MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

APRIL 19, 2023
MEETING SUMMARY

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WEDNESDAY: APRIL 19, 2023

WELCOME AND INTRODUCTIONS

Call to Order/Roll Call

Dr. Grace Lee (ACIP Chair) called to order and presided over the April 19, 2023 Advisory Committee on Immunization Practices (ACIP) meeting. Dr. Lee conducted a roll call, which established that a quorum was present. A list of Members, *Ex Officios*, and Liaison Representatives is included in the appendixes at the end of this summary document. No conflicts of interest (COIs) were identified. The following potential COI was identified:

- ❑ Dr. Camile Kotton is involved in a clinical trial for Takeda for an investigational antiviral that does not involve any work with vaccines.

Announcements

Dr. Melinda Wharton (ACIP Executive Secretary, CDC) noted that copies of the slides for the meeting were available on the ACIP website and were made available through a ShareLink™ file for voting ACIP Voting, *Ex Officios*, and Liaisons Members. The ACIP is, at its heart, a public body. Engagement with the public and transparency in all of its processes are vital to the committee's work. She indicated that there would be 1 oral public comment session during this meeting, which was scheduled for 1:30 PM Eastern Time (ET). To create a fair and more efficient process, individuals interested in making an oral comment were asked to submit a request online in advance of the meeting. Priority is given to these advance requests. If more people make requests 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 may submit written comments via https://www.regulations.gov using Docket Number ID CDC-2023-0028. Information on the written public comment process, including information on how to make a comment, can be found on the ACIP 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 while serving on the committee, CDC may issue 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 those 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/she abstains on all votes related to that company. ACIP members state any COIs at the beginning of each meeting.

Dr. Wharton reported that Since the COVID-19 vaccination program began in the United States (US) in December, 2020, more than 670 million doses of COVID-19 vaccines have been administered to 270 million people. A lot has happened since the original authorizations of COVID-19 vaccines. There have been multiple changes to recommendations for vaccine use as additional vaccines became available and vaccines were authorized for additional age groups. During the February 2023 ACIP meeting, there was discussion of future directions for the COVID-19 vaccination program. This proposal included moving toward a single dose of an

updated vaccine for most people, and additional doses needed only for young children who may not yet have been exposed to COVID, older adults, and immunocompromised people. With the previous day's regulatory action by the Food and Drug Administration (FDA), a large step was taken in this direction. She invited colleagues from the FDA to provide an update on that action.

Peter Marks M., PhD (CBER/FDA) indicated that FDA's ultimate objective is to improve public health by facilitating better updated COVID-19 vaccine coverage and those eligible for vaccination. The previous day's action was an initial effort, based on the totality of evidence available, to simplify the vaccination regimen for most individuals and authorize the current bivalent vaccines to be used for all doses administered to individuals 6 months of age and older, including an additional dose or doses for certain populations. Most individuals, depending on age previously vaccinated with an original or monovalent COVID-19 vaccine, who have not yet received the dose of a bivalent vaccine, may receive a single dose of a bivalent vaccine. Most unvaccinated individuals may receive a single dose of a bivalent vaccine rather than multiple doses of the original monovalent mRNA vaccines in order to be considered protected. Most individuals who have already received a single dose of the bivalent vaccine are not currently eligible for another dose with some exceptions. The FDA intends to make decisions about future vaccination for all of the various populations after receiving recommendations on the strain composition at an FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting to be held in June 2023, at which time strain selection will be discussed for the coming year or season. As noted, individuals 65 years of age and older who have received a single dose of a bivalent vaccine may receive one additional dose of vaccine at least 4 months following their initial bivalent dose. Most individuals with certain kinds of immunocompromise who have received a bivalent COVID-19 vaccine may receive a single additional dose of a bivalent COVID-19 vaccine at least 2 months following a dose of that vaccine. Additional doses may be administered at the discretion of and intervals determined by their healthcare provider (HCP). The one exception is for immunocompromised individuals 6 months through 4 years of age for whom the eligibility for additional doses will depend upon the vaccine previously given to the individual. Children 6 months through 5 years of age who are unvaccinated may receive a 2-dose series of the Moderna bivalent vaccine. Children 6 months through 4 years of age may receive a 3-dose series of the Pfizer-BioNTech bivalent vaccine. Children 5 years of age may receive either 2 doses of the Moderna bivalent vaccine or a single dose of the Pfizer-BioNTech bivalent vaccine. Children 6 months through 5 years of age who have received 1, 2, or 3 doses of a monovalent COVID-19 vaccine may receive a bivalent vaccine, which is essentially to complete that initial vaccination series. FDA realizes that this updated regimen is still somewhat more complicated than desirable but views it as an interim step moving into the next cycle of strain selection, which is coming up in late Spring to early Summer. FDA will further consolidate and simplify the regimen as labeling is further updated for these vaccines. Ultimately, the goal is to have the regimen simple enough for patients to easily understand and providers to easily administer. For now, the key message is that for older children and adults up to age 65, a single bivalent vaccine is appropriate for prevention of COVID-19 under the current Emergency Use Authorization (EUA). In terms of those who have received non-mRNA vaccines, FDA will be discussing with manufacturers how to further update those vaccines so that there will be options available moving forward. The previous day's action does not affect those vaccines at this time.

Dr. Grace Lee (ACIP Chair) thanked FDA colleagues for their continued attention to addressing the COVID-19 pandemic, recognized that this is an evolution of recommendations or authorizations over time, and expressed appreciation for FDA's attempt to a more simplified future state.

COVID-19 VACCINES

Session Introduction

Dr. Matthew F. Daley (ACIP WG Chair) introduced this session on behalf of the ACIP COVID-19 Vaccines Work Group (WG). As they just heard from Dr. Marks, there were FDA authorizations on April 18, 2023 that included updating the COVID-19 Vaccine EUA, including the use of bivalent mRNA vaccines for all doses and indications administered to individuals ages 6 months and older and additional doses for certain specific populations.[1]

Since the February 2023 ACIP meeting, the COVID-19 Vaccines WG reviewed a number of data points around pediatric COVID-19 vaccination. They also reviewed the epidemiology of COVID-19, including among adults ≥65 years of age. The WG heard a number of vaccine effectiveness (VE) updates. In addition, they reviewed preliminary results from pediatric cost-effectiveness analyses and discussed additional doses in vulnerable populations. The February 24, 2023 ACIP meeting included COVID-19 updates and discussions on vaccine safety, VE, and epidemiology and hospitalization data. In addition, there were presentations and discussions on a benefit-risk analysis, considerations for transition to a bivalent primary series, and future directions of COVID-19 vaccines, including updates to vaccine policy.

The session on April 19 included vaccine safety updates, VE data updates, presentations on epidemiology and hospitalization data and a benefit-risk analysis, considerations for transition to bivalent primary series, and discussion on future directions of COVID-19 vaccines—including updates to vaccine policy.

COVID-19 Vaccine Program Updates

Georgina Peacock, MD, MPH, FAAP (CDC/NCIRD) presented COVID-19 Vaccine Program updates. As a reminder, she reviewed the key objectives that were set forward at the beginning of the pandemic, which were to: 1) ensure safety and effectiveness; 2) reduce mortality, morbidity, and the incidence of COVID-19 disease; 3) help minimize disruption to society and the economy, including maintaining healthcare capacity; and 4) ensure equity in vaccine allocation and distribution.

Moving into the next phase, it is important to keep these objectives in mind for the US COVID-19 Vaccination Program. In terms of the reasons for changes in the program, the Public Health Emergency (PHE) will end on May 11, 2023. Regarding what will change, it is possible that there will be reduced submission of vaccine administration data from some jurisdictions on a national level. This is going to limit the completeness of the administration data that can be reported report on a national level. CDC has been working with jurisdictions to sign an extension of their COVID-19 Data Use Agreements (DUAs) that will extend CDC's ability to get data from most states until the end of 2023. It is expected that that a few jurisdictions may not submit those data based on state laws and other issues that are impacted by the end of the PHE. Nevertheless, CDC still will be getting the majority of administration data on COVID-19 vaccines. Other things will not change. CDC will continue to work with public and private partners to learn more about the short- and long-term health effects associated with COVID-19 in terms of who is affected and why and to implement vaccine recommendations to optimize

[1] https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-changes-simplify-use-bivalent-mrna-covid-19-vaccines

protection. FDA's EUAs will remain in place for COVID-19 products, including vaccines, even beyond the PHE. All vaccines purchased by the US Government (USG) will continue to be distributed and available for free. CDC is committed to ensuring a strong immunization program going forward as changes continue to occur.

Commercialization of COVID-19 vaccines is expected to occur in early Fall 2023. Commercialization is the transition of vaccines previously purchased by the USG to established pathways of procurement, distribution, and payment for vaccinations by public and private payers.[2] Considerations include what will be authorized by FDA and recommended by CDC, and the alignment with any strain changes due to potential variants. After commercialization, vaccines will remain free for most people through the Vaccines for Children Program (VFC), the Children's Health Insurance Program (CHIP), most commercial insurance, and Medicare and Medicaid programs.

A focus on vaccination equity has been a very important part of the COVID-19 Program. CDC has been working with national, state, tribal, and territorial health departments; healthcare; and community partners to ensure that all people have fair and just access to vaccination. This effort also has addressed many issues related to vaccine confidence. Given that access and confidence go hand-in-hand, there has been a major emphasis on these over the past couple of years. CDC uses a Social Vulnerability Index (SVI)[3] to support areas that are at increased risk. The SVI allows health departments and others to look at vaccine coverage at the sub-county and Census track levels to determine where there is social vulnerability in order to target efforts to increase vaccine coverage. Making sure that uninsured adults have continued access to COVID-19 vaccines with as few financial barriers as possible is a top priority.

An important announcement was made by the HHS Secretary in the last few days that there will be an "HHS Bridge Access Program For COVID-19 Vaccines and Treatments" for uninsured adults.[4] This program is being put in place to serve the 30 million uninsured adults in the US. This supports the existing public sector vaccine safety net. Traditionally, CDC has worked with state and local health department partners to make vaccines available through the 317 Program that provides vaccines and supportive infrastructure to vaccinate uninsured adults. Funding for this effort will be made available through this existing program. Funding also will be going to Federally Qualified Health Centers (FQHCs). In addition, there will be a funded partnership with pharmacy chains. This will allow another way for uninsured adults to be able to receive vaccines free of charge. A major development over the last couple years and throughout the pandemic is that pharmacies have been a key partner in helping to increase access to COVID vaccine. Pharmacy partners administered COVID vaccine during the pandemic, which is an important model in terms of consideration of the domestic vaccine program. CDC is committed to thinking through and supporting pharmacy networks in terms of moving forward in this new phase of the COVID vaccine program. One of the ways to do this is through the Bridge Program for the uninsured.

[2] https://aspr.hhs.gov/COVID-19/Pages/FAQ-Commercialization.aspx
[3] https://www.atsdr.cdc.gov/placeandhealth/svi/at-a-glance_svi.html
[4] https://www.hhs.gov/about/news/2023/04/18/fact-sheet-hhs-announces-hhs-bridge-access-program-covid-19-vaccines-treatments-maintain-access-covid-19-care-uninsured.html

Another issue that has arisen that affects the COVID-19 Vaccine Program is the Public Readiness and Emergency Preparedness Act (PREP Act) for Medical Countermeasures against COVID-19.[5] HHS recently announced an intention to amend the declaration under the PREP Act for Medical Countermeasures against COVID-19. By issuing this amendment, the HHS Secretary intends to extend immunity liability to pharmacists, pharmacy interns, and pharmacy technicians to administer COVID-19 and seasonal influenza vaccines through December 2024. This amendment will allow for the ability of pharmacists to vaccinate children for routine vaccinations down to 3 years of age.

Another important development is the Inflation Reduction Act,[6] which includes some key provisions that eliminated cost-sharing for all ACIP-recommended vaccinations under Medicaid and Medicare Part D or equivalent plans. This started on January 1, 2023 and is continuing to be implemented. While not yet fully in place, it guarantees that nearly 50 million Medicare beneficiaries and more than 80 million Medicaid beneficiaries will have access to all ACIP-recommended vaccinations for adults without any cost-sharing. This is a very important development for the coverage of vaccines across the lifespan.

