Update From the September 2022 Meeting of the Advisory Committee on Immunization Practices

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Abstract

The Advisory Committee on Immunization Practices (ACIP), a group of medical and public health experts that provides expert advice to the Centers for Disease Control and Prevention (CDC), normally meets three times per year to develop US vaccine recommendations. The ACIP increased their meeting frequency over the past 2.5 years to address vaccine-related issues during the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic. They met to discuss updating COVID-19 booster dose recommendations on September 1, 2022 recommending use of new bivalent Coronavirus Disease-2019 (COVID-19) booster vaccines which include equal amounts of ancestral and Omicron BA.4/BA.5 variant mRNA that encodes the spike protein.

Introduction:

The US Food and Drug Administration (FDA) authorizes vaccines, while the Advisory Committee on Immunization Practices (ACIP) provides recommendations for use. This group of medical and public health experts provides expert advice to CDC. This group normally meets three times per year to develop US vaccine recommendations, but due to the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic, they met many times over the past 2.5 years to make recommendations on COVID-19 vaccine use and to address safety.

The Pediatric Infectious Disease Society (PIDS) is one of 30 organizations that has a liaison (non-voting) member to the ACIP. Dr. Sean O'Leary served in this role over the several years immediately preceding and throughout the pandemic. In the period preceding the pandemic, the PIDS representative chronicled the ACIP meeting details for PIDS membership and the broader community. We report the September 2022 ACIP meeting and will continue to provide updates about subsequent meetings through JPIDS. Importantly, these ACIP meetings can be viewed by webcast and an opportunity exists for public comment [1]. Since the pandemic, all meetings have occurred virtually. The agenda is available before future meetings (scheduled for October 19-20, 2022; February 22-23, 2023; June 21-22, 2023) and meeting slides are available before or shortly after the meeting [1].

In June 2022 the FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) met to discuss variant-containing COVID-19 vaccine boosters, including bivalent boosters containing both the ancestral strain and an Omicron-specific strain. At the meeting, initial data were presented by Moderna and Pfizer about Omicron (BA.1) containing vaccines. Given the anticipated rapid

emergence of Omicron BA.4 and/or BA.5, the FDA requested that BA.4/BA.5 sublineage variant vaccines be developed.

At the time of the September 1, 2022 ACIP meeting, the FDA had just given Emergency Use Authorization (EUA) for the Pfizer bivalent vaccine for ≥12-year-olds and for the Moderna bivalent vaccine for ≥18-year-olds. We provide a summary of the ACIP meeting which focused on providing booster recommendations for adults and adolescents (≥12 years of age) for use of new bivalent Coronavirus Disease-2019 (COVID-19) booster vaccines. These vaccines include equal amounts of mRNA encoding for ancestral (i.e., original, prototype) and Omicron BA.4/BA.5 variant spike proteins.

Updates on COVID-19 Epidemiology and Emergence of the Omicron Variants

A new surge in SARS-CoV-2 infections began in April 2022 and case counts remained elevated throughout the summer before beginning to decline in August 2022. Reported cases poorly reflect actual cases due to increases in home COVID-19 testing. US COVID-19 deaths rose to 1,042,112 according to death certificate data as of August 27, 2022. Case rates were higher in urban populations, while death rates were higher in rural populations.

CDC continues to monitor emerging SARS-CoV-2 variants including the prevalence and impact on disease incidence, severity, and vaccine effectiveness over time. More than 30 mutations in the spike gene (S) have been reported with Omicron with fifteen of those in receptor binding domain (RBD). Although Omicron variants have increased transmissibility and escape from immunological responses induced by prior vaccination, the severity of infections appears to have decreased [2].

Beginning in December 2021, Omicron BA.1 became the predominant circulating variant. Importantly, sublineages of Omicron have emerged and circulated including BA.2, BA.2.12, and now BA.5. The naming does not express the antigenic difference or similarity between the sublineage variants. BA.4 and BA.5 sublineages do not have differences from one another in the spike protein or RBD, but instead differ in non-spike proteins. As of August 27, 2022, about 89% of US circulating isolates were BA.5.

At the meeting, antigenic cartography was discussed. This approach uses convalescent sera and sera from prior vaccine recipients to identify substantial antigenic differences between the ancestral strain and key variants that have emerged (e.g., Beta, Delta, Omicron). When antigenically mapped, the Beta, Delta, and Omicron variants all appear quite different from one another. Evaluation of the Omicron sublineages indicates that although BA.4 and BA.5 viruses are antigenically different than BA.1, they clearly are more related to each other than to other variants that have emerged (e.g., Beta, Delta) [3-5].

