aspr.hhs.gov/COVID-19/Therapeutics/updates/Pages/important-update-27July2022.aspx
[83] https://app.smartsheet.com/b/form/21e4312a2985457f982bb2738cf82744
[84] Levin et al, Intramuscular AZD7442 (Tixagevimab-Cilgavimab) for Prevention of Covid-19, *New England Journal of Medicine*, 2022
[85] a) Tixagevimab/Cilgavimab for Prevention of COVID-19 during the Omicron Surge: Retrospective Analysis of National VA Electronic Data | medRxiv; b) Serum neutralization of SARS-CoV-2 Omicron sublineages BA.1 and BA.2 in patients receiving monoclonal antibodies | Nature Medicine; c) Al Jurdi et al., American Journal of Transplantation;June 2022; d) Association between AZD7442 (tixagevimab-cilgavimab) administration and SARS-CoV-2 infection, hospitalization and mortality | Clinical Infectious Diseases | Oxford Academic (oup.com); and e) Takashita E, et al, Efficacy of Antibodies and Antiviral Drugs against Omicron BA.2.12.1, BA.4, and BA.5 Subvariants. N Engl J Med. 2022
[86] Data source: HHS-Tiberius: https://aspr.hhs.gov/COVID-19/Therapeutics/orders/Pages/default.aspx

authorized for use as a single booster dose administered at least 2 months after either completion of primary vaccination with any authorized or approved monovalent COVID-19 vaccine or receipt of the most recent booster dose with any authorized or approved monovalent COVID-19 vaccine. Along with the authoritarian of bivalent vaccines for persons ≥12 years of age, monovalent mRNA COVID-19 vaccines are no longer authorized as booster doses for individuals ≥12 years of age. This means that monovalent booster doses can no longer be given to people ≥12 years of age, even if the person had not previously received a monovalent booster dose.

Everyone ≥12 years of age is recommended to receive 1 age-appropriate bivalent mRNA booster dose after completion of any FDA-approved or FDA-authorized monovalent primary series or last monovalent booster does. This means that people cannot get a bivalent booster without first completing a primary series. Homologous and heterologous boosters are allowed as long as they are age appropriate, meaning only Pfizer bivalent can be given to people 12–17 years of age. Either Moderna or Pfizer bivalent can be given to people ≥18 years of age. There is no preference. At this time, there are no changes to schedules for children 6 months–11 years of age. Again, the bivalent booster recommendation replaces previous booster recommendations for people ≥12 years of age. This means that everyone ≥5 years of age who are eligible for a booster dose will now be eligible for only 1 booster dose. People 5–11 years of age who received Pfizer are eligible for 1 monovalent booster dose currently, and people ≥12 years of age may are eligible for 1 bivalent booster dose.

In terms of the Fall booster reset, the proposed recommendations are simplified. There is a change in the way they vaccines are thought about from dose counting monovalent boosters to 1 bivalent booster for everyone eligible. This table reinforces that regardless of whether someone had 0, 1, or 2 monovalent boosters, 1 bivalent booster is now recommended:

Vaccination history	→	Next dose
Primary series	At least 2 months →	1 bivalent booster dose
Primary series + 1 booster	At least 2 months →	1 bivalent booster dose
Primary series + 2 booster	At least 2 months →	1 bivalent booster dose

Since some people may already have had 3, 4, or even 5 doses for those who are immunocompromised and had a second booster already, it is important to emphasize that total number of doses will no longer be looked at. In terms of the COVID-19 vaccination schedule for people who are not moderately or severely immunocompromised, people ≥12 years of age who have completed at least the primary series and are 2 months out from the last dose should not be denied a bivalent booster dose based on the number of total doses the person has received.