Despite these advances, a comprehensive Vaccines for Adults (VFA) Program is still needed that will fill in the gaps in places where no coverage is currently available. The proposed VFA would reduce the spread of vaccine-preventable diseases and pave the way for greater health equity. In CDC's FY24 President's Budget Request, there is a request for the proposed VFA Program. This $1.2 billion request for FY24 equates to $12 billion over 10 years that would be utilized for vaccine purchase, program operations, provider administration, and provider fee reimbursement. This would cover all ACIP-recommended vaccines for uninsured adults, which equates to approximately 30 million people in the US. In addition to this, not included in the VFA proposal, is the important provision for the support of vaccine confidence and equity activities need to continue through the discretionary funding related to Section 317.

Discussion Points

Dr. Duchin (IDSA) expressed concern about cessation of reporting of vaccine administration data, given that it seems critical to ensuring equity in access and distribution. He requested information about how this gap would be addressed long-term and whether it is part of the new informatics initiative the CDC is working on. He applauded the movement forward in terms of the Adult Vaccination Program after so many years of advocacy by the National Vaccine Advisory Committee (NVAC) and others and asked what specifically would be provided to state and local health departments that administer these vaccines and carry out many of the relationships with community providers.

Dr. Peacock emphasized that there has not been complete cessation of reporting of administration data. There will be some decreases after this PHE, most of which is related to state laws that prohibit sharing these data with the federal government. CDC is working with its state partners to determine whether there are ways to continue to receive vaccine administration data related to COVID and routine vaccinations. Putting an extension of the DUAs into place for COVID and negotiation of routine vaccination DUAs should be helpful. For COVID vaccines, the CDC COVID-19 Vaccination Program Provider Agreement is still in place. At the peak, over 120,000 providers were providing COVID vaccine. The agreement includes a provision that providers need to report administration data of COVID vaccine. While it is

[5] https://www.hhs.gov/about/news/2023/04/14/factsheet-hhs-announces-amend-declaration-prep-act-medical-countermeasures-against-covid19.html
[6] https://www.cms.gov/newsroom/fact-sheets/inflation-reduction-act-lowers-health-care-costs-millions-americans

probable that CDC will not have the full picture of what is occurring nationally, state health departments will still have these data within their Immunization Information Systems (IISs). It will still be necessary to consider ways to ensure equity moving forward. There will be challenges, but CDC has supported many partners who have been working with community-based organizations (CBOs) to examine access and confidence issues. This work is continuing to be funded and move forward. In relation to the Adult Program and support of state and local health departments, that work is critical. As a domestic program is implemented that serves people across the lifespan, the infrastructure that has been built to serve children over the last 30 years through the VFC Program serves as a basis for providing vaccines for adults through a VFA Program. Built into that is an increase in the infrastructure, which is essentially the jurisdiction awardee that CDC funds. That is an important part of the VFA proposal.

Dr. Sanchez requested clarification with regard to the amendment to the PREP Act in terms of children down to 3 years of age and how that applies to vaccine provided to children and pregnant women.

Dr. Peacock clarified that the PREP Act allowed for a number of vaccinators to vaccinate people all down to 3 years of age. Typically, there are state laws that differ by state that designate who can be vaccinators. The PREP Act extended the ability to vaccinate to pharmacists, pharmacy techs, and pharmacy interns for COVID-19 vaccine, influenza vaccine, and routine childhood vaccination. This has been ongoing throughout the pandemic. The amendment to the PREP Act allows certain provisions to continue. Certain provisions allow influenza and COVID vaccination to continue down to 3 years of age, so there is coverage across the nation for that. That provision was not extended for routine childhood immunization, which now revert back to state laws. She apologized for not having any details on pregnant women.

Dr. Daley expressed gratitude for the continuing advocacy for the VFA Program. Although death from COVID-19 is largely vaccine-preventable, it seems completely unfair that the ability to access that vaccine is related to whether someone has health insurance.

Dr. Peacock stressed that the announcement of the Bridge Program represented an important step forward toward ensuring administrative of a vaccination program that serves people across the lifespan.

mRNA COVID-19 Bivalent Booster Vaccine Safety Update

Tom T. Shimabukuro, MD, MPH, MBA (CDC/NCEZID) described current data on ischemic stroke following mRNA COVID-19 bivalent booster vaccination from the following systems:

- ❑ CDC's Vaccine Safety Datalink (VSD) Rapid Cycle Analysis (RCA) signal assessment for ischemic stroke after Pfizer-BioNTech COVID-19 mRNA bivalent booster dose vaccination in the age group ≥65 years old

- ❑ Vaccine Adverse Event Reporting System (VAERS) data on ischemic stroke following mRNA COVID-19 bivalent booster dose vaccination

As a reminder, the VSD is CDC's active, electronic health record (EHR)-based surveillance system that was established in 1990 as a collaborative project between CDC and 9 integrated healthcare organizations. These analyses included the 9 participating sites that have data on a total of about 12.5 million individuals.

VSD RCA pre-specified outcomes were assessed during weekly sequential monitoring after bivalent booster vaccination. The risk of pre-specified outcomes in 1 to 21 days following vaccination were compared with bivalent vaccinated individuals who were 22 to 42 days out following the bivalent dose. This is a vaccinated concurrent comparator method that assesses cases in vaccinated individuals in the risk window of 1 to 21 days compared to cases in vaccinated individuals in the comparison interval at 22 to 42 days. All analyses were adjusted for age, sex, race and ethnicity, VSD site, calendar time (days), and seasonality (time). The signaling threshold is a 1-sided p-value <0.01.

This table shows the pre-specified outcomes that were monitored in the COVID-19 Vaccine RCA and the settings in which they were monitored:

Prespecified outcomes	Settings
Acute disseminated encephalomyelitis	Emergency dept, Inpatient
Acute myocardial infarction	Emergency dept, Inpatient
Acute respiratory distress syndrome	Emergency dept, Inpatient
Anaphylaxis*	Emergency dept, Inpatient
Appendicitis	Emergency dept, Inpatient
Bell's palsy	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*	Emergency dept, Inpatient
Narcolepsy / cataplexy	Emergency dept, Inpatient, Outpatient
Pulmonary embolism	Emergency dept, Inpatient
Seizures/Convulsions (including 0-7 days for youngest ages)	Emergency dept, Inpatient
Stroke, hemorrhagic	Emergency dept, Inpatient
Stroke, ischemic	Emergency dept, Inpatient
Thrombosis with thrombocytopenia syndrome	Emergency dept, Inpatient
Thrombotic thrombocytopenic purpura	Emergency dept, Inpatient
Transverse myelitis	Emergency dept, Inpatient
Venous thromboembolism	Emergency dept, Inpatient, Outpatient

*All outcomes are first ever in the ICD-10 era, except anaphylaxis which is first in 7 days, and myocarditis/pericarditis which is first in 60 days

In the COVID-19 booster vaccination monitoring, the RCA detected a statistical signal for ischemic stroke after Pfizer-BioNTech bivalent booster vaccination in the age group 65 years and older. No other VSD RCA pre-specified surveillance outcomes have signaled in any age group for either of the mRNA COVID-19 bivalent boosters or when data for the 2 mRNA vaccine types were combined or pooled. VSD investigations of an RCA signal to assess whether it reflects a real effect of vaccination on an outcome include several steps, including the following:

- ❑ Data quality assessment for errors, anomalies, or missing or late-arriving data
- ❑ Analyses using different comparators than the primary concurrence (e.g., un-boosted, unvaccinated, or "historical" comparators) to supplement the primary analyses
- ❑ Additional investigations to provide context, such as background rates
- ❑ Graphic displays of outcome incidents, day-by-day after vaccination, using temporal scan statistics to assess apparent clustering to examine the temporal clustering of outcome events in subgroups defined by demographics, site, or simultaneous exposure (e.g., influenza vaccine)
- ❑ Further analyses by site or subgroup conducted as appropriate if the signal is driven by a strong association in one subgroup or VSD site
- ❑ Chart review to confirm cases and collect additional data, such as date of symptom onset
- ❑ Consideration of epidemiologic studies to further investigate surveillance findings

Moving now to the results of the VSD COVID-19 RCA analyses of ischemic stroke after Pfizer-BioNTech bivalent booster among people ≥65 years of age, substantially more Pfizer-BioNTech (643,372) booster vaccines were administered during the bivalent booster program compared to Moderna (355,767) between 8/28/22 and 4/8/23. There were substantially more doses administered early in the booster program, with the peak of COVID-19 bivalent booster with Pfizer-BioNTech at about the same time as peak influenza vaccination in this age group.

This table reflects the VSD RCA ischemic stroke case definition, onset date, codes to detect prevalence, and exclusion criteria:

ICD-10 CODES TO FIND INCIDENT CASES	ICD-10 CODES FOR LOOKBACK TO ADJUST ONSET DATE (in all settings)	ICD-10 CODES - TO DETECT PREVALENCE (history of, in all settings)	ICD-10 CODES - OTHER CAUSE EXCLUSIONS (in all settings)
Stroke, ischemic (settings = Emergency, Inpatient)	**Codes to adjust Stroke, ischemic onset (if seen within 1 day before case)**	**Stroke, ischemic - Review for Prevalence - 1ST EVER**	**Other possible causes of Stroke, ischemic**
G45.8 Other transient cerebral ischemic attacks and related syndromes G45.9 Transient cerebral ischemic attack, unspecified I63.* Cerebral infarction	**Adjust onset date if occurs in the 1 day prior to incident case:** Z92.82 Status post administration of tPA (rtPA) in a different facility within the last 24 hours prior to admission to current facility R51.* Headache R47.* Speech disturbances, not elsewhere classified R29.810 Facial weakness R53.1 Weakness R42.* Dizziness and giddiness R41.82 Altered mental status, unspecified R40.4 Transient alternation of awareness G81.9* Hemiplegia, unspecified H53.9 Unspecified visual disturbance H53.13* Sudden visual loss	**Exclude if occurs EVER prior to incident case:** Z86.73 Personal history of transient ischemic attack (TIA), and cerebral infarction without residual deficits I69.* Sequelae of cerebrovascular disease	**Exclude if COVID-19 in the last 30 days prior to incident case (not including same day):** COVID-19 DIAGNOSIS **OR** COVID-19 POSITIVE LAB TEST **Exclude if occurs in the time period noted prior to incident case (not including same day):** I48.* Atrial fibrillation and flutter (if seen EVER prior to incident case) I21.* Acute myocardial infarction (if seen within 28 days prior to incident case) S15.* Injury of blood vessels at neck level (if seen within 1 day prior to incident case) I74.* Arterial embolism and thrombosis (if seen within 1 day prior to incident case) D57.* Sickle-cell disorders (if seen EVER prior to incident case) D68.5* Primary thrombophilia (if seen EVER prior to incident case)

In terms of the bivalent RCA concurrent comparator analysis of ischemic strokes during a 1- to 21-day risk interval versus a 22- to 24-day comparison interval, the primary analysis was the vaccinated concurrent comparator, shown for the most current weekly analysis with data through April 8, 2023. This analysis was broken down by age groups 18—64 years and 65+ years. While younger age groups were assessed, ischemic stroke is a very rare outcome and those data are not informative for this analysis. For the most recent sequential analysis by the 2 age groups and by vaccine (Pfizer, Moderna) none of the findings met the signaling threshold, which is a p-value of <0.01. In the nominal analysis, all the 95% confidence intervals included 1.0, so it also was not statistically significant. As Dr. Shimabukuro recalled, the last time he showed these data, the nominal analysis for Pfizer vaccine among persons ≥65 years of age the was statistically significant and the sequential analysis did not hit the signaling threshold.

In the weekly analyses ischemic stroke after Pfizer-BioNTech bivalent booster for persons age ≥65 years from October 16, 2022 through April 8, 2023, the rate ratio was 1.26 with a 95% confidence interval of 0.99 to 1.60 as of April 2, 2023. A statistical signal for ischemic stroke following the Pfizer-BioNTech bivalent booster in this age group was first detected in November 2022. This signal persisted through January 2023, but did not meet the signaling threshold for the last 10 weekly analyses. An important caveat is that in the VSD RCA, once there is a signal, there always is a signal. While the most recent 10 weekly analyses did not meet the statistical threshold for a signal, there still was a signal for this outcome. However, CDC continues to follow these weekly analyses over time because they think it is informative to do so.

