MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

FEBRUARY 22-24, 2023
MEETING SUMMARY

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WEDNESDAY: FEBRUARY 22, 2023

WELCOME AND INTRODUCTIONS

Call to Order/Roll Call

Dr. Grace Lee (ACIP Chair) called to order and presided over the February 22-24, 2023 Advisory Committee on Immunization Practices (ACIP) meeting. Dr. Lee conducted a roll call each day, 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. The following conflicts of interest (COIs) were identified:

- ❑ Dr. Camile Kotton is involved in a clinical trial for Takeda for an investigational antiviral for cytomegalovirus (CMV) but is not involved in any of their vaccine projects.

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 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 2:00 PM Eastern Time (ET) on February 22, 2023. 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-2023-0007. 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.

MPOX VACCINE

Opening Remarks

Dr. Melinda Wharton (ACIP Executive Secretary, CDC) provided opening remarks for the Mpox session. She reminded everyone that in November 2021, ACIP unanimously voted in favor of JYNNEOS as an alternative to the other available vaccine for prevention of Mpox in persons with certain occupational risk of exposure. During this session, ACIP would be asked to vote on an additional use of JYNNEOS vaccine for control of Mpox outbreaks. In 2022, a multinational outbreak of Mpox began with more than 30,000 cases in the United States. In response to this outbreak, JYNNEOS has been successfully used in accordance with recommendations in CDC's interim clinical considerations, and there has been a dramatic reduction in case counts. Dr. Wharton emphasized that the vote for use in outbreaks would not change CDC's recommendations for use of JYNNEOS in the current outbreak but represents an update to ACIP's recommendations that were voted on in late 2021. It is expected that there will be additional decisions coming to ACIP for a vote in future meetings. The recent outbreak has highlighted the risks that infectious diseases can present to communities, the importance of a robust public health response at the state and local levels, the value of engaged partners and communities in responding to public health threats, and the impact that a vaccine can have in helping to bring an outbreak under control.

Session Introduction

Pablo Sanchez MD (The Ohio State University−Nationwide Children's Hospital, ACIP Mpox WG Chair) introduced the Mpox session. He pointed out that from a historical context, Mpox is a rare, sometimes life-threatening infection that is endemic in parts of West and Central Africa. It is caused by the monkeypox virus, which is an orthopoxvirus. There are 2 clades. Clade 1 was previously known as the Congo Basin Clade, while Clade 2 was previously known as the West African clade. Mpox can spread from infected animals to people and then person-to-person from respiratory secretions, skin-to-skin contact with infected body fluids (e.g., fluid from lesions), and fomites (e.g., shared towels, clothing, and bedding).

In terms of the timeline of notable human Mpox events, during 1970 to 2021, Mpox was known to be endemic in 9 African countries: Cameroon, Central African Republic, Côte d'Ivoire, Democratic Republic of Congo, Gabon, Liberia, Nigeria, Republic of Congo, and Sierra Leone. During recent years, there has been a re-emergence of human cases after decades of no reported cases. The first human case was identified in rural settings in 1970. In 2003, there was a US outbreak from pet prairie dogs with 47 cases identified. In 2017, there was an outbreak in Nigeria involving 17 states and 138 cases. In 2018, there were imported cases to the United Kingdom (UK) and Israel with 3 cases identified. In 2019, there were imported cases to the UK and Singapore with 2 cases identified. In 2021, there were imported human cases to the UK and the US with 3 cases identified. A multinational outbreak occurred in 2022.

Person-to-person spread has been seen. Historical outbreaks in Africa have been associated with close skin-to-skin contact and contact with fomites, with zoonotic exposure causing most cases and a few secondary cases among close contacts. In the US, a 2003 outbreak resulted in no secondary cases and no vaccination was offered. In 2021, there were no secondary cases and ACAM2000 was offered to some contacts.[1] In the most recent outbreak in 2022, there were many secondary cases and over 1 million doses of the JYNNEOS vaccine were administered.

In 2021, ACIP voted for the of orthopoxvirus vaccine, JYNNEOS that was licensed in 2019, for pre-exposure vaccination of people at occupational risk for orthopoxvirus exposures. The JYNNEOS vaccine is a 2-dose series that is administered subcutaneously. Recommendations were published in the *Morbidity and Mortality Weekly Report* (*MMWR*) on June 3, 2022.[2] Currently, there is no ACIP recommendation for the use of JYNNEOS during outbreaks. The current US national Mpox vaccine strategy is shown in this table:

Vaccination before exposure to mpox virus	Post-exposure prophylaxis
-Gay, bisexual, and other MSM, transgender or nonbinary people (including adolescents who fall into the aforementioned categories) who in the past 6 months have had: • New diagnosis of ≥ 1 sexually transmitted disease • More than one sex partner -People with the following in the last 6 months: • Sex at commercial sex venue • Sex in association with large public event in geographic area where mpox transmission is occurring -Sexual partners of people with the above risks -People who anticipate experiencing above risks -People with HIV or other causes of immunosuppression who have had recent or anticipate potential mpox exposure	-People who are known contacts to someone with mpox and identified by public health authorities (for example, via case investigation, contact tracing, or risk exposure assessment) -People who are aware that a recent sex partner within the past 14 days was diagnosed with mpox -Gay, bisexual, or other MSM, and transgender or nonbinary people (including adolescents who fall into any of the aforementioned categories) who have had any of the following within the past 14 days: sex with multiple partners (or group sex); sex at commercial sex venue; or sex in association with an event, venue, or defined geographic area where mpox transmission is occurring

The US strategy for vaccination with JYNNEOS during the current outbreak has been that the intradermal route is preferred, but the subcutaneous route can be administered for persons ≥18 years of age or older. The subcutaneous route is recommended for persons <18 years of age. This is a 2-dose series with a second dose administered 1 month after the first dose.

Regarding the tentative timeline for ACIP discussions and votes, during the February 2023 meeting, the ACIP would be voting on the use of 2-dose JYNNEOS for persons ≥18 years of age. In June 2023, ACIP will be discussing the use of 2-dose JYNNEOS for persons aged <18 years of age and would hear updates about vaccine effectiveness (VE) and safety. In October 2023, there will be consideration for a longer-term vaccination strategy for the 2-dose JYNNEOS vaccine. It is important to note that the current US Mpox vaccination strategy remains active, which is that populations at high risk should continue to be vaccinated.

[1] ACAM2000 was offered through a CDC Investigational New Drug Protocol that allows for vaccination after mpox exposure. Only contacts with highrisk exposures were offered vaccine; none accepted.
[2] https://www.cdc.gov/mmwr/volumes/71/wr/mm7122e1.htm

This session included updates from the ongoing outbreak in terms of epidemiology, VE, vaccine safety, community engagement, and equity and implementation; discussion about the use of the 2-dose JYNNEOS subcutaneously during Mpox outbreaks with an Evidence-to-Recommendations Framework presentation and an ACIP vote. Dr. Sanchez presented the following proposed wording for the vote:

> ACIP recommends the 2-dose* JYNNEOS vaccine series for persons aged 18 years and older at risk of Mpox during an Mpox outbreak.§
>
> *Dose 2 administered one month after dose 1
> § Public health authorities determine whether there is an mpox outbreak; a single case may be considered an mpox outbreak at the discretion of public health authorities. Other circumstances in which a public health response may be indicated include ongoing risk of introduction of mpox into a community due to disease activity in another geographic area.

Epidemiology of Mpox During the Current 2022 Outbreak in the United States

Sascha Ellington, PhD, MSPH (CDC/NCCDPHP) presented an update on the epidemiology of the current Mpox outbreak on behalf of the Epidemiology Task Force of CDC's Mpox Response. The first US case associated with the current Mpox outbreak was identified in Massachusetts in May 2022. Cases initially were associated with travel. Since then, cases have been reported from all 50 states, DC, and Puerto Rico. More than 30,000 cases have been reported to date. States with the most cases including California, New York, Texas, Florida, Georgia, and Illinois all reporting more than 1,000 cases. Most cases have occurred in gay, bisexual, and other men who have sex with men(MSM). Cases have also been reported in men who have not reported sex with men, cisgender and transgender women, transgender men, gender diverse people, children, and teens.

US cases peaked in August 2022 and have declined substantially since. Currently, the 7-day moving average is 2 cases per day in the US. As of February 8, 2023, 95% of all cases reported have been amongst cisgender men, 2.9% amongst cisgender women, and a combined 1.7% of cases have been among transgender men, transgender women, and gender diverse people. The age of people with Mpox ranges from 0, with a few cases reported in neonates, up to 89 years of age. The median age is 34 years. Overall, cases have been reported primarily among Black, Hispanic, and White persons, with nearly a third in each of these groups. At the start of the outbreak, about 45% of cases were among White persons, which decreased over time. Cases in Black or African American persons increased and cases among Hispanic or Latino persons have remained fairly stable over the period of the outbreak.

In terms of clinical characteristics and outcomes among cases reported to date, 53% of cases with available data have been among people living with HIV and 47% of cases have been among people who are human immunodeficiency virus (HIV)-negative, though only 30% of cases reported had data on HIV status. Among cases with available data, more than half had rash reported on the genitals or perianal area, trunk or limbs, head, face, or mouth. About a quarter had rash on the palms or soles of the feet. About 7.7% of people with Mpox have been hospitalized and 32 Mpox-associated deaths have been reported, representing 0.1% of cases. Deaths have occurred primarily in severely immunocompromised persons.

During the current outbreak, Mpox has been spread primarily through sexual or close intimate contact. Other routes of transmission also have been reported, including household transmission through injury with a contaminated sharp instrument in a clinical setting, through piercing and tattooing, and perinatal transmission from an infected mother to an infant around the time of delivery. Current evidence suggests that some people can spread Mpox virus to

others 1 to 4 days before they become symptomatic. However, there is no evidence that people who never develop symptoms have spread the virus to others. This table summarizes the specimens in which Mpox has been detected by polymerase chain reaction (PCR), whether replication-competent viruses has been detected, and whether each exposure source has been associated with transmission:

Mpox Virus in Human Samples and Implications for Transmission

Exposure source	Mpox virus DNA detected by PCR	Replication-competent virus detected/isolated	Epidemiologically supported source of infection
Skin	Yes	Yes	Yes
Oropharynx and saliva	Yes*	Yes	Yes
Anorectum	Yes	Yes	Yes†
Semen	Yes*	Yes	Insufficient data
Urine/urethra	Yes	Yes	Insufficient data
Conjunctivae or ocular fluid	Yes	Yes	Insufficient data
Blood/plasma/serum	Yes	Insufficient data	Insufficient data
Feces	Yes	Insufficient data	Insufficient data
Vagina	Yes	Insufficient data	Insufficient data†
Breastmilk	Insufficient data	Insufficient data	Insufficient data
Contaminated sharp‡	Insufficient data	Insufficient data	Yes

* DNA has been detected at Ct values <35 in recovered patients more than 30 days after illness onset in an upper respiratory tract swab, saliva, and semen.
† The preponderance of existing data support exposure to anorectal and vulvovaginal tissues and fluids as capable of transmitting infection; however, it is difficult with current evidence to definitively isolate these exposures from other concomitant exposures (see text).
‡ Includes body modification with piercings and tattooing.
https://www.cdc.gov/poxvirus/monkeypox/about/science-behind-transmission.html

Replication-competent virus has been detected but isolated in skin lesions, oropharyngeal swabs, anorectal swabs, semen, urine, and ocular fluid. Mpox has been transmitted from skin-to-skin contact, oral contact, and from a contaminated sharp. Transmission via exposure to some sources such as semen can be particularly challenging to assess since exposure typically occurs during close intimate contact that also includes skin-to-skin contact. For this reason, many exposure sources listed in the table have insufficient data to conclude definitively they are a source of infection.

As previously mentioned, 95% of cases of Mpox have been reported amongst cisgender men, and cases have occurred primarily among gay, bisexual, and other MSM. Among the cases reported in men with data on recent sexual history, 75% reported sexual or close intimate contact with a man in the 3 weeks preceding symptom onset. However, in 25% of cases among men, no recent male-to-male sexual contact was reported. Over time, the percentage of cases in men that had recent male-to-male sexual contact has declined from over 80% initially to about 60%, increases have been observed in the missingness of sexual contact data, which may contribute at least partially to this decline.

A few specific populations have been less affected overall, but the characteristics of these cases have contributed to the overall understanding of the epidemiology. Based on data from a publication that was published earlier this year reporting on cases in cisgender women,[3] about 3% of the Mpox cases have been in cisgender women. The median age of cases in this group is 32 years, ranging from 15–89 years. Of the cases among cisgender women, 44% were in Black, non-Hispanic women; 25% were in White, non-Hispanic women, and 23% were in Hispanic or Latino women. Of those with available data on HIV status, 8% of cases in cisgender

[3] http://dx.doi.org/10.15585/mmwr.mm7201a2

women were HIV-positive, and 92% were HIV negative. While the data were available for only 22% of cases among cisgender women, this is markedly lower than the percent of total cases that were HIV-positive at 53% and 71% of cases among cisgender women reported a recent sexual or close intimate partner.

The same publication also reported on cases in pregnant people. From May 11—November 7, 2022, a total of 21 cases of Mpox were reported during pregnancy and 2 cases were reported in a recently pregnant person, which was defined as within 3 weeks of pregnancy. Among the 12 with exposure data, 9 reported sexual contact and 3 reported household contact to a person with Mpox. Pregnant people had similar signs and symptoms of Mpox as those among non-pregnant people. Among pregnant people, 4 cases had general lesions during the pregnancy, but none had lesions at the time of delivery. Tecovirimat was provided to 48% of cases during pregnancy, with no adverse events (AEs) reported. None of the pregnant cases received post-exposure prophylaxis (PEP) with JYNNEOS. Outcomes reported to date have included 4 hospitalizations of pregnant people for Mpox indications. All were discharged while still pregnant. No pregnant cases required intensive care, intubation, or unplanned delivery. To date, pregnancy outcomes have been reported among 3 patients. Of these, 2 were uncomplicated live births with no transmission to the infant and 1 pregnancy resulted in a first trimester spontaneous abortion. Two recently pregnant persons experienced symptoms within 3 days of delivery and their newborns developed lesions within a week. The exact timing of transmission for these infant cases is unknown.

In another recent report,[4] the characteristics of Mpox cases were assessed among 466 transgender and gender diverse persons. In this analysis, 43% were transgender women, 42% were gender diverse, and 15% were transgender men. Of the gender diverse persons, 96% were assigned male sex at birth. The median age of the transgender and gender diverse persons with Mpox was 32 years and ranged from 18—71 years. Among the transgender and gender diverse persons with Mpox, 28% were Black, 28% were White, and 37% were Hispanic or Latino. About half of the transgender and gender diverse persons with Mpox were HIV-positive, which is similar to the percentage observed among all persons with Mpox. Among transgender and gender diverse persons with Mpox, 84% reported recent sexual or close intimate partner contact.

In another recent report of 83 cases in children from May 17–September 24, 2022,[5] there were 16 cases in children aged 0—4 years, 12 cases in children aged 5—12 years, and 55 cases in children aged 13—17 years. Adolescents aged 13—17 years were overwhelmingly male and primarily had sexual exposures, mirroring the epidemiology of cases overall. In younger children, cases were more evenly divided by sex and were associated with household contact, frequently from an infected caregiver. While these findings are from a report analyzing data through September, investigation has continued in cases among children, particularly younger children, and findings have been similar.

In terms of vaccine doses administered to date, as of February 7, 2023, a total of 1,185,907 doses were administered. This includes 732,725 first doses. First doses and overall doses administered peaked in August at the same time when Mpox cases reported to CDC peaked. Doses administered have declined substantially since August. In the first week of February, 1,314 first doses and 1,243 second doses were administered. While one-third of Mpox cases occurred among Black or African American persons, just 13% of first dose vaccine recipients

[4] https://www.cdc.gov/mmwr/volumes/71/wr/mm715152a1.htm?s_cid=mm715152a1_w
[5] http://dx.doi.org/10.15585/mmwr.mm7144a4

were Black or African American. While 31% of Mpox cases were among Hispanic or Latino persons, just 22% of first dose vaccine recipients were Hispanic or Latino. Additionally, 29% of Mpox cases were among White persons, while 52% of first dose vaccine recipients were among White persons. Hence, some substantial differences are observed by race and ethnicity when comparing those who have been infected versus those receiving vaccine.

JYNNEOS Vaccine Effectiveness

Anna Chard, PhD, MPH (CDC/NCIRD) presented on JYNNEOS VE on behalf of the Vaccine Task Force of CDC's Mpox Response. The efficacy of JYNNEOS vaccine against Mpox has been inferred from animal and immunogenicity studies, but it has never been demonstrated in clinical trials. Additionally, prior to the multinational outbreak, there were no real-world effectiveness estimates for JYNNEOS against Mpox disease. Therefore, the following key questions related to VE were developed:

1. What is the effectiveness of JYNNEOS vaccine against Mpox disease for partial (1-dose) and full (2-dose) vaccination?
2. Are there differences in VE by route of vaccination administration? On August 9, 2022, an Emergency Use Authorization (EUA) was issued for intradermal administration of a 2-dose series to increase vaccine supply, so it is important to examine the differences in VE by route of administration.
3. Are there differences in VE among persons with immunocompromising conditions? The populations most at risk for Mpox disease are also at higher risk of immunocompromising conditions such as HIV.
4. What is the duration of protection conferred from JYNNEOS vaccine? The duration of protection conferred by JYNNEOS vaccine is unknown.

In this presentation, Dr. Chard presented evidence for the first 2 questions; however, evidence remains limited regarding VE among persons with immunocompromising conditions and the duration of protection from JYNNEOS vaccine.

In terms of vaccine performance, Dr. Chard reviewed a study on the incidence of Mpox among unvaccinated persons versus persons receiving ≥1 JYNNEOS dose in the US.[6] For this analysis, investigators used surveillance data from confirmed and probable Mpox cases, vaccine administration data ascertained from interviews and immunization registries, and jurisdiction-specific estimates of the vaccine-eligible population to compare Mpox instance among persons who were unvaccinated and those who had received either one or two JYNNEOS doses. There were 9,544 reported Mpox cases among men 18─49 years of age from 43 US jurisdictions during the analysis period of July 31─October 1, 2022. Investigators estimated weekly Mpox incidence for persons with partial (1 dose) and full (2 doses) vaccination and persons eligible but unvaccinated. The incidence rate ratio was calculated using negative binomial regression controlling for week. Mpox incidence among unvaccinated individuals was 7.4 (95% CI = 6.0–9.1) times as high as persons receiving 1 dose of JYNNEOS vaccine. Mpox incidence among unvaccinated individuals was 9.6 (95% CI = 6.9–13.2) times as high as persons receiving 2 doses of JYNNEOS vaccine. No difference was observed in vaccine performance between subcutaneous and intradermal administration.

[6] Payne AB, et al. Reduced Risk for Mpox After Receipt of 1 or 2 Doses of JYNNEOS Vaccine Compared with Risk Among Unvaccinated Persons — 43 U.S. Jurisdictions, July 31–October 1, 2022. MMWR Morb Mortal Wkly Rep 2022;71:1560–1564.

The New York City Department of Health and Mental Hygiene (NYC Health) examined the VE of JYNNEOS administered as PEP using a cohort evaluation of individuals ≥18 years of age identified through contact investigations to a case patient with Mpox between March 22─August 24, 2022.[7] PEP was defined as receiving the first dose of JYNNEOS within 14 days of exposure and prior to symptom onset. Case patients were defined as exposed individuals who developed symptom onset within 21 days of exposure and had laboratory confirmation of Mpox. VE was 77% among individuals who received PEP less than 14 days after their last exposure and 79% among individuals who received PEP less than 14 days after their first exposure.

Investigators in Israel evaluated the real-world effectiveness of a single subcutaneous dose of Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN), which uses the trade name JYNNEOS in the US.[8] This was a retrospective, observational cohort study based on data obtained from electronic health records (EHRs) from a single integrated healthcare organization in Israel. The cohort included 2,054 men who were eligible for vaccination on July 31, 2022 when the vaccination campaign began who had completed at least 90 days of follow-up. Specific eligibility criteria were males aged 18─42 years of age who were dispensed HIV pre-exposure prophylaxis(PrEP) for at least 1 month since January 1, 2022, or males aged 18─42 years who were diagnosed with HIV and also were diagnosed with one or more sexually transmitted infections (STIs) since January 1, 2022. The time period for this analysis spans July 31─December 25, 2022 such that all participants were followed for 90 to 120 days after cohort entry. VE was estimated using Cox proportional hazards regression with vaccination status as a time-varying covariate. The model adjusted for sociodemographic and clinical risk factors. During July 31─December 25, 2022 there were 5 cases among vaccinated individuals and 16 cases among unvaccinated individuals. The adjusted single-dose VE was 86% (95% CI: 59%-95%).

In the EPIC-COSMOS case-control study,[9] data were used from EPIC's EHR platform, Cosmos, which includes records from over 169 million patients across the US. This was a case-control design in which cases were defined as patients with an Mpox diagnosis or a positive orthopoxvirus or positive Mpox virus laboratory result from the study period of August 15─October 29, 2022. Controls were defined as patients with an instant HIV diagnosis or HIV PrEP prescription during the same study period and was determined based on the Administration for Strategic Preparedness and Response (ASPR) vaccine distribution guidance. VE was estimated using conditional logistic regression models, adjusting for a priori specified confounders. The analysis also was stratified to examine full and partial VE by route of administration and immunocompromised status. Adjusted VE was 66% for full vaccination and 36% for partial vaccination. Among individuals with no immunocompromising conditions, VE was 76% for those fully vaccinated and 41% for those partially vaccinated. Although the analysis was controlled for immunocompromising conditions, VE could not be estimated among this population because vaccine coverage was low. Less than 1% of immunocompromised individuals were fully vaccinated. When examining VE by route of administration, very few patients were fully vaccinated with 2 subcutaneous doses or 2 intradermal doses. The 95% confidence intervals were wide, but the point estimates were similar to the overall estimate. For fully vaccinated persons with heterologous administration routes, VE was 75%, demonstrating that 2 doses confers protection regardless of the route of vaccine administration.

[7] Unpublished data
[8] Sagy, Y. W. et al. Real-world effectiveness of a single dose of mpox vaccine in males. Nature Medicine https://doi.org/10.1038/s41591-023-02229-3 (2023)
[9] Unpublished data

A multi-jurisdictional case-control study is currently underway. This study examines VE among men 18─49 years of age who have sex with men and live in 12 US jurisdictions. Cases are identified through the jurisdictions' probable and confirmed Mpox case lists. Controls are selected from healthcare settings providing HIV PrEP or from STI clinics. Cases are matched to controls based on time point within 4 weeks of clinic attendance and jurisdiction. Jurisdiction staff members collect data on participants' demographics, exposure history, and vaccination history using electronic surveys. Vaccination status of enrolled participants is confirmed using state immunization registries. VE is estimated using multivariable logistic regression with random intercept for jurisdiction and adjusted for prior specified confounders. Notably, these are interim results as data collection is still underway. Results indicate that VE is 76% for full vaccination among those without immunocompromising conditions. VE is 90% for full vaccination. At this interim stage, there were few individuals with partial vaccination or with immunocompromising conditions. Therefore, data are not sufficiently powered to generate estimates for these strata.

In a case-control study in New York State (NYS), investigators linked case surveillance data to the immunization registry. Cases were adult male Mpox cases diagnosed during July 24─October 31, 2022. Controls were adult male STI cases with rectal gonorrhea or primary syphilis cases during the same time period. Cases and controls were matched on week of diagnosis and VE was estimated using conditional logistic regression. VE was 68% for partial vaccination and 89% for full vaccination.

In summary, the existing body of evidence for VE of JYNNEOS against Mpox disease ranges from 66% to 83% for full vaccination and 36% to 86% for partial vaccination. This evidence indicates that the JYNNEOS vaccine is effective at reducing the risk of Mpox disease. Protection is provided by both 1 and 2 doses of JYNNEOS vaccine, but the highest protection is provided by 2 vaccine doses regardless of administration route. Further research is needed to assess whether immunocompromised status modulates VE. Due to small numbers in this population across studies, there was insufficient power to generate VE estimates among immunocompromised individuals. Additionally, because of a decline in Mpox cases and the limited follow-up period from studies to date, further research is needed to assess the duration of protection conferred by JYNNEOS vaccination.

JYNNEOS Vaccine Safety

Jonathan Duffy, MD, MPH (CDC/NCEZID) noted that while an *MMWR* report about JYNNEOS vaccine safety monitoring was published that included data collected through October 2022, this presentation would include data through January 2023 collected using 3 surveillance systems: 1) the Vaccine Adverse Event Reporting System (VAERS), which is a national passive reporting system; 2) the Vaccine Safety Datalink (VSD), which performs medical visit-based active surveillance for pre-specified adverse events of special interest (AESI) in a population of more than 10 million people; and 3) v-safe^{sm}, which is a smartphone-based system that uses text messaging to initiate web-based survey monitoring for AEs. AEs also were collected as part of single-patient Emergency Investigational New Drug (EIND) procedures for persons <18 years of age who were vaccinated before the JYNNEOS EUA was issued that allowed administration in that age group.

To provide an overview of the VAERS findings, as a reminder VAERS is the national passive surveillance system for AE reporting after vaccination. VAERS accepts reports from healthcare providers (HCP), vaccine manufacturers, and the public. VAERS collects data on any AE following vaccination, be it coincidental or truly caused by a vaccine. The report of an AE to VAERS is not documentation that a vaccine caused the event. The FDA issued an EUA for JYNNEOS on August 9, 2022 that required mandatory reporting to VAERS of vaccine administration errors, regardless of whether they were associated with an AE; serious AEs (SAE), irrespective of attribution to vaccination; cases of cardiac events, including myocarditis and pericarditis; and cases of thromboembolic events and neurovascular events.

The analysis presented during this session included VAERS reports received and processed by January 20, 2023. AE reporting rates were calculated by dividing the number of VAERS reports by the number of vaccine doses administered in the US. During the period May 22–January 13, 2023, a total of 698,188 people received Dose 1 and a total of 426,980 received Dose 2 for a total of over more than 1.1 million doses administered. VAERS received 1,817 reports after JYNNEOS. Most of these reports were for male adults 18─64 years of age and for JYNNEOS given alone without other vaccines on the same day. Most reports were about Dose 1. The most common route of administration was intradermal, followed by subcutaneous. Intramuscular administrations also were reported, most of which were reported as an error in the route of administration. Vaccine administration errors were the subject of 50% of all JYNNEOS VAERS reports. Of these, 96% did not report an adverse health event. Vaccine administration errors have been reported for JYNNEOS about 3 times more often with intradermal compared to subcutaneous administration. The most common issue reported with intradermal administration has been absence of a wheal without vaccine leakage (42%). CDC's Interim Clinical Considerations for use of JYNNEOS state that absence of a wheal without vaccine leakage may be counted as valid administration. After excluding reports of vaccine administration errors alone, adverse health events were reported to VAERS at a similar rate for subcutaneous and intradermal administration. The most common types of events differed slightly by route of administration. Overall, the most common adverse health events reported to VAERS for adults were consistent with those reported in pre-licensure clinical trials.

An SAE event is defined as a report of the occurrence of any of the following: death, a life-threatening AE, hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, a congenital anomaly or birth defect, or another important medical event that based on appropriate medical judgement may jeopardize the individual and may require medical or surgical intervention to prevent one of the outcomes listed above. About 1% of reports to VAERS after JYNNEOS were classified as SAEs. SAEs were reported at a rate of 22 reports per million doses administered. SAEs reported to VAERS after JYNNEOS are listed here:

Myocarditis (n=5)	Dehydration
Death (n=2)**	Idiopathic thrombocytopenic purpura
Pericarditis (n=2)	Injection site discoloration
Urticaria (n=2)	Injection site pain
Appendicitis	Injection site scar
Aseptic meningitis	Methemoglobinemia
Asthenia	Retrograde amnesia
Atrial fibrillation	Rhabdomyolysis
Cellulitis	Sudden hearing loss
Chest pain	

Not all AEs that occur after vaccination are caused by the vaccine. Two deaths were reported to VAERS after JYNNEOS administration. The local Medical Examiners (MEs) determined and reported the causes of death in these cases to be drowning and cocaine toxicity. Hospitalization for myocarditis or pericarditis were the most commonly reported SAEs. The single cases of the other conditions reported do not suggest safety signals for any of these conditions.