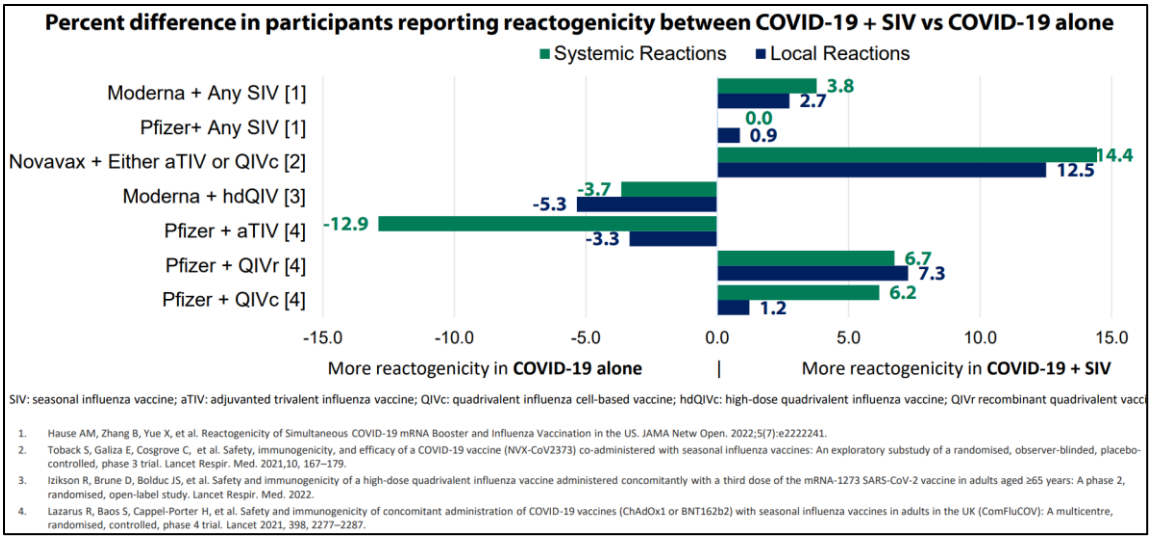
Regarding the COVID-19 vaccination schedule for people who are moderately or severely immunocompromised, people ≥12 years of age are recommended to receive a primary series of either Moderna, Novavax, or Pfizer. This would be followed by an age-appropriate bivalent booster dose at least 2 months or 8 weeks after completion of the primary series or most recent monovalent booster. The bivalent booster is now recommended regardless of how many previous monovalent boosters were received. In certain limited situations, Janssen can be used followed by bivalent booster at least 2 months later.

For people who are moderately or severely immunocompromised, the primary series will remain the same. Moderna, Novavax, or Pfizer is recommended. For Moderna and Pfizer, this is 3 doses. For Novavax, this is 2 doses. The bivalent recommendation is the same for everyone, with 1 bivalent booster dose at least 2 months after completion of the primary series or most recent previous monovalent booster does. Again, Janssen is only used in limited situations for those ≥18 years of age. Those who got a Janssen primary dose should get an additional mRNA followed by a bivalent booster.

In terms of the specifics on timing considerations for bivalent boosters, the current timing guidance for vaccination in persons with current or prior SARS-CoV-2 infection also applies to bivalent boosters. If a person has current or has had a prior SARS-CoV-2 infection, at a minimum, vaccination should be deferred at least until recovery from acute illness and criteria to discontinue isolation have been met. In addition, people who recently had SARS-CoV-2 infection may consider delaying vaccination longer by 3 months from symptom onset or positive test if infection was symptomatic. Individual factors such as risk of COVID-19 severe disease, community-level, or characteristics of the predominant strain should be taken into account when determining whether to delay getting a COVID-19 vaccine after infection.

With new bivalent vaccines, co-administration guidance has not changed. Routine administration of all age-appropriate doses of vaccines simultaneously is recommended as best practice for people for whom no specific contraindications exist at the time of the healthcare visit. Of note, orthopoxvirus vaccine does not follow the same routine guidance, and further information on that very specific situation can be found in CDC's Interim Clinical Considerations. Extensive experience with non-COVID-19 vaccines has demonstrated that immunogenicity and adverse event profiles are generally similar when vaccines are administered simultaneously as when they are administered along. Therefore, providers should offer all vaccines for which a person is eligible at the same visit.

With both influenza and COVID-19 vaccine campaigns, a lot of questions have been received about co-administration of these vaccines specifically. Providers should offer influenza and COVID-19 vaccines at the same visit, if eligible. This includes adjuvanted or high-dose influenza vaccines, but the recommendation in this case is to administer in separate limbs. With both influenza and SARS-CoV-2 circulating, getting both vaccines is important for prevention of severe disease, hospitalization, and death. Getting both vaccines at the same visit increases the chance that a person will be up-to-date with their vaccination. Studies looking at co-administration have shown that immunogenicity is similar between those who received co-administered COVID-19 vaccine and seasonal influenza vaccine and those who received these vaccines separately. Approximately 9.4% (~92,000) of v-safe ™ participants reported simultaneous vaccination with an mRNA COVID-19 vaccine and seasonal influenza vaccine, and 8.7% (~454,000) of persons enrolled in the VSD received simultaneous vaccination with a COVID-19 booster and seasonal influenza vaccine during the 2021-2022 influenza season. To summarize reactogenicity of co-administered COVID-19 vaccine and seasonal influenza vaccine to date, the following chart shows the percent difference in participants reporting reactogenicity between COVID-19 and influenza vaccine versus COVID-19 alone:



Generally, COVID-19 vaccines administered with seasonal influenza vaccine showed similar or only slightly higher reactogenicity and no specific safety concerns were identified.

In terms of best practices for multiple injections, it is recommended to label each syringe with the name and dosage of the vaccine, lot number, initials of preparer, and beyond use time if applicable. Each vaccine should be administered in a different injection site and injection sites should be separated by one inch or more. The COVID-19 vaccine and vaccines that may be more likely to cause a local reaction, such as adjuvanted or high-dose influenza vaccine and COVID-19 vaccine, should be administered in different limbs if possible.