In addition to the primary analysis, supplemental analyses also are performed. The supplemental RCA analyses assessing ischemic strokes in the 1- to 21-day risk interval comparing bivalent boosted to unboosted concurrent comparators can be thought of as a vaccinated versus unvaccinated comparison. A note for this particular analysis is that it is not truly a vaccinated versus unvaccinated: it is a bivalent boosted versus unboosted, but eligible for a booster. These individuals probably are more similar than true vaccinated versus unvaccinated. In the supplemental analyses, the adjusted rate ratio was 1.01 (0.86—1.19) and was not statistically significant.

As mentioned earlier, much of the vaccination with the Pfizer-BioNTech bivalent booster was occurring at the same time as peak influenza vaccination in the VSD in persons ≥65 years of age. A substantial number of the cases in the risk window also had simultaneous influenza vaccination. Most of the individuals ≥65 years of age who had simultaneous influenza vaccination received a high-dose or adjuvanted influenza vaccine, which might be expected because those vaccines are preferentially recommended. A stratified analysis was conducted to assess ischemic stroke incidence during the risk window compared to the comparison window among persons ≥65 years of age, with and without simultaneous influenza vaccination. For individuals who received the bivalent Pfizer-BioNTech booster and simultaneous high-dose or adjuvanted influenza vaccine, the adjusted rate ratio was elevated but not statistically significant at 1.59 (0.99—2.61). The bivalent Pfizer-BioNTech bivalent booster without any same day influenza vaccine had an adjusted rate ratio of 1.01 in February 2023 in the simultaneous group and was statistically significantly elevated. It is now attenuated and is no longer statistically significant.

To summarize, the statistical signal persisted during the November to January timeframe. The rate ratio has slowly attenuated from 1.92 to 1.26 and has not met signaling criteria during the past 10 weekly analyses. Supplemental analyses using an unboosted concurrent comparator showed a rate ratio of 1.01, which was not statistically significant. Analyses evaluating simultaneous high-dose or adjuvanted influenza vaccine showed a rate ratio of 1.59, which also was not statistically significant. Separate analyses did not detect an elevated rate ratio for stroke after influenza vaccine alone. In previous presentations, data from some supplemental analyses suggested comparison interval rates were lower than expected. There can be several reasons an elevated rate ratio might be seen. There may be more than expected cases in the risk window compared to the comparison window, less cases than expected in the comparison window compared to the risk window, or a combination of two. Data previously presented in February suggested that there was some evidence of a lower rate in the comparison interval than would be expected.

Moving on to VAERS. As a reminder, VAERS is the national spontaneous reporting or passive surveillance system that is co-managed by CDC and FDA. This system is good at rapidly detecting safety signals and rare adverse events (AEs). As a spontaneous reporting system, its main limitation is that causality cannot be assessed based on VAERS data alone. In general summary of US reports to VAERS following bivalent booster COVID-19 mRNA vaccination among people ≥5 years as of April 2, 2023 (N=28,363), the distribution by age, sex, and serious status was similar regardless of manufacturer. For both Pfizer-BioNTech and Moderna vaccines, 93% of reports were non-serious. That is consistent with what has been observed with other monovalent booster vaccinations.

In terms of reports to VAERS of ischemic stroke or transient ischemic attack (TIA) after bivalent COVID-19 mRNA vaccination in people ≥18 years of age after bivalent vaccination as of April 2, 2023, there were 252 preliminary reports of ischemic stroke or TIA. Of these, 34 are still under

review, 9 were excluded based on chart review, and 60 were non-ischemic strokes verified by chart review. That left a total of 149 verified reports of ischemic stroke or TIA comprised of 110 ischemic strokes, 35 TIAs, and 4 ischemic stroke + TIA. There are 112 Pfizer BioNTech bivalent cases and 37 Moderna bivalent cases. The median age was 72 years, median time to onset was 13 days, 68 were in males and 81 were in females. All 149 verified reports had at least 1 risk factor for ischemic stroke, with the most common being hypertension. Some of these cases received simultaneous influenza vaccination. In those 18–64 years of age, 6 had simultaneous administration with standard dose influenza vaccine. Among those ≥65 years of age, 1 had high-dose, 3 had adjuvanted, 2 had standard dose, and 1 had an unknown type of influenza vaccine. This table shows VAERS reports and reporting rates of ischemic stroke and TIA in the 3 weeks after bivalent vaccination people 18–39, 40–64, and ≥65 years of age:

		Chart-verified reports			Chart-verified reports + reports under review			Background
Age group (years)	Vaccine	Obs reports	Doses admin*	Reporting rate (per million doses admin)	Obs reports	Doses admin*	Reporting rate (per million doses admin)	Exp cases†
18–39	Pfizer-BioNTech	3	6,334,671	0.5	3	6,334,671	0.5	88
18–39	Moderna	0	3,048,913	0	1	3,048,913	0.3	42
40–64	Pfizer-BioNTech	13	12,419,399	1.0	17	12,419,399	1.4	1,168
40–64	Moderna	4	7,028,873	0.6	5	7,028,873	0.7	661
≥65	Pfizer-BioNTech	51	13,693,161	3.7	60	13,693,161	4.4	4,993
≥65	Moderna	19	9,622,716	2.0	23	9,622,716	2.4	3,509

* Doses administered as of April 5, 2023

† Ramirez et al. Trends in Transient Ischemic Attack Hospitalizations in the United States. *J Am Heart Assoc.* 2016;5(9):e004026. (Estimated expected cases based upon observed annual incidence in 2010 for ages 25–44, 45–54, and 65–84 years, adjusted for period corresponding to 3 weeks after vaccination).

This is limited to reports with onset within the 3 weeks, so the observed reports are the verified VAERS reports in these specific age and vaccine strata. The chart verified reports plus reports under review is essentially a sensitivity analysis in which the reports under review are assumed to be true reports. The easiest way to explain this, focusing on the bottom row, this is saying that within in a hypothetical cohort of individuals ≥65 years of age (9.6 million individuals) about 3,500 stroke or TIA cases would be expected in a 3-week period. The background rates are based on the references at the bottom of the table. These are these observed versus expected cases, which requires some assumptions. While this is not a perfect analysis, it does provide some perspective on what is being observed compared to what would be expected based on background. To provide some information on stroke in general from CDC statistics, about every 40 seconds someone in the US has a stroke and about every 3.5 minutes somebody dies from a stroke. About 87% of strokes are ischemic strokes. In this analysis, no unusual or unexpected reporting patterns were observed and no evidence of a safety concern was detected for ischemic stroke with either mRNA COVID-19 bivalent booster in VAERS monitoring.

In terms of COVID-19 mRNA bivalent booster vaccination safety data from other monitoring systems and programs,[7] FDA monitoring in the Center for Medicare and Medicaid Services (CMS) data and Department of Veterans Affairs (DVA) monitoring in the Veterans Affairs (VA) system have not detected any safety signals using historical comparator designs. Surveillance conducted by international regulatory and public health partners have not detected a safety concern for ischemic stroke. There is no evidence of a safety signal for ischemic stroke in

[7] Note: These surveillance activities did not include analyses to evaluate the effect of simultaneous flu vaccination; different formulations of COVID-19 mRNA bivalent booster vaccinations were used globally.

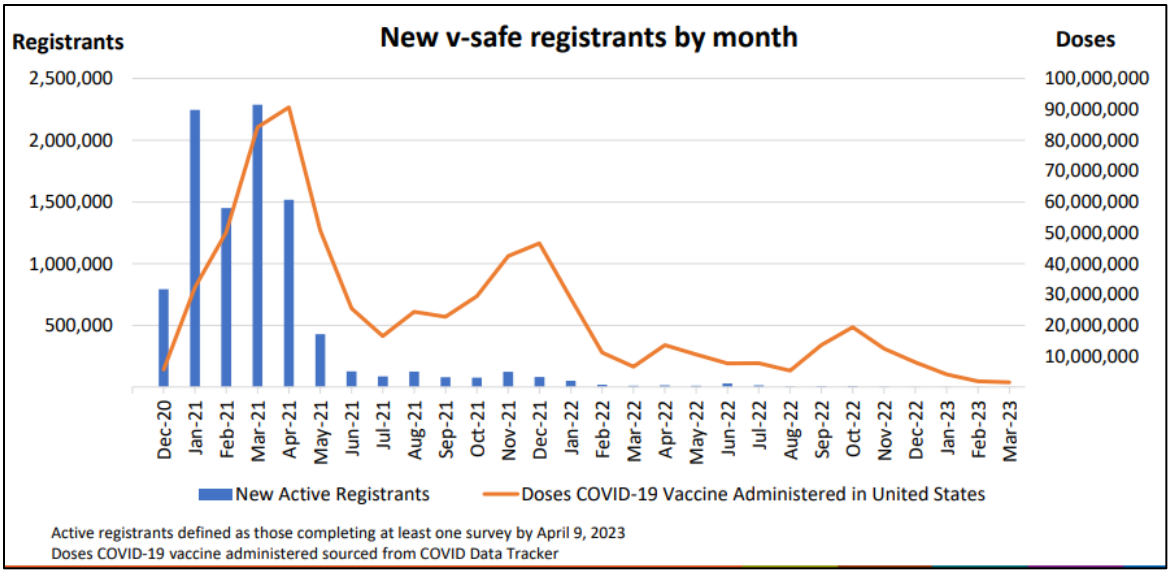
Pfizer's global monitoring of COVID boosters. No safety signals were detected for ischemic stroke for primary series or monovalent boosters for Pfizer-BioNTech or Moderna vaccines in US and global monitoring.

In terms of further evaluation, CDC will continue to consult with other surveillance systems to better understand the possible role of simultaneous high-dose or adjuvanted influenza vaccination with COVID-19 vaccination, as well as the possible decreased rate of stroke observed in the VSD in the 3 to 6 weeks following vaccination. CDC is in the process of chart reviewing a random sample of 100 cases across VSD sites and will continue to monitor VAERS. CDC continues to recommend that everyone eligible for a COVID-19 mRNA bivalent booster or influenza vaccine get vaccinated. CDC and FDA are engaged in epidemiologic analyses regarding simultaneous vaccination with COVID-19 mRNA bivalent booster and influenza vaccines.

v-safe[sm] After Vaccination Health Checker

Tom T. Shimabukuro, MD, MPH, MBA (CDC/NCEZID) next presented an update on the v-safe[sm] after vaccination health checker, including a brief overview of v-safe[sm], contributions of v-safe[sm] to the COVID-19 response, data on historical and current participation in v-safe[sm], planning for the wind-down of the current system and the development of the next version of v-safe[sm], and continued safety monitoring of COVID-19 vaccines. As a reminder, v-safe[sm] was implemented in December 2020. It was designed to collect near real-time data by direct outreach to vaccine recipients. It was initially conceived to rapidly collect basic safety data (e.g., primarily local and systemic reactogenic and health impacts) at the onset of the COVID-19 vaccination program to provide early data while other systems like VAERS and the VSD were accruing data. In addition, v-safe[sm] identified vaccinated pregnant persons for possible enrollment in the COVID-19 Vaccine Pregnancy Registry. It also was useful in rapidly collecting early safety data when authorizations and recommendations expanded to other age and risk groups. It was quickly adapted to capture simultaneous administration of other non-COVID vaccines (e.g., influenza vaccine). It was designed, built, and supported in collaboration with Oracle Health Services under a donation agreement with the Department of Health and Human Services (HHS).

Enrollment in v-safe[sm] is by self-registration on a smartphone, with any dependents added to a guardian's account. Survey completion was prompted by text message reminders for "health check-ins," which had links to online surveys. Call follow-up was performed on all participants who reported a medically attended event. There was robust participation in its first year, with 9.3 million participants and 131 million health surveys completed. Total participation to date has included 10.1 million participants and 151 million health surveys completed. Most of the registration and most of the health surveys occurred in the first year. v-safe[sm] has been particularly effective in characterizing the basic safety of COVID-19 vaccines during early vaccine introduction and following new authorizations and recommendations. v-safe[sm] has successfully accomplished his mission and worked as intended. This graph shows participation in v-safe[sm] over time:



Generally, registrations paralleled doses administered. As noted earlier, most new v-safe[sm] registrations and survey completions occurred in the first year of the vaccination program. Use has waned rapidly and has pretty low uptake at this point. Also noteworthy is that active registration and doses administering paralleled early on when many doses were administered. Then there were peaks in doses administered largely representing new authorizations and recommendations. However, there was not a corresponding surge in v-safe[sm] uptake with these new registrations. There probably were a lot of early adopters early in the program, which is not totally unexpected.