Updates on COVID-19 Vaccination – Uptake, Impact, and Immunogenicity

Vaccine coverage was reported to be highest in those ≥65-years of age and lowest in those <18 years of age. As of August 24, 2022, about 224 million people in the US had received the primary series (72% of the population ≥5 years of age), about 108.5 million people had received a first booster dose (49% of those that completed a primary series), and about 23 million people had received a second booster dose.

Data were presented regarding vaccine effectiveness (VE) against symptomatic infection, emergency department/urgent care (ED/UC), and hospitalizations due to Omicron in the US among different age groups. VE during BA.4/BA.5 predominance was generally comparable to VE observed during the period of BA.2 predominance. A third vaccine dose provides significant additional protection against infection and severe disease in all ages studied, and the VE of a third dose wanes more slowly compared to the two-dose series during Omicron.

Currently, approved SARS-CoV-2 vaccines continue to protect against severe illness and death from COVID-19. In June 2022, unvaccinated adults had 4.6-fold higher COVID-19-associated hospitalization rate compared to those vaccinated with at least one booster dose. Although prior receipt of at least one booster dose provided 20-fold protection against death during January-March 2022, this declined to an 8-fold protection in June 2022. In June 2022, people ≥50 years of age with ≥2 booster doses had 14-fold lower risk of dying from COVID-19 compared to unvaccinated people and a 3-fold lower risk of dying from COVID-19 than people that had received a single booster dose. Most vaccinated people with severe COVID-19 have multiple risk factors for severity. Racial and ethnic minority groups have been disproportionately affected by COVID-associated hospitalization and mortality. Although these inequities have decreased over time, they have not been eliminated.

Updates on COVID-19 Vaccination – Safety

Data supporting the safety of COVID-19 vaccines were presented. There are multiple safety systems that are used to monitor safety including the Vaccine Adverse Event Reporting System (VAERS), V-Safe, and the Vaccine Safety Datalink (VSD). VAERS now has safety data from the primary series in those 6 months – 4 years of age for the Pfizer COVID-19 vaccine, and Moderna for children 6 months – 5 years of age. About 2% of VAERS reports in this population were serious; importantly,

myocarditis was not reported for either vaccine. Reported adverse events included incorrect dose administered, product preparation issues, wrong product administered, and expired product administered, thus emphasizing the importance of addressing vaccine administration issues.

V-safe is a voluntary CDC smart phone-based monitoring program for COVID-19 vaccine safety in the US. It uses text messaging and web surveys to check in with vaccine recipients after vaccination. Reactions and health impacts were not higher after a booster dose than after a second dose of the primary series. In children 6 months - ≤4-5 years of age, data from V-safe were similar to those observed in clinical trials with no unexpected safety findings and no increased risk of myocarditis to date. Injection site reactions were reported in <50% and systemic reactions in <60%. Rates in V-Safe data may be slightly higher for the second boost of Moderna, while rates for the Pfizer second boost may be lower.

Finally, the VSD gathers data from 9 sites that have vaccine administration information along with detailed electronic medical records that are linked across healthcare settings (e.g., primary care, urgent care/emergency department, hospitalization). The active surveillance VSD data through August 13, 2022 showed no statistical signals for any prespecified surveillance outcomes including myocarditis. Data showed few myocarditis/pericarditis cases after booster doses and imprecise risk estimates; risk after booster doses appears similar to risk after a second dose of the primary series. For children 5-11 years of age, there have not been verified cases of myocarditis. Administration of a booster dose in children 5-11 years of age identified 727 reports to VAERS, 99% classified as non-serious. The majority of these reports were product administration issues. For patients ≥12 year of age, there have been fewer administration error reports.

Myocarditis is a rare event following COVID-19 vaccination. CDC has verified 131 myocarditis case reports to VAERS in people ages ≥5 years after over 120 million mRNA COVID-19 booster vaccinations. Risk is primarily observed in adolescent and young adult males. In VAERS data,

reporting rates of myocarditis are lower following the first booster when compared with a second dose of the primary series. In VSD analyses, incidence of myocarditis was similar following a first booster or a second dose of the primary series.