To discuss the myocarditis and pericarditis findings in more detail, myocarditis and pericarditis have occurred following either primary vaccination or revaccination with live vaccinia virus smallpox vaccines in the past. The mechanism is poorly understood, and it was unknown whether persons who received JYNNEOS might experience myocarditis or pericarditis. In this epidemiologic analysis, the cases have been classified into 2 groups. The first is myocarditis with or without pericarditis and the second is acute pericarditis alone. The surveillance risk interval is defined as symptom onset within 30 days after vaccination. In VAERS, 2 cases of myocarditis were reported after Dose 1 for a rate of 2.75 cases per million persons vaccinated, while 3 cases were reported after Dose 2 for rate of 6.74 per million. In the VSD population, there were 37,646 people who received at least one dose of JYNNEOS. There was 1 case of myocarditis observed after each dose. The VSD incidence rate estimates have wide confidence intervals that range from about 1 to 250 cases per million. These confidence intervals overlap published historical population background rates, which range from 2.7 to 21.6 cases per million persons during a 30-day period. For context, the published historical rates after live replicating smallpox vaccines have ranged from 70 cases per million after Dryvax in a 2002 military cohort study, up to 5,000 per million cases after ACAM2000 in a 2018 military cohort study. In summary, the VAERS and VSD data do not suggest an increased risk for myocarditis following JYNNEOS compared to expected published background rates,[10] but the possibility of a small risk cannot be excluded.

In a similar analysis for pericarditis, there were a total of 6 cases reported to VAERS, only 2 of which were classified as serious due to hospitalization. There were 4 cases after Dose 1 and 2 cases after Dose 2 for a rate up to 5.5 cases per million persons during a 30-day period. There were no cases identified in the VSD population. The VAERS reporting rate for pericarditis is similar to expected published historical background rates and less than that observed after live replicating smallpox vaccines in one military cohort study.[11]

The v-safe[sm] platform is a smartphone-based system that uses text messaging to initiate web-based survey monitoring for AEs following vaccination. The data from v-safe[sm] are used to characterize the basic safety profile of a vaccine when given outside of a clinical trial setting and can facilitate reporting to VAERS for medically attended adverse events (MAAEs). This system is meant to supplement CDC's other vaccine safety monitoring systems, VAERS and VSD. In terms of the characteristics of v-safe[sm] participants, there were 181 active participants, defined as having completed at least one survey between November 16, 2022 – January 29, 2023, all of whom were adults and the majority of whom were male. Additional characteristics are shown on the following tables:

[10] References: Halsell, et all. DOI: 10.1001/jama.289.24.3283; Oster, et al. DOI:10.1001/jama.2021.24110; Mandra, et al. DOI: 10.1017/dmp.2020.478

[11] References: Imazio, et al. DOI: 10.1136/hrt.2006.104067; Kumar, et al. DOI: 10.1159/000445206; Engler, et al. DOI:10.1371/journal.pone.011828

Characteristic	N=181 n	(%)
Age in years		
18-49	112	(61.9)
50-64	56	(30.9)
≥65	13	(7.2)
Gender identity		
Male	139	(76.8)
Female	28	(15.5)
Transgender	7	(3.9)
None of the above or unknown	7	(3.9)
Immunocompromised**	32	(17.1)

Characteristic	N=181 n	(%)
Race/Ethnicity		
White, non-Hispanic	111	(61.3)
Hispanic	28	(15.5)
Asian, non-Hispanic	11	(6.1)
Black, non-Hispanic	10	(5.5)
Multiracial, non-Hispanic	10	(5.5)
Other race, non-Hispanic	2	(1.1)
Unknown race or ethnicity	9	(5.0)

In terms of the percentage of participants who reported reactions or health impact events at least once during Days 0 to 7 after vaccination by dose, about 80% reported any injection site reaction and 5% sought medical care. No participants reported SAEs. The most common type of injection site and systemic reaction reported overall was redness at the injection site, reported by 64% of participants. The most common systemic reaction was fatigue, reported by 40%.

Regarding information about AEs in persons <18 years of age, CDC facilitated single-patient EIND authorization from the FDA to make JYNNEOS available for persons <than 18 years of when needed prior to the JYNNEOS EUA being issued on August 9, 2022 that allowed wider use in this age group. CDC solicited information from vaccine providers about AEs occurring in their patients during the 28 days after each dose. Persons vaccinated under the EIND ranged in age from 4 months to 17 years and 58% were male. AEs were reported for 10 (18%) of 57 people after Dose 1 and 5 (21%) of 24 people after Dose 2. The types of events reported included injection site reactions of pain, erythema, swelling, and induration and systemic AEs of fever, fatigue, and headache. No SAEs were collected in this project.

VAERS also was used to collect data on persons <18 years of age. JYNNEOS was administered to 1,245 persons <18 years of age in the US during the surveillance period. VAERS received 25 reports for this age group. Vaccinated persons' ages ranged from 12 through 17 years. Reports of vaccine administration errors accounted for 84% of these reports, with the most common being intradermal administration instead of subcutaneous, which is the authorized route for this age group. The only AE reported was 1 person with syncope and no SAEs were reported.

The overall conclusions about vaccine safety monitoring are that JYNNEOS post-licensure and post-authorization vaccine safety surveillance findings to date are consistent with those observed in clinical trials. No new or unexpected safety concerns have been identified. SAEs were rare among adults and none have been identified among persons <18 years of age. VAERS and VSD data taken together do not suggest an increased risk for myocarditis or pericarditis following JYNNEOS, but the possibility of a small risk of myocarditis cannot be excluded.

Mpox Vaccine Acceptability and Uptake from Cross-Sectional Surveys

Kevin P. Delaney, PhD, MPH (CDC/NCHHSTP) presented Mpox vaccine acceptability and uptake findings from cross-sectional surveys from among clinicians and vaccine interest, intent, and uptake among the general population and populations disproportionately affected by the current outbreak on behalf of the CDC Community Engagement Task Force. One source of information for this is surveys of clinicians. CDC has worked with Sermo to get some insights on this. Sermo is an online community of more than 1.3 million clinicians. At the beginning of August, the company conducted what they call a "Barometer" survey of physicians around the world with over 1,000 physicians total.[12] During this session, Dr. Delaney presented data from the 415 US-based clinicians in that survey. He highlighted that in early August 2022, the majority of clinicians surveyed wanted more access to Mpox vaccine. At short follow-up was conducted on September 12, 2022 at CDC's request that found both high vaccine demand and acceptability, with 76% of respondents saying they knew where to send patients for JYNNEOS vaccine. More importantly, 86% wanted to be able to offer vaccine in their practice.

In terms of information from affected populations, this table provides an outline and overview of the 4 surveys conducted by CDC and partners during the current outbreak:

Study	Timeframe	Population	Methods
Porter Novelli	August – December 16	N= up to 371 LGBTQ+ Data weighted to match census population	Four KAP surveys in the general population including LGBTQ+
AMETHST: **Ame**rican **T**ransformative **H**IV **St**udy	Aug 9th – November 15th	N=8,551 50% Black and Latinx GBMSM	Monthly cross-sectional survey to recruit new cohorts of persons at risk for HIV. Questions related to mpox added in 2022
AMIS: **A**merican **M**en's **I**nternet **S**urvey	August 5 – August 15	N = 824 GBMSM	Emory conducted a one-time KAP survey of 2021 AMIS population. Survey available here
	October 6 – December 31	N=3041 GBMSM	Ongoing recruitment of the 2022 AMIS survey summarized through 12/31
San Francisco study among persons experiencing homelessness (PEH)	Oct 23rd – November 5th	N= 273 57 with higher risk sexual activity 35 GBMSM	Cross-sectional survey among PEH to understand vaccine acceptability and coverage

The first survey is one that CDC conducted in partnership with Porter Novelli. Porter Novelli is a contractor who conducted 4 online general population surveys of US adults through the months of August, September, October, and December 2022 on knowledge, attitudes, and beliefs of Mpox-related topics. The data are weighted to match US Census proportions for age, gender, region, race, ethnicity, and education. They also ask a question about whether the respondent considered themselves to be a member of the lesbian, gay, bisexual, transgender, queer or questioning, or other (LGBTQ+) community. The December survey had the largest sample and asked several questions specifically designed to directly measure Mpox vaccine acceptability and value. In this general population survey, very few people overall disagreed with the statement that "The monkeypox vaccine is safe." Although many of the general population, even those identifying as part of the LGBTQ+ community, said they did not know. For the current outbreak, which overwhelmingly has affected gay and bisexual men, 51% of those who identified as LGBTQ+ thought the vaccine was safe and 50% of that group also thought it was important to get the Mpox vaccine to protect themselves. For the second question, it is

[12] https://app.sermo.com/barometer/unitedstates

interesting that 31% of those who did not identify as LGBTQ+ or a member of the LGBTQ+ community also felt it would be important to get the Mpox vaccine to protect themselves.

The American Transformative HIV Study (AMETHST)[13] collected data from the community most affected by the current outbreak (e.g., gay, bisexual, and other MSM). AMETHYST is a National Institutes of Health (NIH)-funded online cohort that will eventually include 5,000 sexual minority men. This is a diverse group with higher risk of HIV acquisition than the general population, even of sexual minority men, by design. The study will be recruiting such that the cohort is no more than 50% non-Hispanic Whites, the majority-minority, by race and ethnicity. About 60% of the cohort will have reported recent methamphetamine use, which increases bio-behavioral vulnerability to HIV. To achieve the objective of enrolling 5,000 such men, the plan is to screen over 30,000 respondents with an online eligibility survey. Questions about Mpox knowledge, vaccine uptake, and behavior change have been added to the screening enrollment survey. The data presented during this session were from the first 8,500 participants screened from August 6—November 15, 2022.

Regarding the question, "How much have you worried about Mpox infection over the last 2 weeks?" the number who said they worried some or more than half of the days decreased from 66% in August to 35% in November and the number who said they never worry increased from 34% in August to 66.4% in November. While Mpox concern decreased over time, about one-third of participants remain concerned about Mpox. Over 85% of respondents remain interested in vaccine. Vaccine coverage doubled between August and September but then flattened out, which is consistent with vaccine administration data. As of November, 30% of those recruited reported having received at least 1 dose. However, the proportion of people reporting the intent to take vaccine remained strong and there was minimal increase in the proportion of people who said they were unlikely to get vaccinated. Overall, 85% of those enrolled in the survey so far are either vaccinated or reported being likely to get vaccinated. In terms of vaccine uptake by race from August to November 2022 among AMETHYST participants surveyed at the peak of the outbreak, Black men had the highest proportion reporting receipt of at least 1 dose of vaccine. In August, Black participants had higher vaccine coverage than participants from other racial and ethnic groups but did not see the "doubling" in vaccine coverage that were reported overall. It also is important to think about other communities in terms of equity. AMETHYST may be the only or best source for this. There was much lower uptake of vaccine for gender diverse persons and for those who do not identify as gay. Moving forward with plans to improve equity and access, it is important to do a better job of specifically marketing and creating demand for those groups as well as Black men.

The American Men's Internet Survey (AMIS) is an Emory University annual online cross-sectional survey of people who were born and currently identify as male that is typically conducted with recruitment from October to February of a given year. In August 2022, colleagues at Emory University conducted a special one-time survey that recontacted men who participated in the 2021 AMIS survey cycle interviewed between October 2021 and February 2022 to explore knowledge, attitudes, and practices related to the US Mpox outbreak. The survey was conducted between August 5-15, 2022 during the peak of the current outbreak.[14] For those interested, Emory posted all of the questions that were asked in the August survey online. There are questions in this survey about vaccine knowledge, access, and desire to be vaccinated; barriers to vaccination; and sources of information on Mpox. As published in an *MMWR* that first appeared online on August 26th, 53% of AMIS participants reported concern

[13] https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-21-018.html
[14] https://www.cdc.gov/mmwr/volumes/71/wr/mm7135e1.htm

about getting Mpox at that time. At that time, 18.6% of MSM surveyed reported having received at least 1 dose of vaccine. This is consistent with the AMETHYST data. That *MMWR* also reported higher vaccine uptake for Black men compared to all other racial groups, lower vaccine uptake in more rural areas relative to urban areas, and lower vaccine uptake in the South and Midwest. At the time this was published, the *MMWR* called for more equitable vaccine delivery. These quotes are from the discussion section:

> "Equitable vaccine program implementation involve…, engaging diverse partners already working with special populations, delivering vaccines through mobile outreach and pop-up events, and diversifying times and locations for vaccine administration"
>
> "Expanding vaccine availability geographically, including diversifying vaccination locations to include nonurban areas, can help ensure that those who need vaccination have access to it."

Just 4 days after publication of the *MMWR*, the White House announced plans to support expansion of vaccine access through distribution to groups working to provide vaccine at large events and in spaces where they could reach populations who otherwise might not have access.[15] The Mpox Vaccine Equity Pilot Program (VEPP) was created to: 1) support innovative ways to address vaccination disparities; 2) encourage vaccination coordination between health departments and community-based organizations (CBOs); and 3) promote innovation to strengthen existing vaccination infrastructure. The VEPP provided additional vaccine above the original allocation to 15 jurisdictions, 14 states, and Puerto Rico for 28 different vaccination programs and events. These were beyond the threshold supplies provided to states. This project delivered nearly 25,000 doses of vaccine at special vaccine equity events.

The 2022-2023 AMIS is still recruiting. These data are from an abstract developed for submission to the International AIDS Society (IAS) meeting but are not yet published. Recruitment began in early October and by the end of December, over 3,000 men had been enrolled. At that point, 33% reported that they had received 1 dose of vaccine. Again, very consistent with the AMETHYST data for November and December. Vaccine uptake was associated with Mpox awareness and concern and also with factors that might be indicative of concern for or awareness of sexual health and access to sexual health services overall, including HIV care, STI testing, and HIV PrEP use.

A study conducted by the CDC and the San Francisco Department of Public Health (SFDPH) specifically recruited another special population of people experiencing homelessness in San Francisco. This study was fielded from October 23–November 5 and sought to understand Mpox vaccine coverage and acceptability among people experiencing homelessness. This study also collected blood to assess seroprevalence in this community, though Dr. Delaney did not discuss that during this session. The take-home from this analysis is that 56% of those who reported any sexual risk and 74% of MSM, said that they would accept Mpox vaccination. Again, consistent with the AMETHYST data.

[15] https://www.whitehouse.gov/briefing-room/statements-releases/2022/08/30/fact-sheet-white-house-monkeypox-response-team-announces-new-plans-to-support-large-lgbtqi-events-and-equity-interventions-to-reach-communities-at-highest-risk-of-contracting-the-virus/

Interim Clinical Considerations

Rosalind Carter, PhD (CDC/NCIRD) provided a brief overview of CDC's Mpox vaccine Interim Clinical Considerations (ICC) that were developed to guide vaccine implementation during the Mpox outbreak. It is important to remember that the ICC is a living document. As the epidemiology of the outbreak evolved and as feedback was received from the field in terms of new questions and concerns, the guidance was updated or clarified. The latest ICC updates continue to emphasize the importance of vaccination before exposure for those with the highest potential for exposure to Mpox, the importance of identifying and vaccinating persons living with HIV or who have other causes of immunosuppression who have had recent or anticipate potential Mpox exposure, and including explicit language stating that the definitions of risk groups also include adolescents.

From the beginning of the 2022 Mpox outbreak, the US Government (USG) recognized that Mpox vaccine availability was the critical strategy to limit the rapid spread of Mpox. Two vaccines may be used for prevention of Mpox and were available from the Strategic National Stockpile (SNS). They included the JYNNEOS vaccine approved for prevention of smallpox and Mpox and licensed for use among persons 18 years of age and older. On August 9, 2022, FDA issued an Expanded Use Authorization (EUA) for intradermal administration among persons 18 years of age and older. That is the primary vaccine being used during this outbreak in the US. ACAM2000 is an alternative to JYNNEOS and approved to protect against both smallpox and monkeypox. While it is available, it has not been used during this outbreak due to the higher risk of SAEs.

On June 28, 2022, the federal government announced an enhanced nationwide strategy to vaccinate and protect people at risk for Mpox, prioritize vaccines for areas with the highest number of cases, and provide guidance to state, tribal, local, and territorial health officials to aid planning and response efforts. Multiple federal agencies, including the ASPR, SNS, Biomedical Advanced Research and Development Authority (BARDA), CDC, and FDA are working closely with partners to ensure there are enough vaccine doses available to vaccinate all people for whom vaccine is recommended. There are 2 primary strategies, which are 1) vaccination of individuals after known or presumed exposure to someone with Mpox; and 2) vaccination prior to exposure among persons at high risk for potential exposure.

For PEP in the first strategy, CDC has defined people eligible for vaccine in the ICC as follows:

- ❑ People who are known contacts to a person with Mpox, and identified by public health authorities as a "contact" from case investigation, contact tracing, or risk exposure assessment; or
- ❑ People who are aware that a recent (within the past 14 days) sex partner was diagnosed with Mpox; or
- ❑ Gay, bisexual, other MSM, and transgender or non-binary people (including adolescents) who have had sex with multiple partners, at a commercial sex venue, or sex in an association with an event, venue, or defined geographic area where Mpox transmission is occurring.

For PrEP in the second strategy, CDC has defined eligible groups in the ICC as those groups eligible for vaccination prior to Mpox exposure who either have highest potential risk for exposure or who anticipate potential exposure to Mpox:

- ❑ Gay, bisexual, and other men who have sex with men, and transgender or nonbinary people (including adolescents) who, within the past 6 months, have had:
  - A new diagnosis of one or more sexually transmitted diseases (e.g., chlamydia, gonorrhea, syphilis);
  - More than one sex partner
- ❑ People who have had any of the following in the past 6 months:
  - Sex at a commercial sex venue; or
  - Sex in association with a large public event in a geographic area where mpox transmission is occurring
- ❑ Sexual partners of people with the above risks
- ❑ People with HIV † infection or other causes of immunosuppression who have had recent or anticipate potential mpox exposure
- ❑ People in certain occupational exposure risk groups (laboratory personnel working with orthopoxviruses)

This is all in accordance with the ACIP 2022 recommendations. It is important to note that although the language describes the highest risk groups in an effort to improve equitable access to Mpox vaccines, persons who request vaccination can receive it without having to attest to meeting any of these specific criteria.

Health equity principles outlined in the interim clinical guidance are incorporated into the National Vaccine Strategy as well as local implementation efforts. Some of these principles include engaging people from affected communities in the planning and design of vaccination efforts; using non-stigmatizing, plain language; reiterating privacy of information and how data will be used; engaging diverse partners already working with special populations; bringing vaccines to where affected populations are (e.g., pop-up events, mobile outreach); offering multiple appointment times and flexible walk-in opportunities, including evenings and weekends to improve vaccine accessibility; leveraging clinical venues such as the Federally Qualified Health Centers (FQHCs) that serve people who have historically had less access to primary care, sexual health clinics, transgender health clinics, and pharmacies to deliver vaccines; and minimizing systems that are first come, first-served.

Looking quickly at the data, almost 1.2 million doses were administered and reported to CDC through February 7, 2023. This includes 734,000 first doses and 452 second doses. During the week of August 7-13, the EUA for intradermal administration was introduced. At that same time, additional vaccine vials were released from the SNS and provided to the states. Intradermal dosing greatly expanded the number of people vaccinated with first and second doses during the peak of the outbreak when demand was highest. Looking at data comparing Mpox cases to those vaccinated by race and ethnicity and whether vaccine equity improved over time, notably completeness for race and ethnicity data in vaccine administration database was very good quality. Over 91% of this information was completed. Summarizing the overall data from May through the end of January 2023 compared to the time periods of mid-June to mid-July and mid-July to mid-August, the proportion vaccinated who were Hispanic increased from 19% to 23% and the proportion of people vaccinated who were Black non-Hispanic increased from 7% to 13%. While these proportions were maintained over time, improvements in vaccine equity in subsequent months have been modest. It is important to note that these data summarize the

national picture and individual jurisdictions, including many of the highest burden states that have made substantial progress in addressing equity gaps. Nonetheless, there is much work ahead in implementation to improve vaccine equity.

To highlight a few elements of the current vaccine implementation as best practices for future outbreaks, vaccine strategies and implementation were adapted to local situations, local epidemiology, and population needs. This included adapting the eligibility criteria for local contexts. Some examples of this are that some states included sex workers in their definition of vaccine eligibility. Many others removed sexual orientation labels from eligibility criteria and reduced potential stigma by allowing people to self-attest to eligibility. The interim guidance for eligibility also evolved as the epidemiology, which was very dynamic, changed over time. CDC recognizes that vaccination offered in the context of broader prevention activities, as well as sexual health care, including HIV testing and PrEP initiation, increased access to vaccines as well as acceptance of vaccines. The importance of the key role that CBOs had cannot be emphasized enough in the success of vaccine implementation, both as trusted messengers and in logisticians in helping set up vaccine events in their neighborhoods and communities. It also is important to highlight the importance of planning resources for data collection, including collecting vaccine status and dates of vaccination on monkeypox reporting forms, which allowed CDC to measure vaccine performance early in the rollout. Including race and ethnicity data on vaccination reports, including on reports shared with CDC, is essential in driving program actions and course correction.

In addition to the success stories, there were many challenges, most notably the limited supply of vaccine at the peak of the outbreak in mid-July when demand was high. The intradermal route of administration was an important public health intervention, increasing the vaccine supply 300% to 500% when it was most needed. CDC's ASPR colleagues handled the complex logistics of moving JYNNEOS vaccine from the federal SNS to the jurisdictions. However, at the beginning, the SNS was limited to only 5 shipments per week during the outbreak peak, leaving the jurisdictions to manage redistribution to providers in critical areas. However, within about 6 weeks, ASPR was able to increase their shipping capacity to provide directly to providers. The change from subcutaneous to intradermal administration required jurisdictions to provide skills training to vaccinators. However, on average, these jurisdictions were able to begin implementation of intradermal within 2 to 3 weeks of the EUA, which was a significant accomplishment and heavy lift. Initially, health departments and public clinics were the primary vaccine providers, providing more than 50% of all vaccinations. As the outbreak has subsided, the jurisdictions have increasingly engaged STI and HIV care providers, as well as pharmacies in some states to take on these roles. Despite these challenges, it is important to acknowledge the dedication and the hard work of the jurisdictional health departments that are truly responsible for the successful implementation of Mpox vaccines.

EtR: Use of JYNNEOS During Mpox Outbreaks

Agam Rao, MD (CDC/NCEZID) presented the EtR Framework for vaccination with JYNNEOS vaccine during any monkeypox outbreak that could be spread through travelers from countries where it is endemic, imported animals such as prairie dogs or other animals, et cetera. It is important to understand that even though a vote is being proposed for JYNNEOS for any outbreak, the current outbreak is not over and people are encouraged to continue to be vaccinated based on the ICC that Dr. Carter summarized for specific populations for whom JYNNEOS is recommended during the current outbreak. Dr. Rao cautioned that this presentation included photographs that might be difficult for some viewers and that she would provide advanced notice before showing them.

As a reminder, the EtR Framework is a structure to describe information considered in moving from evidence to ACIP vaccine recommendations. It provides transparency around the impact of additional factors on deliberations when considering a recommendation. There are 7 EtR domains: Public Health Problem, Benefits and Harms, Values, Acceptability, Equity, Feasibility, and Resource Use. Dr Rao presented the WG's interpretation of the data for each of these domains and the response to the associated questions for each domain. The EtR question is:

> Does ACIP recommend the2-dose* JYNNEOS vaccine series for persons aged 18 years and older at risk of Mpox during an Mpox outbreak? §
>
> *Dose 2 administered 1 month after Dose 1
> §Public health authorities will determine whether there is an Mpox outbreak; a single case may be considered an Mpox outbreak at the discretion of public health authorities. Other circumstances in which a public health response may be indicated include ongoing risk of introduction of Mpox into a community due to disease activity in another geographic area.

In terms of the Public Health Problem domain, there have been several notable public health events involving Mpox since it was first recognized in humans in 1970. Early cases were in rural settings in certain forested regions of Africa where the presumed animal reservoirs reside. The first outbreak outside of Africa occurred in the US in 2003 from pet prairie dogs that were co-housed with infected small mammals from Ghana. There were 47 cases associated with that outbreak. Going forward, cases continue to occur in Africa. The 9 African countries are the countries where we know that cases had occurred. Cameroon, Central African Republic, Côte d'Ivoire, Democratic Republic of Congo, Gabon, Liberia, Nigeria, Republic of Congo, and Sierra Leone. In 2017, there was a large outbreak in Nigeria involving 17 states. At that time, it was considered a very large outbreak involving 138 cases. During 2018–2021, there were imported cases in travelers from Nigeria to various countries, to the UK and Israel in 2018, and to the UK and Singapore in 2019. In 2021, there were 3 cases, 2 of which occurred in the US. In 2022, a multinational outbreak occurred. All of this to say that Mpox does seem to be of public health significance and importance. There have been a lot of cases, including a reemergence of human cases in recent years after decades of no reported cases in some countries.

Even before the 2022 multinational Mpox outbreak, investigations for even a single case of Mpox have been intense. During the July 2021 investigation, in one of the investigations in the US 223 contacts had to be monitored. Fortunately, there were no high-risk exposures or secondary transmissions. There were a lot of contacts, including flight crew and fellow passengers on international and domestic flights and friends of the affected patient and a rideshare driver. All of these individuals were monitored by public health authorities. There were 2 imported cases to the UK in 2019 and 2021 that resulted in secondary infections. In 2019, a HCW developed Mpox after presumed exposure while changing the bedding of an Mpox patient. In 2020, 2 household contacts of an Mpox patient developed Mpox. This outbreak is obviously involved in many cases that peaked in early August. Case counts are decreasing at this time, but this outbreak is not over.

The typical presentation manifestation of Mpox during the current outbreak are small, firm, deep-seated, well-circumscribed lesions that can occur on the palms, soles, and other parts of the body. They often have been scattered or focused on one body part, most commonly the genitals. Prodromal symptoms, including fever and lymphadenopathy, have inconsistently occurred. When lesions have occurred in the perianal or genital region, the pain from lesions has been particularly pronounced. Rectal pain, abdominal pain, rectal bleeding, and tenesmus have all been reported. Typically, symptoms resolve with supportive care alone, including pain control. However, severe manifestations are occurring in some patients who have severe outcomes. Severe manifestations include ocular lesions, neurologic complications,

myopericarditis, and certain mucosal lesions that can affect patients regardless of immune status. Myopericarditis cases have been seen in people who developed Mpox. not just in individuals. Keratitis and conjunctival ulcer are associated with ocular Mpox. Ocular lesions can be very serious and can even cause blindness, as in other countries where classic Mpox has occurred in Africa. Myopericarditis and neurologic complications have been reported in a small number of patients who are uncertain of the reasons for this. It has occurred in individuals who have been immunocompetent. Encephalitis and transverse myelitis have occurred in patients with Mpox. When lesions occur on certain mucosal surfaces (e.g., urinary meatus, penis) they can cause complications, including obstruction.

Lesions can be severe, necrotic, and require consultation from medical subspecialists such as urologists, gastroenterologists, and general surgeons depending upon the location of the lesions. While these are considered severe manifestations, the most severe and the life-threatening lesions occur in patients with severe immunocompromise. Patients who are severely immunocompromised due to advanced HIV in particular have had the most severe manifestations of Mpox during the current outbreak. The etiology is believed to be uncontrolled viral spread in severely immunocompromised patients. Dr. Rao shared some images to illustrate the progression of illness and how different the lesions in these patients can be from the typical presentation. Medical therapeutics such as tecovirimat and brincidofovir may be helpful, but an optimized immune system through antiretroviral therapy, temporary halting of immunomodulator therapies, or some other mechanism is still the most critical aspect of care. Deaths have occurred because of these illnesses, often many weeks after hospitalization because of the progression and despite therapeutics. Therefore, the WG determined Mpox outbreaks to be of public health importance based on all of the data presented.

Regarding the Benefits and Harms domain, there are early estimates and population-based estimates of VE. Vaccine performance has been evaluated through comparison of incidence of Mpox between vaccinated and unvaccinated persons in 43 US jurisdictions. Mpox incidence among unvaccinated was 7.4 times that among persons who received only 1 dose of JYNNEOS vaccine ≥14 days earlier, and 9.6 times that among persons who received Dose 2 ≥14 days earlier. Population-based adjusted measures of VE using EMRs also have been performed. A retrospective population-based cohort study conducted in Israel showed that 5 Mpox infections occurred among subjects vaccinated with 1 subcutaneous dose and 16 infections occurred among unvaccinated subjects. The VE for Dose 1 was calculated as 86% with the confidence interval of 59% to 95%. A nationwide US case-control study with a 1:4 ratio of cases matched to controls had an adjusted VE of 35.8% with a 95% confidence interval of 22.1% to 47.1% for 1 dose and 66% with a 95% confidence interval of 47.7% to 78.1% for 2 doses, regardless of the vaccination route. In terms of population-based adjusted measures of VE using case-control studies, a case-control study of adult MSM 18–49 years of age in 12 US jurisdictions had an adjusted VE of 76% with a confidence interval of 48% to 89% for the 2 doses. Those are interim results. This study is ongoing, so the WG hopes to have more information to present during the June 2023 ACIP meeting. Unpublished preliminary results from a NYS case-control study of adult male Mpox cases matched to STI controls had an adjusted VE of 68% with a confidence interval of 25% to 86% for 1 dose and 89% with a confidence interval of 44% to 98% for 2 doses. These also are preliminary results and the analyses are ongoing.