It is important to understand what v-safe[sm] is and is not. v-safe[sm] was designed to rapidly monitor and assess common outcomes (e.g., local and systemic reactogenicity and health impacts)—the basic safety profile of the vaccine. It is not designed to be a signal detection or signal assessment system. Those systems are primarily VAERS, VSD, FDA's Biologics Effectiveness and Safety (BEST) System, and FDA, CMS, and VA active surveillance systems.

In terms of the next step for v-safe[sm], the timing for the final registration and completing of surveys will be announced soon. Follow-up will continue on reports of medically attended health events. The next generation v-safe[sm] is under development. CDC plans to collect data on new vaccines. Once developed and implemented, the new v-safe[sm] will allow greater flexibility for surveys and use of CDC information technology (IT) infrastructure. It will be designed to permit longer-term support for collecting data rapidly from a large number of vaccine recipients. v-safe[sm] is one of the several complementary systems at CDC and one of many complementary systems that the USG uses to monitor vaccine safety. CDC's standard established systems will continue to monitor and assess the safety of COVID-19 vaccines. That includes VAERS, the VSD, and the Clinical Immunization Safety Assessment (CISA) Project.

Discussion Points

Dr. Virginia Caine (NMA) observed that according to the VAERS data, Blacks have a 50% greater stroke incidence than their White counterparts and asked whether stroke incidence side effects data were broken down by race and ethnic populations to understand whether there would be higher risk among Blacks over the age of 65.

Dr. Shimabukuro indicated that data on race and ethnicity are collected in VAERS, but because VAERS is passive, the data on these variables is dependent upon the reporters filling in that information. While the data are not analyzed by race and ethnicity, these data are collected. This information is also collected in the VSD, but the ability to analyze at that level is limited in the VSD because of small numbers. He acknowledged the importance and said that consideration can be given to exploring ways of getting better visibility on race and ethnicity. At least for the VSD RCA, race and ethnicity are not the primary variables in the RCA because the finer the data are sliced, the greater the small numbers problem.

While he was glad the signal had not persisted and that there would be continuing epidemiologic analyses regarding simultaneous vaccine with the high-dose influenza and COVID bivalent booster, Dr. Sanchez asked if any changes were anticipated in the recommendation that they can be administered simultaneously or if there should be a cautionary note saying that there should be an interval of separation between the two.

Dr. Shimabukuro said he did not think the data were sufficient to conclude that there is a safety problem for ischemic stroke with the Pfizer vaccine in this age group, or that there is a safety problem with simultaneous administration of COVID and influenza vaccines. Additional work is being done. FDA has a study in progress and CDC and its VSD partners will continue to evaluate the data. At this time, the feeling is that the data are not sufficient to conclude that there is a safety problem requiring make a change in recommendations.

Dr. Lee reflected on the importance of sustaining these vaccine safety surveillance efforts beyond COVID-19. She reminded everyone that during H1N1, there was a similar effort in place akin to v-safe[SM] to monitor safety rapidly with the initial implementation of H1N1 vaccines, but it was difficult to sustain. With COVID-19, it was not clear how v-safe[SM] would be able to contribute. However, it has been quite impactful—especially for pregnant populations. She expressed gratitude to CDC for continuing to sustain important and complementary safety surveillance tool for the future. It gave her confidence and she found it incredibly reassuring that based on the number of complementary systems at CDC for vaccine safety and in partnership with other federal agencies (FDA, DoD, IHS, VA, and others) that ACIP is are able to emphasize the importance of vaccine safety to vaccination programs.

COVID-19 Vaccine Effectiveness Updates

LCDR Ruth Link-Gelles, PhD, MPH (USPHS/CDC) presented a summary of vaccine effectiveness data available from CDC studies, including VE of the original monovalent vaccines and updated bivalent vaccines. This included presentations on updated estimates of VE of monovalent vaccines for symptomatic infection in young children aged 6 months–4 years (Pfizer-BioNTech) and 6 months–5 years (Moderna), as well as an update on monovalent and bivalent VE against severe disease in adults with and without immunocompromising conditions. For background, she shared the national coverage estimates from CDC's COVID Data Tracker[8] for the primary series among young children showing that young children have the lowest coverage for either a single dose or a completed primary series, with just over 10% for 1 dose and 6% for the complete primary series in children 2 to 4 years of age. Coverage is even lower among those under 2 years of age. Children vaccinated early may be meaningfully different from those who remained unvaccinated, which may impact VE estimates.

[8] https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends

The Increasing Community Access to Testing (ICATT) platform includes community-based testing data from pharmacies and partners nationwide. It uses a test-negative design with self-reported vaccine history at the time of test registration. For these analyses, only children whose caregivers reported symptoms and who were between the ages of 3 and 5 years for the Moderna analyses and 3 and 4 years of age for the Pfizer-BioNTech analyses were included. Children whose caregivers reported that the child being tested had immunocompromising conditions were excluded. These data are for tests from July 4, 2022 through April 8, 2023, although the analysis start date varied depending upon the dose analyzed. This was a period when Omicron BA.4/BA.5 and XBB related sub-lineages predominated.

Looking at preliminary estimates of VE against symptomatic infection for monovalent Moderna vaccine among children 3 to 5 years of age, VE was 40% (95% CI: 25-52) for 1 dose or a partial series during the interval between the first and second doses. VE for the complete 2-dose primary series of Moderna was 47% (95% CI: 37-54) over the entire 2 weeks to 6 months after the dose. Broken down by time since dose, VE decreased from 61% (95% CI: 47-71) during the first 2 weeks to 1 month after the dose to 18% (95% CI: -6-37), with confidence intervals crossing the null during the 4 to 6 months after the dose. Looking at the same information for Pfizer-BioNTech in children 3 to 4 years of age for a 1-dose partial series, VE was 20% with a confidence interval that just crossed the null (95% ci: 0-36). For 2 doses, which for Pfizer-BioNTech also is a partial series, VE was 40% (95% CI: 28-50) in the interval between doses 2 and 3. For 3 doses, a complete Pfizer-BioNTech primary series, VE was 27% (95% CI; 4-45) in the 2 weeks to 6 months after the dose. There was not enough statistical power to break down the Pfizer- BioNTech complete series estimates by time since last dose.

There are a number of limitations for this analysis. As noted earlier, vaccine coverage is low in children 5 years of age and under. When coverage is low, vaccinated children may be meaningfully different than unvaccinated children, potentially biasing early VE estimates and making the estimates less stable. The prevalence of prior infection among children is high. Based on CDC seroprevalence data through December 2022, more than 92% of children 6 months through 17 years of age had a prior infection. If unvaccinated children have protection from prior infection, it may lead to an underestimation of VE. However, the prevalence of prior infection is so high that these estimates are likely to represent the current situation among young children in the US. While the goal of the US COVID-19 vaccination program is to prevent severe disease, the ICATT platform estimates VE for symptomatic infection only. To date, low vaccination coverage in this age group has prevented estimation of VE against more severe disease. However, other VE platforms may impact future ability to estimate VE in this group, including against severe outcomes. Given this context, VE against symptomatic infection can provide important insight into vaccine protection.

In conclusion, a complete monovalent primary series vaccination helped provide protection for children 3 through 5 years of age against symptomatic SARS-CoV-2 infection for at least the first 3 months after vaccination. Some waning of the monovalent Moderna primary series appears to occur by 4 to 6 months after the second dose. These patterns are similar to patterns observed in older children and adults in the first months after vaccination. Waning of monovalent Pfizer-BioNTech against symptomatic infection could not be assessed, but also is likely based on analyses in older children and adults. Children should stay up-to-date with COVID-19 vaccines. CDC will continue to monitor VE in this age group, including against severe disease and for bivalent doses if possible.

Moving to updated estimates of bivalent VE against ED and urgent care (UC) encounters and hospitalizations in adults 18 years of age and older, the VISION VE Network is a multi-state network based on EHRs. Like ICATT, it uses a test-negative design with cases having COVID-like illness and a positive PCR for SARS-CoV-2 and controls having COVID-like illness (CLI) with a negative PCR. VE is adjusted for age, sex, race, ethnicity, geographic region, calendar time, and local rates of SARS-CoV-2 circulation. Vaccination is determined via EHRs and state and city registries. In terms of the absolute VE of monovalent and bivalent vaccines against ED and UC encounters among immunocompetent adults among adults 18–64 years of age and ≥65 years of age, for those who received only monovalent doses, roughly a year has passed since their last dose. For those receiving bivalent doses, the time since last dose is much shorter. For monovalent doses, there is little remaining protection. For bivalent vaccination, the trends across the age groups are similar with bivalent VE at 53% (95% CI: 48-58) for adults 18–64 years of age and 61% (95% CI: 57-64) for adults ≥65 at 7 to 59 days after the first dose. Estimated VE declines by 120 to 179 days after the bivalent dose to 15% (95% CI: 2-26) for the younger group and 25% (95% CI: 16-34) for the older group.

For hospitalizations, there was some residual protection. In contrast to the ED, effectiveness of a monovalent dose was 21% (95% CI; 10-30) for younger adults and 25% (95% CI: 18-31) for older adults. For bivalent doses, trends were similar across age groups. However, there was not enough statistical power to interpret estimates for 120 to 179 days out from the bivalent dose in the younger group. In older adults, there was waning at a higher point estimate than against ED/UC encounters. Regarding absolute VE of bivalent booster doses against hospitalization among immunocompromised individuals ≥18 years of age, there was little remaining residual protection of the monovalent vaccine. VE estimates for bivalent vaccines started lower than for those of immunocompetent individuals at 30% (95% CI: 12-44), but the same patterns of waning have not been seen in this group thus far.

To provide a snapshot of who is being hospitalized with COVID-19 and the VISION VE Network, it is important to note that this analytic population does not match the population used in the VA analysis precisely. It does give an overall sense of who is being hospitalized and who has critical illness defined as “admission to intensive care or in-hospital death within the VISION Network. The median age is approximately 75 years. Eighteen percent of those hospitalized and 24% of those with critical illness had an immunocompromising condition. This is compared to roughly 3% in the overall US population. Thirty percent of those in the hospital and 34% of those with critical illness are entirely unvaccinated, which is particularly notable when considered along with the median age of this population and the fact that in the US as a whole, 94% of those aged 65 and up have completed at least a primary series. Also notable is that 17% of those hospitalized and 15% of those with a critical hospitalization had received a bivalent booster compared to about 43% of the overall US population over 65 years of age.

The next update is on data published by CDC in December 2022 looking at the effectiveness of the bivalent boosters against hospitalization in adults ≥65 years of age through the Investigating Respiratory Viruses in the Acutely Ill (IVY) Network, which is a multi-state VE platform that uses a prospective test-negative design. For this analysis, participants were enrolled from 25 hospitals in 20 states with hospitalization between September 8, 2022 and April 1, 2023. Note that this analysis includes data beyond what was published in the *MMWR* in December 2022. Participants are adults hospitalized with COVID-like illness. Cases have a SARS-CoV-2 positive PCR or antigen test and controls are negative for SARS-CoV-2 and influenza by PCR. Models are adjusted for age, sex, race, ethnicity, admission date, and HHS region.

In terms of updated IVY results among adults ≥65 years of age for absolute VE against hospitalization, comparing people with at least 2 monovalent doses but no bivalent dose to unvaccinated people, VE was 13% with a confidence interval crossing the null (95% CI: -9-30). This is consistent with the limited to no residual protection of the monovalent doses. Absolute VE of a bivalent booster followed a similar pattern, with high initial protection and apparent waning. Looking at the relative VE of a bivalent booster comparing individuals who received a bivalent booster to individuals with at least 2 monovalent doses but no bivalent booster, the additional protection offered by a bivalent booster was 60% (95% CI: 45-71) with waning apparent with more time since the dose. Note that as with the VISION estimates, the median time since last dose was over a year for monovalent only recipients.