Regarding the look of the bivalent products the monovalent and bivalent cap and border label colors will be identical for the Pfizer product, both of which are gray. Most characteristics are the same in that they are authorized for persons ≥12 years of age at 30 micrograms. The injection volume is 0.3 mL. Dilution is not required for these specific products, although other Pfizer products require dilution and they have the same beyond use of 12 hours and the same storage requirements. The monovalent is primary series and the bivalent is booster doses. The monovalent and bivalent labels are almost identical aside from the name being different. It is important to be aware of the potential for errors. CDC will have education on strategies to prevent administration errors to try to reduce errors.

For Moderna, Dr. Hall highlighted 2 different vials in comparison to the bivalent, the one for the older age group (≥12 years of age) and the one with the most similar appearance (6–11 years of age). The first monovalent product authorized for persons ≥12 years of age and is fairly visually distinct from the bivalent product authorized for ages ≥18 years of age. The monovalent is in a red-capped vial with a light blue labeled border color and is now only authorized for primary doses. Comparatively, the bivalent product for booster doses in people ≥18 years of age is in a vial with a dark blue cap and a gray labeled border. The injection volume, beyond use date of 12 hours, and storage requirements are the same. The labels for the 2 products just highlighted are much more visually distinct. The bivalent booster is clearly labeled “BOOSTER DOSES ONLY” in all caps, and there are different colors on these labels. The vial that looks the most similar is actually the monovalent product authorized for primary doses in people 6–11 years of age. This vial also uses a dark blue cap, and the visual distinction is the purple label border. Of note, the monovalent vial authorized for primary doses in ages 6–11 years is not authorized for booster

doses. The main distinction is the name of the vaccine and the color of the border, and the background for the booster dose is only text and is purple.

CDC continues to encourage people to stay up-to-date with their COVID-19 vaccines. Staying up-to-date keeps people current with the COVID-19 vaccine recommendations. With new recommendations, people are up-to-date if they have completed a primary series and received the most recent booster dose recommended for them by CDC.

COVID-19 Vaccines WG Interpretation

Sara Oliver, MD, MSPH (CDC/NCIRD) summarized the overall WG interpretations. As Dr. Daley mentioned at the beginning of the day, the WG has met frequently over the course of the last several months to review data that would inform these recommendations. In addition, the WG has had broad policy discussions around the use of the updated bivalent COVID-19 vaccines for people in age groups currently recommended for booster doses. As a reminder, based on the current FDA authorizations, the current recommendations would be for Pfizer-BioNTech COVID-19 vaccine bivalent for individuals ≥12 years and older and the Moderna vaccine bivalent for individuals ≥18 years of age. However, it is expected that additional authoritarians for other ages and vaccines may follow over the next several weeks to months. The WG discussed that the current population recommended for these boosters is very heterogenous. Many in the US have had Omicron infection over the past 9 months. In addition, individuals recommended for the bivalent COVID-19 booster doses may have previously received a primary series and only 1 booster dose, while the population ≥50 years of age who are immunocompromised may have received a primary series and 2 booster doses. The WG also noted that the balance of benefits and risks for individuals may vary by age, by previous receipt of booster, or by recent SARS-CoV-2 infection. There are uncertainties around the incremental benefit for some individuals including those with recent infection or recurrent vaccine receipt.

The WG also discussed recommendations in the setting of prior infection. COVID-19 vaccines are recommended even for those who have had prior infection. Rates of reinfection increased during Omicron period. Bivalent COVID-19 vaccines in the setting of prior SARS-CoV-2 infection, sometimes called “hybrid immunity,” results in the highest antibody titers. Encouragingly, these high and diverse titers may result in a longer duration of protection and increased need for frequent COVID-19 vaccine booster doses. Studies have shown that increased time between infection and vaccination may result in an improved immune response to vaccination. Those with recent SARS-CoV-2 infection may consider delaying the vaccine does by 3 months from symptom onset or a positive test.

The WG also discussed that time since most recent vaccine dose may be more important than total cumulative number of doses. They also fully acknowledged that there will be a time of transition as the recommendations move from counting dose number to optimal timing of the vaccination campaigns. They know clearly and have learned for the last 2 years that vaccine recommendations that are simple and easy to communicate are important. The WG also discussed that if SARS-CoV-2 becomes seasonal virus, and annual vaccine program could be an effective strategy for the future. All of this highlights that there is a distinct effort to simplify vaccine recommendations through a transition to what could be a more sustainable and long-term COVID vaccination program.

To highlight the new framework for the equity data used during this session, a key important part of the discussion through equity is that equity is not a yes/no question but requires considerations for implementation. Discussions among the WG also identified several of these implementation considerations, some of which have been discussed already such as ensuring supply, ordering, and provider readiness through an equitable distribution of the vaccine. Communications is also integral for equitable implementation, creating COVID communication plans that understand existing data around attitudes and perceptions for COVID vaccines and adjusts actions accordingly, leveraging trusted partners to deliver the vaccines as well as trusted messengers to communicate with a broad population.