In terms of PEP effectiveness and infections following a single JYNNEOS dose
10% (11 out of 108 subjects) in France who were administered JYNNEOS after Mpox exposure became symptomatic with Mpox disease soon after vaccination. The interquartile range was 1 to 6 days, with a median of 5 days. Notably, the clinical course was mild among those persons. Also in France, there was an observational study involving people who received a single subcutaneous dose. In this study, 4% were infected during the month after the vaccination and none had serious infection. In a NYC cohort study of individuals with high-risk exposure, VE was 77% with PEP <14 days after last exposure and 79% with PEP <14 days after the first exposure. Based on all of this information that seemed to support the benefits of the vaccine, the WG's interpretation was that the desirable anticipated effects of Mpox vaccine during an outbreak are large.

Vaccine safety is focused on the subcutaneous route of administration during May 22, 2022 through January 13, 2023. A total of 1,125,168 JYNNEOS vaccine doses were administered. CDC monitored JYNNEOS safety using VAERS and VSD for vaccine recipients of all ages. The most common AEs reported were non-serious and included injection site reactions consistent with pre-licensure studies. These were reported at similar rates for doses received by intradermal and subcutaneous administration and SAEs were rare among adults. The WG's interpretation is that the undesirable anticipated effects of Mpox vaccine during an outbreak are small. The WG's interpretation of the balance between the desirable and undesirable effects was that the desirable effects outweigh the undesirable effects and favored the intervention of vaccination with JYNNEOS.

Regarding the Values domain, surveys have been used to assess the values of the individuals who are being vaccinated during the 2022 outbreak. Even though this vote is for Mpox outbreaks in general that may not be specific to male-to-male sexual contact, there are data from this outbreak to rely on to answer this question. In terms of populations at highest risk of Mpox, and August AMIS survey found that 53.1% of respondents had concerns about getting Mpox. During October–December, an AMIS survey showed that those with high Mpox concern had a 3.5 times odds of being vaccinated. Interest in the vaccine seemed to be high during August–November when greater than 85% of respondents in the AMETHYST study were interested in the vaccine. During August–December, 50% of Porter Novelli survey responders who identified as LGBTQ+ felt that the vaccination is important to protect from Mpox. That includes not only MSM, but also other LGBTQ. During October–November, greater than 70% of MSM in a San Francisco survey of persons experiencing homelessness reported that they would accept or have accepted vaccination. This is important because a disparity has been observed in that individuals experiencing homelessness have experienced a disproportionate number of cases just as those who are Black and Hispanic have. The WG's interpretation was that the target population probably feels that the desirable effects are large relative to the undesirable effects.

There is some uncertainty or variability in how many people might value the vaccination. During the 2022 Mpox outbreak, willingness to be vaccinated was dynamic and depended upon perceived vulnerabilities. Clear demand for JYNNEOS vaccination occurred, but many still remain unvaccinated for unclear reasons. The demographics of future outbreaks also would be unclear, which is why the WG believes there might be some uncertainty or variability. It is unknown what the demographics of future outbreaks might be, who the affected populations might be, and whether the values expressed by the population most affected by the 2022 Mpox outbreak can be extrapolated to all other populations. For this reason, the WG's interpretation was that there is possibly important uncertainty or variability.

Moving to the Acceptability domain, stakeholder perceptions are very important to this question. Sermo is an online community of greater than 1.3 million clinicians. During July 31─August 1, 2022, survey results of US clinicians (n=415) showed that 69% felt that the US was without enough Mpox vaccine to handle the outbreak, indicating that they wanted vaccine to be available. A September 12, 2022 survey among 62 US clinicians showed that 66% had treated at least 1 Mpox patient, 76% knew where a patient could get JYNNEOS vaccination, and 86% wanted to be able to provide vaccination to their office. Taken together, the WG interpreted this as the clinician stakeholders being supportive of vaccination.

In terms of health departments and CBOs, health departments have been requesting JYNNEOS and organizing vaccination campaigns. Approximately 70% of the allotted JYNNEOS vaccine doses already have been requested and shipped to states in response to requests from stakeholders. In addition, the VEPP has enabled jurisdictions to request more than their allotted amount of JYNNEOS vaccine. It was established to support innovative ways to address vaccination disparities, encourage vaccination coordination between health departments and CBOs, and promote innovation to strengthen existing vaccination infrastructure. A total of 28 programs involving 15 jurisdictions and approximately 25,000 doses have been associated with the VEPP. This is above and beyond the initially allotted amounts, all of which illustrates that there seems to be support among stakeholders, health departments, and CBOs. The WG's interpretation is that the intervention is acceptable to key stakeholders.

Regarding the Resource Use domain, JYNNEOS vaccine is provided from the HHS SNS free of charge. Vaccines are a good use of resources during an outbreak and this EtR and ACIP vote are intended for any outbreaks. However, there are costs and challenges associated with mobile pop-up vaccination sites. A cost-effectiveness analysis of vaccine implementation during the current outbreak is not currently available. As comments during previous sessions have indicated, use of the SNS is sometimes not as efficient as would be preferred. The WG was split on their interpretation of whether the intervention is a reasonable and efficient allocation of resources. Some WG members felt that it was reasonable, but that the efficient element was uncertain. Therefore, the interpretation was that it varies.

With respect to the Equity domain, no groups or settings are disadvantaged by a recommendation for JYNNEOS use during Mpox outbreaks. Effectiveness is the same for all immunocompetent persons. Implementation to assure equitable access will be important, particularly among persons who are at high risk for severe outcomes. This recommendation by ACIP might facilitate broad acceptance of the vaccine (e.g., by insurance companies and health departments) because it is an endorsement by ACIP after rigorous review of the evidence. The WG's interpretation was that interpreting equity as independent of implementation challenges, the impact on health equity is that equity probably would be increased.

In terms of the Feasibility domain, the feasibility of conducting vaccine campaigns in communities, at events, and within the public health facilities was demonstrated in 2022. Vaccinations can be integrated into provider' practices. Standing orders are available, the IIS requirements for reporting vaccinations are the same as for COVID-19 vaccines, and JYNNEOS can be stored refrigerated for 8 weeks. A wide range of vaccinators can administer JYNNEOS unlike the other orthopoxvirus vaccine, which some clinicians are hesitant to administer. All of these elements support the feasibility of vaccines and the vaccine recommendation.
which some clinicians are hesitant to administer. The WG thought carefully about this and felt that the JYNNEOS vaccination probably is sustainable during outbreaks. Vaccine access is an important concern. There needs to be increased, convenient, and low stigma access for all persons who might be at risk. Considerations to ensure vaccine equity include strong ties with

CBOs, support for vaccination events, engagement of trusted messengers, and ensuring that there is access, including in rural areas. The WG's interpretation was that the intervention is feasible to implement.

To summarize the responses to all of the EtR questions, the WG felt that there was possibly important uncertainty or variability, mostly because they did not have data about stakeholders who might be affected during other types of Mpox outbreaks. The WG felt that it is reasonable to have vaccines during an outbreak if it would prevent infections, which the Mpox vaccine does. There was some concern about whether use of this intervention is an efficient allocation of resources, so the WG's interpretation of whether the intervention is reasonable and efficient allocation of resources is that this varies. In terms of the balance of consequences, the WG felt that the desirable consequences clearly outweigh the undesirable consequences in most settings and drafted the following proposed recommendation language for ACIP's consideration:

> ACIP recommends the 2-dose* JYNNEOS vaccine series for persons aged 18 years and older at risk of Mpox during an Mpox outbreak? §
>
> *Dose 2 administered 1 month after Dose 1
> §Public health authorities will determine whether there is an Mpox outbreak; a single case may be considered an Mpox outbreak at the discretion of public health authorities. Other circumstances in which a public health response may be indicated include ongoing risk of introduction of Mpox into a community due to disease activity in another geographic area.

The WG also proposed the following Clinical Considerations:

- ❑ In an outbreak setting, vaccine is ideally given pre-exposure but may also be given as post-exposure prophylaxis (PEP), although evidence has not been reviewed by ACIP for PEP at this time.
- ❑ The complete 2-dose vaccine series should be given regardless of the timing of the exposure.
- ❑ Although ACIP has not reviewed the evidence, if there are vaccine supply shortages, the intradermal route of administration can be used.

The WG will be talking more about data for the intradermal route of administration during the June ACIP meeting. The entire outbreak language from this meeting and the June meeting will be consolidated into one *MMWR* after that. During the June ACIP meeting, the WG will provide updates about VE and safety and will propose a separate vote for administration of the JYNNEOS vaccine in people less than the age of 18 years. The focus during this meeting was on persons ≥18 years partly because that is simply an expansion of the 2022 ACIP recommendations for persons at occupational risk. It is the same age range, but for a different group of people. Depending upon the epidemiology of this outbreak, if cases are continuing to occur in large numbers, there will be more discussion and consideration for a longer-term vaccination strategy with the 2-dose JYNNEOS series during the October 2023 ACIP meeting.

ACIP Discussion Points, Observations, Suggestions on Mpox Vaccine

Following Dr. Ellington's Presentation

- It would be beneficial to have additional details on the individual who had a spontaneous abortion.

Following Dr. Chard's Presentation

- Concern was expressed about the large difference in the estimates of single dose coverage.

- It would be beneficial to have information about whether delivering vaccine too deeply affects VE.
- Concern was expressed about very few people being able to administer intradermal vaccine anymore. Dr. Rao emphasized that early on the intradermal route was recommended due to the shortage of vaccine. There is more vaccine available now and route of administration should not be a reason someone is not vaccinated.
- In the future, it would be helpful to share VE estimates of people with different organ transplants taking different pharmaceutical medications and HIV diagnosis codes.
- As more information is collected on intradermal versus subcutaneous administration, it would be useful, if possible, to look at that combined with full versus partial vaccination to understand if there is any differential impact in the setting of an outbreak if there is a preference for one or the other.

Following Dr. Duffy's Presentation

- While it is reassuring that the rate of myocarditis/pericarditis is lower than following Dryvax, the numbers of people vaccinated are still very small.
- In response to a request for the benefit of the public to explain what it means to have an absence of wheal without vaccine leakage, Dr. Buffy indicated that with intradermal administration, the idea is that there will be a wheal or small area where the skin is raised after an injection. Some people have reported to VAERS that when they have attempted intradermal administration but have not seen a wheal forming. That is why CDC issued some guidance to indicate that just because the wheal is not seen does not mean that the intradermal vaccination was not successful.
- This is another example that reveals that the US has a multifaceted safety surveillance system in which each platform complements the other in terms of strengths and limitations.
- Though v-safe^{sm} had low uptake for Mpox, with the understanding that this likely was a timing issue, it is laudable that CDC plans to use this system in the future for other types of vaccines and that in non-emergency response and routine vaccination programs, it is expected to be available early in the launch of new vaccines.
- It would be beneficial to have information on JYNNEOS vaccine in pregnancy. Dr. Buffy indicated that v-safe^{sm} has a question about pregnancy.
- Monitoring vaccine safety in general in pregnancy and among immunocompromised persons is crucial. The lessons learned from COVID-19 in terms of these populations have been very positive and reassuring, which is extremely helpful in terms of communication efforts.

Following Dr. Delaney's Presentation

- Regarding a question about what types of practices were involved in the Sermo cross-sectional surveys, Dr. Delaney indicated that most clinicians surveyed were from primary care or infectious disease practices. In terms of geography and racial distribution, they were primarily in the Northeast. The survey was quick and was open for only about 48 hours. The follow-up survey included a more diverse pool of respondents from the US. The data are available online.
- Looking at safety data, efficacy data, and outreach is a good approach in general in terms of how ACIP views a theoretical upcoming vote on this vaccine.
- It would be beneficial to hear more about the reason African Americans had the highest rate of vaccine uptake at the beginning but the lowest rate as time progressed in terms of whether it was related more to access or lessening interest in the vaccine. Dr.

Delaney noted that the AMETHYST questions could unpack that more, though intention to get vaccine has not yet been assessed by race and ethnicity.

- It seems that more education is needed to make at risk populations aware of the problem, given that the target populations do not know much about the vaccine and/or Mpox disease. Dr. Delaney acknowledged that the AMETHYST and AMIS cohorts showed that there were gaps in knowledge, so CDC adapted its messaging based on those early survey results to be more sex-positive and to ensure that the vaccine was being talked about as a sexual health intervention, because most of the places where the vaccine was available outside of the health equity events were STI and PrEP clinics and HIV care sites. The Community Engagement Task Force developed the materials and the social media marketing and worked with CDC's community partners to get the message out to the most affected communities. He agreed that more needs to be done.
- The difference between the number of people who are interested in the vaccine and the number who actually have taken the vaccine is striking. That disconnect suggests that there is creative work to be done.
- One approach to address the equity issue is positive deviance; that is, highlight successes and figure out how to learn from them.
- From a local public health standpoint, the aspect of achieving equity is often a matter of having adequate resources for local public health and their partners to conduct effective outreach to those who are at higher risk. ACIP's guidance and identification of potential equity issues can help to direct resources accordingly.
- Equity always has been increased in terms of pediatric vaccines because of the Vaccines for Children Program (VFC). Because there is not a comparable program for adult vaccines, barriers can increase equity among adult populations.

Following Dr. Carter's Presentation

- The launch of this response was very difficult because the vaccine distribution system was totally different from what all of the public health immunization programs had been utilizing beforehand. In terms of the issue of equity, states were only allowed to have 5 sites receive vaccine. That is one of the reasons why there was such limited distribution of the vaccine. If the SNS is going to be used via ASPR, consideration must be given to the efficiency of that distribution system.
- This presentation highlighted the complexity of the response and how many people were involved, both on the frontline and behind the scenes. The data with doses by month addressed the equity issue and demonstrated clearly that the concerted efforts were effective. All jurisdictions should be encouraged to look at their data in a similar way.
- Immunization registry reporting is critical to determine what doses have been given and to avoid errors.
- The lessons learned from Mpox should be applied to other outbreaks to inform quick mobilization versus spending months gearing up for an unexpected outbreak.
- It would be nice to have an overall statement saying that ACIP does not recommend routine HCP vaccination for frontline workers, along with more guidance about when PEP should be offered to frontline HCP who perhaps were not using personal protective equipment (PPE) and later finds out a patient has Mpox. Dr. Carter indicated that CDC worked closely with its Healthcare Worker Task Force and NIOSH colleagues to review this carefully and the conclusion was that PPE recommendations provided adequate protection against the risk of Mpox transmission and therefore, JYNNEOS vaccine was not recommended for HCP. Certainly, someone who is exposed to Mpox who was not adequately protected could be offered PEP.

- It would be beneficial to continue to have the flexibility to offer either the intradermal or subcutaneous route of administration, especially since intradermal can be stigmatizing.

Following Dr. Rao's Presentation

- Looking at the entire picture, this is a common disease. Even now at its lowest, there are still 2 cases per week. That is higher than the number of cases per week in the past few years, and there is a fairly high death rate. There is a very effective vaccine with good data.
- It was observed that case counts also have decreased in many countries where no vaccine is available. While vaccine is certainly playing a role, behavioral changes also may be having an impact.
- Significant information is still lacking for immunocompromised patients. In general, it seems that immunocompromised patients need additional doses. Perhaps during the October ACIP meeting, consideration can be given to additional doses of JYNNEOS for immunocompromised patients. Dr. Rao indicated that CDC is collaborating with other partners to try to conduct some immunogenicity studies to better understand the role of JYNNEOS for immunocompromised patients and plans to discuss this with the WG. Clinicians on the WG have raised this concern for HIV, immunocompromised, transplant, and other patients who have higher risk.
- Concern was expressed that having a risk-based recommendation could limit access, be stigmatizing to some extent, and present inherent challenges for future Mpox outbreaks or other infectious diseases with similar characteristics. While education will help, it will not solve the problem to the extent that someone who is not aware they are at risk needs to be seen in a clinical setting and that their risk needs to be assessed. CDC and the WG emphasized that the ICC explains that individuals should not have to explain their rationale for wanting to be vaccinated and that there is a need for continual community engagement and education to keep Mpox in the public eye.
- It will be important for longer-term recommendations and the ICC to address booster dosing, which will be part of the WG's discussion after June 2023.
- The question often arises about whether someone who recovered from Mpox should be vaccinated, which the WG is not currently recommending because it is believed that these individuals will have protection from their natural illness. There are booster studies underway that will inform booster dosing recommendations in the coming years.
- There can be complicated political considerations in declaring an outbreak. The proposed recommendation language is broad and as such offers the flexibility to implement more aggressive vaccination measures if state and local health departments feel that is needed.
- It is impressive that over 90% accurate data were captured on race and ethnicity. It would be great to capture that information and information on disabilities in all clinical trials and other studies in order to inform and enhance access.

Vote: Mpox Vaccine

Agam Rao, MD (CDC/NCEZID) displayed and read the proposed vote language following the public comment period. The vote was combined with the Mpox session for ease of reading:

> ACIP recommends the2-dose* JYNNEOS vaccine series for persons aged 18 years and older at risk of Mpox during an Mpox outbreak? §
>
> *Dose 2 administered 1 month after Dose 1
> §Public health authorities will determine whether there is an Mpox outbreak; a single case may be considered an Mpox outbreak at the discretion of public health authorities. Other circumstances in which a public health response may be indicated include ongoing risk of introduction of Mpox into a community due to disease activity in another geographic area.

Motion/Vote: Mpox Vaccine

Dr. Loehr made a motion to approve the recommendation as stated, which Dr. Poehling seconded. No COIs were declared. The motion carried with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

RESPIRATORY DISEASE SURGE, FALL 2022, UNITED STATES

José R. Romero, MD (CDC, Director NCIRD) emphasized that it was a pleasure to speak to ACIP in his role as Director of NCIRD. Having previously served as a member and the Chair of the CDC's ACIP, he truly understands and greatly appreciates the time and effort required by its members to convene a meeting of the ACIP. He observed that over the course of the meeting, the committee would hear presentations on influenza and COVID-19 vaccines, as well as novel RSV vaccines. To set the scene for the next few sessions, he wanted to give a brief overview of the co-circulating respiratory viruses that are observed over the Winter and Fall and highlight how they are of critical importance in terms of vaccination. This past Fall and Winter, the US saw high co-circulation of respiratory syncytial virus (RSV), influenza virus, and SARS-CoV-2. These put significant stress on healthcare systems and the drug supply chain. After a brief and anticipated uptick of hospitalizations and cases around the holidays, there is now a continued decrease in COVID, influenza, and RSV cases and hospitalizations nationally.

For those who are not pediatricians, he explained that RSV is a well-recognized respiratory pathogen of infants and a common cause of respiratory disease in older adults. In adults, RSV can be difficult to differentiate from COVID-19 and influenza based on symptoms alone and is frequently overlooked as a diagnosis for viral respiratory disease in adults. In the elderly or in those with certain comorbid conditions, RSV infections can be significant and life-threatening. Typically, adults experience mild cold-like symptoms, although some can develop a lower respiratory tract infection (LRTI) such as pneumonia. Older adults, adults with chronic heart and lung conditions or diseases, and those with weakened immune systems are at higher risk for

severe RSV infections. RSV is also known to lead to worsening of chronic conditions common in adults, such as asthma, congestive heart failure, and chronic obstructive pulmonary disease (COPD). Each year in the US, it is estimated that between 60,000 and 160,000 hospitalizations occur and 6 to 10,000 deaths result in older adults due to RSV infections. This past fall, the CDC surveillance team saw an increase in RSV detections, RSV-associated emergency room department visits, and hospitalizations, including among older adults. Current national trends for RSV activity indicate that it has returned to baseline levels. For seasonal influenza, the activity continues to decline across the country. While influenza activity is declining, it remains possible that a second wave may occur later in the season as it has in the past.

CDC has responded to the increase in co-circulating respiratory viruses in multiple ways, but Dr. Romero thought the most important way to bring before the ACIP was that in January 2023, CDC released 2 new respiratory diseases surveillance dashboards that are accessible to public health medical professionals and the public in general. The first is the Respiratory Virus Hospitalization Surveillance Network (RESP-NET), which is an interactive dashboard that displays respiratory virus-associated hospitalizations from 3 existing surveillance platforms: Coronavirus Disease 2019 (COVID-19) Hospitalization Surveillance Network (COVID-NET), Influenza Hospitalization Surveillance Network (FluSurv-NET), and Respiratory Syncytial Virus Hospitalization Surveillance Network (RSV-NET). The second dashboard is the National Emergency Department Visits for COVID-19, Influenza, and Respiratory Syncytial Virus, which displays data on emergency room visits for multiple respiratory conditions as tracked by the National Syndromic Surveillance Program (NSSP). This dashboard presents data captured from approximately 75% of all emergency departments (EDs) in the US, so it is a very robust database. These dashboards allow users to easily see hospitalizations and ED data for these 3 viruses by age and track and compare the trends for SARS-CoV-2, influenza, and RSV disease.

Recent outbreaks highlight the importance of remaining vigilant about prevention. CDC continues to conduct outreach to clinicians, public health, and school partners and the public to raise awareness about the importance of vaccination for COVID-19 and influenza for everyone 6 months of age and older. Dr. Romero noted that during the first day of this meeting, there would be presentations and discussion on pediatric and maternal RSV vaccines that may become available for the prevention of RSV-related disease in the near future. Since the detection of the first case of SARS-CoV-2 virus over 3 years ago, more than 1 million Americans, including 2,000 children, have tragically died as a result of COVID-19 infection. Nearly 6 million individuals have been hospitalized and many more continue to suffer from long-COVID conditions. Fortunately, due to the rapid development of safe and effective vaccines, the position is very different from 3 years ago. COVID-19 vaccinations have prevented millions of severe illnesses, hospitalizations, and deaths since their introduction in December 2020. Many current members of the ACIP were on the committee at that time. Now 80% of Americans have received at least 1 dose of the primary COVID-19 vaccine series and over 667 million doses of vaccine have been administered. However, despite the introduction of a bivalent booster in September 2022, uptake has been low with only 15% of the US population having received an updated booster. The numbers are even lower for pediatric patients. Vaccinations and antivirals continue to be the best protection against serious illness for COVID-19.

Unfortunately, during the COVID-19 pandemic, there was a concerning decrease in routine immunizations for both adults and children. Routine vaccinations are rebounding, although unevenly, and have yet to fully recover in all groups. A significant and extremely concerning example is that the percentage of uninsured children not vaccinated by their second birthday was recently found to be 8 times that of privately insured children. That is even in the context of VFC, a program that is designed to address these inequities in healthcare insurance. While continuing to investigate the impact of the pandemic on routine immunizations, it is imperative to take steps to help get everyone back on track with their routine immunizations. Everyone must continue to work together to improve vaccination coverage by reducing barriers, increasing access, and strengthening vaccine confidence. For influenza and COVID-19, safe, effective, licensed or authorized vaccines are currently available for the prevention of serious disease. It is very possible that in the not-too-distant future, Americans also may have options for the prevention of a third respiratory virus, RSV. With that, Dr. Romero thanked ACIP and wished them good luck with their deliberations and discussions.

Discussion Points

Before opening the floor for discussion, Dr. Lee emphasized Dr. Romero's key points. First, context is everything. Many families with children and/or older adult members have had multiple respiratory viral illnesses this Winter. On top of that, pediatric providers had such a significant respiratory surge during a certain period of time, all due to multiple respiratory illnesses, they had to divert and redirect many of the children who were very ill and needed care. There also were other children who needed to come in for other reasons. This has had a major impact on the healthcare delivery system and families. One reason the ACIP was so grateful to Dr. Romero for being willing to speak about this context was that for the first time in a long time, ACIP had the opportunity during this meeting to review data on influenza vaccines, RSV, COVID-19, and pneumococcal vaccines. All of those are important preventive measures for ACIP to consider as part of a potential respiratory disease prevention platform. While they would take each of these vaccines into consideration on an individual basis, it also is important to think through the broader implementation context for young children and older adults to ensure that as the committee is making these recommendations, they also are thinking ahead about how these programs would be deployed in the various populations.

In response to Dr. Loehr's request to speak further to Dr. Romero's revelation that the percentage of uninsured children not vaccinated by their second birthday was recently found to be 8 times that of privately insured children, Dr. Romero said that given that the VFC was in place and functioning well pre-pandemic, this suggests a major problem. The VFC was established to address barriers in access, yet this problem of lower vaccine rates has been particularly severe among racial and ethnic populations, rural areas, and areas experiencing poverty.

Dr. Talbot expressed excitement about viral vaccines coming online for older adults, but lamented how complicated vaccines are for adults over 65 years of age because of Medicare. She asked whether any processes are in the works to streamline vaccines under Medicare Part B so that physicians can vaccines while patients are in the clinic.

Dr. Wharton indicated that there have been some changes in policy with recent legislation. She called upon Mary Beth Hance to make some brief comments about the changes to Medicare vaccine reimbursement issues under Medicare Part B and D from the Inflation Reduction Act (IRA).

Mary Beth Hance (HRSA) indicated that the IRA made changes to coverage of vaccines for adults in Medicare. COVID-19 was added as a Part B covered vaccine. For Part D, there is no cost sharing for patients. Covered Part B vaccines now include influenza, pneumococcal, hepatitis B for individuals at high and intermediate risk, COVID-19 vaccines, and vaccines that are reasonable and necessary to treat an injury or exposure to a disease. There is coverage of ACIP-recommended vaccines with no cost-sharing under Part D.

Dr. Romero added that while this benefits those with insurance, there is still a large population of adults in the US who do not have insurance. Serious consideration of a program that would offer vaccine to those individuals, a Vaccines for Adults (VFA) modelled in some way after the VFC, is something the American public needs to consider moving forward in order to catch all Americans up on vaccinations and make these vaccinations available to all.

Dr. Daley asked what is known about vaccination rates for adults without insurance and if there is a comparable figure for influenza or COVID vaccination, and what would be required to establish a VFA program.

Dr. Romero indicated that he could share specific data during the Agency Update session, but that rates are substantially lower for those who are uninsured. Even a co-pay can be a deterrent to accessing vaccines. Establishment of a VFA would need to be appropriated for within the President’s Budget and legislated by Congress.

Dr. Goldman (ACP) asked whether it would be within CDC’s purview to handle certain state jurisdictions deliberately spreading disinformation regarding the safety and efficacy of the vaccines.

Dr. Romero responded that CDC, as always, is engaged with educating the public and providing information that is scientifically correct and sound. It is not within the realm of CDC to actively involve itself within jurisdictions. Simply put, these are decisions made by the jurisdiction or jurisdictions involved.

Dr. Hogue (APhA) said he was struck by the inequities that still exist in US society and emphasized that they should all do what they could to address them. He reported that America's pharmacies are having significant issues with the Part D plans and the inconsistency with which the Part D plans cover the administration of vaccines. They treat vaccines as drugs because they have a National Drug Code (NDC) number, but many of the Part D plans either try to bundle the administration fee with the vaccine for administration simplification or they pay very little or no administration fee at all. His concern is that during the pandemic, people have become quite dependent upon community-based pharmacies to improve access points, especially in rural areas of the country. If the Part D plans are not held to account by CMS to consistently pay a meaningful administration fee and stop clawbacks, which are very common in the pharmacy world for drugs, it could result in a situation of pharmacies being unable to offer vaccines for Medicare beneficiaries under the Part D plan in the future. Therefore, he wanted to raise this awareness and an alarm bell so that colleagues at CMS would work with them to try to correct this situation in the coming Part D Call Letter.

INFLUENZA VACCINE

Introduction

H. Keipp Talbot, MD, MPH (ACIP, WG Chair) indicated that this session would include presentations focused on influenza activity, interim influenza VE against inpatient, ED, and outpatient illness in the 2022-2023 season, interim estimates of 2022-2023 influenza VE from 2 studies in Wisconsin, and published estimates of live attenuated influenza vaccine (LAIV).

US Influenza Activity Update

Lisa Grohskopf MD, MPH (CDC/NCIRD) presented a brief update of the 2022-2023 US influenza activity. In terms of virological surveillance data, results of influenza-positive tests are reported weekly to CDC from a very large network of clinical and public health laboratories. The percent of positive influenza tests is one of the indices of influenza activity. For 2022-2023, the percent of positive tests peaked in late November/early December at about 26%. The percent positive has been decreasing for about the 9th consecutive week to 1.7%. The peak of 26% is roughly comparable to other recent seasons. However, the peak shifted earlier than is typical. The peak also was higher than the 2 seasons immediately preceding 2022-2023. The other component of this system, Public Health Laboratories (PHLs), provides a sense of the influenza viral types and subtypes in circulation. H3N2 viruses have predominated, although there also has been appreciable co-circulation of H1N1pdm09-like viruses. About 99.4% of the viruses characterized thus far have been influenza A. Very little influenza B has been seen at this point in the season.