Regarding the durability of monovalent VE protection against the most critical illness, invasive mechanical ventilation (IMV) and death among adults ≥18 years of age in the IVY Network, this analysis assessed VE of 2 to 4 monovalent mRNA vaccine doses against IMV or death among immunocompetent adults ≥18 years of age through January 31, 2023. Overall, this group is at approximately 8 months since their last monovalent dose. For the overall group, VE was 62% (95% CI: 52-70) against critical illness. This does not vary substantially by age group. VE started at 76% (95% CI: 66-83) in the first 179 days since the last monovalent dose, with evidence of waning early on. However, that VE at a median of 455 days or about 15 months since the last dose remained relatively high at 56% (95% CI: 36-69), showing the lasting durability of COVID-19 vaccines against the most critical illness. Looking at these same data broken down by time since last dose of 7 to 179 days or 180 plus days and number of monovalent doses received, there was a slight decline in VE by time since last dose, but sustained protection overall against the most critical illness. Substantial variation is not seen by number of doses received in either the earlier or the later period.

The results presented from both the VISION and IVY VE Networks have several limitations. Regarding the estimates of absolute VE, if unvaccinated individuals are meaningfully different than vaccinated individuals, estimates may be biased. For interpretation of estimates of relative VE, residual protection from prior doses is an important consideration and likely varies by severity of outcomes studied. There is limited information on prior infection, although just as with young children, rates of prior infection in adults and older children are known to be high. Therefore, the VE estimates presented during this session represent a snapshot of how well the vaccine is working under current conditions. Finally, VE against COVID-19-associated hospitalization from the IVY and VISION platforms represent individuals hospitalized with COVID-19 disease, but may underestimate protection against critical illness.

In summary, current data from CDC VE platforms demonstrate that bivalent booster doses provide added protection compared to earlier monovalent doses against ED and UC encounters and hospitalizations in adults, though there is evidence of waning protection. For most adults, both in the platforms shown and in the general population, more than a year has passed since they last received a monovalent COVID-19 vaccine. These individuals may have limited residual protection against hospitalization and should receive a bivalent booster dose. However, results from the IVY analysis show durability of protection against the most critical COVID-19 disease requiring IMV or causing death. CDC will continue ongoing monitoring of VE, including for all outcomes of interest and for all authorized vaccines in the US, including Pfizer, Moderna, Janssen, and Novavax, with a focus on assessing new policy recommendations and VE in populations at higher risk of severe COVID-19 disease.

Discussion Points

Dr. Chen inquired as to why the original Wuhan strain was being included in the vaccines, given that there is evidence the more recent doses are more effective—certainly with the bivalent vaccines. This seemed like an opportunity to comment on thoughts about strain match and selection going forward for the bivalent versus monovalent vaccines for mRNA and other vaccine constructs as well.

Dr. Link-Gelles pointed out that the goal of this presentation was to summarize what is known about currently available vaccines and that she would defer questions about strain selection and the make-up of current and future vaccines to later conversations among the ACIP and VRBPAC.

Referring to Slide 7 regarding monovalent vaccine, Ms. Bahta asked whether there were any theories about why efficacy decreased or was not remarkable after the third dose of the Pfizer BioNTech vaccine and there was no boost at all from the second dose.

Dr. Link-Gelles indicated that it was important to keep in mind that the confidence intervals between the estimates overlap quite a bit so she was not sure it could be called a decrease. In addition, the time for follow-up is quite a bit different. For the 2-dose estimate, the analysis looked only at the interval before the third dose out to 3 months. The estimate for the third dose goes out to 6 months. That was because there were not enough children who received all 3 doses, so there was not enough power to break it down by time since dose. Therefore, the third dose is getting dinged for having more extensive follow-up time. It is known from older children and adults that VE against symptomatic infection wanes by time since dose. If there were comparable follow-up times after the second and third doses, the point estimates probably would be more comparable.

Referring to Slide 14 regarding hospitalization among immunocompromised adults ≥18. Dr. Kotton observed that while there was some overlap in the various timeframes that showed potential waning, it was not as much as might have been expected. She asked if there were any thoughts about this, especially in the context of considering another bivalent booster for the immunocompromised population ≥18.

Dr. Link-Gelles said she thought in part this was a precision issue, especially at the furthest follow-up time where the confidence interval was quite wide and there may be missing waning just because of that. In addition, the immunocompromised populations being studied in these platforms are fairly heterogeneous and includes the span of potential immunocompromise. It is known from earlier studies that the vaccine works much better in some immunocompromised populations and worse in others, such as bone or organ transplant recipients. In this case, because of precision issues, there are not enough data to break it down by type of immunocompromised. What this analysis was showing probably was the result of a relatively heterogeneous group combined with those that who probably are at highest risk of severe COVID being earlier adopters probably having different numbers of monovalent doses previously received, and different times since those monovalent doses previously received. What she would read from this comparison to immunocompetent individuals was that VE is lower at the beginning in immunocompetent individuals and similar patterns of waning would be observed if broken down by some of the variables mentioned previously, which has not been possible due to precision.

Dr. Long observed that there did not seem to be much evidence of herd protection. With the effects of bivalent vaccine boosters apparently being modest and short-lived based on these analyses, it seemed the hope with this kind of vaccine and disease the hope would be to protect against death and mechanical ventilation.

Dr. Link-Gelles agreed that the goal of the COVID-19 vaccination program is to prevent severe disease, including hospitalization and the critical outcomes discussed. VE for symptomatic infection has been shown in cases where there is a lack of data to show VE against more severe illness. This presentation showed VE for symptomatic infection in young children because to date, there has not been sufficient statistical power to assess that against severe disease.

Recognizing that there is a very small proportion of the population vaccinated and that it is difficult to assess effectiveness with the small numbers, Dr. Long asked whether the vaccine manufacturers and possibly FDA could comment on post-market Phase 4 studies that might address effectiveness in these populations. There continues to be a strong need for additional data on the levels in durability of protection for children, pregnant people, and immunocompromised populations.

Dr. Rituparna Das from Moderna responded that the effectiveness work is ongoing within the Kaiser Permanente Southern California Health System. Moderna presented some early data on bivalent effectiveness in adults during the January 2023 VRBPAC meeting and hopes to receive an update soon on pediatric VE and the immunocompromised. As noted, the ability to do this will depend on the uptake in that system.

Alejandro Chevalier from Pfizer indicated that Pfizer also is working with Kaiser Permanente Northern California and are seeking to bring the data soon.

Updates to COVID-19 Vaccine Policy: Considerations for Future Planning

Sara Oliver, MD, MSPH (CDC/NCIRD) first reviewed COVID vaccine uptake over time, pointing out that the overall population received vaccine shortly after recommendations have been updated, but uptake overall has declined over time with additional vaccine recommendations. In terms of current vaccination coverage by vaccine and age group, 16.7% of the population overall has received a bivalent booster dose to date, with higher coverage in older age groups. However, even among adults ≥65 and over, over half of the population has not received a bivalent dose to date. Regarding trends in variant proportions over time, the most recent surveillance shows that most isolates are related to the XBB sub-variant. Even with the newer variants, there has not been a larger increase in cases as seen in previous years. Looking at overall hospitalization rates by age from COVID-NET, the highest hospitalization rates continue to be among older adults.

Building on what was discussed in February 2023, the goal is simple recommendations. Aspects of this include how frequently people should get a COVID vaccine and groups or populations who may benefit from possibly more than one vaccine a year. During this session, Dr. Oliver discussed steps toward simple recommendations, noting that this is a journey that likely will include several steps. In terms of a single formulation for mRNA COVID-19 vaccines, a single annual dose possibly will be needed for most individuals, with flexibility for vulnerable populations. It is important to note that many of the monovalent COVID-19 vaccine products already have expired and others will expire soon. FDA has removed the authorizations from monovalent mRNA COVID19 vaccine products and harmonization across the recommendations

with the bivalent mRNA COVID-19 vaccines was discussed at the VRBPAC meeting in January 2023 and the ACIP meeting in February 2023. Both advisory committees expressed support.

To summarize data that have been presented during previous ACIP meetings, the bivalent COVID vaccines are able to induce an immune response, whether given as a primary series in individuals who are previously unvaccinated or when given as a booster dose. When given to unvaccinated children, the immunogenicity data of a BA.1 vaccine induced antibody titers to BA.1 that were 25 times higher than the original monovalent vaccine. The percent of patients who reported local or systemic events were similar to or less than what was seen after the monovalent vaccine. However, this may be a result of the larger percent of seropositive participants in the bivalent vaccine group. There are limited data to directly compare COVID-19 outcomes after a monovalent versus a bivalent vaccine. Most studies showed an improvement in neutralizing antibodies for Omicron variants with a bivalent vaccine. However, it is difficult to correlate that improvement to defined clinical outcomes. When evaluating antigen cartography that was presented in September 2022, the bivalent vaccines expanded the immune response and provided increased diversity in antibody response. Data from a United Kingdom (UK) study found around a 10% increase in VE for COVID-19 infections with a bivalent vaccine. The transition will reduce the mRNA products from 11 vials to 5 vials and will eliminate the lookalike vials between the monovalent and bivalent products.

To summarize discussions from the last ACIP meeting, receiving COVID-19 vaccines continues to be important for prevention of COVID-19 severe disease, hospitalization, and death. However, many children and adolescents remain unvaccinated for COVID. COVID-19 vaccine recommendations that are simple to implement may remove some barriers to uptake. Overall, ACIP was supportive of a transition of the mRNA COVID-19 vaccine primary series from monovalent to bivalent vaccines. As discussed earlier, FDA removed the authorization from monovalent mRNA products. The BLAs are still in place, but the vaccines are either expired or have very limited doses in circulation. At this point, the bivalent mRNA COVID-19 vaccines are now authorized for all indications and there were no changes to the current language in the other COVID-19 vaccine authorizations, such as Novavax or Janssen COVID-19 vaccines. In terms of what this all means for CDC recommendations, a transition to bivalent COVID-19 vaccines could simplify presentations, reduce errors, and allow continued access for vaccine with the expiration of monovalent products. Bivalent mRNA COVID vaccines would now be recommended for all indications.

The next step toward simple recommendations perhaps would be a single annual dose for most individuals. Looking at data from blood donors to assess the proportion of the population by type of immunity and how they have transitioned over time, the proportion has continued to decline over time. Overall, hybrid immunity has increased over time. Separated out by age groups, there are 2 things to note. The proportion with no prior infection or vaccination is low across all age groups in the most recent data. The proportion with hybrid immunity, which may at this point provide the strongest protection, is actually the lowest in that oldest age group. Highlighting timing for increases in cases or hospitalizations, overall increases have been seen during the winter months, due to the emergence of new escape variants, or when both have occurred at the same time.

To summarize previous discussions regarding the possibility of a single annual dose, future doses for most people would be an additional boost after prior infection, prior vaccination, or both. An update to the benefit-risk analysis shown in February demonstrated that time since the last COVID-19 vaccine dose may both increase the incremental benefits of a COVID vaccine and decrease the risk of myocarditis. As shown by VE studies, vaccine protection likely declines over time. Winter months and immune escape variants have impacted COVID-19 epidemiology. It is known that a simplified annual recommendation could help reduce vaccine and message fatigue. A plan for a fall booster dose could provide added protection at a time when many would be about a year from their last dose. The future epidemiology in SARS-CoV-2 virus evolution could help determine the need for continued annual boosters.

Again, FDA authorized a single age-appropriate dose of mRNA COVID-19 vaccine for most individuals. A single age-appropriate dose of a bivalent Moderna COVID-19 vaccine is authorized for individuals ages 6 years and older who are unvaccinated, or at least 2 months after receipt of any monovalent COVID-19 vaccine. A single age-appropriate dose of a bivalent Pfizer COVID-19 vaccine is authorized for individuals ages 5 years and older who are unvaccinated, or at least 2 months after receipt of any monovalent COVID-19 vaccine.