The WG reviewed the totality of the data presented throughout this session. As a reminder, this was the summary of the WG judgements for EtR:

EtR Domain	Question	Work Group Judgments
Public Health Problem	Is COVID-19 of public health importance?	Yes
Benefits and Harms	How substantial are the desirable anticipated effects?	Moderate
	How substantial are the undesirable anticipated effects?	Small
	Do the desirable effects outweigh the undesirable effects?	Favors intervention
Values	Does the target population feel the desirable effects are large relative to the undesirable effects?	Moderate
	Is there important variability in how patients value the outcomes?	Probably important uncertainty or variability
Acceptability	Is the Bivalent COVID-19 vaccine booster acceptable to key stakeholders?	Probably yes
Feasibility	Is the Bivalent COVID-19 vaccine booster feasible to implement?	Probably yes
Resource Use	Is the Bivalent COVID-19 vaccine booster a reasonable and efficient allocation of resources?	Probably yes

As the WG reviewed the totality of the data presented and acknowledged uncertainties around aspects of the data, they felt that the desirable consequences probably or clearly outweighed the undesirable consequences. The WG proposed to ACIP to recommend the intervention. With that in mind, the WG posed the following question to ACIP:

> Should the updated or bivalent vaccines be recommended for persons already recommended to receive a vaccine booster dose broadly, very specifically pointing out the votes for today would be for the Moderna vaccine in persons ≥18 and over and the Pfizer vaccine in persons ≥12 years of age and over?

The WG also asked for ACIP feedback on and overall updated recommendation strategy that is more in line with traditional ACIP recommendations and a broad summary of the program. CDC will review any additional data to consider expansion of age groups recommended for bivalent COVID-19 vaccines. Future recommendations would necessarily follow updates to the EUAs issued by FDA.

Vote #1: Pfizer-BioNTech COVID-19 Bivalent Vaccine in Individuals ≥12 Years of Age

Sara Oliver, MD, MSPH (CDC/NCIRD) presented the proposed recommendations for a Pfizer-BioNTech COVID-19 bivalent vaccine in individuals ≥12 years of age as follows:

> *A single booster dose of bivalent Pfizer-BioNTech COVID-19 vaccine is recommended for individuals **ages 12 years and older** at least **2 months** after receipt of a primary series or prior monovalent booster dose, under the EUA issued by FDA.*
>
> *ACIP repeals its previous recommendations for administration of monovalent Pfizer-BioNTech COVID-19 vaccine boosters for persons ages 12 years and older.*

Motion/Vote #1: Pfizer-BioNTech COVID-19 Bivalent Booster Vaccine in Individuals ≥12 Years of Age

Dr. Poehling made a motion for ACIP to adopt the verbiage of the recommendation stating that, "A single booster dose of bivalent Pfizer-BioNTech COVID-19 vaccine is recommended for individuals **ages 12 years and older** at least **2 months** after receipt of a primary series or prior monovalent booster dose, under the EUA issued by FDA. ACIP repeals its previous recommendations for administration of monovalent Pfizer-BioNTech COVID-19 vaccine boosters for persons ages 12 years and older." Ms. McNally seconded the motion. No conflicts of interest (COIs) were declared. The motion carried with 13 affirmative votes, 1 negative vote, and 0 abstentions. The disposition of the vote was as follows:

13 Favored:	Bahta, Bell, Brooks, Chen, Cineas, Daley, Kotton, Lee, Loehr, Long, McNally, Poehling, Talbot
1 Opposed:	Sanchez
0 Abstained:	N/A

Vote #2: Moderna COVID-19 Bivalent Vaccine in Individuals ≥18 Years of Age

Sara Oliver, MD, MSPH (CDC/NCIRD) presented the proposed recommendations for Moderna COVID-19 bivalent vaccine in individuals ≥18 years of age as follows:

> *A single booster dose of bivalent Moderna COVID-19 vaccine is recommended for individuals ages 18 years and older at least 2 months after receipt of a primary series or prior monovalent booster dose, under the EUA issued by FDA.*
>
> *ACIP repeals its previous recommendations for administration of monovalent Moderna COVID-19 vaccine boosters for persons ages 18 years and older.*

Motion/Vote #2: Moderna COVID-19 Bivalent Vaccine in Individuals ≥18 Years of Age

Dr. Poehling made a motion for ACIP to adopt the verbiage of the recommendation stating that, "A single booster dose of bivalent Moderna COVID-19 vaccine is recommended for individuals ages 18 years and older at least 2 months after receipt of a primary series or prior monovalent booster dose, under the EUA issued by FDA. ACIP repeals its previous recommendations for administration of monovalent Moderna COVID-19 vaccine boosters for persons ages 18 years and older. No conflicts of interest (COIs) were declared. The motion carried with 13 affirmative votes, 1 negative vote, and 0 abstentions. The disposition of the vote was as follows:

13 Favored:	Bahta, Bell, Brooks, Chen, Cineas, Daley, Kotton, Lee, Loehr, Long, McNally, Poehling, Talbot
1 Opposed:	Sanchez
0 Abstained:	N/A

Discussion Summary

Subsequent to the vote, Dr. Lee invited ACIP members to make a statement about the rationale for their vote and/or to share any additional general comments:

Dr. Long said that as a clinician making a decision for individuals, she would be on Dr. Sanchez's side. She makes this decision for most people, considering and hoping that the advantages will outweigh any risks that are not yet anticipated.