Safety and Immunogenicity of Variant-Containing Vaccines

Manufacturers have developed vaccines to address emergence of multiple prior variants of concern including Beta, Delta, and Omicron (BA.1). These variant vaccines were tested in clinical trials [3], but variant evolution and circulation of new variants/sublineages has outpaced the development of new variant vaccines and the clinical trials conducted to evaluate them.

In June 2022, the FDA requested that both Pfizer and Moderna develop a bivalent vaccine containing equal amounts of ancestral vaccine (original vaccine) along with the BA.4/BA.5 subvariant. Prior variant vaccine clinical trial data and new preclinical data for these new bivalent vaccines were submitted to the FDA by both Moderna and Pfizer. These new bivalent vaccines received an EUA from the FDA before the ACIP meeting. Each vaccine has an equal amount of mRNA coding for spike protein from ancestral SARS-CoV-2 vaccine and Omicron BA.4/BA.5 sub-lineages. The goals of these bivalent vaccines include retaining neutralization against the ancestral SARS-CoV-2 strain, providing a stronger immunological response against circulating variants, as well as a broader cross-neutralizing response against potential future variants, and extending the durability of immunological responses.

At the ACIP meeting, data from multiple clinical trials of bivalent boosters were presented. This included data from studies of bivalent vaccines containing Omicron BA.1 that demonstrated safety

and immunogenicity in >1,700 adults. These trials included subjects with and without prior SARS-CoV-2 infections, and >1,400 individuals that had received Omicron BA.1 variant containing vaccine. The FDA EUA of the Moderna and Pfizer modified mRNA COVID-19 bivalent booster vaccines used clinical data supporting the safety and immunogenicity from all prior variant vaccine studies. These bivalent vaccines replace prior approved ancestral booster doses for populations eligible to receive them.

Moderna Data

Moderna presented data for variant-containing vaccine candidates evaluated in clinical trials in individuals ≥18 years of age. They noted prior clinical trials of 3 monovalent and 4 bivalent variant containing vaccines with >7,000 individuals receiving various variant-containing vaccines. Their bivalent vaccine candidates have included Beta-containing vaccine, Omicron BA.1, and Delta-containing vaccine (data not presented) [3]. Of note, enrollment into a bivalent ancestral-BA.4/BA.5 containing vaccine study was completed the week prior to the ACIP meeting, and data are expected later in 2022. Local and systemic reactogenicity of the Omicron BA.1 containing bivalent vaccine administered as a 4th total dose was similar to or lower than the second dose of the primary series and the first booster dose of ancestral vaccine in adults. The Omicron BA.1 neutralizing titers following this booster were significantly higher than those observed with ancestral vaccine. The BA.1 neutralizing geometric mean titers (GMTs) at day 29 in previously uninfected participants were 2,480 for bivalent vaccine versus 1,421 with ancestral vaccine for the booster dose (ratio of 1.75) with seroresponse of 100% noted versus BA.1. When evaluated versus the ancestral strain (D614G) in previously uninfected participants, the GMTs were 6,422 with bivalent vaccine versus 5,287 with ancestral vaccine (GMT ratio of 1.22) with seroresponse of 100%. The vaccine resulted in immune

responses in all ages, including those >65 years of age. Preclinical studies of BA.4/BA.5 bivalent vaccine show better Omicron responses with reduced replication in the lungs and nasal turbinates of mice with subsequent BA.5 SARS-CoV-2 challenge. Studies of BA.4/BA.5 Omicron bivalent booster in adults and the Omicron BA.1 bivalent booster in children 6 months – 5 years of age are ongoing.

Pfizer Data

Pfizer presented data for their bivalent ancestral and Omicron BA.1 variant vaccine compared with a fourth dose of ancestral vaccine. They presented data about the use of BA.1-containing vaccine which had local reactogenicity with pain and other systemic symptoms that were similar to those observed with ancestral vaccination. At the time of the meeting, BA.4/BA.5 clinical safety and reactogenicity data were pending in those 12 – 55 years. With bivalent vaccine containing Omicron BA.1, there was a broad, balanced immune response. There was a superior response to BA.1-containing vaccine with GMTs of 711 versus 456 (GMR of 1.56) with improved seroresponse by 14.6% with bivalent vaccine compared to ancestral against BA.1. The immune response to ancestral virus was similar for bivalent vaccine in comparison to ancestral vaccination (GMR of 0.99). Pfizer presented data about the GMTs observed against BA.4/BA.5 sublineage which were lower when compared to BA.1 GMTs.