School children nearly all have had prior infection, vaccine-induced, or hybrid immunity. The proportion with immunity is lower in the youngest age groups. Based on these and other data, some populations of young children likely still need a prime and a boost to optimize immunity. In addition, young children will continue to age into the vaccine recommendations at 6 months and could be SARS-CoV-2 naïve. Additional data are forthcoming to evaluate the benefits of a multi-dose primary series in all children ages 5 and younger, or if those recommendations could be simplified further. The WG looks forward to presenting a cost-effectiveness analysis in children and additional antibody data in children during future ACIP meetings. In the pediatric population, FDA has authorized 1, 2, or 3 doses of a bivalent vaccine for children 6 months through 4 or 5 years. The number of doses depends on age and the number and type of prior COVID-19 vaccines received.

The overall implications for CDC recommendations are that a COVID-19 vaccine framework for a single dose could be easy for COVID-19 vaccine providers to implement and for the public to understand. The current recommendation for a single dose may evolve over time and could move to an annual recommendation. With these updates, a single bivalent dose would be recommended for everyone ages 6 years and over. For most people, the implication of this update means no change, and. the actions taken after this are exactly the same. If someone has not received a bivalent vaccine yet, they are recommended to receive one regardless of their previous vaccine history. Children 6 months through 5 years of age would receive at least 2 COVID-19 vaccine doses, including at least 1 bivalent vaccine. Detailed guidance for this will be published in the Interim Clinical Considerations.

In terms of flexibility for vulnerable populations, the rates of hospitalization for those 65 years of age and over have seen several increases over the past year. Unlike what was seen previously in the pandemic, these increases have not been nearly as high in the other younger age groups as they were earlier. However, rates of COVID-19 death by vaccination status among older adults 65—74 years of age and ≥80 years of age are highest among the unvaccinated and lowest are among those with an updated or bivalent booster dose. Many adults who already received a bivalent booster dose were eager for the option to receive another one. In a survey

of boosted adults in January,[9] over half said that they were awaiting new guidelines for additional doses and 86% said that they felt it was an important or top priority to receive additional doses. While it is known that many in the population are experiencing vaccine fatigue, there is a subset who are eager to continue to receive additional doses.

To summarize overall what was discussed in February, it is known that older adults continue to have higher rates of hospitalization than younger adults. Among older adults, vaccination rates with bivalent COVID-19 vaccines remain low and it is known that it is critical for older adults to be up-to-date on current recommendations, including receiving a bivalent booster. ACIP discussed that at the time, the data were insufficient to support a routine recommendation for older adults to receive a COVID vaccine dose every 6 months long-term, but acknowledged that the population may continue to be more vulnerable to severe COVID-19 and likely needs flexibility with COVID-19 vaccine recommendations. Updates from FDA's authorizations for adults ≥65 years of age are that a single dose of a bivalent mRNA COVID vaccine, either Pfizer or Moderna, may be administered at least 4 months following the first bivalent dose. In terms of implications for CDC recommendations, bivalent COVID-19 vaccines continue to provide protection against severe disease and rates of hospitalization or death among adults who have received a bivalent booster continue to be low. However, some older adults may benefit from an additional updated COVID-19 vaccine dose prior to future recommendations for updated vaccines this fall. Adult ≥65 years of age may now choose to receive another updated COVID-19 vaccine dose if it has been 4 months since their first bivalent dose.

For immunocompromised persons, data presented in February showed that immunocompromised adults can have a less robust immune response to COVID-19 vaccines. Unfortunately, there are no currently authorized prophylactic monoclonal antibody products for populations at highest risk for COVID-19. ACIP discussed that while the data were insufficient to support a routine recommendation for people who are immunocompromised to receive a COVID vaccine every 6 months long-term, they acknowledged that this population continues to be vulnerable and needs flexibility with COVID-19 vaccine recommendations. FDA has provided that flexibility. For people who are immunocompromised, additional doses have been recommended previously and current updates continue to allow additional protection to a vulnerable population. Updates also allow flexibility to adjust to an individual's specific circumstances, including timing of immunosuppression as well as the possible need for re-vaccination after particular events (e.g., stem cell transplant). Additional guidance is to be published in Interim Clinical Considerations. People who are immunocompromised may choose to receive another updated COVID-19 vaccine dose and have the flexibility to receive additional doses based on their clinical circumstances.

To recap, steps toward the goal of simple recommendations include the single formulation mRNA COVID-19 vaccines and a single (possibly annual) dose for most individuals, with flexibility for vulnerable populations. However, this cannot be achieved in a single action, so it is important to acknowledge that future steps may be possible. While the updates during this session were focused on mRNA vaccines, it may be possible to simplify all COVID-19 vaccines. While looking to the possibility of updated vaccines this fall, the WG will continue to evaluate data-driven ways to simplify the pediatric program and present related data during upcoming meetings. As always, the goal will be to continue to work toward a goal of flexibility and simple guidance.

[9] KFF COVID-19 Vaccine Monitor: January 2023. https://www.kff.org/coronavirus-covid-19/poll-finding/kff-covid-19-vaccine-monitor-january-2023/ Accessed February 7, 2023

In summary, COVID-19 vaccines continue to be the most effective tool available to prevent serious illness, hospitalization, and death from COVID-19. Simple recommendations are easier to communicate, which may improve uptake. It is anticipated that an updated fall vaccine could be available. The WG will continue to review data to inform possible recommendations. Based on available data at this time, it is anticipated that there would be benefits of COVID-19 vaccines this fall. Updates to COVID-19 vaccine policy also can acknowledge the possibility of future recommendations. For most individuals, the current doses needed remain unchanged. A single bivalent vaccine is recommended and there could be an updated vaccine and recommendations this fall. In direct response to feedback from previous discussions, there is flexibility for vulnerable populations in the current recommendations. Young children continue to be recommended for multiple doses for the prime/boost immune response. The WG will continue to review additional data to optimize those recommendations.

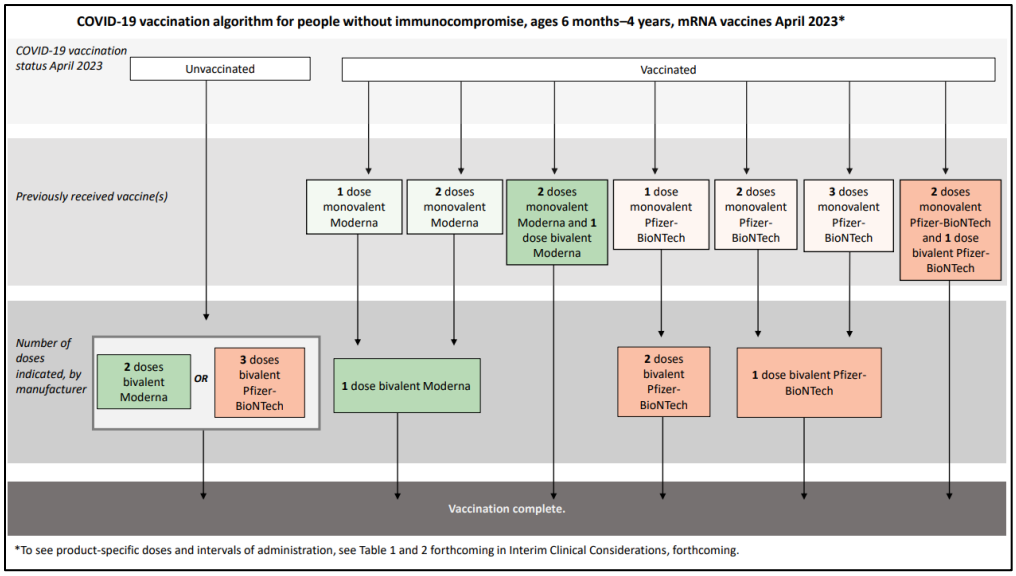
To summarize the WG discussions overall: the WG will continue to review data and evaluate the COVID-19 vaccine program in the context of evolving epidemiology. To date, the COVID-19 Vaccine WG has had 112 calls in which they have reviewed the data and discussed the COVID-19 vaccine program. Early COVID-19 vaccine recommendations were made in light of a highly susceptible immune-naïve population who had limited treatment options. Increases in population-level immunity through vaccine and infection, SARS-CoV-2 virus evolution, availability of antiviral treatments, and the review of COVID-19 epidemiology and hospitalization rates can lead to evidence-based updates in vaccine policy. This does not change decisions that were made then but highlights that the program can continue to evolve as these data evolve as well. Work will be ongoing to review additional data and continue efforts for simplification. When reviewing the totality of the data, the WG was supportive of simplified recommendations and flexibility for vulnerable populations.

Updates to Interim Clinical Considerations for Use of COVID-19 Vaccines

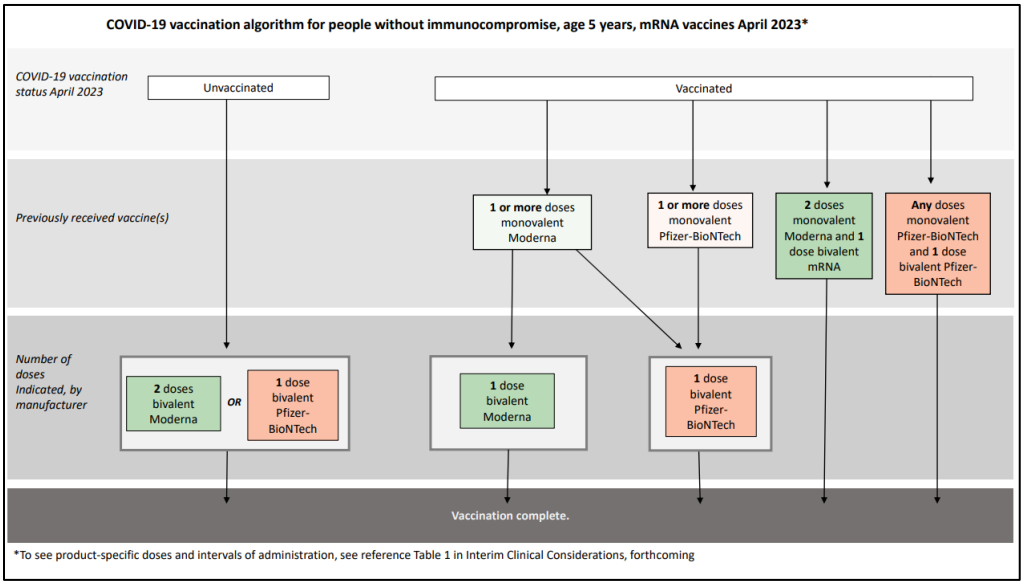
Evelyn Twentyman, MD MPH (CDC/NCIRD) presented updates to the Interim Clinical Considerations for the use of COVID-19 vaccines that are anticipated as a result of the authorized revisions the previous day. First, these new recommendations are simple and singular for most people. The previous recommendations were for people ages 6 through 11 years without immunocompromise, including specific recommendations for a primary series and booster, with variation by age and by product. The new recommendation for people aged ≥6 years without immunocompromise who have not yet received a bivalent mRNA dose is extremely simple: receive one bivalent mRNA dose regardless of COVID-19 vaccination history. The good news is that vaccination is complete for people who already have received a bivalent Pfizer or Moderna mRNA dose and no doses are indicated at this time.