Laboratory-confirmed influenza-associated hospitalizations come from FluSurv-NET. Cumulative hospitalizations have leveled off at about 59.5 per 100,000 and have stayed flat in recent weeks. As with the peak shift, influenza-associated hospitalization activity shifted earlier in the season as well. Deaths of children associated with laboratory-confirmed influenza has been reportable in the US since 2004. Thus far, as of the weekend ending February 11, 2023, a total of 111 pediatric deaths have been reported through the Fluview mechanism. This is unfortunately more than in 2020-2021, for which 1 pediatric death was reported and 2021-2022, for which 45 pediatric deaths were reported.

To summarize influenza activity as of the week ending February 11, 2023, US influenza activity rose early, peaking nationally during late November/early December. The percent that tested positive peaked at about 26% and is currently down to about 1.7%. Influenza A(H3N2) virus has predominated so far with co-circulation of A(H1NI)pdm09. The cumulative influenza-associated hospitalization rate has leveled in recent weeks to about 59 per 100,000. A total of 111 influenza-associated pediatric deaths have been reported thus far this season. Overall influenza activity is increased compared with the previous 2 seasons. US influenza activity is currently low.

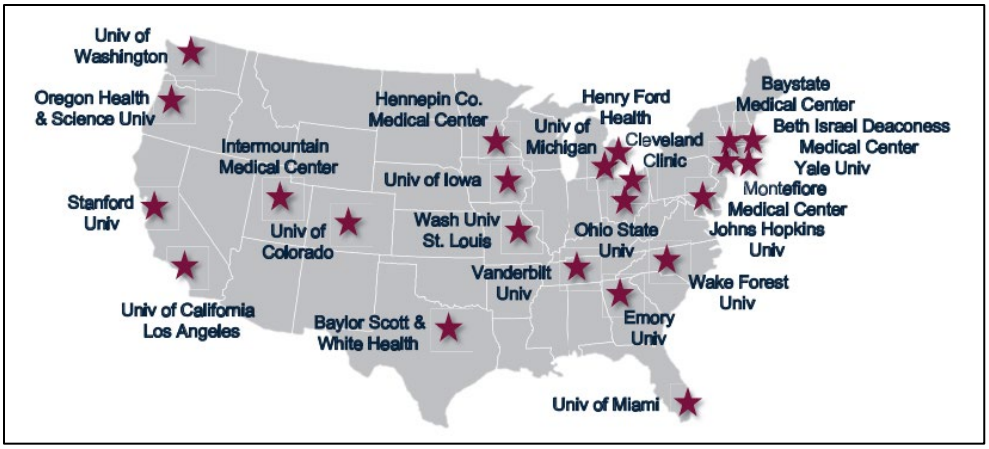
Preliminary 2022-2023 Influenza Vaccine Effectiveness: CDC Networks

Samantha Olson, MPH; Nathaniel Lewis, PhD; and Mark Tenforde, MD, PhD (CDC/NCIRD) presented preliminary 2022-2023 influenza VE results from 3 CDC networks: New Vaccine Surveillance Network (NVSN), Investigating Respiratory Viruses in the Acutely Ill (IVY), and the VISION Vaccine Effectiveness Network. Ms. Olson explained that CDC uses these 3 networks to evaluate VE against laboratory-confirmed influenza-associated outpatient visits, emergency department visits, and hospitalization. Across all 3 networks, the methods are similar. For this analysis, patients were enrolled with acute respiratory illness (ARI) from Fall 2022 through early 2023. Each study has a test-negative design comparing vaccination odds among case patients with influenza A confirmed by molecular assay versus control patients testing negative for influenza and SARS-CoV-2. Vaccination status was defined as the receipt of any 2022 through 2023 influenza vaccine according to medical records, immunization registries, claims data, and/or a self-report. For each analysis, VE was calculated as (1 ─ the adjusted odds ratio) x 100.

The NVSN analysis calculated VE against influenza-associated hospitalizations and ED visits among children 6 months through 17 years of age. NVSN conducts active surveillance at 7 sites across the country: Seattle Children's, Children's Mercy Hospital Kansas City, Texas Children's Hospital Houston, Vanderbilt University Nashville, Cincinnati Children's, University of Rochester, and Children's Hospital of Pittsburgh. NVSN enrolled inpatient and ED patients 6 months through 17 years of age with acute respiratory illness within 10 days of illness onset from September 13─January 25 for this analysis. A test-negative design was used in which patients were considered vaccinated if they received at least 1 dose regardless of their age and relied on verified vaccination or self-report. Logistic regression was used for this analysis, adjusting for site, age, and calendar time of admission.

In terms of preliminary VE estimates against pediatric hospitalizations and emergency department visits among children 6 months through 17 years of age. There were 640 influenza-positive cases and 2,256 controls included in this analysis. Nineteen percent of cases versus 33% of controls received a seasonal influenza vaccine. Overall VE was 49% among inpatients, with a higher-point estimate of 68% observed. Among ED visits, 42% VE was calculated. When stratified by subtype, effectiveness against H3N2 was 45% and against H1N1 was 56%. To summarize, based on preliminary estimates for the 2022─2023 influenza season, influenza vaccinations significantly reduced laboratory-confirmed medically-attended influenza in children. Effectiveness against pediatric hospitalizations was 68%. Effectiveness against pediatric ED visits was 42%, and important protection was observed against both H3N2- and H1N1-associated illness.

Dr. Lewis explained that the IVY analysis assessed VE against influenza-associated hospitalization among adults ≥18 years of age receiving inpatient medically-attended treatment for influenza. This analysis was drawn specifically from patients at 24 medical centers in 19 states in the IVY network shown in the map below:



The methods used in IVY are very similar to the NVSN methods. The data rage for the analysis was October 1—January 31, 2023. This analysis used a test-negative case-control method that assessed the odds of vaccination among cases versus controls. This analysis was adjusted for Census region, age, sex, race/ethnicity, and month of illness onset. Fairly encouraging results were seen in this analysis of 219 cases who tested positive for influenza and 921 controls who tested negative for both influenza and SARS-CoV-2. Vaccination coverage was 31% among cases and 43% among controls. Overall, VE was 43% for persons ≥18 years of age. As expected, there was some variation by age group, with lower protection among those ≥65 years and older of 35% versus 51% among those 18—64 years of age. Importantly, significant protection was observed in the immunocompromised subgroup that was very similar to that of overall VE in the network, albeit with a wider and overlapping confidence interval. About two-thirds of the 77 specimens analyzed through the end of 2022 were H3N2 and the remaining third were H1N1. The important takeaway is that influenza vaccination significantly reduced medically-attended hospitalized influenza at a VE of 43%. Significant protection was observed in the older adult population and among immunocompromised adults.

Dr. Tenforde presented preliminary results from the VISION network on influenza VE results against influenza-associated hospitalizations and ED or urgent care (UC) visits. VISION is an electronic VE network that consists of health systems with integrated laboratory, clinical, and vaccination records. The 3 partners contributed data for this analysis, including Kaiser Permanente Northern California (KPNC), Intermountain Healthcare, and HealthPartners in 4 states. For this analysis, encounters included ED or UC visits or hospitalizations between October 15—January 24, 2023 among adults ≥18 years of age who received clinical testing for influenza and had 1 or more ARI-associated discharge codes. Using a test-negative design, VE was estimated by comparing influenza vaccination odds among patients who tested positive for influenza A versus controls who tested negative for influenza and SARS-CoV-2. VE models applied inverse-propensity-to-be-vaccinated weights and adjusted for potential confounders including patient age, study site, and calendar time.

Preliminary VE estimates against adult ED or UC visits were calculated for 14,011 influenza-positive cases and 43,196 influenza-negative controls included in this analysis. Twenty-three percent of cases versus 36% of controls had received a 2022-2023 seasonal influenza vaccine. Overall VE was 44% in all adults ≥18 years of age, including 46% in adults 18—64 years and 39% in adults ≥65 years of age. A lower point estimate of 30% was seen among adults with immunocompromising conditions. In terms of VE estimates against adult hospitalizations, the analysis included 1,760 influenza-positive cases and 9,377 influenza-negative controls. Thirty-

eight percent of cases versus 49% of controls had received a seasonal influenza vaccine. Overall VE was 39%, including 29% in adults 18–64 years of age and 42% in adults ≥65 years of age. VE was 31% among adults with immunocompromising conditions.

In summary, through almost the end of January 2023, influenza vaccinations significantly reduced laboratory-confirmed medically-attended influenza with an estimated VE of 39% against adult hospitalizations and 44% against adult ED or UC visits. Effectiveness was observed across all age groups and in those with immunocompromising conditions. These estimates were higher than VISION Network VE estimates against hospitalization and ED or UC visits from the same sites during the prior 2021-2022 season when mostly vaccine mismatched H3N2 viruses were circulating. A limitation of this analysis was a lack of data to estimate VE by influenza A subtype including H1 and H3 viruses.

In conclusion, across 3 influenza VE platforms, very consistent influenza VE was observed during the early 2022-2023 influenza season. Vaccination provided substantial protection against inpatient ED and outpatient illness across all ages. Influenza vaccination also provided substantial protection among important high-risk groups, including older adults and those with immunocompromising conditions.

Preliminary 2022-2023 Influenza Vaccine Effectiveness: Wisconsin

Huong McLean PhD, MPH (Marshfield Clinic Research Institute) presenting interim estimates of influenza VE from 2 studies in Wisconsin: A test-negative case-control study funded by CSL Seqirus and a community cohort study funded by CDC. The methods of the test-negative case-control study are similar to what was presented for the 3 CDC networks, except that the enrollees are outpatients who presented for COVID-19 testing aged 6 months through 64 years with ARI with a cough of ≤7 days duration. Data presented are from enrollments from December 2, 2022 through February 10, 2023. Influenza vaccination was defined as documentation in the patient's health record of current season influenza vaccine receipt ≥14 days before illness onset according to the ACIP recommendations. VE estimates were adjusted for age, month of illness onset, and presence of high-risk conditions.

Influenza positive RT-PCR results were highest at the beginning of the enrollment period in December and have declined since. Of the viruses, 73% were A(H3N2) and 26% A(H1N1pdm09). All of the 43 characterized viruses were genetically similar to the vaccine components. A total of 545 patients with medically-attended ARI were included in this analysis. Among participants, 34% were vaccinated, of whom the majority (84%) received cell-culture based vaccine (ccIIV4). The percentage vaccinated differed by sex, high-risk conditions, and COVID-19 vaccination status. Among the 116 participants positive for influenza, 22% were vaccinated compared to 37% of 429 participants who tested negative for influenza and SARS-CoV-2. The adjusted VE against outpatient medically-attended influenza A was 54%, with a 95% confidence interval of 23% to 73%. VE against influenza A(H3N2) viruses was 60%, with a 95% confidence interval of 25% to 79%.

The prospective community cohort study is an ongoing study in Central Wisconsin of 241 children who have been followed weekly since September 5, 2022. Each week, children or their guardians report the absence or presence of the following symptoms over the past 7 days: fever, cough, loss of smell or taste, sore throat, muscle or body aches, shortness of breath, diarrhea, nasal congestion or runny nose, or nausea or vomiting. New symptom onset prompts self- or guardian-collection of anterior nasal swab for influenza and SARS-CoV-2 research testing. Other relevant information collected from surveys and extracted from EHRs include

vaccination history and clinic influenza test results. To estimate VE against symptomatic influenza infection in the cohort, a Cox proportional hazards model was used with time-varying vaccination status. The at-risk window began October 23, 2022 (7 days before the first case was identified) and ended February 10, 2023 (positive influenza infection date)—whichever occurred first. Vaccinated person time began ≥14 days after receipt of the influenza vaccine. Unvaccinated person-time was the time before receipt of influenza vaccine. Person-time was censored for the 13 days after receipt of influenza vaccine. An influenza case was defined as a positive influenza result from a research or clinical test during the at-risk period. VE effectiveness was calculated as 1 minus the adjusted hazards ratio x 100% where the hazards ratios represented the ratio of influenza infections in the vaccinated to unvaccinated person-time. The model adjusted for age, higher at-risk condition, and COVID-19 vacation. Among the 241 children in the cohort, 39% were vaccinated, of whom 84% received ccIIV4 and 65% received 2 or more doses of COVID-19 vaccine. A total of 34 (14%) of children were positive for influenza.

In terms of influenza and SARS-CoV-2 infections by week of onset, influenza incidence was highest late November and early December and has declined since. Of the influenza infections, 85% were caused by A(H3N2), 3% were caused by A(H1N1pdm09), and the remaining 12% were influenza A with unknown subtype. The characterized A(H3N2) viruses in this population were genetically similar to the vaccine component. Regarding VE against symptomatic influenza among children, there were 6 influenza A infections during the 7,292 vaccinated person days of follow-up, resulting in an incidence of 0.82 infections per 1,000 person-days. A total of 28 cases occurred during the 15,678 unvaccinated person-days, resulting in an incidence of 1.79 infections per 1,000 person days. VE against symptomatic influenza A virus infection was 71% with a 95% confidence interval in 31% to 90% among children in this cohort.

There are several limitations to consider for these studies. First, both studies were conducted in a single geographic area, Central Wisconsin. However, the viruses that predominated in the study population was similar to those that predominated across the US. Second, adults ≥65 years of age who generally have lower VE estimates against A(H3N2) were excluded. Third, the sample sizes were small. This resulted in wide confidence intervals, so it was not possible to estimate VE against A(H1N1pdm09) or by age groups. Finally, confounding and bias are concerns with observational studies. However, estimates were comparable across the 2 study designs.

To summarize, interim results indicate substantial vaccine-induced protection against influenza A during the current season. VE effectiveness was 54% against medically-attended influenza A in children and working-age adults and 71% against symptomatic influenza A infection in children. These estimates are consistent with reported estimates from the 4 CDC networks and in Canada and are consistent with a good vaccine match. All characterized viruses from the study population belong to the same genetic subclade as the viruses included in the 2022-2023 Northern Hemisphere influenza vaccine.

Update on Published Estimates of LAIV4 Effectiveness: Background

Lisa Grohskopf MD, MPH (CDC/NCIRD) presented a brief update of published estimates of live attenuated influenza vaccine (LAIV) effectiveness, noting that these are not CDC data. LAIV4, the quadrivalent LAIV, was initially approved in the US in 2012 and came into use during the 2013-2014 season after having had a trivalent formation available since 2003 in the US. LAIV4 was not recommended in the US for use during the 2016-2017 and 2017-2018 seasons following observation of low effectiveness specifically against H1N1pdm09-like viruses among

children 2–17 years of age that was noticed during the 2013-2014 season and during the 2015-2016 season, both of which had some H1N1 predominance. It was not clear what was going on when this first was noticed. The 2013-2014 season was the first H1N1-predominant season that had occurred since the 2009 influenza pandemic. It also was the first season the quadrivalent product was available. However, subsequent studies suggested decreased replicative fitness of the LAIV4 H1N1pdm09-like vaccine virus. Live virus vaccine such as this requires replication of the virus in the nasopharyngeal mucosa in order to be effective. Following those studies, the vaccine virus was updated and replaced in the vaccine. LAIV4 was again a recommended option in the US starting in 2018-2019 after a discussion of 3 streams of data during the February 2018 ACIP meeting. These included a combined US individual patient level VE analysis that consisted of data from several US sources, a systematic review of post-2009 US and non-US LAIV VE estimates, and MedImmune data on the new H1N1pdm09-like vaccine virus that indicated a better immunogenicity and fitness of that new virus.

Unfortunately, subsequently LAIV4 use within the CDC US VE networks has been low since the 2018-2019 season, which has precluded assessment of vaccine-specific VE in the US from these networks. However, LAIV VE estimates have been published from non-US observational studies.[16] For comparison, an effort was made to pool from the same papers where available, either IIV inactivated vaccine quadrivalent VE estimates, or if such were not available, estimates for all vaccines. These estimates are all for children for whom the age groups vary somewhat, given that they represent the age groups for whom vaccine was licensed. Starting with Finland for 2018-2019, LAIV4 VE estimate for children 2–6 years of age was 36% and VE for IIV4 for children 6 months–6 years of age was 54%. For UK, 2018-2019 VE for LAIV VE was 49% for children 2–17 years of age and 53% for all vaccines in this same age group. For 2019-2020, estimated LAIV4 VE of 45% was reported in the UK for children 2–17 years of age. For 2021-2022, estimated LAIV4 VE of 72% was reported in the UK for children 2–17 years of age. For 2021-2022 in Denmark, VE for all vaccines among non-hospitalized children 2–6 years of age was 64% and was 63% for hospitalized children of the same age. This paper notes that these children were offered LAIV4, which 92% received. Others received inactivated vaccine, so these are predominantly LAIV4 estimates.

ACIP Discussion Points, Observations, Suggestions on Influenza Vaccine

Following Dr. Grohskopf's First Presentation

- Regarding questions about whether the pattern of the 111 pediatric death cases was similar to prior years with 50% having no co-morbidities, Dr. Grohskopf indicated this was not yet known for this season. It takes a while for this information to come in, but the 50% that was published in a 2018 paper from her group is fairly typical.
- In terms of questions about why influenza began and peaked so early this season, Dr. Grohskopf noted that influenza seasons are unpredictable, and this is not the first time an early influenza season has occurred. She referred to a chart on the CDC webpage that covers about 39 influenza seasons to date that shows a couple of seasons that peaked as early as October.
- The hospitalization rate seems somewhat low despite the brisk influenza season, which raised questions about whether this was due to better diagnostics and therapeutics and/or better recognition of viral disease. Dr. Grohskopf indicated that this cannot be discerned form the type of data that come from that system, but it is certainly plausible to

[16] A) Stuurman et al Vaccine 2020;38:6455-64632; B) Pebody, Vaccine 38 (2020) 489–4; C) Stuurman et al Vaccine 2021;39:3964-3973; D) https://webarchive.nationalarchives.gov.uk/ukgwa/20220401215804/https://www.gov.uk/government/statistics/annual-flu-reports; E) https://www.gov.uk/government/statistics/annual-flu-reports/surveillance-of-influenza-and-other-seasonal-respiratory-viruses-in-winter-2021-to-2022; and F) Emborg, Euro Surveill2022;27:pii=2200278

think that people have a lower index of wanting to get checked by a medical provider given all that everyone has been through over the last couple of years. Certainly, influenza seasons vary in severity. H3N2 seasons are generally more severe than H1N1, and there appears to be a reasonably good vaccine match.

Following Presentations by Ms. Olson, Dr. Lewis, and Dr. Tenforde

- Regarding an inquiry about what percentage of persons ≥65 years of age in the IVY and VISIONS studies received the preferentially recommend high-dose vaccine, Dr. Tenforde indicated that most persons 18─64 years of age received standard-dose inactivated quadrivalent vaccines and the majority (90%) of individuals ≥65 years of age received either a high-dose vaccine or adjuvanted vaccine product. Dr. Lewis added that while they are awaiting more complete product data for IVY, the breakdown in the past has been similar with the majority of persons 18─64 years of age receiving standard-dose inactivated quadrivalent vaccines and the majority (90%) of individuals ≥65 years of age receiving some type of enhanced vaccine product.
- With regard to an inquiry about how many children received LAIV, Ms. Olson indicated that LAIV uptake has been low within the NVSN Network facilities.
- In terms of why SARS-CoV-2 was excluded from the analyses and if that changed the comparisons to past years, Dr. Tenforde indicated that patients had to be negative for influenza and SARS-CoV-2 to be part of this analysis. Most patients who received influenza testing also received testing for SARS-CoV-2. The reason they were excluded as controls was because there is a potential for a confounding relationship where receipt of influenza vaccination is correlated with receipt of COVID-19 vaccination. Essentially, controls can be enriched with patients who had COVID-19 and potentially bias VE estimates.
- It is important to highlight that among the pediatric deaths, only about 22% were fully vaccinated with 2 doses.
- With respect to whether the WG is aware of any new influenza vaccines on the horizon with less disappointing efficacy, Dr. Talbot pointed out that everyone would like to find the Holy Grail. A unique aspect of influenza infection in adults is that adults have been exposed to RSV and influenza many times in their lives. Yet, the vaccine is still being expected to do something that the human immune system has not figured out. There are multiple components to this, including the aging immune system, the changing virus, and the vaccines primarily induce a B-cell response. There is some T-cell response, but there is very little internal protein in current vaccines that would stimulate the T-cells. While many scientists including herself are looking for a universal influenza vaccine, they still have the vaccine that was developed originally for military recruits. It is somewhat cleaner and less reactogenic than it was when it was first discovered, and it still prevents a fair number of hospitalizations and deaths each year. Therefore, it will continue to be used until the Holy Grail appears.

Following Dr. McClean's Presentation

- The prospective cohort study is intriguing. The incidence per 1,000 person-days of 0.82 for the vaccinated and 1.79 for unvaccinated persons results in approximately 1 per 1,000 person days. Based on a 3-month influenza season, the number needed to vaccinate (NNV) would be 10 people to prevent 1 illness.
- Notably, the test-negative case-control study began in December and likely missed some cases due to the early start of the influenza season.

Following Dr. Grohskopf's Second Presentation

- Notably, the measures, definitions, and criteria vary in the non-US studies. Dr. Grohskopf emphasized that some variations are expected because there are variations in matches from season-to-season and in methods, especially among observational studies.
- There appears to be a theme that this vaccine is unlike Coronavirus vaccine in that it does not seem to protect better against worse outcomes. It may be somewhat different for ARI and hospitalization, but not as dramatically. It was not clear whether this was real or the way that people are being investigated. Dr. Grohskopf said that to be completely honest, she was not sure. Much of the data she is familiar with on prevention of severe outcomes focuses more on influenza vaccines broadly, while she was less familiar with the specifics on LAIV. She will look this up and provide a response at a later time.
- One of the major challenges that will need to be addressed is that because people are able to test themselves at home, they may be less likely to go to their doctor. Those who do present to medical settings are getting multiplex testing. As more point-of-care diagnostics move into the home setting, consideration will have to be given to how meaningful surveillance can continue to be conducted in that context. These data are needed in order to continue to ensure the benefit-risk balance of prevention programs.
- It would be beneficial to include LAIV information in any publications regarding VE, given that many parents have questions and would like to see these data.

PNEUMOCOCCAL VACCINES

Introduction

Katherine A. Poehling, MD, MPH (ACIP WG Chair) reminded everyone that pneumococcal vaccines currently recommended for use in the US include PCV13 and PCV20 for adults. PCV13 and PCV15 are recommended for children. PPSV3 has a risk-based recommendation for children. PPSV3 is recommended for adults who previously received PCV13 or PCV15, but not for those receiving PCV2020. The goal is to move forward with fewer differences. As a reminder, all children under 2 years of age have the same pneumococcal vaccine recommendation for 3 primary series and a booster, often known as the 3 + 1 schedule. The primary series doses are administered at 2, 4, and 6 months and the booster is given at 12 to 15 months later. Currently, either PCV13 or PCV15 can be given to US children. Children with certain underlying conditions are recommended to receive PPSV23. Children with chronic medical conditions (CMC), cerebrospinal fluid (CSF) leak, and cochlear implants are recommended to receive PPSV23 ≥8 weeks after the conjugate vaccine. Children with immunocompromising conditions are recommended to receive PPSV23 ≥8 weeks after the conjugate vaccine. Then ≥5 years later, a second dose of PPSV23 is recommended. Children 6–8 years of age with CMC can receive PPSV23 if they did not receive pneumococcal conjugate vaccine. Of note, CMC includes chronic heart disease (CHD), chronic lung disease (CLD),and diabetes mellitus (DM).

Approval of PVC20 use among children is anticipated later this year. It is anticipated that later in Quarter 2 of 2023, pediatric PCV20 will be approved. Pediatric PCV15 use was approved in June 2022. With that in mind, the WG is considering the following policy questions:

- ❑ Should PCV20 be recommended as an option for pneumococcal conjugate vaccination according to currently recommended dosing and schedules for US children aged <2 years?

- ❑ Should PCV20 without PPSV23 be recommended as an option for pneumococcal vaccination for US children aged 2–18 years of age with underlying medical conditions that increase the risk of pneumococcal disease?

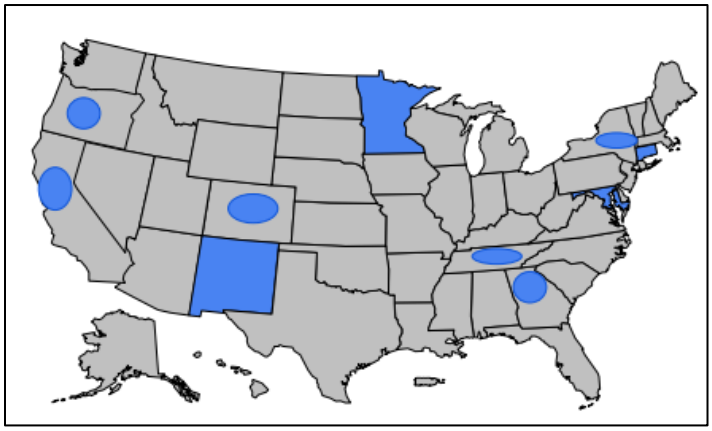
Presentations during this session focused on the epidemiology of pneumococcal disease among US children, pediatric outpatient ARI visits and antibiotic use attributable to serotypes in higher valency pneumococcal conjugate vaccines, PCV20 Phase 2/3 study results among children, preliminary EtR for PCV20 use in children, and WG considerations and next steps.

Epidemiology of Pneumococcal Disease among US Children

Ryan Gierke, MPH (CDC/NCIRD) presented an update on the current epidemiology of pediatric pneumococcal disease in the US, beginning with a background on the spectrum of pneumococcal disease. Pneumococcus is transmitted through airborne droplets from person-to-person. It can colonize in the nasopharynx and can be spread locally to the ears to cause otitis media. It also can be aspirated and cause pneumonia. Pneumococcus also can infect the blood and cause septicemia. These different infections can be characterized as either noninvasive disease or invasive disease. Invasive pneumococcal disease (IPD) is a less frequent but severe form of the illness. Noninvasive disease is more frequent. In children, otitis media is one of the most common forms of pneumococcal disease. Note that pneumococcal pneumonia can be either invasive or noninvasive, depending on whether a sterile body site like blood becomes infected in addition to the lungs.

This presentation focused on: 1) IPD data in terms of the impact of pneumococcal conjugate vaccines (PCVs) and IPD incidence and serotype distribution; IPD incidence caused by serotypes covered in the new conjugate vaccines, PCV15 and PCV20; and changes in IPD incidence and serotype distribution resulting from the COVID-19 pandemic; 2) the impact of PCV13 on acute otitis media (AOM) and incidence estimates; and 3) the impact of PCV13 on all-cause and pneumococcal pneumonia in children and recent estimates of pneumonia incidence.

In terms of the impact of pneumococcal conjugate vaccines on pediatric IPD incidence and serotype distribution among children in the US, data on IPD are obtained from the Active Bacterial Core (ABCs) surveillance system, which provides population-based surveillance at 10 sites across the US. Those are defined as pneumococcus-isolated from a normally sterile site in residents of the 10 surveillance areas shown in the map below:



Isolates are serotyped at reference laboratories using whole-genome sequencing (WGS), Quellung, or PCR at reference laboratories. For analysis purposes, serotypes are grouped by vaccine types. US Census Bureau estimates were used as denominators to calculate incidence rates for overall and serotype-specific IPD and are presented as cases per 100,000 persons. From 1998–2019, before introduction of conjugate vaccines in the US, incidence rates of IPD among children <5 years of age were approximately cases per 100,000 persons. PCV13-type IPD caused the majority of disease. Note that 6C included with the PCV13 serotypes due to cross-protection provided from the 6A antigen included in the vaccine. After the introduction of PCV7 in 2000, rates of IPD declined significantly. There were additional declines in disease following PCV13 introduction in 2010. Around 2013, declines in PCV13-type IPD rates plateaued at <2 cases per 100,000. This trend continued onward through 2019. Rates of overall IPD are now <10 cases per 100,000 persons, with much of the remaining disease caused by non-PCV13 serotypes.

Focusing on more recent years from 2007–2021, the COVID-19 pandemic resulted in a 50% reduction in rates of overall IPD in 2020 compared with 2018–2019. However, rates began to rebound in 2021 with a 30% increase compared to 2020 rates. Data for 2022 are not yet finalized, but looking at 2021 data by month, the monthly rates of IPD were back to the pre-pandemic levels after around August 2021. IPD rates were examined for individual serotypes in PCV13 among children <5 years of age from 2011–2021. After PCV13 introduction in children, rates of IPD declined for many PCV13 serotypes. However, reductions were not seen in serotypes 3 or 19F. Together, these serotypes accounted for almost 80% of remaining PCV13-type disease in 2018 and 2019. The impact of the COVID-19 pandemic led to a change in the serotype distribution of PCV13-type disease. In 2020 and 2021, serotype 19F rebounded quickly and now accounts for the majority of remaining disease, while the proportion caused by serotype 3 has declined. This will continue to be monitored to determine whether these changes continue.