Summary of Data Across Manufacturers

Data presented at the meeting did not include clinical trial data for the Moderna and Pfizer bivalent ancestral and BA.4/BA.5 vaccines in humans. However, the antigenic differences in the new bivalent ancestral and BA.4/BA.5 vaccines were relatively small when compared to the tested Omicron-containing bivalent BA.1 and when compared to the substantial differences that exist with the other SARS-CoV-2 variant vaccines (e.g., Beta, Delta) that have already been tested in other clinical trials.

Importantly, the immunogenicity of variant-containing vaccine was generally better against SARS-CoV-2 variants and possibly more durable than with an ancestral boost. Available data suggest that bivalent vaccines result in antibody titer increases against ancestral strain at least as great as monovalent variant vaccines. Initial and post-vaccination antibodies were consistently higher in those that had prior infection than in those without prior infection. The safety profile of BA.1 variant-containing vaccine boost was generally similar to ancestral vaccine.

As the manufacturing process for the bivalent variant-containing vaccines is unchanged for both Moderna and Pfizer, significant changes in reactogenicity or safety are not expected. Bivalent vaccine contains a 1:1 mix (ancestral vaccine: Omicron BA.4/BA.5) of mRNA encoding for the spike proteins.

Other considerations:

Equity continues to be critical in COVID-19 vaccine administration and uptake, and this was again highlighted in the September 1, ACIP meeting. The COVID-19 ACIP Work Group engaged in a critical review and gathered extensive input and feedback on strategies to improve equity. The need for a systematic, reliable and action-oriented review of evidence toward enhanced equity was made clear as significant disparities remain in equity. It was stated that structural problems require structural solutions and that the recommendations of individual healthcare providers remain particularly important in impacting uptake.

Modeling predicted that more hospitalizations and deaths would be averted when booster doses are recommended for all populations rather than targeting booster vaccine updates to only certain populations. It was estimated that even without emergence of a new variants, beginning vaccination in September instead of November could prevent 137,000 hospitalizations, and 9,700 deaths.

Proposed ACIP Language and Vote:

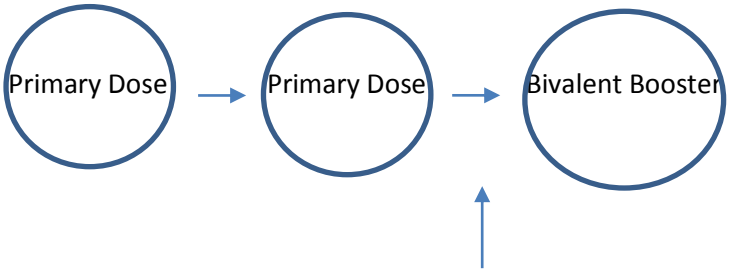
The following was posed to the ACIP: Does ACIP support the use of updated (bivalent) COVID-19 vaccine booster doses, for individuals in age groups currently recommended to receive doses?

Current recommendations:

The current recommendations are for individuals 5 – 49 years of age to complete the primary series followed by a single booster dose. The current recommendations are that those ≥50 years of age should complete the primary series followed by 2 booster doses.

New simplified recommendation:

People ≥12 years of age



Regardless of previous booster doses given (≥2 month interval)

The discussion at the meeting and the ACIP vote only included those ≥12 years of age. Variant-containing booster recommendations may be imminently forthcoming for those 5 - <12 years of age, which has also been suggested by recent news reports [6].

The FDA provided Emergency Use Authorization (EUA) of the Moderna and Pfizer bivalent vaccines (containing equal amounts of ancestral and BA.4/BA.5 variant vaccine) shortly before the ACIP meeting as a single booster dose administered at least 2 months after completing the primary series or 2 months after any prior boost. The proposed votes were to recommend a single booster dose of Pfizer bivalent (ancestral and BA.4/BA.5 combination) vaccine in those ≥12 years of age and a single booster dose of Moderna bivalent (ancestral and BA.4/BA.5 combination) vaccine in those ≥18 years of age. In addition, the proposed vote for ACIP was also to withdraw the Pfizer authorization for ancestral booster in those ≥12 years of age and the Moderna authorization for ancestral booster in those ≥18 years of age. The age difference between the Pfizer and Moderna booster authorization

was because the Moderna vaccine had not been granted approval as a booster dose in those 12 – 17 years of age.