Dr. Sanchez explained that he voted "no" because he feels that human data are needed and are very important. This is a new vaccine and a new platform. There is a lot of vaccine hesitancy already. While human data are needed, he thinks the vaccine will have similar safety as already seen with the previous vaccines with mRNA. He personally is of the age group that is at higher risk and is almost sure that he will take the vaccine. However, he feels that this vote was premature without having seen human data.

Dr. Poehling said she thought this was a huge step forward in simplifying the recommendations and hopefully enhancing coverage. It does put a lot of pressure on the distribution of the vaccine because of switching from bivalent to monovalent for boosters among people ≥12 years of age. Her sincere hope is that this will be expedient and not impair access for all who want the bivalent vaccine.

Dr. Brooks expressed appreciation for Dr. Oliver's synopsis of the EtR Framework showing the beauty of how important that is and the addition of equity on each of the line items, because the WG struggled with equity. The only reason he voted "yes" was because of thinking about how influenza vaccines are handled on a yearly basis. While they have data, it is based on the last vaccine.

Dr. Oliver confirmed that all of the discussion and deliberation will be captured in the Clinical Considerations to make sure that it fully reflects the diverse opinions of this committee in the vote.

Dr. Lee expressed appreciation for all of the input throughout the day on the booster recommendations and the move toward. Like one of the members mentioned earlier, they might not be “out of the woods yet” but she remains optimistic as this becomes a solution that is one that can be sustained. If anything changes substantively about the benefit-risk balance or if there are any new safety considerations, she assured everyone that the ACIP most certainly would meet. She assured members of the public that the ACIP and CDC systems and teams continue close monitoring. She recognized and acknowledged the uncertainty, but expressed her hope that despite that, hopefully this recommendation will make a huge impact in the ability to continue to weather the pandemic together.

Dr. Wharton thanked the ACIP, speakers, and public for sticking with them throughout the day for this very long meeting. This is a big step forward for simplification and hopefully in moving toward something that is a more normal set of vaccine recommendations and a cadence of changes to recommendations. The hope is for simplicity and less frequent changes going forward. As a reminder, this meeting originally was scheduled for 2 days. However, given that all of ACIP’s business for this meeting was completed, adjournment at this time ended the meeting and the ACIP would not reconvene the next day.

CERTIFICATION

Upon reviewing the foregoing version of the September 1, 2022 ACIP meeting minutes, Dr. Grace Lee, ACIP Chair, certified that to the best of her knowledge, they are accurate and complete. Her original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

ACIP MEMBERSHIP ROSTER

CHAIR
LEE, Grace M, MD, MPH
Associate Chief Medical Officer for Practice Innovation
Lucile Packard Children's Hospital
Professor of Pediatrics, Stanford University School of Medicine
Stanford, CA
Term: 8/4/2021 – 6/30/2023

EXECUTIVE SECRETARY
WHARTON, Melinda, MD, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, GA

MEMBERS

BAHTA, Lynn, RN, MPH, CPH
Immunization Program Clinical Consultant
Infectious Disease, Epidemiology, Prevention & Control Division
Minnesota Department of Health
Saint Paul, Minnesota
Term: 7/1/2019 – 6/30/2023

BELL, Beth P, MD, MPH
Clinical Professor
Department of Global Health, School of Public Health
University of Washington
Seattle, WA
Term: 7/1/2019 – 6/30/2023

BROOKS, Oliver, MD, FAAP
Chief Medical Officer
Watts HealthCare Corporation
Los Angeles, CA
Past President, National Medical Association
Term: 7/26/2021 – 6/30/2025

CHEN, Wilbur H, MD, MS, FACP, FIDSA
Professor of Medicine
Center for Vaccine Development and Global Health
University of Maryland School of Medicine
Baltimore, MD
Term: 12/23/2020 – 6/30/2024

CINEAS, Sybil, MD, FAAP, FACP
Associate Professor of Medicine, Pediatrics, and Medical Science (Clinical)
The Warren Alpert Medical School of Brown University
Associate Program Director
Brown Combined Residency in Internal Medicine and Pediatrics
Providence, RI
Term: 7/28/2021 – 6/30/2025

DALEY, Matthew F, MD
Senior Investigator
Institute for Health Research, Kaiser Permanente Colorado
Associate Professor of Pediatrics
University of Colorado School of Medicine
Aurora, CO
Term: 1/4/2021 – 6/30/2024