Now to review the current pediatric IPD burden among PCV15 and PCV20 serotypes, this table shows the serotypes contained in the 3 conjugate vaccines and PPSV23. Serotypes covered by PCV13 are shown in yellow; additional serotypes covered by the new conjugate vaccines, PCV15 and PCV20, are shown in green; and PCV15 contains the 13 serotypes included in PCV13 plus serotypes 22F and 33F:

For analysis purposes:

- ❑ PCV13+6C: includes serotype 6C with PCV13 types due to cross protection from 6A antigen
- ❑ PCV15 non-PCV13: includes serotypes 22F and 33F
- ❑ PCV20 non-PCV15: includes serotypes 8, 10A, 11A, 12F, and 15B
- ❑ PPSV23 non-PCV20: includes serotypes 2, 9N, 17F, and 20

Rates of IPD incidence among children <5 grouped by vaccine type from 2011–2021 remained relatively stable for PCV15/non-PCV13 and PCV20/non-PCV15 serotypes in recent years before the COVID-19 pandemic. Although rates of IPD were lower in 2020 and 2021, PCV15/non-PCV13 and PCV20/non-PCV15 serotypes still account for a similar proportion of IPD at around 15% each. There has been great variability over the years among children 5–18 years of age, which is likely due to having much fewer number of cases. Unlike what was observed for younger children, IPD did not start to rebound in 2021 among children 5–18 years of age. Children with immunocompromising conditions are at increased risk of IPD. In terms of IPD among children with select immunocompromising conditions, children <5 years of age with a hematologic malignancy had rates of IPD around 230 times higher than children without a hematologic malignancy. African-American children with sickle cell disease had rates of IPD at around 30 to 70 times higher than African-American children without sickle cell disease, depending upon their age. Among children with immunocompromising conditions, a higher proportion of IPD is caused by non-vaccine serotypes compared to children without immunocompromising conditions.

To review the impact of PCV13 on AOM and available data on incidence estimates for AOM,[17] AOM is a major cause of childhood morbidity and pneumococcus is a common cause of AOM, accounting for around a quarter of bacterial AOM. Studies have shown that AOM incidence has decreased after PCV13 introduction, with declines ranging from 11% to 14% depending on the age groups and years examined. AOM estimates vary among studies, but incidence is consistently highest among children <5 years of age.

Regarding the data on the impact of PCV13 on all-cause and pneumococcal pneumonia and estimated incidence of pneumonia in children, multiple studies have shown reductions in all-cause and pneumococcal pneumonia among children following introduction of PCV13. Reductions in all-cause pneumonia range from 17% to 35% among children, depending on the age group, with reductions largest among children <2 years of age. There was an estimated 40% reduction in pneumococcal pneumonia among children <1 year of age and a 51% reduction in pneumonia among children 5–17 years of age. To summarize all-cause pneumonia and all-cause inpatient pneumonia incidence estimates in cases per 100,000 person years among children, pneumonia incidence is lower than AOM incidence but higher than IPD incidence. Again, the highest incidence is observed among children <5 years of age.

In conclusion, the use of PCVs has significantly decreased the incidence of pneumococcal disease in US children. However, risk of disease remains higher among children with immunocompromising conditions compared to those without. In 2018 and 2019, the proportion of IPD caused by vaccine serotypes was about 15% of IPD for PCV15/non-PCV13 serotypes and about 30% of IPD for PCV20/non-PCV13 serotypes.

[17] Tong et al. BMC 2018; King et al. ASHE 2021; Casey et al Clin Pediatr 2014; Kaur et al. EJCMID 2022

Estimating the Impact of Higher-Valency PCVs on Pediatric Outpatient ARI Visits and Antibiotic Use

Laura King, MPH (UC Berkeley) presented results from a University of California Berkeley study estimating pediatric outpatient ARI visits and antibiotic use attributable to serotypes in higher valency PCVs. This presentation focused on pediatric outpatient visit and antibiotic prescription incidence, AOM vaccine serotype attributable proportion and incidence, and sinusitis and pneumonia vaccine serotype attributable proportion and incidence. In terms of background, ARIs account for a large proportion of all outpatient visits and antibiotic prescriptions among children. Previous work looking at a commercially-insured population established that there were over 1,200 ARI visits per 1,000 children in 2018.[18] A separate study established that there were about 250 ARI-associated antibiotic prescriptions per 1,000 children issued from US doctors' offices and EDs per year in 2014 and 2015.[19] *Streptococcus pneumoniae (S. pneumoniae)* is a known etiology of several ARIs, including AOM, sinusitis, and pneumonia. However, the contribution of pneumococcus to the total burden of these conditions and the visits and antibiotic prescriptions associated with them is still unknown.

Time series data demonstrate decreases in outpatient visits and antibiotic use associated with PCVs. A previously published study examining the number of all antibiotic prescriptions per 1,000 persons stratified by age group[20] showed that the rate of antibiotic prescriptions decreased from 2011 to 2014, coinciding with uptake of PCV13 after its introduction in 2010. This decrease was especially pronounced in children <2 years of age, the age group eligible for vaccination. In considering PCV20 and PCV15 for pediatric use, it is important to better understand the potential impacts of these higher valency vaccines on outpatient visits and antibiotic use. This was the impetus for the current study with an overall objective to estimate the incidence of pediatric outpatient visits and antibiotic prescriptions for AOM, sinusitis, and pneumonia caused by *S. pneumoniae* serotypes found in the new higher valency PCVs, PCV15 and PCV20. This study focuses on the additional serotypes in PCV15 and PCV20 that are not in PCV13 to quantify the additive potential of these vaccines. These are referred to as PCV20-13 and PCV15-13 serotypes.

The study focuses specifically on AOM, abbreviated AOM, sinusitis, and pneumonia as these are ARIs with established pneumococcal involvement. The overall study objective is composed of two parts, which are to: 1) estimate the incidence of all-cause visits and antibiotic prescriptions for these conditions; and 2) estimate the proportion of outpatient disease caused by PCV15-13 and PCV20-13 serotypes. Multiplying the results from these 2 components will provide the incidence of visits and antibiotic prescriptions for these conditions attributable to PCV15-13 and PCV20-13 serotypes.

Beginning with the first project component to estimate all-cause visit and antibiotic prescription incidence for AOM, pneumonia, and sinusitis, 2 data sources were used to capture visits and antibiotic prescriptions across all outpatient settings in the US. Visits to and antibiotic prescriptions from physician offices and EDs were estimated using the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS). These are nationally representative surveys administered by CDC's National Center for Healthcare Statistics (NCHS). Data were used from 2016 and 2018, as later years and in 2017 were not available in NAMCS at the time of the analysis. Because NAMCS and

[18] King LM, et al. Antimicrob Steward Healthc Epidemiol. 2021;1(1):1-8. doi: 10.1017/ash.2021.230
[19] Hersh AL, et al. Clin Infect Dis. 2021;72(1):133-137. doi: 10.1093/cid/ciaa667
[20] King et al., Clin Infect Dis. 2020; 70(3):370-377). doi: 10.1093/cid/ciz225

NHAMCS only cover physician offices and EDs, the MarketScan Commercial and Medicaid Databases were used to estimate visits and prescribing in alternative outpatient settings such as urgent care and retail health clinics. In both datasets, a single diagnosis was assigned to each visit using an established tiered methodology that prioritizes diagnoses most likely to result in an antibiotic prescription. All incidence estimates were standardized per 1,000 person-years at risk and total incidence was estimated by combining the sum of the estimates from NAMCS, NHAMCS, and MarketScan. Using those methods, total incidence of outpatient visits for all 3 conditions was estimated to be 208 visits per 1,000 person-years. Total incidence of outpatient antibiotic prescriptions was estimated to be 181 prescriptions per 1,000 person-years. Notably, overall incidence was driven primarily by AOM.

In terms of the second project component and estimating vaccine serotype attributable proportions and incidence, it is important to note that there are several major challenges in evaluating pneumococcal and serotype-specific contributions to outpatient disease. First, children are frequently colonized with pneumococcus. Published estimates of nasopharyngeal pneumococcal carriage range from 11% to 60% in healthy children from high-income countries. Second, samples from infection sites are not regularly obtained for outpatient pneumococcal disease. There are some studies using samples of middle ear fluid in children with AOM. However, the children sampled in these studies often have severe or recurrent disease. Third, few studies have been conducted for non-AOM ARIs in pediatric outpatients.

Given these challenges, 3 methods were used to estimate the proportion of outpatient AOM attributable to PCV15-13 and PCV20-13 serotypes. All of these methods have their own limitations, and no one method is likely definitive. However, using multiple methods allowed for estimation of ranges of likely values, taking into account the uncertainties inherent in estimating etiology in outpatient disease. For all methods, previously published data were used to generate estimates. The first method used was a vaccine probe approach. In vaccine probe studies, VE against vaccine type in all-cause disease is used to estimate the proportion of disease attributable to a specific pathogen, in this case, the vaccine serotypes. The second approach used considered pneumococcal prevalence and serotype distribution for middle ear fluid sampled from children with AOM to estimate attributable proportions. The third approach used differential nasopharyngeal carriage prevalence in children with AOM and healthy children to estimate the pneumococcal attributable proportion and combined this with the distribution of serotypes and carriage in children with AOM.

Using these 3 methods, pneumococcus was estimated to account for 14% to 22% of outpatient AOM cases, PCV15-13 serotypes accounted for 0.7% to 1% of outpatient AOM, and PCV20-13 serotypes accounted for 3.7% to 5.1% of outpatient AOM. The highest attributable percents were observed from the approach using pneumococcal prevalence and serotype distribution in middle ear fluid. Regardless of method, the distribution of vaccine serotype groups remained fairly constant, with PCV20-13 serotypes accounting for about 5 times the proportion of outpatient disease covered by PCV15-13 serotypes. Using these attributable percents and the all-cause AOM visit and prescription incidence data presented earlier, incidence was estimated for outpatient visits per 1,000 person-years and the annual number of outpatient AOM visits in children. It was estimated that 76,000 to 109,000 visits per year were attributable to PCV15-13 serotypes and 397,000 to 543,000 visits were attributable to PCV20-13 serotypes. Looking at the same data for AOM-associated antibiotic prescriptions, PCV15-13 serotypes were associated with 65,000 to 93,000 outpatient antibiotic prescriptions annually and PCV20-13 serotypes were associated with 340,000 to 464,000 outpatient antibiotic prescriptions annually.

Regarding the attributable proportion and incidence estimates for pneumonia and sinusitis, less data were available for these conditions. The ability to estimate attributable proportions in pneumonia and sinusitis was limited to the vaccine probe and differential carriage approaches. Using these methods, 12% to 18% of pediatric outpatient pneumonia were estimated to be attributable to pneumococcus. PCV15-13 serotypes accounted for less than 1% of outpatient pediatric pneumonia cases and PCV20-13 serotypes accounted for 2.8% to 4.4% of outpatient pediatric pneumonia cases. The attributable proportions were multiplied by the all-cause visit and antibiotic prescription estimates presented earlier, which estimated that PCV15-13 serotypes accounted for 9,000 to 14,000 visits and 7,000 to 11,000 antibiotic prescriptions for outpatient pediatric pneumonia per year. PCV20-13 serotypes account for 43,000 to 68,000 visits and 34,000 to 53,000 antibiotic prescriptions for outpatient pediatric pneumonia per year. For sinusitis, it was estimated that 12% to 30% of all outpatient pediatric cases were attributable to pneumococcus. PCV15-13 serotypes accounted for 0.6% to 1.5% of sinusitis cases and PCV20-13 serotypes accounted for 2.8% to 7.3% of sinusitis cases. The differential carriage estimates were the same for pneumonia and sinusitis because the same estimates were used for all non-AOM ARIs in that approach given the scarcity of data. For sinusitis, it was estimated that PCV15-13 serotypes accounted for 17,000 to 44,000 visits and 16,000 to 43,000 antibiotic prescriptions per year. PCV20-13 serotypes accounted for 82,000 to 216,000 visits and 79,000 to 209,000 antibiotic prescriptions per year.

To summarize the ranges of point estimates for each condition by vaccine serotype group estimated using the multiple methods described earlier, for all 3 conditions, PCV15-13 serotypes accounted for 1.9% to 3.4% of outpatient disease in children, translating to 103,000 to 168,000 pediatric outpatient visits and 90,000 to 148,000 outpatient antibiotic prescriptions annually in the US. PCV20-13 serotypes account for 9.4% to 16.8% of outpatient AOM, pneumonia, and sinusitis, translating to 527,000 to 831,000 pediatric outpatient visits and 458,000 to 731,000 outpatient antibiotic prescriptions annually in the US.

This study had several limitations. First, it relied upon previously published data to estimate attributable proportions. Consequently, although data on pneumococcus in all outpatient conditions was limited, this was especially true for sinusitis and pneumonia. Therefore, it was necessary to rely on AOM as a proxy for these conditions in some cases. Additionally, due to data limitations at the time of the analysis, the incidence estimates were based on all-cause incidence data from 2016–2018. Finally, it was assumed that healthcare utilization was constant across serotypes for outpatient disease.

In conclusion, this study estimated that the additional serotypes included in PCV15 and PCV20 accounted for approximately 100,000 to 830,000 outpatient visits and 90,000 to 730,000 outpatient antibiotic prescriptions for AOM, pneumonia, and sinusitis in US children annually. Specifically, PCV15-13 serotypes accounted for 103,000 to 168,000 visits and 90,000 to 148,000 antibiotic prescriptions. PCV20-13 serotypes account for 527,000 to 831,000 visits and 458,000 to 731,000 antibiotic prescriptions. The percent of outpatient disease attributable to PCV20-13 serotypes was greater than the percent attributable to PCV15-13 serotypes. As a result, the estimated incidence of outpatient pediatric visits and antibiotic prescriptions attributable to PCV20-13 serotypes was 4 to 5 times that attributable to PCV15-13 serotypes.

PCV20 Phase 2/3 Study Results among Children

Wendy Watson, MD (Pfizer) presented key results from Pfizer's PCV20 Pediatric Clinical Development Program from the Phase 2/3 trial. PCV20 is built on the 20-plus year legacy of PCV7 and PCV13. PCV20 contains all of the components of PCV13, with 7 additional conjugates. Pfizer is seeking to expand PCV20 currently licensed in adults to include the same pediatric indications as PCV13. PCV20 builds upon the clinical experience of previous generations of PCV7 and PCV13. PCV7 was licensed based on a randomized controlled clinical (RCT) efficacy trial of IPD in California. In this study of 38,000 infants, high efficacy was demonstrated. Subsequently, high VE was shown following PCV7 introduction. When PCV13 was developed to expand protection against 6 additional serotypes, it was not considered feasible to perform an efficacy trial. Therefore, a licensing pathway similar to other vaccines, like a conjugate vaccine, was pursued. Immunogenicity bridging comparing PCV13 to PCV7 was used to support licensure globally. Similarly, PCV20 licensure for pediatrics will be based on immunogenicity bridging with non-inferiority comparisons to PCV13—a vaccine that now has more than 10 years of demonstrated effectiveness against disease due to vaccine serotypes.

This table shows the studies Pfizer submitted to the FDA to support the PCV20 pediatric indication:

Phase 2	Senders et al. 2021	2, 4, 6 and 12 months of age	460 Participants	Demonstrate safety, tolerability, and immunogenicity of PCV20 • Concomitant administration with Pediarix • United States	IMMUNOGENICITY / SAFETY
Phase 3	Pivotal Infant Study	2, 4, 6 and 12–15 months of age	1997 Participants	Demonstrate noninferiority of immune response of PCV20 vs PCV13 • Concomitant administration with Pediarix, Hiberix, M-M-R II, Varivax • United States, Puerto Rico	
	Pediatric Single Dose Study	Single dose (15 months–<18 years of age)	831 Participants	Characterize safety and immunogenicity in children 15 months to 17 years of age • United States	
	Safety Study	2, 4, 6 and 12–15 months of age	1511 Participants	Further characterize safety profile of PCV20 • Concomitant standard vaccines allowed • United States, Puerto Rico, Canada, Chile, Argentina, European Union	

These pediatric studies were generally modeled on the PCV13 pediatric studies and consisting of Phase 2 and Phase 3 studies. The studies listed in the table were conducted in children in the US, including Puerto Rico, except for the safety study on the bottom row that also included infants from other countries. For this presentation, Dr. Watson focused on the pivotal immunogenicity study in infants in the second row and the single dose study in children in the third row.

The Phase 3 pivotal infant trial was a multi-center, randomized, double-blind study enrolling infants in the US, including Puerto Rico. The study enrolled approximately 2,000 participants who were randomized equally to receive 4 doses of PCV20 or PCV13. PEDIARIX and HIBERIX were given concomitantly with the first 3 doses and MMR and varicella vaccines were given with the fourth dose. Influenza and rotavirus vaccines were permitted to be given with study vaccine in age-eligible participants. Blood was collected for immunogenicity assessments 1 month after the third dose, before the fourth dose, and 1 month after the fourth dose. The primary study objectives were to: 1) describe safety; 2) evaluate the immunogenicity of PCV20, including non-inferiority comparisons of PCV20 to PCV13; and 3) assess responses of specific concomitantly

administered vaccines. In terms of the disposition and demographics of the study population, the groups were well-balanced with respect to sex, race, and ethnicity.

PCV generate complex and diverse cellular and humoral immune responses that play a role in imparting protection. The primary and key secondary objectives that were agreed to prospectively with the FDA include 2 co-primary objectives to assess noninferiority of immunoglobulin G (IgG) geometric mean concentrations (GMCs) after the toddler dose and assess noninferiority of the percentage of participants with IgG above predefined levels after the infant series. The key secondary objective was to assess noninferiority of IgG GMC after the infant series. Other aspects of the responses also were assessed, including other IgG responses, functional antibodies measured as opsonophagocytic activity (OPA) titers, and boosting of IgG and OPA antibody levels that are indicative of immune memory. The assessment of the totality of data for serotypes that missed non-inferiority was agreed to prospectively by the FDA. An example of how important this assessment is comes from the previous experience with PCV13 and serotypes 6b and 9b. These 2 serotypes missed a co-primary objective for non-inferiority compared to PCV7, but the totality of immunogenicity data supported licensure and subsequent real-world effectiveness has shown that PCV13 protects against IPD caused by these two serotypes.

For the co-primary objective percentage of participants with the predefined IgG concentration after dose 3, non-inferiority was declared if the 95% confidence interval of the difference was greater than -10%. The additional 7 serotypes were compared to the lowest result in the PCV13 group, excluding serotype 3. In this case, the comparison was to serotype 23F result in the PCV13 group. For this objective, non-inferiority was met for 14 serotypes and 6 serotypes missed non-inferiority, although serotypes 1, 4, 9V, and 23F missed statistical non-inferiority by only a small margin. Serotypes 3 and 12F missed by a greater margin, but the totality of data was supportive. Additionally, public reference standard that was used to calculate 12F IgG concentrations may be underestimating 12f IgG results. Pfizer has shared these findings with the FDA.

Continuing to look at the response after Dose 3, the IgG GMC ratios in the PCV20 group compared to the PCV13 group for each vaccine serotype was the key secondary objective in the study. Non-inferiority was to be declared for this objective if the lower bound of the 95% confidence interval of the ratio was greater than 0.5. All 20 serotypes met non-inferiority for this comparison, including serotypes 3 and 12F. There also was comparison of the 7 additional serotypes to the result of a vaccine serotype in the PCV13 group. The IgG GMCs to those 7 additional serotypes in the PCV13 group after Dose 3 were low. The IgG GMCs for the 7 additional serotypes were substantially higher in the PCV20 group compared to the PCV13 control group. This was also the case after Dose 4. Functional antibodies elicited by the vaccine after Dose 3 also were assessed. The OPA GMC responses for the 13 matched serotypes were similar between groups, even for serotypes that missed the co-primary IgG objective for this dose. PCV20 also elicited very robust functional activity to the 7 additional serotypes, including 12F.

Moving on to the response after the toddler dose, Dose 4 in the study, non-inferiority was declared if the lower confidence interval was above 0.5. Similar to the result for the IgG GMC ratios after Dose 3, all 20 vaccine serotypes met non-inferiority after Dose 4. An important property of conjugate vaccines is their ability to elicit memory responses. Looking at the antibody levels in the PCV20 group after Dose 3 and after Dose 4, it is clear that there were numerically higher antibody levels after the toddler dose than after the infant series. This was observed for both IgG GMCs and OPA GMTs for the vaccine serotypes. This indicates that

immune response after the toddler dose is a significant marker indicating that a memory response has been induced after the infant series by PCV20.

In addition to evaluating the pneumococcal responses, Pfizer evaluated responses to concomitant vaccines. Regarding the difference in percent of participants with pre-specified antibody levels to the different antigens in PEDIARIX and HIBERIX given with the 3 infant doses of PCV20 or PCV13, all met the non-inferiority criteria. In terms of the responses to MMR and varicella vaccines given with Dose 4 of PCV20 or PCV13, all met the non-inferiority criteria. These data support PCV20 use in routine pediatric schedules.

Regarding safety, injection site pain, drowsiness, and irritability were the most common events. Most reactions were mild or moderate, rates were similar across both groups, and were consistent with the historical experience with PCV13. As mentioned previously, another important Phase 3 study assessed the safety and immunogenicity of a single dose of PCV20 in children 15 months to less than 18 years of age. This study was conducted in the US to support the use of PCV20 in children through 17 years of age. This multi-center, single arm trial enrolled approximately 800 healthy participants of approximately 200 per age group. Participants 15 months–5 years of age were required to have documentation of at least 3 doses of PCV13 prior to enrollment. In terms of IgG GMCs for the 2 age groups less than 5 years of age, 1 dose of PCV20 elicited a robust IgG response to all 20 serotypes in children 15 to <24 months and 2 to <5 Years previously vaccinated with PCV13. Data from the youngest group also supports the potential for replacement of PCV13 with PCV20 in the schedule. There was a similar pattern in the functional antibody responses in these age groups, as well as IgG and OPA responses in older children. The safety data were consistent with historical experience with PCV13. There were no clinically significant differences in the AEs in the PCV20 and PCV13 control group. SAEs were reported in 4.5% of PCV20 recipients and 3.7% of PCV13 recipients in the infant studies supporting US licensure. No SAEs in this dataset were considered to be related to vaccine and no deaths were reported.

In summary, PCV20 is well-tolerated when administered as a 4-dose series to infants and as a single dose to toddlers through older children, with a safety profile similar to PCV13. The totality of data shows that PCV20 elicits IgA, IgG, and OPA responses in infants for all vaccine serotypes consistent with PCV13. A single dose of PCV20 elicited IgG and functional immune responses to all 20 serotypes in children 15 months to less than 18 years of age, including those with prior PCV13. PCV20 is compatible with routine pediatric vaccines. PCV20 is currently under review by the FDA for use in pediatric populations 6 weeks to less than 18 years of age, with a target action date in April 2023. PCV20 has the potential to address the substantial burden of pneumococcal disease in children.

Preliminary EtR/GRADE for PCV20 use in US Children

Miwako Kobayashi, MD, MPH (CDC/NCIRD) provided the EtR Framework for PCV20 use in US children, pointing out that while the EtR includes 7 domains, the focus of this session would cover 3 of the domains: Public Health Problem, Benefits and Harms, and Equity. Currently, all children under 2 years of age have the same pneumococcal vaccine recommendations to receive either PCV13 and PCV15 using a 3-dose series at 2, 4, and 6 months of age and a booster dose at 12 to 15 months of age. Children ≥2 years of age with certain underlying conditions are recommended to receive PPSV23 in addition.

For this EtR analysis, there were 2 policy questions:

- ❑ Should PCV20 be recommended as an option for pneumococcal conjugate vaccination according to currently recommended dosing and schedules for US children aged <2 years?

- ❑ Should PCV20 without PPSV23 be recommended as an option for pneumococcal vaccination for US children aged 2–18 years with underlying medical conditions that increase the risk of pneumococcal disease?

Combined into the PICO question regarding whether PCV20 should be recommended as an option for pneumococcal vaccination for US children, the population is all US children aged <2 years and US children aged 2–18 years with underlying medical conditions. The comparison is the current recommendations for the respective groups. The critical outcomes include: Vaccine-Type IPD (VT-IPD), VT-Pneumonia, VT- AOM, VT-Pneumococcal Deaths, and SAEs Following Vaccination.

Beginning with the Public Health domain, use of pneumococcal conjugate vaccines significantly decreased the incidence of pneumococcal disease in US children. Outpatient acute respiratory illness caused by pneumococcus such as AOM, sinusitis, and pneumonia are common causes of outpatient visits and antibiotic prescribing. The risk of disease remains high in children with underlying conditions that increase the risk of pneumococcal disease. In 2018─2019, the proportion of IPD caused by vaccine serotypes was approximately 30% for additional serotypes contained in PCV20 but not in PCV13 and 15% for additional serotypes contained in PCV15 and not in PCV13.[21] The WG determined that pneumococcal disease is of public health importance for both groups of children. There was variability in the WG's interpretation for children <2 years of age due to the significant reductions in pneumococcal disease among these children. However, most WG members agreed that pneumococcal disease continues to be of public health importance due to the remaining disease burden.

For the Benefits and Harms domain, the WG interpretation of this domain was informed primarily by the great evidence profile for the PICO question. The outcomes deemed critical were VT-IPD, VT-pneumonia, VT-AOM, and VT-pneumococcal deaths. Given that there are currently no studies assessing PCV20 effectiveness against these clinical outcomes, PCV20 immunogenicity studies were used as evidence for these outcomes. To supplement this, the WG also reviewed post-licensure PCV13 and PPSV23 effectiveness data against these outcomes as a background.

Regarding outcomes related to harms, WG members deemed SAEs as being of critical importance. Evidence of SAEs was available and reviewed for PCV20. First, a summary of the post-licensure PCV13 VE data. Several post-licensure studies assessed PCV13 effectiveness against IPD. In general, these studies showed that PCV13 is highly effective against VT-IPD. Data on PCV13 effectiveness against VT-pneumonia in children are limited. Based on the 2 studies done in China and Israel, PCV13 is likely to be protective against VT-pneumococcal pneumonia, but with a wide confidence interval. Data on PCV13 effectiveness against VT-pneumococcal AOA also are limited. Estimates from these studies also tend to have wide confidence intervals, though the data suggest that PCV13 is likely protective against VE-pneumococcal AOM.

[21] Gierke. February 2023 ACIP meeting presentation; King. February 2023 ACIP meeting presentation

Data on PPSV23 effectiveness against pneumococcal disease in children with underlying conditions are limited.[22] A study conducted before the introduction of PCV in the US showed that PPSV23 is protective against VT-IPD among children with underlying medical conditions.[23] Data on PPSV23 effectiveness against non-invasive pneumococcal disease in children are even more limited. In a recent systematic review, no studies were identified that assessed PPSV23 VE against AOM. Two RCTs that evaluated the efficacy of administrating both PCV7 and PPSV23 against AOM did not show any efficacy in the intervention groups.[24]

To summarize the data on PCV20 use in children, the WG conducted a systematic review of literature on PCV20 use among children.[25] Overall, 4 studies were included for GRADE (Grading of Recommendation Assessment, Development and Evaluation). Of these, 3 were considered for evidence of routine PCV20 use and 1 was considered for evidence of PCV20 use in children with underlying medical conditions. Evidence of benefits of PCV20 use among children <2 years of age was informed by 2 RCTs (Phase II and III) that randomized healthy children to receive either PCV13 or PCV20.[26] In the pivotal trial, PCVs were given using the 3-dose primary series followed by a booster dose. The study showed that PCV20 had numerically lower immune responses compared with PCV13 for most of the 13 shared serotypes. Post-dose 3, PCV20 did not meet the non-inferiority criteria compared with PCV13 for some serotypes for the primary immunogenicity outcome. Post-dose 4, PCV20 met the non-inferiority criteria compared with PCV13 for all 13 shared serotypes and for all 7 additional serotypes. Evidence of harms was informed by findings from 3 RCTs.[27] Across the 3 studies, SAEs were reported in 4.5% of the PCV20 recipients compared with 3.7% of the PCV13 recipients, but none were considered to be vaccine-related.