The new recommendations also offer flexibility for people at higher risk. One of the groups of people at higher risk of severe COVID-19 disease is people ages 65 years and older. People ages 65 years and older who have not yet received a bivalent mRNA dose are recommended to receive that dose. Additionally, they have the option of receiving an additional bivalent mRNA vaccine dose when it has been at least 4 months following their first bivalent mRNA dose. That means that those aged 65 years and older who have already received a bivalent mRNA dose, for example, who received their updated booster when they were authorized in September 2022 or sometime thereafter, are already up to date. Vaccination is complete.
With the new flexible recommendations, they have the option of receiving an additional bivalent mRNA vaccine dose when it has been at least 4 months following the initial bivalent dose. There also is flexibility for people at higher risk of severe COVID-19 disease due to immunocompromise. For those people aged 6 years and older who have already received a

bivalent mRNA dose, an optional additional bivalent mRNA dose may be administered at least 2 months after their first bivalent mRNA dose and additional bivalent mRNA doses may be administered as needed. The changes additionally offer customized recommendations for young children as illustrated here. The new recommendations are customized by COVID-19 vaccination history such that all children receive at least 2 vaccine doses in total, including at least 1 bivalent dose. This flow chart was developed to depict how to easily determine what customized recommendation is relevant to a child given their personal COVID-19 vaccine history. For the Interim Clinical Considerations to be posted to the CDC website, a complete table has been developed of the recommendations for vaccine doses moving forward, given any particular history of COVID-19 vaccination:



The other group of children who have customized recommendations are 5-year-olds. These recommendations are extremely similar to those for children ages 6 months through 4 years:



To summarize it means to be up-to-date with COVID-19 vaccines in the context of the new recommendations, adults and children aged 6 years and older are up-to-date with COVID-19 vaccines if they got a bivalent (updated) COVID-19 vaccine. Children 6 months through 5 years of age who received the Pfizer-BioNTech COVID-19 vaccine are up-to-date if they are 6 months to 4 years of age and got at least 3 COVID-19 vaccine doses, including at least 1 bivalent (updated) COVID-19 vaccine dose or they are 5 years of age and got at least 1 bivalent (updated) COVID-19 vaccine dose. Children 6 months through 5 years of age who got the Moderna COVID-19 vaccine are up-to-date if they got at least 2 Moderna COVID-19 vaccine doses, including at least 1 bivalent (updated) COVID-19 vaccine dose. Persons may be eligible for additional COVID-19 vaccine doses if they are 65 years of age and older and got their first bivalent (updated) COVID-19 vaccine booster 4 or more months ago and/or are moderately or severely immunocompromised and received a bivalent (updated) COVID-19 vaccine booster 2 or more months ago. Someone who is unable or chooses not to get a recommended bivalent mRNA vaccine will be up-to-date if they got the Novavax COVID-19 vaccine doses approved for their age group.

In terms of implications for vaccine providers, the new recommendations result in fewer total COVID-19 vaccine products in use, which might be very helpful for vaccine providers. There will now be 5 total bivalent products in use and 1 monovalent product in use. The supply of the 1 remaining monovalent COVID-19 vaccine will be expired on May 6, 2023. Additional help for providers is on the way. CDC is working to serve providers the very best way possible. Interim Clinical Considerations are being updated with comprehensive tables of vaccine doses and dosages indicated for each age group, and by history of COVID-19 vaccines received for children aged 6 months through 5 years. CDC is working to revise additional clinical guidance materials and will present these new recommendations and their implications for providers in greater depth during an upcoming Clinician Outreach and Communication Activity (COCA) call on May 11, 2023.

In terms of implications for public health, one of the most important messages is that although the new recommendations are simplified and although everyone ages 6 years and older will now be up-to-date following receipt of an updated mRNA vaccine, most people in the US have not yet received an updated mRNA vaccine. Just 16.7% of the entire US population and just over 20% of adults or 4 out of 5 adults have not yet received a bivalent mRNA vaccine and are not up-to-date with COVID-19 vaccination at this time. Bivalent COVID-19 vaccine coverage tends to decrease with decreasing age. Unfortunately, coverage is not even 50% among people ages 65 years or older who may be at higher risk of severe COVID-19 disease because of their age. Unfortunately, racial disparities in receipt of bivalent mRNA vaccines persist. Bivalent COVID vaccine coverage is lowest among Black, non-Hispanic, Hispanic/Latino, and Native Hawaiian or other Pacific Islander populations. It also is important to point out that bivalent COVID-19 vaccine coverage is lower among those with lower income. It is evident that providing these vaccines free of cost to the recipient has not yet resulted in equitable coverage by income. Unfortunately, bivalent COVID-19 vaccine coverage is also lower among those without health insurance. It is important to underscore here that a person does not need to have health insurance in order to receive a bivalent COVID-19 vaccine. It does appear that there is still work left to be done in achieving equitable coverage for those without health insurance.

To provide some reflections and next steps, COVID-19 vaccines continue to be the most effective tool to prevent serious illness, hospitalization, and death from COVID-19. However, uptake of the updated bivalent COVID-19 vaccines is not yet equitable and remains generally

low. Simple recommendations are easier to communicate, which hopefully may improve vaccine uptake. CDC is continuing to work toward additional materials for vaccine providers, clinicians, and the general public to make it easy for everyone to get up-to-date and stay up-to-date with COVID-19 vaccines.

Discussion Points (Oliver & Twentyman)

Ms. Bahta asked whether ethnic and racial background information related to hospitalization and death are available and expressed concern that there might be a missing gap of individuals who are vulnerable between 50 to 65 years of age.

Dr. Oliver recalled a presentation in February from the COVID-NET team, which is where those data come from at CDC. While she did not remember specifically whether those data showed race and ethnicity, she will engage in discussions looking forward to future meetings to determine whether additional data can be provided on that.

Based on the comments that have been made via the Federal Registry, Ms. Bahta pointed out that it is important to understand why the recommendations are not being updated and especially why there is no booster for Novavax. While Dr. Marks addressed this, she thought it was important to re-explain that.

Dr. Twentyman indicated that there is a Novavax booster that is authorized in some situations, specifically including among those who are unable or unwilling to receive a bivalent mRNA vaccine dose and who have not received previous booster doses. This is part of the authorization of that vaccine dose and is why it is stated as such. In terms of updating the Novavax vaccine itself, she called upon the sponsor to comment.

Dr. Raburn Mallory, Novavax, indicated that they are working to provide an updated vaccine for the upcoming full winter season. They have been engaged in discussions with the FDA and other regulatory authorities about what kind of updates might be made to the vaccine.

Dr. Kotton asked whether the FDA could provide any additional explanation for children who are immunocompromised regarding the number of vaccine doses that they can receive, which seemed somewhat different from what ACIP had been thinking. In addition, she asked whether there would be additional guidance from FDA or CDC through Clinical Considerations. While she understand that the intent was to provide an individual clinician flexibility with some of the more extenuating circumstances, she wondered if there would be any specific language provided regarding that, because as an immunocompromised host provider, she was not necessarily entirely clear on what the flexibility actually would provide.

Dr. David Kaslow, FDA, indicated that immunocompromised children and adults can receive an additional bivalent dose after they have gotten their first bivalent dose. FDA has provided flexibility for additional doses at the discretion of the HCP and taking into consideration an individual's clinical circumstances.

Dr. Twentyman clarified that Moderna recipients ages 6 months through 5 years of age have the option to receive further additional doses of bivalent Moderna COVID-19 vaccine as informed by the clinical judgment of a HCP, personal preference, and circumstances. Those ages 6 years and older who received Moderna also have the option to receive further additional age-appropriate doses of bivalent Moderna COVID-19 vaccine as informed by the clinical judgment of a HCP, personal preference, and circumstances. Pfizer recipients ages 5 years and older

have the option to receive further additional age-appropriate doses of bivalent Pfizer COVID-19 vaccine informed by clinical judgment, personal preference, and circumstances. Novavax recipients ages 12 years and older have the option to receive further additional age-appropriate doses of bivalent mRNA COVID-19 vaccine informed by the same considerations. Children 6 months through 4 years of age who are immunocompromised who received Pfizer are not perceived to be authorized at this time.

Dr. Marks emphasized that the FDA has to make decisions based on data and there were not sufficient data to support the additional dose. Updates will be made when data are available. That means that immunocompromised children 6 months through 4 years of age who had a prior Pfizer dose cannot receive additional vaccine doses moving forward until such time as FDA has the data, which is anticipated to be toward the fall vaccination campaign once strain selection is decided.

Dr. Kotton stressed that this potentially leaves this immunocompromised vulnerable population at higher risk for at least the next 6 months, which sounded potentially devastating for a high-risk immunocompromised population. Certainly, during the pandemic there have been times when the best decisions have been made at the time based on the preponderance of data in the interest of public health. She spoke strongly in favor of trying to protect this vulnerable pediatric population.

Dr. Marks indicated that FDA is happy to take this into consideration and to speak with their CDC colleagues.

Regarding the bivalent Moderna being a lower dose than the primary series, Dr. Lee asked what the potential impact would be now that the lower bivalent dose would be allowed for use as a primary series even though an additional dose is allowed. Immunocompromised children and adult patients are presenting with severe consequences and have been hospitalized for prolonged periods of time. For the immunocompromised population, there are not good choices right now or the data to support that it will be possible to optimally protect that population. Given that, she asked what guidance FDA would give providers who are caring for these patients.

Dr. Marks replied that they allowed the additional dose for Moderna because of the way previous doses were administered and the situation they were in. It was a challenge to sort out what would be best to do, given the various doses of the vaccine that were used in the initial series and in subsequent ones. FDA will take this under advisement.

Dr. Lee emphasized the need to highlight the gap that Dr. Kotton identified and provide some guidance to clinicians about how to manage these patients because right now, there are not optimal ways to protect those who are immunocompromised who are 5 years of age and younger.

Dr. Das, Moderna, responded that the primary series is 25µg for children, but the booster dose is 10µg for children 6 months to 5 years of age. The 10µg bivalent booster dose is also the dose for 6 years of age plus. Dr. Lee noted that the question would be whether to provide the 25µg dose for those who might be immunocompromised if they are felt to need the additional doses versus the one that is now approved for those 6 months to 5 years of age.

Dr. Sanchez expressed appreciation for the flexibility, echoed what had been said about immunocompromised children, and agreed that clarification was needed. Given VE in immunocompetent children with the Pfizer and Moderna products, he would think that

immunocompromised children need further dosing and would appreciate not only further, but also more protection in that age group. In terms of scheduling, the bivalent dosing of 10µg was still confusing to him.

Dr. Twentyman indicated that this would be addressed in the forthcoming Interim Clinical Considerations. CDC is creating a table of precise dosage by both microgram, intervals by age, and COVID-19 vaccine history so that providers will be able to look up exactly where their patient is sitting on the table and provide exactly the dosage indicated from the vial indicated. To speak to the Moderna issue, the chart indicates that children 6 months to 4 years of age who have not previously received COVID-19 vaccine are recommended to receive 2 doses of Moderna COVID-19 bivalent vaccine at a dosage of 25 µg from the dark blue cap gray label bordered vial at an interval of 4 to 8 weeks between Dose 1 and Dose 2. That is just one example, but the plan is to provide this guidance for every age and by history where relevant among children ages 6 months through 5 years. The 10µg dose remains in use for children with a history of receipt of 2 doses of monovalent Moderna COVID-19 vaccines. In other words, that recommendation has not changed from the previous recommendation, and they can receive the 10µg dose from the existing booster dose vial for that age group.

Dr. Marks, FDA, clarified that for the Moderna vaccine, children between the ages of 6 months and 4 years have received 2 doses at 25µg. As in some adult situations, there can be a third dose given to the immunocompromised at the same 25µg dose. A third 25µg dose of Moderna may be given in that population. Immunocompromised children who have not received any doses could receive up to the 3 doses of Moderna at 25µg each. That information is included in the Fact Sheet.

Dr. Caine pointed out that the Biden Administration has a Bridge program for the 30 million uninsured adults, and there is an effort to get funding for the vaccine for adults. One of the slides showed that only 9% of Blacks overall have had bivalent COVID-19 vaccine. She asked whether there are any recommendations and/or funding from ACIP for community-based organizations (CBOs) engaged in outreach to get folks vaccinated. She is concerned about those who are not connected to a medical home such as FQHCs or providers and about how to get them connected to a medical home. Also concerning is that there has been a substantial increase in undocumented immigrants.

Dr. Peacock indicated that throughout the pandemic, a fairly large amount of funding has been provided to CBOs and various state and local health departments to focus on this type of work. One of the activities that CDC has funded is through the Partnering for Vaccine Equity (P4VE) program. That is COVID-19 supplemental funding that is still in place and is scheduled to go through FY24. CDC is continuing to work with CBOs, which is a critical need. Overall, there has been fairly low uptake of updated vaccine and a lot of work needs to be done to improve confidence and access for these vaccines.

Dr. Hackell seconded the comments about addressing pediatric patients whose age group changes, especially during the Moderna primary series because the dose is different. Pediatricians often are asked a lot of questions by families, parents, and grandparents. Anticipating a possible update in the vaccine in the fall and thinking about whether the optional second booster should be received now, there could be an impact on eligibility for a booster in the fall if the composition of the vaccine changes.