KOTTON, Camille Nelson, MD, FIDSA, FAST
Clinical Director, Transplant and Immunocompromised Host Infectious Diseases
Infectious Diseases Division, Massachusetts General Hospital
Associate Professor of Medicine, Harvard Medical School
Boston, MA
Term: 12/23/2020 – 6/30/2024

LOEHR, Jamie, MD, FAAFP
Owner, Cayuga Family Medicine
Ithaca, New York
Term: 7/26/2021 – 6/30/2025

LONG, Sarah S, MD
Professor of Pediatrics
Drexel University College of Medicine
Section of Infectious Diseases
St. Christopher's Hospital for Children
Philadelphia, Pennsylvania
Term: 12/24/2020 – 6/30/2024

MCNALLY, Veronica V, JD
President and CEO Franny
Strong Foundation
West Bloomfield, Michigan
Term: 10/31/2018 – 6/30/2023

POEHLING, Katherine A, MD, MPH
Professor of Pediatrics and Epidemiology and Prevention
Director, Pediatric Population Health
Department of Pediatrics
Wake Forest School of Medicine
Winston-Salem, NC
Term: 7/1/2019 – 6/30/2023

SÁNCHEZ, Pablo J, MD
Professor of Pediatrics
The Ohio State University – Nationwide Children's Hospital
Divisions of Neonatal-Perinatal Medicine and Pediatric Infectious Diseases
Director, Clinical & Translational Research (Neonatology)
Center for Perinatal Research
The Research Institute at Nationwide Children's Hospital Columbus, Ohio
Term: 7/1/2019 – 6/30/2023

SHAH, Nirav D, MD, JD
Director
Maine Center for Disease Control and Prevention
Augusta, ME
Term: 9/26/2022 – 6/30/2026

TALBOT, Helen Keipp, MD
Associate Professor of Medicine
Vanderbilt University
Nashville, TN
Term: 10/29/2018 – 6/30/2023

EX OFFICIO MEMBERS

Centers for Medicare and Medicaid Services (CMS)
HANCE, Mary Beth
Senior Policy Advisor
Division of Quality, Evaluations and Health Outcomes
Children and Adults Health Programs Group
Center for Medicaid, CHIP and Survey & Certification Centers
for Medicare and Medicaid Services
Baltimore, MD

Food and Drug Administration (FDA)
FINK, Doran, MD, PhD
Deputy Director, Clinical, Division of Vaccines and Related Products Applications
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration
Silver Spring, MD

Health Resources and Services Administration (HRSA)
GRIMES, Reed, MD, MPH
Chief Medical Officer
Division of Injury Compensation Programs
Rockville, MD

Indian Health Service (IHS)
CLARK, Matthew, MD, FAAP, FACP
Physician
Chair, IHS National Pharmacy & Therapeutics Committee
Durango, CO

Office of Infectious Disease and HIV/AIDS Policy (OIDP)
KIM, David, MD, MA
Director, Division of Vaccines, OIDP
Office of the Assistant Secretary for Health
Department of Health and Human Services
Washington, DC

National Institutes of Health (NIH)
BEIGEL, John, MD
Associate Director for Clinical Research
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases (NIAID)
Bethesda, MD

LIAISON REPRESENTATIVES

American Academy of Family Physicians (AAFP)
ROCKWELL, Pamela G, DO
Associate Professor, Department of Family Medicine, University of Michigan Medical School
Medical Director, Dominos Farms Family Medicine
Ann Arbor, MI

American Academy of Pediatrics (AAP)
O'LEARY, Sean, MD, MPH
Professor of Pediatrics
Pediatric Infectious Diseases
General Academic Pediatrics
Children's Hospital Colorado
University of Colorado School of Medicine

American Academy of Pediatrics (AAP)
Red Book Editor
KIMBERLIN, David, MD
Professor of Pediatrics
Division of Pediatric Infectious Diseases
The University of Alabama at Birmingham School of Medicine
Birmingham, AL

American Academy of Physician Assistants (AAPA)
LÉGER, Marie-Michèle, MPH, PA-C
Senior Director, Clinical and Health Affairs
American Academy of Physician Assistants
Alexandria, VA

American College Health Association (ACHA)
CHAI, Thevy S., MD
Director of Medical Services
Campus Health Services
University of North Carolina at Chapel Hill Chapel Hill,
NC

American College Health Association (ACHA) (alternate)
MCMULLEN, Sharon, RN, MPH, FACHA
Assistant Vice President of Student & Campus Life for Health and Wellbeing
Cornell Health
Ithaca, NY

American College of Nurse Midwives (ACNM)
HAYES, Carol E., CNM, MN, MPH
Lead Clinician
Clinical Quality Compliance and Management
Planned Parenthood Southeast Atlanta, GA

American College of Nurse Midwives (ACNM) (alternate)
MEHARRY, Pamela M., PHD, CNM
Midwifery Educator, Human Resources for Health
In partnership with University of Rwanda and University of Illinois, Chicago