The overall certainty of evidence was moderate. Certainty of evidence for benefits was downgraded since these are immunogenicity studies and there are no correlates of protection established for most outcomes of interest. For harms, certainty of evidence was downgraded for imprecision due to lack of vaccine-related SAEs being reported. The WG determined that the desirable anticipated effects of PCV20 were moderate. PCV20 provides the broadest serotype coverage among available PCVs, so it is expected to prevent more disease. However, it is unknown how substantial the protection conferred from PCV20 will be based on available data. The undesirable anticipated effects were considered to be minimal. The WG's interpretation of whether the desirable effects outweigh the undesirable effects was split between "favors intervention" of PCV20 use and "favors both" the intervention and the comparator of either PCV13 or PCV15 use. Those who favored the intervention believe that PCV20 is expected to prevent more disease compared with current PCVs. Those who favored both considered the uncertainties of the clinical implications of the lower immunogenicity of PCV20 and improved immunogenicity of PCV15 against serotype 3 compared with PCV13.

[22] Marra et al. Value Health 2022
[23] Fiore et al. EID 1999
[24] Veenhoven et al. Lancet 2003; and Van Kempen et al. Int J Pediatr Otorhinolaryngol 2006
[25] The search strategy and search terms used are available in the supplementary slides from this presentation
[26] Senders et al. PIDJ 2021; and Pfizer unpublished data from B7471011
[27] Senders et al. PIDJ 2021; Pfizer B7471011, unpublished data; Pfizer B7471013, unpublished data, limited to US and Puerto Rico sites

Findings from the pediatric PCV15 immunogenicity studies were presented during the February 2022 ACIP meeting.[28] No studies were conducted among children 2─18 years of age with underlying medical conditions. Evidence on benefits was informed by 1 Phase 3 non-randomized clinical trial with no comparator that evaluated the safety and immunogenicity of PCV20 use in healthy children 15 months─17 years of age. This included children <5 years of age who received at least 3 doses of PCV13. All participants received a dose of PCV20. The study showed that PCV20 was immunogenic for all 20 vaccine serotypes when assessed 1 month after vaccination compared with pre-vaccination baseline. SAEs after vaccination was reported in 0.6% of the participants and none were considered to be vaccine-related.

The overall certainty of evidence was very low. Certainty of evidence was downgraded further for this study since this was an open-label non-randomized controlled trial with no comparator group and did not include children with underlying conditions. The WG determined that the desirable anticipated effects of PCV20 use were moderate, the reasons for which were similar to those for routine use for children <2 years of age. In addition, there are no data on PCV20 use among children with underlying medical conditions. The undesirable anticipated effects were considered to be minimal. The WG's interpretation of whether the desirable effects outweigh the undesirable effects was split between "favors intervention" of PCV20 use and "favors both" the intervention and the comparator of PPSV23 use after currently recommended PCV doses. Those who favored the intervention believed that PCV20 is expected to prevent more disease compared with current recommendations. Those who favored both considered the fact that there are no data on PCV20 use in this population and that the clinical implications of improved immunogenicity of PCV15 against serotype 3 compared with PCV13 are unknown.

For the Equity domain, data were reviewed of estimated pneumococcal conjugate vaccine coverage by 24 months of age among children born during 2018─2019 by health insurance status using data from the National Immunization Survey-Child (NIS-Child). Compared with coverage among children with private insurance only, children who were uninsured and those insured by Medicaid and other insurance was lower. Nationally representative PPSV23 vaccine coverage data among children with indications are limited. In a study among children enrolled in the Michigan Medicaid program,[29] 64% of children with sickle cell anemia received 4 doses of PCV followed by a dose of PPSV23 as recommended by 5 years of age and 53% received 4 doses of PCV followed by 2 doses of PPSV23 as recommended by 10 years of age. Other studies that assessed PPSV23 coverage among children with underlying medical conditions were much lower, ranging from 20% to 40%.[30]

An unpublished analysis using CDC's ABCs data assessed the incidence rate difference of IPD among children ≤17 years of age in the highest and the lowest Census tract poverty categories by year for all serotypes, PCV13 serotypes, PCV15/non-PCV13 serotypes, PCV20/non-PCV13 serotypes, PCV20/non-PCV15 serotypes, and non-vaccine serotypes from 2010─2019. For all serotypes in PCV13 serotypes, incidence rate difference decreased after 2010 after PCV13 was recommended for use in children. There was essentially no incidence rate difference for PCV15/non-PCV13 serotypes in 2018─2019. The IPD incidence rate difference for the additional serotypes contained in PCV20 remained, and there was a slightly larger incidence rate difference for non-vaccine serotypes.

[28] Banniettis. February 24, 2022 ACIP meeting presentation
[29] Reeves et al. Pediatric Blood & Cancer, 2018
[30] Tran et al. Frontiers in Pediatrics, 2021; Mirza et al. The Ochsner Journal, 2022; Harris et al. Pediatrics, 2022

The WG believed that PCV20 use among children in both groups will "probably increase" health equity. However, there were some differences in the interpretation among WG members. For routine PCV20 use among children <2 years of age, some believed that new interventions like PCV20 are likely to be accessible to the wealthy communities first and, therefore, could reduce health equity. However, others believed that programs such as VFC and school requirements allow for high vaccine coverage across the population and post-PCV13 data showed that vaccine can reduce disparities due to VT-pneumococcal disease. Some WG members believed that there probably is no impact since remaining disparities in VT-pneumococcal disease seem to be minimal. Some believed that equity will be increased based on the experience post-PCV13. For PCV20 use in children with underlying conditions, some WG members believed a risk-based recommendation is less likely to be equitable compared with routine vaccine recommendations. Others believed that PCV20 use could simplify the current risk-based pneumococcal vaccine recommendations and improve vaccine coverage.

In terms of the preliminary summary of the WG's interpretation of the 3 EtR domains for the 2 policy questions, the WG believed that pneumococcal disease is of public health importance. Compared with the current recommendations, the benefits of PCV20 use were considered to be moderate and have minimal undesirable effects. The WG's interpretation was split between "favors intervention" of PCV20 use and "favors both" the intervention and current recommendations. The certainty of evidence was moderate for benefits and harms for routine PCV20 use in children <2 years of age, while the certainty of evidence was very low for children 2–18 years of age with risk-based recommendations. PCV20 use was considered to probably increase health equity, although some WG members expressed different opinions.

Pneumococcal Vaccines WG Considerations and Next Steps

Miwako Kobayashi, MD, MPH (CDC/NCIRD) reminded everyone that the policy question under consideration are:

- ❑ Should PCV20 be recommended as an option for pneumococcal conjugate vaccination according to currently recommended dosing and schedules for US children aged <2 years?

- ❑ Should PCV20 without PPSV23 be recommended as an option for pneumococcal vaccination for US children aged 2–18 years with underlying medical conditions that increase the risk of pneumococcal disease?

In addition, a cost-effectiveness analysis will be conducted to assess the incremental benefit of PPSV23 use in addition to PCV20 in children 2–18 years with underlying medical conditions, and the incremental benefit of PCV20 use in children who completed the recommended PCV series with either PCV13 or PCV15. The WG also is reviewing evidence to revisit some of the conditions for risk-based pneumococcal vaccine recommendations. Here are the specific questions that are being considered by the WG:

- ❑ Are children with asthma at increased risk of pneumococcal disease regardless of high-dose oral corticosteroid use?
- ❑ Are children with CLD at increased risk of pneumococcal disease?
- ❑ Are children with CKD of any stage at increased risk of pneumococcal disease?

Currently, there are differences between the pediatric and adult recommendations regarding the indications for pneumococcal vaccine use for people with asthma. The current pediatric recommendation[31] states, “Including asthma if treated with high-dose oral corticosteroid therapy.” The current adult recommendation states, “Includes chronic obstructive pulmonary disease, emphysema, and asthma.[32]

There are certain conditions or risk factors that currently are part of adult risk-based recommendations, but not for the pediatric recommendations. These include alcoholism, CLD, and cigarette smoking. The WG is considering whether to add CLD as part of pediatric risk-based recommendations. Chronic renal failure historically has been interpreted as those on dialysis or about to be on dialysis. The WG is discussing whether the risk-based recommendation should be expanded to children with all CKD stages.

The next steps for the WG are to:

- ❑ Review of evidence and WG interpretation of the remaining EtR domains (e.g., Values, Acceptability, Resource Use, Feasibility).
- ❑ Review findings from cost-effectiveness analyses by CDC and other groups.
- ❑ Review draft policy options for PCV20 use in US children for consideration by the committee.

Questions for the ACIP include the following:

- ❑ Does the Committee agree with the policy questions being considered by the WG?
- ❑ Are there additional data the Committee would like to see before deciding on policy options for a vote?

Merck Comments

Richard Haupt (Head, Global Medical & Scientific Affairs, Merck) commented on the pneumococcal disease burden in children in the US, emphasizing that the day’s discussion highlighted the importance of maintaining important epidemiological vigilance as the pneumococcal vaccine landscape evolves. This was the first time post-COVID disease burden trends have been seen. It is notable that serotypes 3, 19A, and 19F remain important in causing disease in children and underscores the need to maintain protection against these PCV15 and PCV13 vaccine serotypes. The trends also were notable for the disease burden of the youngest age group. The CDC presentation included estimates for pneumonia in children less than a year of age, and similar trends have been observed for other outcomes such as IPD in children less than one year of age, highlighting the importance of early vaccine protection. Pneumococcal vaccination coverage rates revealed persistent disparities. This was particularly true for the fourth dose where roughly 20% of Medicaid children missed that booster dose, therefore relying on early protection from the 3-dose primary series. The vaccine community clearly needs to address this vaccine series completion rate disparity for all pneumococcal vaccines that are developed or used.

[31] Nuorti et al. MMWR RR 2010; Kobayashi et al. MMWR 2022. 71(37); 1174–1181
[32] Matanock et al. MMWR 2019; Kobayashi et al. MMWR 2022. 71(4); 109–117

ACIP Discussion Points, Observations, Suggestions on Pneumococcal Vaccine

Following Mr. Gierke's Presentation

- There appears to be a differential even after vaccine introduction for children 2–4 years of age in terms of why it seems protective for the younger and older children and not as much for children 2–4 years of age. It may just be that there is a lot of variability in these studies in terms of the age groups, so the numbers might have been too small. While there seems to be a downward trend, it was not found to be significant. It would be helpful to see the references and review the data.
- It will be helpful to see a further breakdown of the children <5 years of age for whom a decrease was seen that was followed by a rebound in terms of immunization information when it is updated for 2021.
- In terms of whether more data are anticipated from 2022 that could help to better understand more complicated pneumonias that were see this winter than any other winter, Mr. Gierke indicated that this was assessed, but the data were not complete, especially for the latter part of the year. They could assess just pneumonia and just IPD. They are working to update the 2022 data on IPD. Dr. Kobayashi added that they also tried to look at this through the NDSS for which an uptick was observed in children <5 years of age, so there definitely is a trend. A limitation of the NDSS data is that they are self-reported.

Following Ms. King's Presentation

- It would be beneficial to have the NNV.
- Regarding the "big picture" in terms of trying to understand how the various vaccines together could reduce the overall impact of respiratory disease in young children, Dr. King emphasized that because it is a nasty respiratory season with horrific pneumonia and influenza, increasing vaccinations for both should significantly improve the health of children and keep them out of the hospital.
- Perhaps it could be an aspirational goal for the respiratory disease prevention platform to increase vaccination for influenza and pneumonia.

Following Dr. Watson's Presentation

- Regarding a request to provide more detail about the types of SAEs, Dr. Watson indicated that the SAEs were comprised of a multitude of other infections that had a diagnosed etiology, accidents, traumatic injuries, dehydration, failure to thrive, and malnutrition in both groups. There were more SAEs in the 20-valent group.
- In terms of an inquiry about why for the GMR on Slide 7 a lower confidence interval of 0.5 was used for most of the comparisons versus 0.67, Dr. Watson indicated that this is a longstanding endpoint and criteria that they have used for pneumococcal conjugate vaccines. That means that the actual point estimate has to be within 2-fold or closer to the actual control. When measuring multiple valencies and making 40 to 60 comparisons, having too rigid of a lower bound criterion like 0.67 probably would run into feasibility and, by chance, prevent a good vaccine from being licensed.
- With regard to a request to describe the Grade 3 fevers that occurred post-vaccination with PCV-20, Dr. Watson reported that there were 7 cases in the 20-valent group and 2 cases in the 13-valent group of fevers greater than 104°F. None of these had febrile seizures. There were 9 febrile seizures total over the course of the 4 pediatric studies, which comprised 0.2% in the PCV20 group and 0.1% in the PCV13 group. There were 2 cases of febrile seizure within 2 weeks of vaccination. In one case, the child also had a concurrent COVID illness. In the other case, fever occurred 14 days after Dose 4. The

investigator considered this possibly related to MMR and varicella but did not consider it related to vaccination. The remaining febrile seizures occurred much further out from vaccination.

- Given that the ACIP will be making a decision based on immunogenicity data, concern was expressed that there potentially could be a tradeoff between functional antibody response and quality of the response, as well as opportunity costs, even though there would be a gain of 7 additional serotypes. Dr. Watson said she thought the quality of the response is most important rather than the absolute IgG level. Both have to be taken into consideration in terms of responses. Functional antibody and memory responses both play a big role. Functional antibody was assessed in subsets of participants because there would not have been sufficient volume from infants for the OPA sample size as needed. It is important not to base things solely on one end point, which is known from Prevnar 13 for which non-inferiority was missed for 2 serotypes but protection of those 2 serotypes was good. The reverse cumulative distribution curves for IgG are reassuring in that protection was added for additional serotypes and IgG concentrations were kept fairly similar. Even though one data point showed missed non-inferiority for serotype 3 compared to the lowest Prevnar 13 serotypes, it was well above the Prevnar 13 group.
- Recalling a theoretical concern with respect to PCV7 and PCV13 that there is biological plausibility to the argument that response to 1 serotype could compete against response to another serotype, Dr. Watson responded that this was a concern in moving from PCV7 to PCV13, but there have not been any problems observed with containing or controlling the shared serotypes between PCV7 and PCV13. They are seeing a small increment in the immune response—not a large magnitude.
- Regarding an inquiry about whether there are any concerns about immunogenicity and/or efficacy and effectiveness among individuals who are immunocompromised or by race/ethnicity, Dr. Watson indicated that Pfizer did not conduct specific studies with immunocompromised children or those with sickle cell disease. They have a lot of experience with Prevnar 7 and Prevnar 13 showing that safety is acceptable in those populations comparable to the general population. They have some safety data for late preterm infants of 34─37 weeks gestation for which the safety looks very similar to term infants. Immunocompromised infants were not included in the trials for PCV20. They also looked at subgroups of African Americans, which is the largest single population in addition to the White population, and no significant differences were seen. If anything, immunogenicity was slightly higher for some serotypes, but it is important to keep in mind that those were smaller datasets.

Following Dr. Kobayashi's Presentations

- It appears that PCV20 could help to eliminate about a quarter of what is left of the remaining disease, most of which was addressed with the prior 2 vaccines. It would be beneficial for ACIP to see data regarding how cost-effective this would be. Dr. Kobayashi indicated that the plan was to present cost-effective analyses during the next ACIP meeting.
- Given the concern regarding a possible tradeoff being less serotype 3 or 19F disease, Kobayashi reiterated that the WG's interpretations of whether the benefits outweigh the harms was split between "favors intervention" with PCV20 and "favors both." Among those who favored both, one concern was that the clinical implication of the immunogenicity studies are not yet known. There also were concerns regarding last year's presentation from Merck representatives about the PCV15 data and how that would translate in terms of clinical protection. The remaining unknowns were reflected in the WG's interpretation.

- Reflecting on the EtR framework itself, the indirect impact of vaccinating children on older adults is potentially substantial. It feels like at least acknowledging the potential indirect impact on herd immunity would be an important aspect of the benefits of pneumococcal conjugate vaccines.
- The pneumococcal vaccine experts on the WG did not think PPSV23 vaccine has the immunogenicity or "legs" to be considered as an addition to or replacement of a PCV. Given that PCV20 induces immunologic memory and gets T-cells to participate, the experts all believe that it is so superior to PPSV23 that this would be desirable even at the expense of potentially losing PPSV23.
- The incidence among children with immunocompromising conditions of 270 times greater risk, even with vaccination, is striking.
- It is important to remember that even after the *MMWR* is published following an ACIP vaccine recommendation, insurance companies have a year before they have to start covering the vaccines. Some insurance companies are still not covering PCV15 for children. This is frustrating, delays care, and has resulted in some practices and hospitals continuing to give PCV13. In addition, there were delays in getting VFC PCV15. Difficulty getting coverage and delays in VFC vaccine may occur with PCV20 as well.
- Regarding whether PCV13 would be removed from the market if there is a PCV20 indication, Alejandro Cané from Pfizer confirmed that once PCV20 is approved for the pediatric indication, PCV13 will be phased out in the US.

PUBLIC COMMENTS

The floor was opened for public comment on February 22, 2023 at 2:00 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 rather than comments directed at individuals. 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 Number ID CDC-2023-0007. Visit http://www.regulations.gov for access to the docket or to submit comments or read background documents and comments received.

Mr. Jack Baker
National Foundation for Infectious Diseases

Good afternoon. I am Jack Baker with the National Foundation for Infectious Diseases, or NFID. As NFID commemorates its 50th anniversary during 2023, we celebrate the remarkable impact that vaccines have had in protecting public health and saving lives. As a long-standing partner of CDC, NFID appreciates the valuable work of ACIP in guiding US immunization policy to protect public health through the ongoing review and analysis of vaccine safety and advocacy data. Our comments today focus on 2 respiratory viruses of concern, influenza and RSV. Now influenza, or flu, is not just a cold but can cause potentially life-threatening complications—even in healthy children and adults. During the current flu season, estimates show that at least 25 million people in the US have become sick with flu; 280,000 have been hospitalized; and 17,000 have died from flu and related complications, including more than 100 children. Those affected are far more than just numbers, as clearly illustrated by the dozens of personal stories that NFID has collected of people whose lives have been impacted by vaccine-preventable diseases. Data also show that flu has a disproportionate impact on communities of color. Black adults are more likely to be hospitalized with flu-related complications and are less likely to get vaccinated

against flu than White and Asian adults. In fact, during most flu seasons in the past decade, hospitalization rates among Black adults have been about 2 times higher than among White adults. To help address these disparities, NFID is working with partner organizations to increase awareness of the importance of annual flu vaccination through the #ShowUp and #FightFlu campaign. Another respiratory virus of concern in the US, RSV, also has a substantial impact on individuals of all ages. Each year in the US, RSV causes an estimated 58,000 hospitalizations and 100 to 500 deaths among children younger than age 5 years, as well as 177,000 hospitalizations and 14,000 deaths in adults aged 65 years and older. In 2022, NFID issued a Call to Action on reducing the burden of RSV across the lifespan, which outlined key strategic priorities to drive progress in RSV surveillance, diagnosis, prevention, and treatment. Like flu, RSV also has a disproportionate impact on communities of color. As the ACIP evaluates new interventions to protect both infants and older adults against RSV, swift action will be essential to ensure equitable access through private and public payors, including the Vaccines for Children program. Additionally, developing clear, consistent communications will be critical in building public confidence and ensuring that these potentially life-saving new tools are available to all who need them. NFID values its long-standing partnership with CDC, and we look forward to continued collaboration to raise awareness about the importance of disease prevention through vaccination. On behalf of NFID, thank you for your dedicated service.

Mrs. Angie Bluford
Vaccine-Injured Individual

Thank you. Good afternoon. I am Angie Bluford, a 49-year-old mom of 2. At the beginning of 2021, I was in the best shape of my life due to a recent found love of kickboxing. On April 15th of 2021, I gladly took my second Moderna vaccine to protect my family, friends, and return to the gym. Since that day, I feel like I'm wearing a lead suit. The migraines, excruciating head pressure, and bone pain keep me from smiling as much as I used to. The shortness of breath, fatigue, cognitive, and speech issues have forced my second leave of absence since the vaccine. I've been denied short-term disability and most likely will be again, considering that no one wants to acknowledge our injuries. The mRNA vaccine has put me and my family in financial, emotional, and physical strain. It robs the injured of our families, friends, employment, and hobbies. Why would we, the injured, choose to make this up? Per the CDC's website, verified again today, the mRNA from the vaccines is broken down within a few days after vaccination and discarded from the body. I have a test result showing that the spike protein was still present and wreaking havoc in my body 603 days after my last Moderna vaccine, and I've never had COVID. Per Dr. David Wiseman, Moderna disclosed at September's ACIP that their bivalents produced non-natural spiked heterotrimers, something acknowledged to React19 by FDA's Dr. Marks. EMA papers reveal Pfizer's bivalents likely do the same. Since this is new chemistry and new immunology, how can you recommend tetravalent vaccines with new, untested toxicology? Dr. Wiseman also shared that the CDC and FDA's statement at January's VRBPAC that an ischemic stroke signal was only found in one database, FSD, is incorrect. Highly significant values for the PRR safety signals in VAERS emerge from CDC's recent FOIA disclosure and an NIH-sponsored calculator. How can CDC withhold this information from unsuspecting seniors it is studying without informed consent? Last year, the German Ministry of Health publicly acknowledged post-vac syndrome, a disease like long COVID that occurs after COVID vaccination. Post-COVID vaccine syndrome is most certainly happening to Americans, too. Why is the CDC silent with these important side effects? I implore you to remove the COVID vaccines from the schedule of recommended vaccinations for children until further study of adverse effects. Please hear, acknowledge, and help us. Thank you.

Ms. Sarah Regenspan
Vaccine-Injured Individual

Hello. Thank you very much to the committee for the opportunity to speak, and I acknowledge that I didn't have the time to be as prepared as our previous speaker. I was also injured by the COVID vaccine. I took my third Pfizer vaccine on January 7, 2022 and within hours, I developed burning chest pain and called my primary care doctor. I've never been hospitalized, but I was diagnosed by a cardiologist with vaccine-induced pericarditis. Over 13 months later, I am still suffering from symptoms that are preventing me from exercising normally and having a normal quality of life. My cardiologist has told me that they don't know why I'm still experiencing symptoms and that they have no more help to offer me. My primary care doctor says the same, although I'm very lucky that I have providers who do believe that this is a vaccine-induced injury. I made a VAERS report. I've applied to the Counter Measures Injury Compensation Program. I would be happy to submit my medical records and proof of those filings to any members of the committee here who would like to see them. And I just want to point out that even vaccine injuries that do not result in hospitalization are extremely traumatic and lead to a great loss of quality of life. And there are no answers being provided for people like me. And I would really love to see the CDC and this committee offer some support to those in the community like me who rolled up our sleeves and took not 1, not 2, but 3 of these vaccines because we were told it was for the greater good and we wanted to be of service to the community. I've now spent close to $25,000 of my own money and gone into credit card debt doing experimental treatments to try to recover, as traditional cardiology medications have not solved the problem for me. So, this has been an extremely painful and traumatic time in my life. It's been a very, very lonely journey. And it's disappointing to not see more support from government entities like the CDC. And my worry is that it is going to continue to produce resistance to public health measures in the future, as friends and family of those who are injured see that we are getting no support and no options for medical treatment and no acknowledgement from the CDC. So, I really would urge you to look into these injuries and take them seriously so that the public will trust and be part of public health measures in the future. Thank you.

Christina LaBette
Vaccine Injured Individual

Good afternoon. My name is Christina LaBette. On April 21, 2021, I freely received my second dose of the Pfizer COVID vaccine. Within 36 hours, my nightmare began being rushed to the hospital experiencing stroke symptoms. Today marks the 22-month anniversary of my injury and I wish for you to please listen to my story. Prior to my injury, I traveled, did many outdoor activities, was the mom who volunteered at school whenever needed, a cheer mom, a devoted wife, an active person who was free to do what I needed without assistance. Now, 22 months later, my life has forever changed struggling to live with debilitating cardiac and neurological symptoms, having to take multiple medications, and needing assistance with daily basic needs. Not only has my health deteriorated, I'm no longer able to be the mother or the wife that I was prior to the Pfizer injection. I have accrued over $35,000 in traditional medical bills and I have no improvement. I am begging for help to heal from these injuries. I now suffer from over 30 new diagnoses with conditions such as blood-clotting issues, tachycardia, dysautonomia, hemiplegic migraine disorder, diastolic dysfunction, small fiber neuropathy—these are just to name a few. I have been suffering unimaginable symptoms. These conditions are without question from my COVID vaccine. My life is consumed by appointments, testing, treatments. I'm just trying to survive this nightmare. It is a full-time job managing all of my health issues from the Pfizer vaccine. During our infertility journey in 2020, I had extensive clotting workups prior to starting treatments. All indicated I had no clotting genetics or factors. And now, my labs are riddled with

clotting issues and worse yet, my husband and I can no longer pursue our dream of having another child due to the Pfizer vaccine. I am mostly bedridden and housebound now. I can't garden or provide for my family as I did previous to my injection. I just can't up and go, as my body now dictates if I am capable of doing anything, including driving. I live in fear if I'm going to live or die, as well as my child fears losing her mother—so terrified she is in counseling now. I did my job getting the vaccine, so I ask you, why aren't you doing your job to help us get better? Why aren't you giving us a chance to recover from these injuries? We know you know this is happening. Why aren't you helping us? Here is a question for you all. What if this was your child? Your parent? Your loved one? What would you be doing to help them if they were injured by these vaccines? Why aren't you doing that to help me? To help us? We are real, we matter, and we need your help. The German government has even acknowledged these reactions as post-vax COVID syndrome, like a long COVID-like disease after COVID vaccination. So, I ask you again, why aren't you helping us?

THURSDAY: FEBRUARY 23, 2023

AGENCY UPDATES

Centers for Disease Control and Prevention

José R. Romero, MD noted that during the upcoming ACIP sessions, the audience would hear the most current information on many of CDC's efforts. Because of this, he kept his CDC update brief and limited to comments on updates on polio, measles, and childhood vaccination coverage. As a reminder, a case of paralytic poliomyelitis was confirmed in an unvaccinated person in Rockland County, New York on July 21, 2022. Shortly thereafter, CDC deployed staff to New York's Rockland and Orange Counties to assist with the investigation and vaccination efforts. CDC continues to support these efforts. CDC also is partnering with select jurisdictions on plans to expand wastewater testing where communities are at risk for poliovirus transmission. It is encouraging to note that for more than 7 months, no new paralytic poliomyelitis cases have been identified in the US. The last poliovirus detection was in December 2022.

Moving to measles, provisional data indicate that there were 121 cases of measles in the US in 2022. As of January 27, 2023, there have been 2 cases in two US jurisdictions. Early in February 2023, Columbus Public Health Department in Ohio declared the measles outbreak over after 85 cases were identified. As a reminder, a measles outbreak is declared over when 2 incubations periods, 42 days, have passed without another case. Jurisdictions at highest risk for measles continue to be those communities with persistently low vaccination coverage and at risk for importations from locations outside the US where measles is endemic or experiencing outbreaks.

Turning to current efforts for maintaining childhood vaccination coverage, in January 2023, CDC published new data providing an updated assessment of the impact of the COVID-19 pandemic on routine childhood immunization. To highlight some of the key findings of these reports, vaccination coverage has dropped a total of 2 percentage points since the start of the pandemic, decreasing from 95% reported in the 2019-2020 school year to 93% in the 2021-2022 school year. This steady decline means that nearly 250,000 kindergarteners are potentially not protected against measles. MMR vaccination coverage for kindergarten children is now the lowest it has been in over a decade. It is additionally concerning that the percentage of uninsured children not vaccinated by their second birthday is 8 times that of privately insured

children—even with the VFC Program in place. There were differences in vaccination coverage among children living below poverty and in rural areas, with a 4% to 5% decrease in coverage among children in those groups during the pandemic. These data add to previous research that highlights the impact of the COVID-19 pandemic on routine childhood vaccinations and ongoing disparities in coverage and reinforces the importance of vaccination to protect children from serious illness and death. While overall routine vaccination remains high, the recent outbreaks of measles and polio underscore that under- and un-vaccinated children are at risk for serious illness. To help address pandemic-related declines in routine immunizations, CDC has recently launched Let's RISE (Routine Immunizations on Schedule for Everyone), an effort to equip partners and HCP with actionable strategies, resources, and data to support getting all Americans back on schedule with routine immunizations. It is important to continue to work together and remain vigilant in efforts to ensure that children receive the vaccines they need in order to protect them against serious and sometimes deadly disease.

In terms of vaccination rates among adults with insufficient insurance coverage, individuals with incomes less than $20,000 a year compared to those with incomes of $40,000 or more were less likely to receive influenza vaccination. Adults with an out-of-pocket payment of $30 for an influenza vaccine are 58% less likely to get vaccinated than adults who have no out-of-pocket payment. Current estimates suggest that approximately 35%, one-third, of adults ages 18–64 years of age were uninsured (14%) or underinsured (21%) for the first half of 2001. There are ethnic and minority disparities and these groups are less likely to be vaccinated, even if they are covered by insurance. Uninsured adults have the lowest rates of those reporting having received a vaccine for influenza in the previous 2 months. This supports the need for a VFA Program similar to the VFC Program.