The vote was 13 voting yes, and 1 voting no for both the Pfizer and the Moderna vaccines. The cited reason for voting against the vaccine was due to concern over the lack of clinical trial data with the bivalent ancestral-BA.4/BA.5 vaccine. Although several other committee members also expressed some reservations, they voted for the recommendation.

The ACIP recommendation implicitly agreed to a fundamental change in the basic framework for making recommendations about new COVID-19 variant vaccines. Given the data available with other variants, the ACIP agreed that recommending ancestral + BA.4/BA.5 bivalent vaccination is of greater benefit than potential risk. As such, this could pave the way for making minor updates in COVID-19 vaccine to better cover currently circulating variants without requiring clinical trial data. This change will result in an approach that is similar to seasonal influenza in which minor updates in the seasonal vaccine strain are made without requiring repeated clinical trials of the new seasonal vaccine strain prior to use.

Points of Discussion and Need for Additional Data

The ideal timing for a new booster vaccination after recent booster vaccination was discussed extensively. Many ACIP members discussed the theoretical benefits of waiting longer than the minimum 2 months (e.g., reactogenicity, safety, immunogenicity), but solid data remain limited. The optimal timing for vaccination after recent infection remains uncertain, but the consensus is that this may be delayed by 3 months from symptom onset or positive test. It is not known whether there

could be additional risk of myocarditis with COVID-19 boost vaccination in the setting of recent SARS-CoV-2 infection.

Studies of administration of a Moderna ancestral (mRNA-1273) booster dose in children 6 – 17 years of age are ongoing with data submitted to the FDA in September 2022 [6]. The lack of data about booster vaccination in pregnant women and in the immunocompromised was highlighted. Variant-containing vaccine clinical trials are just beginning in those 12 – 17 years of age with the Pfizer vaccine. The proposed framework for simplifying booster vaccination suggests that use of variant-containing vaccine might extend soon into children as young as 5 years of age. The timeline for availability of bivalent booster vaccines in children <5 years of age remains uncertain but will likely wait until additional clinical trial data are available in this population.

Finally, practical implementation issues were extensively discussed. It was noted that the current vaccine manufacturer labeling of vaccine vials could result in a high risk of administration errors due to the similarity of labeling and vial colors. The particular concern was related to accidental administration of a primary series dose with variant-containing vaccine, and the potential concern about an inadvertent boost with ancestral vaccine. Administration errors should be reported to VAERS (https://vaers.hhs.gov/).

Final Additional Considerations

It is known that the immunocompromised do not respond as well to the primary vaccination series and remain at increased risk of COVID-19. The availability of monoclonal antibodies for preexposure prophylaxis in certain high-risk individuals was emphasized. EvuSHELD is available for those ≥12

years of age with moderate-to-severe immunocompromising conditions. EvuSHELD is also available for those whom vaccination with any available COVID-19 vaccine is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine or its components. EvuSHELD should be administered at 6 month intervals. Although other monoclonal antibodies have been previously available, the spike protein mutations in variants have adversely impacted the ability of these antibodies to bind.

The coadministration of other vaccines with COVID-19 vaccine is acceptable. Immunogenicity and reactogenicity is generally similar. Influenza vaccine and COVID-19 vaccine can be coadministered and should be offered at the same visit if the individual is eligible. Vaccines should be separated at the administration location by 1 inch or greater. If the high dose or adjuvanted vaccine is administered (e.g., to an older adult), it is recommended that the vaccine should be administered in different limbs. It was noted that 9.4% of V-safe participants received simultaneous influenza vaccine administration last fall (2021) without increased safety concerns. Limited data suggest that the immunogenicity is similar when co-administered.

Disclosures:

E.J.A has consulted for Pfizer, Sanofi Pasteur, GSK, Janssen, Moderna, and Medscape, and his institution receives funds to conduct clinical research unrelated to this manuscript from MedImmune, Regeneron, PaxVax, Pfizer, GSK, Merck, Sanofi-Pasteur, Janssen, and Micron. He serves on a safety monitoring board for Kentucky BioProcessing, Inc. and Sanofi Pasteur. He serves on a data adjudication board for WCG and ACI Clinical. His institution has also received funding from NIH to conduct clinical trials of COVID-19 vaccines. C.G.A's institution has received funds to conduct clinical COVID-19 vaccine clinical trials sponsored by Moderna.

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