American College of Obstetricians and Gynecologists (ACOG)
ECKERT, Linda O, MD, FACOG
Professor, Department of Obstetrics & Gynecology
Adjunct Professor, Department of Global Health
University of Washington
Seattle, WA

American College of Physicians (ACP)
GOLDMAN, Jason M, MD, FACP
Affiliate Assistant Professor of Clinical Biomedical Science
Florida Atlantic University, Boca Raton, Florida
Private Practice
Coral Springs, FL

American Geriatrics Society (AGS)
SCHMADER, Kenneth, MD
Professor of Medicine-Geriatrics Geriatrics
Division Chief
Duke University and Durham VA Medical Centers
Durham, NC

America's Health Insurance Plans (AHIP)
GLUCKMAN, Robert A, MD, MACP
Chief Medical Officer, Providence Health Plans
Beaverton, OR

American Immunization Registry Association (AIRA)
COYLE, Rebecca, MSEd
Executive Director, AIRA
Washington, DC

American Medical Association (AMA)
FRYHOFER, Sandra Adamson, MD
Adjunct Associate Professor of Medicine Emory
University School of Medicine
Atlanta, GA

American Nurses Association (ANA)
RITTLE, Charles (Chad), DNP, MPH, RN Assistant
Professor, Nursing Faculty
Chatham University, School of Health Sciences
Pittsburgh, PA

American Osteopathic Association (AOA)
GROGG, Stanley E, DO
Associate Dean/Professor of Pediatrics
Oklahoma State University-Center for Health Sciences
Tulsa, OK

American Pharmacists Association (APhA)
HOGUE, Michael D., PharmD, FAPhA, FNAP
Dean and Professor of Loma Linda University School of Pharmacy
Director, Center for Interprofessional Education & Practice
Loma Linda, CA

Association of Immunization Managers (AIM)
HOWELL, Molly, MPH
Immunization Program Manager
North Dakota Department of Health
Bismarck, ND

Association for Prevention Teaching and Research (APTR)
ZIMMERMAN, Richard, MD, MPH
Professor
University of Pittsburgh School of Medicine
Department of Family Medicine and Clinical Epidemiology
Pittsburgh, PA

Association of State and Territorial Health Officials (ASTHO)
TBA

Biotechnology Industry Organization (BIO)
ARTHUR, Phyllis A, MBA
Senior Director, Vaccines, Immunotherapeutics and Diagnostics Policy
Washington, DC

Council of State and Territorial Epidemiologists (CSTE)
HAHN, Christine, MD
State Epidemiologist
Office of Epidemiology, Food Protection and Immunization Idaho
Department of Health and Welfare
Boise, ID

Council of State and Territorial Epidemiologists (CSTE) (alternate)
LETT, Susan, MD, MPH
Medical Director, Immunization Program
Division of Epidemiology and Immunization
Massachusetts Department of Public Health
Boston, MA

Canadian National Advisory Committee on Immunization (NACI)
DEEKS, Shelley, MD, MHSc, FRCPC, FAFPHM
Deputy Chief Medical Officer of Health, Department of Health and Wellness, Nova Scotia
Associate Professor, Dalla Lana School of Public Health, University of Toronto
Chair, National Advisory Committee on Immunization
Halifax, Nova Scotia

Infectious Diseases Society of America (IDSA)
BAKER, Carol J., MD
Professor of Pediatrics
Molecular Virology and Microbiology
Baylor College of Medicine
Houston, TX

International Society for Travel Medicine (ISTM)
BARNETT, Elizabeth D, MD Professor of
Pediatrics
Boston University School of Medicine
Boston, MA

National Association of County and City Health Officials (NACCHO)
ZAHN, Matthew, MD
Medical Director, Epidemiology
Orange County Health Care Agency
Santa Ana, CA

National Association of County and City Health Officials (NACCHO) (alternate)
DUCHIN, Jeffrey, MD
Health Officer and Chief, Communicable Disease
Epidemiology and Immunization Section
Public Health - Seattle and King County
Professor in Medicine
Division of Allergy and Infectious Diseases
University of Washington School of Medicine and School of Public Health
Seattle, WA

National Association of Pediatric Nurse Practitioners (NAPNAP)
STINCHFIELD, Patricia A, RN, MS, CPNP
Director
Infectious Disease/Immunology/Infection Control
Children's Hospitals and Clinics of Minnesota
St. Paul, MN

National Foundation for Infectious Diseases (NFID)
SCHAFFNER, William, MD
Chairman, Department of Preventive Medicine
Vanderbilt University School of Medicine
Nashville, TN

National Foundation for Infectious Diseases (NFID) (alternate)
DALTON, Marla, PE, CAE
Executive Director & CEO
National Foundation for Infectious Diseases (NFID)
Bethesda, MD