Dr. Oliver emphasized that changes are being made to the recommendation in anticipation that there still may be additional changes this fall. Overall, especially for children, the additional doses that would be recommended would be for immunocompromised people. This would be up to the clinician, but if there is a desire and potential benefit, especially based on the level of immunocompromise, then she would encourage someone to get all available doses. It is not anticipated that getting a dose now would preclude somebody from getting a dose in the fall. Reasonably healthy and perhaps older adults may want to wait until the fall, which is an option.

To clarify some continuing confusion, Dr. Twentyman explained that the transition from the era of monovalent mRNA vaccines to bivalent mRNA vaccines is slightly different for 5-year-olds because these children were previously recommended to receive either 2 or 3 primary series doses and then at least 1 bivalent dose. For 5-year-olds who have started the Moderna series, there are now customized recommendations to make sure that they all receive at least 2 vaccine doses in total, including at least 1 bivalent dose. Pfizer recipients who have turned age 5 who received Pfizer or who will receive Pfizer have the very simple recommendation of receiving a single bivalent dose.

PUBLIC COMMENT

Overview

The floor was opened for public comment on April 19, 2023 at 1:30 PM ET. Given that many more individuals registered to make oral public comments than could be accommodated during this meeting, selection was made randomly via a lottery. Dr. Lee provided a gentle reminder 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 ID CDC-2023-0028. Visit http://www.regulations.gov for access to the docket or to submit comments or read background documents and comments received.

Public Comments

Donna Treubig
Licensed Child Care Provider
Family Traditions Child Care

Thank you. Hello. I am a licensed childcare owner/provider. I have worked very hard over the last 3 years and continue to work to protect the very young children I care for, including my young grandchildren, from this virus. I have no conflicts. I'm also a proud member of Protect Their Future, a non-profit grassroots advocacy organization made up of parents, doctors, and scientists dedicated to ensuring that children are prioritized regarding the development of vaccines. While I am a member, the following comments are my opinions. Our children need your commitment to the early approval of the next round of fall vaccines before school starts in August. We need all children, including children under 5, to be vaccinated and have immunity before starting school and daycare this fall. Please simplify the process. Families across the country are actively looking to vaccinate their young children, but pharmacies will not administer them and pediatric offices cannot manage a large stock of vials. All vaccine trials and next generation solutions should include all age groups simultaneously. We know that the vaccines are safe and effective. We also know from the data that children under 1 are at a higher risk for COVID complications. Babies cannot wear a mask to protect themselves. Even based on

today’s discussion, please do not continue to leave them behind. It would be beneficial for those who haven't been infected, pregnant women, people with high BMI, and others to have access to another bivalent booster before the late summer spike. There shouldn't be an age range or immunocompromised requirement to get a second bivalent booster today. It is too early to move to a once-a-year flu shot-type schedule for COVID. COVID is still mutating. The vaccine manufacturers need to be ready and free to produce a variant specific booster that is quickly available to all age groups. Thank you very much.

Ms. Crescent Martin
Pregnant Person

Good afternoon and thank you for the chance to comment today. I urge the ACIP and CDC, in coordination with colleagues at FDA as needed, to immediately grant pregnant people permissive access to an additional COVID booster based on their pregnancy status. Recently, the WHO updated its recommendations to include pregnant people as a high priority group and to recommend that pregnant people receive an additional booster dose if their last dose was more than 6 months ago. I was heartened to hear Dr. Sara Oliver state at the February ACIP meeting that a deeper dive into the emerging data on vaccination among pregnant individuals, with a view towards assessing what data is needed to make recommendations for that population, is among CDC’s top priorities for upcoming meetings. But I'm here to remind you that people who are currently pregnant do not have the luxury of waiting for full consideration of all of the emerging data. I received a bivalent booster as soon as I could get an appointment in September—more than 7 months ago. I'm currently in my third trimester of pregnancy and I recently received a Tdap booster as recommended to protect my infant against whooping cough. However, under current restrictive US authorizations, I'm not eligible to receive an additional COVID booster to maximize the maternal antibodies I could be passing on to my infant. These antibodies could help reduce her risk of serious COVID complications before she is eligible for her own vaccination. For context, this is my second pandemic pregnancy. My first pandemic baby was born in Summer 2020, a truly scary time to be pregnant, before any vaccines were available. My family tried hard to shield my son from getting COVID until after he was finally eligible to be vaccinated in June 2022. In large part, our concerns were about the unknown long-term consequences of infection with a novel pathogen, especially with a naïve immune system. In 2023, we're now fortunate to have the tools of vaccination and so it should be much easier to protect this pandemic baby. However, the current move to an annual vaccination schedule does not have enough flexibility to optimally protect the vulnerable groups of pregnant people and infants under 6 months. As we wait for sufficient evidence to support an affirmative policy recommendation that a COVID booster is absolutely necessary in each pregnancy, we do have very strong safety data. The currently available evidence suggests that the known and potential benefits of an additional booster are likely much higher than the known and potential risks. It would be a reasonable choice under a shared clinical decision-making model for a pregnant person to choose an additional booster dose during pregnancy. CDC and FDA policy should not stand in the way of that decision, but instead should ensure that pregnant people have authorized access to additional booster dose if they wish to receive one. This, of course, is in addition to continuing to promote and provide access to vaccination for the many, many pregnant people who are not otherwise up-to-date. Thank you for your consideration and I look forward to hearing your discussion this afternoon.

Dr. Jonathan Vigh
Project Scientist
National Center for Atmospheric Research

Thank you so much, Dr. Lee and ACIP members. Thank you for the opportunity to provide input on this very important subject. I'm a Project Scientist at the National Center for Atmospheric Research in Boulder, Colorado. I'm also a wildfire survivor. My family lost their home in the Marshall Fire. My 2 children attend elementary school here in Colorado and there has been a frightful amount of illness at their school this year, including COVID, RSV, flu, and strep. Although no one in my family has tested positive for COVID so far, my son has been sick for weeks and we worry he could be suffering from post-viral syndrome. I've learned that resilience is vital, and that health cannot be taken for granted. I had Moderna for my first 3 vaccinations. After my second shot, I experienced a strong reaction which included fever, malaise, heart palpations, and chest pain. My first booster was only somewhat better. It was miserable to have to miss a day of work each time I got vaccinated. Last fall, I was due for my second booster, so I decided to try Novavax. The difference was night and day. The only side effects I experienced were a sore arm, a slight tingle in my scalp, and feeling a little tired in the evening. I was able to work the next day and for me, Novavax was a game changer. From everything I've heard, I understand that Novavax's monovalent vaccine has effectiveness on par with the bivalent vaccines. Recent real-world data shows that the mRNA protection starts strong and begins fading as early as 4 months. In contrast, Novavax offers durable, lasting protection and excellent protection against severe disease with fewer side effects. Also, many people suffering long-COVID have reported that Novavax improved their symptoms. The weight of evidence that we have in hand shows that Novavax is an effective and safe vaccine. Therefore, it is inexplicable why the current guidelines make it nearly impossible for Americans to get Novavax as a second booster. I have not seen any scientific justification that supports this restriction. I'm asking for 4 changes to vaccine immunization practice today: 1) Please allow all age groups to get vaccinated more than once per year, if desired; 2) Please speed up the timeline for kids under 12 to be able to get Novavax. I would like my kids to get it; 3) allow kids to get their booster a full month before the school year starts; and 4) Please, please change the guidelines to allow people to get Novavax without regard to their previous vaccination history. We won't achieve full vaccine equity until all Americans have the freedom to choose the vaccine that is best for them. Once we achieve this, I believe that we will see improved uptake of boosters. This will move the needle toward stopping transmission and finally ending this pandemic. Thank you very much.

Ms. Gwendolyn Kull
Attorney & Contributing Author
Brownstone Institute

Thank you. My name is Gwendolyn Kull, I'm an Attorney and a Contributing Author for Brownstone Institute. I'm here today to speak about the policy requiring COVID-19 vaccination for foreign travelers to the United States. And for those of you who might not be aware, the CDC has an Amended Order mandating that all travelers, non-citizen, non-immigrants, to the United States be vaccinated before boarding an airplane. If this policy were truly for preventing disease, shouldn't we instead mandate testing? This policy has failed at its purpose and is costing thousands, precious time with their family members, and the US economy billions in revenue. As of August 19, 2022, the CDC public policies should not differentiate by a person’s vaccination status because of breakthrough infections. Yet this policy continues, leaving those of us harmed by it to question why. Vindictive punishment for the exercise of medical autonomy or religion? The CDC has a duty to the American public and the US Constitution to rescind the

policy regardless of President Biden's proclamation because it is unconstitutional. It is an unlawful delegation under Title 3 since Director Walensky was not appointed through Senate confirmation. It is not rationally related to the purpose of disease prevention since vaccines do not prevent the disease, and it further causes families to be separated. It oversteps authority vested by Congress under the Administrative Procedures Act by creating additional requirements for entry into the United States than are actually legislated under Title 8, Section 1182a, which only requires proof of vaccination against vaccine-preventable diseases prior to entry. Even if the vaccine did prevent disease, the policy is still ineffective because it doesn't apply to Americans who can travel nearly anywhere in the globe unvaccinated, free to transmit the disease. In reality, the policy fails because the vaccines do not prevent disease and it allows people with active COVID infections to fly to the US so long as they present proof of vaccination. As a result of this policy, bi-national families have been kept apart—some for more than 3 years. Unvaccinated visa holders living in the United States have been trapped here for fear they will be denied re-entry and lose their jobs or education. Tourists choose non-US destinations. The vaccine is now also senselessly on the immigration schedule for adults and children, again violating 1182a and the PREP Act. Probable reciprocity is not maintained with other nations and the US lost nearly $100 billion between lost tourism revenue and the cost of enforcement in the last year alone. Stop wasting resources and taxpayer dollars on this moot and unlawful policy that's causing real harm to innocent, healthy people while not preventing transmission. Resend the amended order implementing Proclamation 10294. Thank you.

CERTIFICATION

Upon reviewing the foregoing version of the April 19, 2023 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

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Term: 8/4/2021 – 6/30/2023

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ACRONYMS USED IN THIS DOCUMENT

Acronym	Extension
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
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
ARI	Acute Respiratory Illness
ASTHO	Association of State and Territorial Health Officers
BEST	Biologics Effectiveness and Safety System
BLA	Biologics License Application
CBO	Community-Based Organizations
CDC	Centers for Disease Control and Prevention
CHIP	Children's Health Insurance Program
CISA	Clinical Immunization Safety Assessment
CMS	Center for Medicare and Medicaid Services
COI	Conflict of Interest
CSTE	Council of State and Territorial Epidemiologists
DFO	Designated Federal Official
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DUA	Data Use Agreement
DVA	Department of Veterans Affairs
ED	Emergency Department
EHR	Electronic Health Record
ET	Eastern Time
EtR	Evidence to Recommendation
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FQHC	Federally Qualified Health Center
GBS	Guillain-Barré Syndrome
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
HCP	Healthcare Personnel / Providers
HHS	(Department of) Health and Human Services

IDSA	Infectious Disease Society of America
IHS	Indian Health Service
IIS	Immunization Information System
MMWR	*Morbidity and Mortality Weekly Report*
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
NCHS	National Center of Health Statistics
NCIRD	National Center for Immunization and Respiratory Diseases
NFID	National Foundation for Infectious Diseases
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NMA	National Medical Association
NP	Nasopharyngeal
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
NVSN	New Vaccine Surveillance Network
OIDP	Office of Infectious Disease and HIV/AIDS Policy
PCP	Primary Care Provider/Practitioner
PCR	Polymerase Chain Reaction
PHAC	Public Health Agency Canada
PHE	Public Health Emergency
PICO	Population, Intervention, Comparison, Outcomes
PIDS	Pediatric Infectious Disease Society
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SAHM	Society for Adolescent Health and Medicine
SHEA	Society for Healthcare Epidemiology of America
SME	Subject Matter Expert
SVI	Social Vulnerability Index
UK	United Kingdom
US	United States
USG	United States Government
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VFA	Vaccines for Adults
VFC	Vaccines For Children
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VSD	Vaccine Safety Datalink
WG	Work Group
WHO	World Health Organization