Centers for Medicare and Medicaid Services

Mary Beth Hance reported that a major change to Medicare under the Inflation Reduction Act provisions was to eliminate cost-sharing for the Part D vaccines that started in January 2023. Part D plans may not apply a deductible to co-insurance or other enrolling cost-sharing requirements for Part D-covered adult vaccines recommend by the ACIP. CMS issued an MLN Fact Sheet in December 2022 highlighting this called "Medicare Part D Vaccines."[33] There is a larger change coming for adult coverage in Medicaid as a result of the Inflation Reduction Act. Beginning in October 2023, the Inflation Reduction Act expands coverage of ACIP-recommended adult vaccines without cost-sharing for adults in Medicaid and the Children's Health Insurance Program (CHIP). In the expansion population for Medicaid, there already is coverage without cost-sharing for ACIP-recommended vaccines. For pre-adults who are eligible under the pre-expansion, referred to as traditional Medicaid, coverage of vaccines for adults is a state option. While most states cover some vaccines, they may not have covered all of the recommended vaccines or may do so but not necessarily without cost-sharing. This will be a significant change for the Medicaid Program. CMS is in the process of working on guidance that will be released prior to the October 2023 start date. In terms of childhood immunization rates, CMS continues to work closely with CDC to address the immunization gaps and to work hard to ensure that children in Medicaid and CHIP and others who are eligible for the VFC program have access to and obtain their childhood immunizations.

[33] https://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network MLN/MLNProducts/Downloads/Vaccines-Part-D-Factsheet-ICN908764.pdf

Health Resources and Services Administration

CDR Reed Grimes, MD, MPH reported that the National Vaccine Injury Compensation Program (VIPC) continues to process an increased number of claims. In fiscal year 2022, petitioners filed 1,029 claims with the VICP. Nearly $196 million was awarded to petitioners and $34.2 million was awarded to pay attorney's fees and costs. As of February 1, 2023 in fiscal year 2023, petitioners have filed 380 claims with the VICP and $61 million has been awarded, including petitioners' attorney's fees and costs. As of February 15, 2023, the VICP has a backlog of 1,453 claims alleging vaccine injury that are awaiting review. More data about the VICP can be obtained at www.hrsa.gov/vaccinetackcompensation/data/index.html. As of February 21, 2023, a total of 11,196 claims alleging injuries or death from COVID-19 countermeasures have been filed with the Countermeasures Injury Compensation Program (CICP), including 8,447 claims alleging injuries from COVID-19 vaccines. CICP has rendered decisions on 543 COVID-19 countermeasure claims, all of which are COVID-19 vaccine claims, have been determined to be eligible for compensation and are pending a review of eligible expenses. Among the COVID-19 countermeasure claims, 524 have been denied compensation because requested medical records were not submitted. Of those, 144 missed the filing deadline, and 141 did not specify CICP-covered products. For 251, the standard of proof for causation was not met and/or a covered injury was not sustained. More information about the CICP can be found at www.hrsa.gov/CICP.

Indian Health Service

Matthew Clark, MD, FAAP, FACP reported that the IHS continues to prioritize access, quality, and equity in vaccine distribution and administration for American Indian/Alaskan Native (AI/AN) tribal communities served by the IHS system of care. During the COVID pandemic, IHS has worked closely with its federal and tribal partners to ensure vaccine access and support vaccine acceptance. IHS is currently engaged in efforts to promote primary series and bivalent booster vaccination in all age groups in every region. Throughout the Mpox public health emergency, IHS took a proactive approach to the distribution and administration of JYNNEOS vaccine among high-risk persons in tribal communities. Recognizing the potential impacts on its service population, IHS was among the first of the jurisdictions to expand access to JYNNEOS vaccine as PrEP as part of its Mpox PrEP initiative, which was implemented broadly across the IHS system of care. Multiple IHS areas and facilities also implemented equity pilot projects to enhance vaccine access for the most vulnerable patients. In November, IHS announced a new national vaccine strategy, the E3 Vaccine Strategy, which is designed to promote access for every patient at every encounter to every recommended vaccine when appropriate. This includes all ACIP-recommended vaccines in all age groups, which are provided at no cost to IHS's AI/AN service population. Working in collaboration with key stakeholders, especially tribal communities, IHS seeks to leverage the lessons learned from the COVID vaccine campaign to improve general vaccination rates in tribal communities. The E3 Operational Plan includes a bottom-up approach to encourage innovation, incentivize efforts, and recognize success, drawing on the adaptability of the comprehensive healthcare system to cross-pollenate federal, tribal, and urban Indian programs using best practices developed in Indian Country for Indian Country. The IHS looks forward to continued collaboration with its tribal, urban, and federal partners to ensure safe access to effective vaccines across the age spectrum for AI/AN populations served by the IHS.

National Institutes of Health

John Beigel, MD reported that the NIH continues to support basic and clinical research to improve human health. A large part of that involves preventing infectious diseases by developing new and better vaccines. He highlighted a few studies that may be of interest to the ACIP. For COVID-19, in a pre-print for early serologic responses from a randomized trial comparing a COVID wild-type BA1 versus wild-type BA4/BA5 bivalent, there is a lot of discussion about whether the BA1 or the BA4/BA5 bivalent is a better. While this is not an efficacy study, a detailed immunologic response helps inform that discussion. For Ebola, a group at the NIH has developed a vaccine against Sudan Ebola virus disease (SEVD) that was causing outbreaks in Uganda that completely protected against SEVD challenge. It has not yet entered into human studies. While fortunately the outbreak seems to be under control, having an effective vaccine is important and this represents the first step. A group at the NIH developed an experimental Marburg virus vaccine that was put into Phase I trials. Human trials showed it was safe and achieved a robust immune response. Marburg virus has periodic outbreaks, so having an effective vaccine is quite important for prevention of this disease. This also is a tremendous first step. HIV continues to be elusive for vaccines. Many people were interested in a large study on the Mosaic HIV vaccine, which was an investigational HIV vaccine that was used in MSM and transgender. While it was found to be safe, it was not protective. Therefore, the DSMB recommended that study be stopped. The study is still in follow-up, but reporting of the reasons it was stopped has been made public. Regarding malaria, a monoclonal antibody has been shown to be safe and protective. It was 82% effective in preventing infection in non-pregnant adults in Mali. This is the first time that monoclonal antibody prevented malaria infection in an endemic region. This is a tremendous first step and hopefully a target toward a more effective malaria vaccine strategy.

Office of Infectious Disease and HIV/AIDS Policy

Dr. David Kim, MD, MA
CDR Valeria Marshall, MPH, PMP reported that in January 2023, the *Vaccines Federal Implementation Plan* (VFIP) was approved by the HHS Secretary, Xavier Becerra, and Assistant Secretary for Health, Admiral Rachel Levine. The VFIP is a companion document to the *Vaccines National Strategic Plan* (VNSP or Vaccine Plan) published in January 2021, which describes specific actions that federal agencies will take to eliminate vaccine-preventable diseases. The actions described in the VFIP align with the VNSP across the 5 stated major goals. The VFIP was developed in collaboration with the Federal Interagency Vaccine Workgroup (IVWG), which consists of senior leadership from 11 US Departments, 11 US HHS agencies and 3 additional federal departments. The VFIP highlights vaccine development, administration, and policy based on the federal agencies' missions, priorities, regulatory and legislative directives, resources, and capacities. The Office of the Assistant Secretary for Health (OASH) will host a webinar entitled "The Importance of Preventive Services and Lessons Learned from the Pandemic" on March 21. 2023. The program will discuss the following Healthy People 2030 objectives: 1) Immunization and Infectious Diseases (IIS) Objective 9, which is to increase the proportion of persons who are vaccinated annually against seasonal influenza; 2) Maternal, Infant, and Child Health (MICH) Objective 8, which is to increase the proportion of pregnant women who receive early and adequate prenatal care; and 3) STI Objective 4, which is to reduce congenital syphilis. As a reminder, the vaccination rate against seasonal influenza has been identified in Healthy People 2030 as a leading health indicator for the IIS sub-component of Healthy People 2030. The National Vaccine Advisory Committee (NVAC) met on February 2-3, 2023. During this virtual 2-day meeting, the NVAC heard from experts and scientists who presented information on immunization equity, vaccine safety, vaccine

innovation, and other topics. This meeting supported in the subcommittees that are working to address the charges Admiral Rachel Lavigne, the Assistant Secretary for Health, gave the committee on vaccine safety and innovation and immunization. There are 2 other in-person meetings scheduled for 2023, one in June and one in September. Additional information about these meetings will be posted on the website.

MENINGOCOCCAL VACCINES

Introduction

Katherine Poehling, MD, MPH (WG Chair) provided an introduction on behalf of the Meningococcal Vaccines WG. She reminded everyone that during the October 2022 meeting, the WG reported on the Menveo 1-vial presentation and the 2 new MenABCWY vaccines, one that will be produced by GSK and the other by Pfizer. The MenABCWY vaccines presentations described the WG policy questions, PICOs, and the WG's plans for the near future. Results from GSK's clinical trials were not available in time to review for that meeting, so both would be reviewed during this session but would be decoupled moving forward. The WG will continue to aim to be ready for an ACIP vote on the Pfizer vaccine during the October 2023 meeting, presuming licensure occurs before then. There is now some additional time to prepare for the GSK vaccine vote. The revised proposed timeline for the next few ACIP meetings include presentations during this meeting on the epidemiology of meningococcal disease in the US and Pfizer clinical trial. The June 2023 meeting will include GRADE, EtR, and cost presentations for the Pfizer vaccine and GSK clinical trial data. In October 2023, the WG will prepare for an ACIP voted on the Pfizer vaccine if it is licensed by then and GRADE, EtR, and cost-effectiveness presentations for the GSK vaccine. GSK has not confirmed when its vaccine will be ready for a vote, but the WG will be prepared.

Since the October 2022 ACIP meeting, GSK and Pfizer presented to the WG on their pentavalent vaccines in the WG asked clarifying questions. The WG also considered whether to revisit the current adolescent immunization schedule based on the discussions during the October ACIP meeting. These topics are somewhat intertwined, so the WG needed to determine how to proceed. During the January 2023 WG meeting, the WG decided to postpone the assessment of the schedule until after both pentavalent vaccines have been reviewed. Because of the complexity of these reviews and an unclear picture of how meningococcal disease epidemiology might be evolving after 2 years of COVID-19, the WG will plan to revisit this topic in Spring 2024 when another year of epidemiologic data is available to better inform this discussion.

Epidemiology of Meningococcal Disease in the United States

Amy Rubis, MPH (CDC/NCIRD) described the current epidemiology of meningococcal disease and reviewed recent notable cases and outbreaks during this session. Meningococcal disease cases are reported to CDC through the National Notifiable Diseases Surveillance System (NNDSS). Additional serogroup, outcome information, and clinical characteristics are collected nationally from all jurisdictions through Enhanced Meningococcal Disease Surveillance (EMDS). All available isolates are also submitted to CDC for WGS as part of the EMDS.

Meningococcal disease surveillance data are typically finalized in the fall of the following year. Because of the COVID-19 pandemic, there have been delays in obtaining and finalizing NNDSS and EMDS data. 2020 data are finalized, but 2021 and 2022 are not yet final. Cases are known to have been low in 2020 and 2021 because of COVID-19 mitigation measures, but there is not yet a complete sense of what happened in 2022. For 2022, preliminary case counts have been collected with age and serogroup information. However, these data are less complete than the final data are expected to be. Additionally, CDC has not yet received and tested all available isolates for 2021 and 2022 to confirm serogroup and antimicrobial susceptibility.

Since the last 1990's, a sustained decline has been observed in the US in the incidence of meningococcal disease with a decrease from 1.2 to 0.11 cases per 100,000 population from 1996–2019. This decline in incidence began prior to the introduction of a quadrivalent meningococcal conjugate, MenACWY, vaccine in adolescents or the availability of serogroup B or MenB vaccines. During the COVID-19 pandemic, cases declined to a preliminary incidence of 0.06 cases per 100,000 population in 2021. In 2022, cases increased almost 50% to a preliminary incidence of 0.09 cases per 100,000 population. Incidence is still below pre-pandemic levels, but it is unknown whether cases will stabilize at this level or will continue to rebound. Incidence decreased over time in all 3 primary disease-causing serogroups B, C, and Y, while the incidence of serogroup W and other serogroups remained stably low. During 2020 and 2021, the largest declines in incidence were observed for serogroup B. In 2022, there was an increase in serogroup C to above pre-pandemic levels, driven largely by 1 outbreak.

Looking at incidence age group and serogroup from 2010–2019, incidence in serogroup distribution varied by age group, with the highest incidence observed in children <2 years of age and adults 85+ years. A peak in incidence also was observed among adolescents and young adults 16–25 years of age. Serogroup B was the predominant group in children <5 years of age. In children in adolescence 5–20 years of age, serogroup B accounted for approximately half of cases. Among adults >20 years of age, serogroups C, W, and Y caused the majority of disease. In 2020–2022, a slightly different incidence distribution was seen across age groups. While overall incidence during this time period was lower, declines in adults 26–64 years of age were not as pronounced as in other age groups.

Now to highlight some recent unusual developments in meningococcal disease epidemiology in the US. Historically, resistance to any of the antibiotics used for treatment or prophylaxis of meningococcal disease was rare. In 2020, ciprofloxacin- and penicillin-resistant serogroup Y cases were identified. To date, 27 ciprofloxacin- and penicillin-resistant serogroup Y cases have been reported for 2019–2022 and have occurred primarily (78%) among Hispanic or Latino persons. The age ranges for these cases was <1 year of age through 97 years of age. Only 1 case occurred in individuals 11–20 years of age. This is consistent with the expectation not to see cases in this age group since they are routinely recommended to receive ACWY vaccine and should be protected from serogroup Y. None of the ciprofloxacin- and penicillin-resistant serogroup Y cases were in vaccinated individuals. Taking a more detailed look at the ciprofloxacin- and penicillin-resistant serogroup Y cases and dual-resistant cases, large declines were reported in meningococcal disease incidence in 2020 and 2021. While preliminary incidence for 2021 is approximately half, the incidence of 2019 had the same number of dual-resistant cases reported for 2021 compared to 2019. As previously mentioned, CDC has not received and tested all available isolates for 2021 and especially for 2022, so the number of resistant cases may increase.

Some unusual outbreaks have occurred over the past year. During 2022 in Florida, the largest outbreak that has been reported to CDC to date occurred of cases predominantly among MSM. There have been 43 serogroup C cases, including 9 deaths for a case fatality rate (CFR) of 21% in this ongoing outbreak since January 2022. All 43 cases are genetically closely related. Of the 43 cases, 12 were either in men not known to be MSM or were female. The isolates from these cases are genetically closely related to those from the MSM cases. Of the 43 cases, 14 occurred in people living with HIV. The age of cases ranges from 20─77 years, with a mean of 35 and median of 31. The second unusual recent outbreak is a community outbreak caused by what appears to be an unusually lethal strain of serogroup Y. Since mid-June 2022, a total of 11 cases have been reported with 3 deaths, for a CFR rate of 27%. The average CFR for serogroup Y cases for the past 5 years was 12%. Of the 11 cases, 10 were in Black or African American persons. The age range is 30─78 years. No connections have been identified among any of the cases to date. In the past few months, cases of this strain have been observed in other states that have affected a similar population to this outbreak, with a similarly elevated CFR, but with no known epidemiologic connections to the outbreak. Outbreaks also have continued to be seen among people experiencing homelessness, with 1 small serogroup C outbreak each year in 2021 and 2022.

In summary, incidence of meningococcal disease declined in 2020 and 2021, but increased in 2022. In recent years, new strains have been emerging in the US. Both new serogroup Y strains are predominantly affecting racial and ethnic minority groups. Given these unusual new strains, it is unclear how meningococcal disease epidemiology may change in the coming years. More complete 2022 data will be available in Fall 2023 and these data, combined with additional years of data post-pandemic, will provide a clearer picture of current meningococcal disease epidemiology. An increase in cases has been observed following the COVID-19 pandemic, but more years of data are needed to understand whether the number of cases will level off and if so, when.

Pfizer Pentavalent Meningococcal Vaccine

Jason D. Maguire, MD, MPH (Pfizer) presented an update on Pfizer's meningococcal pentavalent vaccine safety and immunogenicity data. Pfizer is seeking licensure for its pentavalent meningococcal MenABCWY vaccine as 2 doses administered at least 6 months apart in individuals 10─25 years of age prevent invasive meningococcal disease (IMD) caused by all 5 serogroups. MenABCWY vaccine is composed of 2 vaccines:1) Trumenba® (MenB-fHbp), which is licensed in the US for the prevention of invasive disease caused by *Neisseria meningitidis* group B in individuals 10─25 years of age; and 2) Nimenrix® (MenACWY-TT), which is licensed outside the US for the prevention of invasive disease caused by *Neisseria meningitidis* serogroups A, C, W, and Y in individuals 6 weeks of age and older.

In terms of the adolescent meningococcal vaccination platform options for MenABCWY vaccine, the current US recommendation is for ACWY administered at 11─12 years of age and ACWY and B at 16─23 years of age. The pentavalent development program was designed to generate data that would inform how MenABCWY might generally be incorporated across the platform and provide the maximum protection against all 5 serogroups. One option of how MenABCWY could be incorporated would be as a single dose in early adolescence at 11─12 years of age to protect against IMD caused by serogroups ABCWY or 2 doses administered 6 months apart in later adolescents among individuals 16─23 years of age to boost ACWY and protect against MenB. The pentavalent development program includes studies supporting the proposed pathology for 2 doses administered 6 to 12 months apart to protect against all 5 serogroups and

a single dose to protect against ACWY, as well as a study including a booster dose administered 4 years after completing the primary series.

The MenABCWY vaccine clinical program consists of 3 main studies involving more than 4,000 participants 10─25 years of age who are naïve to prior MenB vaccination. In the Phase 3 study (C35110001), 80% of the participants were Caucasian, 10% were Black or African American, and 25% were Hispanic or Latino. The Phase 3 study evaluated MenABCWY vaccine administered on a 0,6 month schedule in approximately 2,400 ACW naïve and ACWY primed adolescents and young adults compared to Trumenba® administered on a 0,6 month schedule and co-administered with Menveo® at Dose 1. This study is now complete, so ACWY responses after 1 or 2 doses of MenABCWY in naïve and primed individuals and B responses after 2 doses in all participants are available. A Phase 2 study (C3511004) of safety and immunogenicity in approximately 300 ACWY naïve children 11─14 years of age were dosed with MenABCWY on a 0, 12 month schedule. This group is in the persistence follow-up phase. A 0,36 month schedule group will be receiving their second dose later in 2023, For this session, results were available for ABCWY responses after 2 doses (0,12 months). The third study (B1971057) is a Phase 2 MenABCWY 0,6 month 2-dose study in approximately 1,600 participants 10─25 years of age that includes a 4-year immune persistence phase and booster dose safety and immunogenicity evaluation, which is now complete and for which the persistence and booster data were available to present during this session.

Beginning with reactogenicity for the Phase 3 study (C35110001) primary vaccination series by vaccine and group, there were no clinically significant differences between ACWY-naïve and primed individuals or between the primary vaccination schedule and the booster dose. E-diaries were used to collect reactogenicity data for 7 days following each vaccination. Local reactogenicity was measured in the arm where either pentavalent or Trumenba® were administered. Local reactogenicity to Menveo® administered in the contralateral arm was not evaluated. Pain, swelling, and redness at the injection sites event were mild to moderate in severity, with slightly higher proportions experiencing events in the pentavalent group compared to Trumenba®. There was a reduction in both groups between vaccination 1 and 2. Pain at the injection site was the most frequently experienced local event and proportions are consistent with what already is known for Trumenba®. Minor differences in point estimates were considered not clinically significant and there were no withdrawals from the Phase 3 study due to either local or systemic reactogenicity events.

For systemic reactogenicity events, the pattern was consistent with what is already known for Trumenba®. Fatigue and headache were the most frequently experienced systemic events and were mostly mild to moderate in severity, with no clinically significant differences between either group or vaccination 1 and 2. Frequencies of other systemic events are even lower and no fevers >40° C occurred in any participants in this study. For unsolicited AEs, rates were similar between the pentavalent and Trumenba® + Menveo® groups for AEs at around 20% for MAAEs at around 15%. There also were very few related or severe events in this study. Although there were 7 SAEs in the pentavalent group during the vaccination phase and none in the Trumenba® + Menveo® group, none of these were considered to be vaccine-related. There were slightly more newly diagnosed chronic medical conditions occurring in the pentavalent group compared to the Trumenba® + Menveo® groups, of which the majority were psychiatric disorders and in particular attention deficit hyperactivity disorder (ADHD), for which further investigation confirmed that for most of these cases, symptoms of ADHD were present prior to study entry and formal diagnosis.

In terms of the immunogenicity objectives, Dr. Maguire focused on the hypothesis testing endpoints agreed upon with the FDA:

- ACWY evaluation (non-inferiority after 1 and 2 doses of MenABCWY vaccine versus MenACWY-CRM) defined as a proportion of participants achieving a ≥4-fold rise in hSBA titers above baseline.

- B evaluation (non-inferiority after 2 doses of MenABCWY vaccine versus MenB-fHbp) defined as the proportion achieving protective titers ≥1:8 or ≥1:16 depending on the strain for all 4 group B test strains combined.

Non-inferiority was achieved for serogroups ACWY and the 4 MenB test strains when the lower bound confidence interval for the difference between the proportion of participants achieving seroresponses was greater than -10%. The approach taken for assessment of MenB bactericidal responses for pentavalent was the same as that which supported the licensure of Trumenba® in the US and non-inferiority was defined the same as for ACWY. Looking specifically at data supporting that a single dose of MenABCWY vaccine can be used as an alternative to ACWY vaccines in ACWY-naïve adolescents in the Phase 3 study, 1 dose of MenABCWY vaccine was noninferior to 1 dose of MenACWY-CRM in ACWY-naïve participants. Approximately 82% to 99% of participants had serogroups ACWY hSBA titers ≥1:8 after 1 dose of MenABCWY vaccine.

Given that Pfizer also is seeking licensure of MenABCWY vaccine as a 2-dose series to provide protection against all 5 serogroups, it also was important to evaluate the ACWY responses following 2 doses administered relatively close together. As expected, 2 doses of MenABCWY vaccine elicited higher responses versus a single dose of MenACWY-CRM in ACWY-naïve participants. Approximately 83% to 99% of participants had serogroups ACWY hSBA titers ≥1:8 after 2 doses of MenABCWY vaccine. In addition, 2 doses of MenABCWY vaccine elicited higher responses versus 2 doses of MenB-fHbp in B-naïve participants. The 2 doses of MenABCWY vaccine were noninferior to 2 doses of MenB-fHbp. Approximately 83% to 98% of participants had serogroup B hSBA titers ≥1:8 after 2 doses of MenABCWY vaccine across the board against all 4 test strains as well as the composite response. Responses were statistically higher for 2 of the test strains, B24 and B44, and the composite response.

For the second study (C3511004) among adolescents 11—14 years of age naïve to all 5 serogroups MenABCWY vaccine protected against all 5 serogroups with 2 doses given 6 to 12 months apart. Approximately 98% to 100% of participants had serogroups ABCWY hSBA titers ≥1:8 following 2 doses of MenABCWY vaccine given 12 months apart. Serogroup B responses were generally higher for the 12-month schedule compared with the 6-month schedule, albeit under different study conditions. The key take-away from the data presented thus far is that in ACWY-naïve individuals 11—12 years of age when they would be receiving their first dose of an ACWY conjugate vaccine in the US, a single dose of MenABCWY can be used as an alternative and 2 doses at either 6 or 12 months apart provide protection against all 5 serogroups.

Given that the current platform of preventing IMD caused by serogroups ACW and Y is based on the consensus that the first dose in early adolescents provides protection until a second dose is administered later in adolescents to maintain protection through early adulthood, the Phase 2 proof-of-concept study (B1971057) included a 4-year immune persistence follow-up phase in a booster stage. During the 4 years following a 2-dose series of MenABCWY or 4.5 years following a single dose of Menveo®, proportions of participants with protective titers for ACWY declined to a lesser degree in the MenABCWY compared to Menveo® recipients. Overall, they remained high, with a substantial proportion still protected 4 years out. After a MenABCWY booster dose, the GMT rose above those following the primary series, with 100% seroprotection across all 4 serogroups. Proportions with protected titers for the 4 MenB test strains over the 4 years following the 2-dose primary series were similar between the MenABCWY and Trumenba® groups and, similar to what has been observed in prior Trumenba® studies, declined over the first year and remained stable thereafter. Again, a very robust response was seen of 95% to 100% seroprotection following the booster dose.

Considering older adolescents who have received a single dose of an ACWY conjugate vaccine in early adolescents, a single dose of MenABCWY vaccine potentially could be used as an alternative to ACWY vaccines in ACWY-primed adolescents. A single dose of MenABCWY vaccine was noninferior to 1 dose of MenACWY-CRM in ACWY-primed participants. Approximately 99% to 100% of participants had serogroups ACWY hSBA titers ≥1:8 after 1 dose of MenABCWY vaccine. These data are from Study C3511001 among adolescents 11—14 years of age. Data from the same study show that 2 doses of MenABCWY vaccine can be used as an alternative to 1 dose of MenACWY-CRM and 2 doses of MenB-fHbp in ACWY-primed adolescents. Data showed that 2 doses of MenABCWY vaccine were noninferior to 1 dose of MenACWY-CRM in ACWY-primed participants. Approximately 99% to 100% had serogroups ACWY hSBA titers ≥1:8 after 2 doses of MenABCWY vaccine. As a reminder, 100% of ACWY-primed participants had protective titers 4 years after 2 doses of MenABCWY vaccine (Study B1971057).

In conclusion, MenABCWY vaccine was well-tolerated and safe. A single dose of MenABCWY vaccine could be used as an ACWY conjugate alternative in naïve and primed individuals. Two doses administered on a 0,6 or 0,12 schedule provide a high degree of protection against all 5 serogroups. After 2 doses of MenABCWY vaccine administered at 11—12 years of age, a single dose produced all 5 serogroups at age 16. A single dose of MenABCWY vaccine could be used as a booster for ACWY at around age 16. Immunopersistance after 2 doses of MenABCWY vaccine is similar to a single dose of ACWY conjugate and 2 doses of Trumenba®.

Workgroup Considerations

Sam Crowe, PhD, MPH (Pfizer) presented the WG's interpretation of Pfizer's MenABCWY vaccine clinical trials data. As a reminder, the policy questions for each pentavalent vaccine are as follows:

- ❑ Should a pentavalent vaccine be included as an option for MenACWY/MenB vaccination in people currently recommended to receive both vaccines? For example, 16-year-olds are recommended to get MenACWY and can receive MenB based on shared clinical decision-making.

- ❑ Should the pentavalent vaccine be included as an option for people currently recommended to receive MenACWY only. For example, this would include adolescents 11—12 years of age.

- ❑ Should the pentavalent vaccine be included as an option for people currently recommended to receive MenB only? An example would be during a serogroup B outbreak.

The WG decided to add the second and third policy questions because of concern that some providers might not carry MenACWY and MenB vaccines once the pentavalent vaccine becomes available.

To provide an overview of the Pfizer MenABCWY vaccine and trials, Pfizer's pentavalent vaccine is comprised of Nimenrix® (serogroups ACWY) and Trumenba® (serogroup B). Trumenba® is currently licensed and available in the US and Nimenrix®. Nimenrix® is used extensively in Europe and elsewhere. Two related clinical trials have been completed (NCT03135834, NCT04440163) that assess the safety immunogenicity of the pentavalent vaccine by comparing it to Trumenba® (serogroup B) and Menveo® (MenACWY). The trials included participants 10─25 years of age and studied single and 2-dose (0,6 month) schedules. Four-year persistence and a booster dose also were evaluated. An extended interval study (NCT04440176) is currently underway with 2 arms: Study arm 1 — 0, 12 months (data available) and Study arm 2 — 0, 36 months.

Vaccine safety was assessed by monitoring for and comparing local reactions, systemic events, MAAEs, SAEs, and newly diagnosed chronic medical conditions (NDCMC). Local reactions include pain, redness, and swelling and were compared using the pentavalent vaccine and the MenB vaccine because the latter is usually more reactogenic than the MenACWY vaccine. A slightly higher percentage of participants had a local reaction to the pentavalent vaccine for both first and second doses than the MenB vaccine. The percentage of systemic events were similar between the pentavalent vaccine and the MenACWY/MenB comparison. The percentage varies slightly between groups by systemic event and by dose, with the comparison group having slightly more systemic events after Dose 1 and the pentavalent group had slightly more after Dose 2. There were similar percentages of MAAEs between the study groups of than 15%. More SAEs were reported for the pentavalent group at 0.4% versus 0%, but none were assessed to be related to the pentavalent vaccine (e.g., hospitalization due to other medical conditions). NDCMC were reported for the pentavalent vaccine of 1.1% versus 0.3%. Pfizer staff explained that a higher number of participants with ADHD were in the pentavalent group, most of whom had related symptoms before entering the study. Of note, higher risk patients were not included in the trials (e.g., competent deficiency).