National Medical Association (NMA)
WHITLEY-WILLIAMS, Patricia, MD Professor and Chair
University of Medicine and Dentistry of New Jersey Robert Wood
Johnson Medical School
New Brunswick, NJ

Pediatric Infectious Diseases Society (PIDS)
ANDERSON, Evan, MD
Professor of Pediatrics and Medicine
Pediatric and Adult Infectious Diseases
Children’s Healthcare of Atlanta and Emory University Hospital
Emory University School of Medicine
Atlanta, GA

Pediatric Infectious Diseases Society (PIDS) (alternate)
SAWYER, Mark H, MD
Professor of Clinical Pediatrics
University of California, San Diego School of Medicine
San Diego, CA

Pharmaceutical Research and Manufacturers of America (PhRMA)
ROBERTSON, Corey, MD, MPH
Senior Director, US Medical, Sanofi Pasteur
Swiftwater, PA

Society for Adolescent Health and Medicine (SAHM)
MIDDLEMAN, Amy B, MD, MSEd, MPH
Professor of Pediatrics
Chief, Section of Adolescent Medicine
University of Oklahoma Health Sciences Center
Oklahoma City, OK

Society for Healthcare Epidemiology of America (SHEA)
DREES, Marci, MD, MS
Chief Infection Prevention Officer & Hospital Epidemiologist
ChristianaCare
Wilmington, DE
Associate Professor of Medicine
Sidney Kimmel Medical College at Thomas Jefferson University Philadelphia, PA

ACRONYMS USED IN THIS DOCUMENT

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
AE	Adverse Event
AESI	Adverse Event of Special Interest
AHIP	America's Health Insurance Plans
AI/AN	American Indian/Alaskan Native
AIM	Association of Immunization Managers
AIRA	American Immunization Registry Association
AMA	American Medical Association
AOA	American Osteopathic Association
APhA	American Pharmacists Association
AR	Adverse Reaction
ASPR	Administration for Strategic Preparedness & Response
ASTHO	Association of State and Territorial Health Officers
BEST	Biologics Effectiveness and Safety System
BLA	Biologics License Application
CDC	Centers for Disease Control and Prevention
CISA	Clinical Immunization Safety Assessment
CLI	COVID-like illness
CMS	Center for Medicare and Medicaid Services
COD	Cause of Death
COI	Conflict of Interest
CSTE	Council of State and Territorial Epidemiologists
CVD	Cardiovascular Disease
DFO	Designated Federal Official
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DVA	Department of Veterans Affairs
ECG/EKG	Electrocardiogram
ED	Emergency Department
EHR	Electronic Health Records
EMR	Electronic Medical Record
ET	Eastern Time
EtR	Evidence to Recommendation
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GBS	Guillain- Barré Syndrome
GMT	Geometric Mean Titers
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HCP	Healthcare Personnel / Providers
HCW	Healthcare Workers

HHS	(Department of) Health and Human Services
HIV	Human Immunodeficiency Virus
HRSA	Health Resources and Services Administration
ICATT	Increasing Community Access to Testing
IDSA	Infectious Disease Society of America
IHS	Indian Health Service
IM	Intramuscular
IVY	Influenza and Other Viruses in the Acutely Ill
J&J	Johnson & Johnson
KFF	Kaiser Family Foundation
LTCF	Long-Term Care Facilities
MAAE	Medically Attended Adverse Event
MedDRA	Medical Dictionary for Regulatory Activities
MMWR	*Morbidity and Mortality Weekly Report*
MSA	Metropolitan Statistical Area
NAAT	Nucleic Acid Amplification Tests
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization Canada
NAPNAP	National Association of Pediatric Nurse Practitioners
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCIRD	National Center for Immunization and Respiratory Diseases
NEJM	*New England Journal of Medicine*
NFID	National Foundation for Infectious Diseases
NHP	Non-Human Primate
NIH	National Institutes of Health
NIS-ACM	National Immunization Survey Adult COVID-19 Module
NMA	National Medical Association
NVSS	National Vital Statistics System
PCP	Primary Care Provider/Practitioner
PCR	Polymerase Chain Reaction
PHAC	Public Health Agency Canada
PIDS	Pediatric Infectious Disease Society
PrEP	Pre-exposure Prophylaxis
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RR	Relative Risk
SAE	Serious Adverse Event
SAHM	Society for Adolescent Health and Medicine
SDOH	Social Determinants of Health
SES	Socioeconomic Status
S-Gene	Spike Gene
SHEA	Society for Healthcare Epidemiology of America
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
SSR	Summary Safety Report
SVI	Social Vulnerability Index
TTS	Thrombotic Thrombocytopenia Syndrome
UC	Urgent Care
UK	United Kingdom

US	United States
USG	United States Government
UTD	Up-To-Date
VA	(US Department of) Veteran's Affairs
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VOC	Variants of Concern
VRBPAC	Vaccine and Related Blood Products Advisory Committee
VSD	Vaccine Safety Datalink
WG	Work Group