The immunogenicity standard for serogroups A,C,W, and Y was the percentage of participants achieving MenACWY seroresponse in hSBA titer 1 month after 1 dose and 1 month after 2 doses. Seroresponse was defined as a 4-fold increase in titer over baseline. The immunogenicity standards for serogroup B was the percentage of participants achieving MenB seroresponse in hSBA 1 month after 2 doses, with a composite response provided. Seroresponse was defined as a 4-fold increase in titer over baseline.

For serogroups A,C,W,Y, 1 dose of the pentavalent vaccine was noninferior to 1 dose of MenACWY and both ACWY-naïve and ACWY-primed participants 1 month after administration. In addition, 2 doses of pentavalent given 6 months apart were noninferior to 1 dose of MenACWY in both naïve and primed participants 2 month after administration. For persistence of immunity after 2 doses, data are available out to 4 years. Seroprotection persists for that time period in vaccine-naïve participants. Seroprotection also persists for up to 4 years in primed participants. This also is true after a 2-dose series of pentavalent vaccine compared to 1 dose of MenACWY vaccine. For serogroup B, 2 doses of pentavalent vaccine given 6 months apart are non-inferior to 2 doses of MenB in naïve participants. Primed individuals were not assessed.

Waning of immunity for the pentavalent vaccine is very similar to that observed with MenB, dropping substantially by 12 months post-Dose 2. The WG noted that data were not presented on a 3-dose schedule pentavalent vaccine. However, a 3-dose schedule of Trumenba® is currently recommended for certain high-risk groups (e.g., people affected by a serogroup B outbreak). Data also were not available in people older than 25 years of age. This is the same as Men B vaccines, which are licensed for individuals 10–25 years of age. MenACWY vaccines are licensed up to 55 years of age and older depending upon the vaccine.

Based on the clinical trials data presented, Pfizer's MenABCWY vaccine appears to be noninferior to the MenACWY+MenB comparison based on the clinical trial data presented. There are some data gaps at this point in terms of the 3-dose schedule for high-risk populations and adults older than 25 years of age. In terms of next steps, the WG will be reviewing additional immunologic persistence data for a single dose of pentavalent vaccine. After that, the WG will turn to GRADE and the EtR Framework, with a focus on pentavalent vaccine studies. A cost-effectiveness study also will be conducted.

ACIP Discussion Points, Observations, Suggestions on Meningococcal Vaccines

Following Ms. Rubis's Presentation

- Regarding an inquiry about whether any of the cases in the Florida outbreak were known to be vaccinated with a conjugate vaccine, Ms. Rubis reported that 3 of the cases in the MSM outbreak in Florida were known to be vaccinated. However, the most recent dose of vaccine was received 7 to 10 years previously among the 3 cases. None of the cases in the serogroup Y group were known to have received vaccines.
- With respect to a question about whether the specific cases of resistance were in some way geographically clustered, Ms. Rubis indicated that the resistance cases were not geographically clustered in one area. While several cases have been reported in 1 metropolitan area, the 27 cases are spread across the country.

Following Dr. Maguire's Presentation

- Regarding a request for more specifics about the SAEs and MAAEs, Dr. Maguire responded that there were 9 events among 7 participants following pentavalent vaccination. These included salmonella, depression with anxiety and suicide attempts, postural orthostatic tachycardia syndrome (POTS), dyspnea, head injury, traumatic spinal cord injury, and depression with suicidal ideations. There were no events in the MenB-fHbp + MenACWY-CRM group. In the vaccination follow-up phase, there were 5 events in 4 participants in the pentavalent group. These included post-tonsillectomy hemorrhage and oral intolerance, open tibia fracture, depression, and disruptive mood dysregulation disorder. In the MenB-fHbp + MenACWY-CRM group, events include appendicitis, *E-coli* UTI, drug overdose, and migraine headache. POTS is not an AESI given that this individual had a history of fainting episodes.
- In terms of a request for details about age, gender, ethnicity, and immunocompromised status among participants, Dr. Maguire indicated that participants were fairly equal across genders, approximately 78% were White, 10% were Black/African American, 2.5% were Asian, 1.6% were multi-racial, and 25% were Hispanic or Latino. Based on the design of the study, about two-thirds of the participants were children and one-third were adults. The mean age at first vaccination was about 16 years and 75% of the participants were from the US and the remaining were from the European Union (EU). Immunocompromised individuals were excluded from the study. This included individuals who had immune diseases that potentially would put them at increased risk

by participation in the study or who were not likely to mount a specific immune response to the vaccine.

- It is important to remember that the ACIP currently does not have an indication for MenB at age 11, so this is information outside of the normal schedule. The case incidence rate is 1 in a million, which is highly relevant.
- Regarding whether any studies are planned to assess vaccine response among the population of people who are getting complement inhibitors like eculizumab, Dr. Maguire indicated that Pfizer is not planning to conduct such studies at this time.
- In terms of a question about what Pfizer attributes what look to be statistically significant increases in hSBA titers ≥1:8, Paul Balmer from Pfizer indicated that they do not yet have an explanation for some of the higher titers observed with the pentavalent vaccine—particularly for the group B response. They speculate that the combination is increasing immunogenicity.
- With respect to whether the recommendation would be for all individuals 10─25 years of age to receive pentavalent vaccine, even though the immunocompromised were excluded from the study, Dr. Maguire indicated he could not give a recommendation but the indication Pfizer is seeking in that age group is for 2 doses to protect against all 5 serogroups or 1 dose to protect against ACWY only.
- Regarding whether persistence was going to be assessed beyond 4 years, Dr. Maguire indicated that there have been some discussions internally about how modeling might be used out to longer time frames based on the data they have.
- ACIP is interested in information about cost per dose, given that this should factor into the committee's considerations. Alejandro Cané from Pfizer reminded everyone that the pentavalent vaccine has not yet been approved by FDA and the list price has not yet been finalized. As part of the regulatory process, Pfizer is taking a value-based pricing approach and will inform the ACIP of the price as soon as this is known.
- Consistency across clinical trials presentations from all manufacturers would be extremely beneficial for the ACIP in terms of demographics and immunocompromised individuals.

Following Dr. Crowe's Presentation

- The potential for needing to stock numerous meningococcal vaccines may be overwhelming to providers, particularly those in adult clinics. More data are needed as soon as possible on adults, especially immunocompromised hosts and those who receive eculizumab.
- Additional data would be appreciated on the immunogenicity experience with the vaccine that is not licensed in the US but has been used extensively in Europe to better understand what is being inferred with regard to that vaccine.
- Close attention should be paid to data on vulnerable populations with high-risk factors (e.g., sickle cell disease, splenectomy for whatever reason, age ≥85 years, et cetera). Recognizing that it is difficult to do, it is surprising that studies are not planned in vulnerable populations.
- Vaccines should be tested among those for whom they actually will be used.
- Cost information will be imperative to have, especially for the cost-effectiveness evaluation so that true economic models will be available.

POLIO VACCINES

Introduction

Oliver Brooks, MD, FAAP (WG Chair) pointed out that the Polio Vaccination WG was formed because of 1 case identified in New York City that was determined to be an outbreak and that this would be the first presentation to the ACIP. The WG's Terms of Reference (TOR) policy topics under consideration are to determine: 1) whether more specific guidance on adult vaccination, including use of adult booster doses, can be provided in the context of circulating poliovirus; 2) whether adults who are immunocompromised should be recommended an additional adult booster of a polio-containing vaccine; 3) whether fractional doses of inactivated polio vaccine (IPV), as prequalified by WHO, should meet polio vaccination requirements, including for people immigrating to the US; and 4) which criteria under which novel oral polio vaccine type 2 (nOPV2) might be used in areas with outbreaks or persistent circulation of poliovirus. During this session, the WG presented on the first TOR.

Recommendations for Adult Polio Vaccination

Sarah Kidd, MD, MPH (CDC/NCIRD) presented on behalf of the Polio Vaccination WG. As Dr. Brooks mentioned, the WG was established in October 2022. Dr. Kathleen Dooling presented some background on the WG's TOR during the last ACIP meeting in October 2022. During this session, Dr. Kidd briefly summarized the WG's deliberations on adult polio vaccination to date, presented some proposed language for adult polio vaccination recommendations in anticipation of an ACIP vote during the June 2023 meeting, and solicited ACIP's feedback and identifications of areas where more data are needed prior to an ACIP vote. As background, the most recent ACIP statement on adult polio vaccination was published in 2000 and contains some ambiguous and outdated language. The 2000 statement states the following:

- ❑ Vaccination is recommended for certain adults who are at greater risk for exposure to polio viruses than the general population.

- ❑ Unvaccinated adults who are at increased risk should receive a primary vaccination series with IPV.

- ❑ Adults who have had a primary series of OPV or IPV and who are at increased risk can receive another dose of IPV.

Multiple problems and questions with the recommendations came to light last year when the New York poliomyelitis case was identified. First, the 2000 statement focused almost exclusively on adults who were at increased risk of exposure to polio virus. Second, it was unclear how increased risk should be defined in the setting of circulating vaccine-derived poliovirus in the US. Third, the recommendations for unvaccinated adults who were not considered to be at increased risk of exposure were unclear. Fourth, the recommendation for vaccinated adults and when or if a booster was advised also was unclear. The first policy question the WG addressed follows:

Policy Question #1

- ❑ Should completion of a primary polio vaccination series with IPV be recommended for unvaccinated and incompletely vaccinated adults in the US?
  - **Population:** Unvaccinated and incompletely vaccinated (with OPV or IPV) US adults >18 years.
  - **Intervention:** Completion of a primary vaccination series with IPV.
  - **Comparison:** No vaccination or partial series completion.
  - **Outcomes:**
    - Prevention of paralytic poliomyelitis
    - Serologic immunity to polio viruses types 1, 2, and 3
    - SAEs following a vaccination
    - Indirect effects (e.g., community transmission, impact on health systems)

In terms of the current definition of "fully vaccinated," an adult is considered fully vaccinated if they received:

A primary series of ≥3 doses of trivalent OPV (tOPV) or IPV in any combination administered ≥4 weeks apart

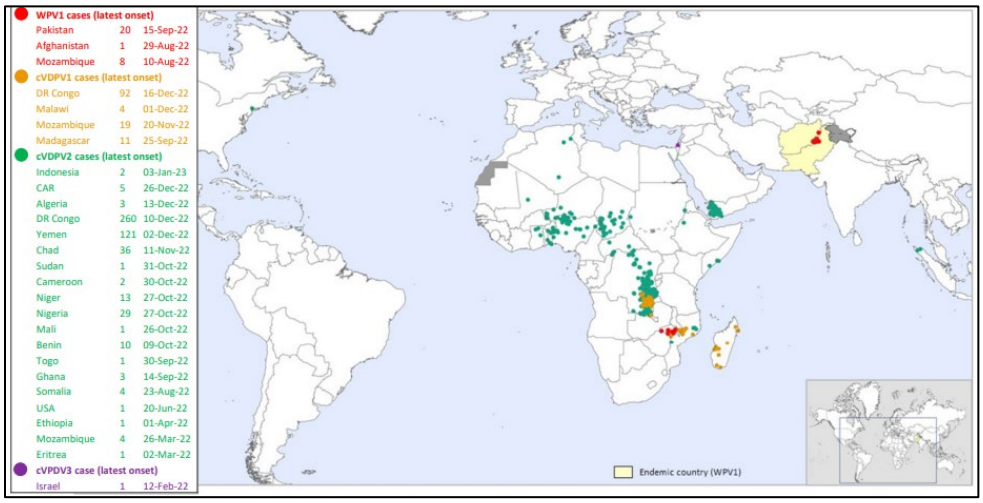
AND

The last dose in the series was given on or after the 4th birthday

AND

The last dose in the series was given ≥6 months after the previous dose

In terms of the public health problem, poliovirus infection can cause poliomyelitis and lifelong paralysis. Paralytic disease occurs in fewer than 1% of infections, with the exact frequency varying by serotype. Most poliovirus infections are asymptomatic. The incidence of paralytic polio decreased rapidly in the US after introduction of the Salk IPV quickly followed by the Sabin polio vaccine. Sabin vaccine was used for routine childhood immunization in the US for decades. In 1997, an enhanced potency IPV was introduced as part of a sequential schedule with OPV. In 2000, the US moved to an IPV only schedule. IPV has been the only polio vaccine recommended in the US since that time. Wild poliovirus type 1 (WPV1) and vaccine-derived poliovirus (VDPV) types 1, 2, and 3 still circulate in certain parts of the world. This graphic shows the distribution of paralytic polio cases in the last 12 months:



Approximately 650 paralytic cases have been identified globally in the last 12 months. A case of paralytic polio caused by vaccine-derived poliovirus type 2 (VDPV2) was confirmed in an unvaccinated young adult from Rockland County, New York on July 21, 2022. Genetic sequencing has indicated a linkage of the virus from this case to polioviruses collected in wastewater in Israel, the United Kingdom (UK), and Canada. Of note, Rockland County has reported overall low vaccine coverage for over 20 years. In the Summer of 2022, 60% of children under 2 years of age had received the recommended 3 doses of IPV. However, zip code-level coverage was as low as 37% in some areas. Poliovirus related to the case was detected in wastewater in Rockland and several other New York counties and in New York City. Retrospective testing detected poliovirus in the area as early as April 2022. The most recent positive sample was collected on December 15, 2022. Samples collected in the last 7 to 8 weeks have all been negative and no additional paralytic polio cases have been identified.

There are no reliable data on vaccination coverage for people who are currently adults in 2023. The best estimate of adults who are protected against paralytic polio comes from serosurveys. Serosurveys indicate that a large majority of Americans have protected antibodies to poliovirus. In a National Health and Nutrition Examination Survey (NHANES) survey that was conducted in 2009 to 2010, seroprevalence varied by poliovirus serotype, but was high in all the age groups studied. Seroprevalence for Type 3 was consistently the lowest but remained high even in the oldest age group studied.

The effectiveness of enhanced potency IPV has been established. The presence of detectable neutralizing antibody is an accepted correlate of protection against paralytic disease. However, immunity against paralytic disease may be present even in the absence of detectable antibodies. Studies of the serologic immunogenicity among infants and children show that 70% to 100% are seropositive after 2 doses and 88% to 100% are seropositive after 3 doses.[34] There are limited data on the VE of the current IPV formulation, but estimates range from 36% to 89% for 1 dose and 89% to 98% for 2 doses.[35] Not surprisingly, because this is a routine childhood vaccine, there is a paucity of data for adults who receive a primary series.

In addition to serologic immunity, which protects against severe disease and paralysis, it is also important to consider mucosal immunity and the potential effect of IPV on transmission. IPV does not decrease the proportion of people who will shed poliovirus when exposed. In terms of intestinal immunity, multiple studies[36] have shown that there is no significant difference between IPV and unvaccinated individuals in terms of the odds of shedding from the intestines. IPV vaccination does appear to reduce the quantity and perhaps the duration of shedding, although a recent modeling study indicated no impact of IPV on the duration of shedding. There are fewer data on nasopharyngeal (NP) immunity following IPV vaccination. But data from 2 studies[37] suggest that rates of NP shedding are similar and low among both OPV and IPV vaccinees.

The safety of IPV is also well-established and IPV is well-tolerated. Local reactions at the injection site were reported during trials, with up to a third reporting erythema, induration, and tenderness at the injection site. Combining IPV with other vaccines has not been associated with increased frequency or severity of reported adverse reactions compared to when the other vaccines are administered alone. No AEs have been causally associated with the use of the current formulation of IPV. In a paper that looked at 2000-2012 data[38] from VAERS during a

[34] Vidor et al review, PIDJ 1997
[35] Stoeckel et al, Rev Infect Dis 1984. CDC, MMWR 1988. John, Rev Med Virol 1993
[36] Hird and Grassly meta-analysis, PLoS Pathogens 2012
[37] Kok et al, Bulletin of WHO 1992. Onorato et al, JID 1991; and Brouwer et al, J R Soc Interface 2022
[38] Iqbal et al, Lancet ID 2015

period when more than 250 million IPV containing vaccine doses were distributed, a total of 41,792 AE reports were submitted for IPV-containing vaccines. The majority of these were for non-serious events. Not surprisingly, 95% were among persons under 7 years of age. Most events were associated with IPV co-administered with other vaccines. Standalone IPV accounted for just 0.5% of reports. It is important to remember that VAERS is a passive reporting system and cannot assess causal associations between vaccination and AEs. Reported AEs were similar and proportional to those reported for other vaccines.

Most of the WG deliberations focused on whether the recommendation for unvaccinated adults should be a risk-based recommendation or a uniform recommendation for all unvaccinated adults. Currently, situations that are considered to put adults at increased risk of poliovirus exposure include international travelers, laboratory and healthcare workers, and healthcare workers or other caregivers. In addition, unvaccinated or incompletely vaccinated adults whose children will be receiving an OPV or unvaccinated or incompletely vaccinated adults who are living or working in a community where poliovirus is circulating are considered to be at increased risk of exposure. During the WG's deliberations, it became clear that there is a difference and that most of these situations pose risk at the individual-level and that there would be an opportunity to anticipate the risk and vaccinate prior to potential exposure. The situation is somewhat different for unvaccinated and incompletely vaccinated adults in a community where poliovirus is circulating, given that this would affect an entire population and the community already would be at increased risk at the time the risk is recognized. This means there potentially would be missed opportunities for vaccination prior to exposure if the recommendation remained risk-based.

When considering the pros and cons of a uniform versus a risk-based recommendation, the pros of a uniform recommendation are that it allows unvaccinated adults and their healthcare providers to take advantage of opportunities to get vaccinated before they are at increased risk of exposure. It also brings adult polio vaccination policy closer in line with other routine childhood vaccines (e.g., MMR and varicella vaccines). In addition, it is a less complicated policy to communicate and understand in that a recommendation regarding who is at increased risk does not change based on the latest wastewater data. The cons of a uniform recommendation are that most adults in the US have a low risk of poliovirus exposure and paralytic polio, and most adults already received a primary polio vaccination series as children. In addition, demand for IPV potentially could exceed supply, particularly if a large number of adults without documentation of polio vaccination status were to assume they were not vaccinated. However, this issue could be mitigated by providing guidance for this group in the Clinical Considerations. In terms of proposed language for unvaccinated and incompletely vaccinated adults, the majority of the WG members believe the pros of uniform recommendation outweigh the cons and support a uniform recommendation. However, approximately one-third of the WG favor maintaining a risk-based recommendation. For the majority, the proposed recommendation language and Clinical Consideration would be as follows:

Majority Recommendation:
Adults who are known or suspected to be unvaccinated or incompletely vaccinated against polio should complete a primary vaccination series with IPV.

Clinical Considerations:
In general, unless there are specific reasons to believe they were not vaccinated, most adults who were born and raised in the US can assume they were vaccinated against polio as children.

Policy Question #2

- Should a booster IPV dose be recommended for adults in the US who have previously completed a primary polio vaccination series?
  - **Population:** US adults aged >18 years who have completed a primary polio vaccination series (with trivalent OPV, IPV, or a combination of both)
  - **Intervention:** Booster dose of IPV
  - **Comparison:** Adults who completed a primary series but did not receive a booster dose
  - **Outcomes:**
    - Prevention of paralytic poliomyelitis
    - Serologic immunity to poliovirus types 1, 2, and 3
    - SAEs following vaccination
    - Indirect effects (e.g., community transmission, impact on health systems)

The current recommendation regarding adult boosters is as follows:

- 2000 Statement: "Adults who have had a primary series of OPV or IPV and who are at increased risk can receive another dose of IPV. Available data do not indicate the need for more than a single lifetime booster dose with IPV for adults."

In terms of the rationale, this has been a longstanding recommendation since trivalent OPV (tOPV) was used in routine immunization. While the actual need for a supplementary dose has not been established, it was thought that "there is value in assuring protection against infection with wild polioviruses when exposure can reasonably be expected" (1977 ACIP Statement). Of note, there have been at least 2 reported cases of paralytic polio in adult travelers who have completed a primary series with either Salk IPV or tOPV. However, further details on these cases are not available and it is not clear whether a booster dose would have prevented these cases. It is unclear whether previously vaccinated adults need an IPV booster for protection. Looking again at the results of the NHANES serosurvey, the seroprevalence of neutralizing antibodies is high for all 3 serotypes and all the age groups studied.[39] While there are no data on the comparative VE of a primary series plus booster compared to a primary series only, serologic studies[40] in adults with heterogenous pre-booster vaccination histories and heterogenous seropositivity have shown that 98% to 100% were seropositive 1 month after receiving an IPV-containing booster. One study also followed up trial participants 10 years later and 98% to 100% were still positive at that time for those who followed up.

The majority of the WG agree with the current recommendation for adult IPV boosters. This recommendation is risk-based and is based on shared clinical decision-making. The proposed language includes some slight edits to modernize the language, namely substituting the word "may" for "can" from the 2000 statement. The proposed recommendation language would be as follows:

Proposed Recommendation:
Adults who have received a primary series of tOPV or IPV in any combination and who are at increased risk of poliovirus exposure may receive another dose of IPV. Available data do not indicate the need for more than a single lifetime booster dose with IPV for adults.

[39] Wallace et al, BMC Public Health 2016
[40] Broderick et al, Vaccine 2015; Domenicus et al, Vaccine 2014; Fukushima et al, Vaccines 2022; Grimprel et al, Vaccine 2005; Kovac et al, Vaccine 2015; Larnaudie et al, Human Vaccines 2010; Zimmermann et al, Vaccine 2013.

ACIP Discussion Points, Observations, Suggestions on Polio Vaccines

Following Dr. Kidd's Presentation

- Many immunocompromised persons in their 60s and 70s are traveling, which calls into question the recommendation for a single lifetime booster. For instance, persons who received a booster 20 or 30 years ago who are immunocompromised might be more vulnerable. Dr. Kidd indicated that the WG is planning to address immunocompromised persons in the next few months, so they will consider this.
- Regarding an inquiry about someone born in 1940 who now would be 83 years old, Dr. Kidd indicated that they have data for estimated coverage for people born in 1950 and later for whom seroprevalence data indicate that a high percent are protected. That could be from primary immunization or secondary immunization from exposure to somebody who received OPV. The seroprevalence data indicate high levels of protection in terms of neutralizing antibodies. They also have some Salk vaccination coverage data for people who were children and adults during that campaign that indicate coverage of 50% to 60% in young adults.
- Concern remains that many adults have no idea whether they were vaccinated, so the Clinical Considerations will need to clearly state who will be considered protected. For instance, there are people born in the US who do not have vaccine records, refugees, and others for whom guidance will be needed about whether a primary series or one-time booster is needed.
- Some international travelers may be required to have another booster dose to comply with a particular country's international standard. Travel clinics and others will need some guidance about this niche question.
- Clarification will be beneficial on proof of polio vaccination for those who immigrate to the US, those who have visitor visas, those who enter through refugee programs, et cetera.
- It seems like there is a lot of opportunity for the Clinical Considerations to provide specific guidance for particular circumstances.
- Equity and access are likely going to be issues, so understanding the numbers of people who are unvaccinated or under-vaccinated seems crucial. It is important to be able to offer reasonable access to individuals who may want vaccines who are unvaccinated or under-vaccinated, particularly if these individuals do not have medical homes and/or insurance coverage. It seems that the ACIP has a responsibility to those individuals in terms of making sure that they have the ability to get covered.

RSV VACCINES: PEDIATRIC/MATERNAL

Introduction

Sarah S. Long, MD (Chair, Maternal/Pediatric RSV WG) emphasized that the WG process and decisions are remarkable and complex. While other WGs and the ACIP realize the complexity of the decisions, RSV is even more complicated. The Maternal/Pediatric RSV WG has presented the epidemiology and burden of RSV disease in infants in terms of RSV seasonality in the US and outpatient, ED visits, hospitalization and deaths. The WG also has presented to the ACIP on the virology and immunology of the organism. In addition, the WG has begun to present safety and efficacy data on nirsevimab, the first passive immunization. Nirsevimab is a prefusion RSV antibody with neutralizing capacity that is potent and of long duration. The WG has previously presented the Phase 3 study in infants born near-term at ≥35

weeks gestation,[41] the 2b study of infants born prematurely 29–34 weeks gestation, and the Phase 2/3 safety and pharmacokinetic study in infants at high risk for RSV disease who were eligible for palivizumab.

The agenda for this session was broad and deep, with presentations on the following topic areas:

- ❑ Cost-effective analysis: CDC Model
- ❑ Cost-effective analysis: Comparison of the CDC and manufacturer models
- ❑ EtR Framework for nirsevimab
- ❑ Clinical considerations for the monoclonal antibody
- ❑ Safety and efficacy of RSV Bivalent A and B Prefusion (PreF) maternal vaccine
- ❑ WG consideration

Dr. Long clarified that neither of the products has been approved by the FDA. The FDA has not completed the evaluation of either the monoclonal antibody or the maternal vaccine. Any recommendation that ACIP would make would follow licensure of the products.

Cost-Effectiveness Analysis for Nirsevimab: CDC Model

David W. Hutton, PhD, MS (University of Michigan) shared the results of economic analysis of nirsevimab in pediatric populations referred to as the CDC Model, which included collaborators from the University of Michigan and CDC, many of whom have extensive RSV expertise. The overall goal was to evaluate the cost-effectiveness of nirsevimab by: 1) evaluating the population burden of disease in the pediatric US population by examining the outcomes of annual resource utilization, total cases, total costs, deaths, and quality-adjusted life years (QALYs) lost from RSV; 2) comparing the incremental cost-effectiveness ratio (ICER) of nirsevimab to no prevention; and 3) exploring scenario analyses to examine key areas of uncertainty related to these questions.

In order to conduct this analysis, a decision-tree model was used. The target population was a US pediatric population <7 months of age entering their first RSV season. In a secondary analysis, high-risk infants were examined in their second season at 7─18 months of age. The intervention compared were no nirsevimab (natural history) to nirsevimab against RSV illness. The time horizon was one RSV season. A lifetime analytic horizon was used to look at outcomes that might last beyond that year, like years lost due to deaths. In order to conduct the analysis, the decision tree incorporated several components. With no prophylaxis, individuals can become infected. The infection can lead to hospitalization, ED visits, outpatient visits, or none of these. Children who are hospitalized potentially could die. Receiving the nirsevimab intervention may involve any of several or no AEs and individuals could experience the same RSV outcomes as with no prophylaxis. However, the likelihood of those RSV outcomes is lower with nirsevimab. Using a decision tree, it is possible to calculate numbers of events and costs, QALYs, numbers needed to prophylax for different outcomes, and cost per QALY life year gained. Because this is a decision-tree model, it does not take into account reductions in RSV transmission. As such, the named results were not dependent on uptake of nirsevimab. The model also does not take into account infections that were not medically attended.

[41] Initial results from start of trial until pause for COVID-19 pandemic and updated results that included entire sample

The estimation of RSV hospitalization incidence came from CDC's NVSN from the season starting in 2016 and ending in 2020. The rates were higher for younger age groups and dropped off for older children. In the base case, it was assumed nirsevimab only reduces lower respiratory tract infections (LRTI). Therefore, an assumption had to be made about how many of visits were due to LRTI. It was assumed that 100% of these hospitalizations are from LRTI based on a study by Rainisch, et al. In terms of incidence of ED and outpatient visits per 100,000 children, rates were higher for the youngest age groups and dropped as children get older. These rates come from studies by Lively, Hall, and Jackson. Assumptions also were made about the proportion of these ED and outpatient visits that were due to LRTIs. These estimates also came from the study by Rainisch. In this model, RSV mortality was linked to hospitalization. The model incorporated information in monthly time periods to track incidence of RSV along with the timing of nirsevimab administration, and waning protection was tracked over time. Regarding the seasonality of RSV each month throughout the year, most of the infections occur from November through April. The seasonality data came from the National Respiratory and Enteric Virus Surveillance System (NREVSS) for 2015─2019.

With regard to modeling efficacy, the average efficacy in the first 5 months was equivalent to the efficacy observed in the trial. The efficacy in months 6─10 was lower and then assumed to drop to 0 after month 10. A majority of the high efficacy was in the first few months. For the precise numbers for the efficacy assumptions, the initial efficacy in months 1─5 was 80% based on the MELODY trial and the phase 2b recommended dose. For months 6─10, the base efficacy assumption was 25%, but was varied from 0.0% to 50% in the sensitivity analysis. Efficacy was assumed to be 0.0% in month 10 and after. The model assumed that nirsevimab was given at birth for those born during the RSV season from October─March. For all children born outside the RSV season, nirsevimab would be given at the regularly schedule at approximately their 2-, 4-, or 6-month visits, which would occur in October or November depending upon when the child is born.

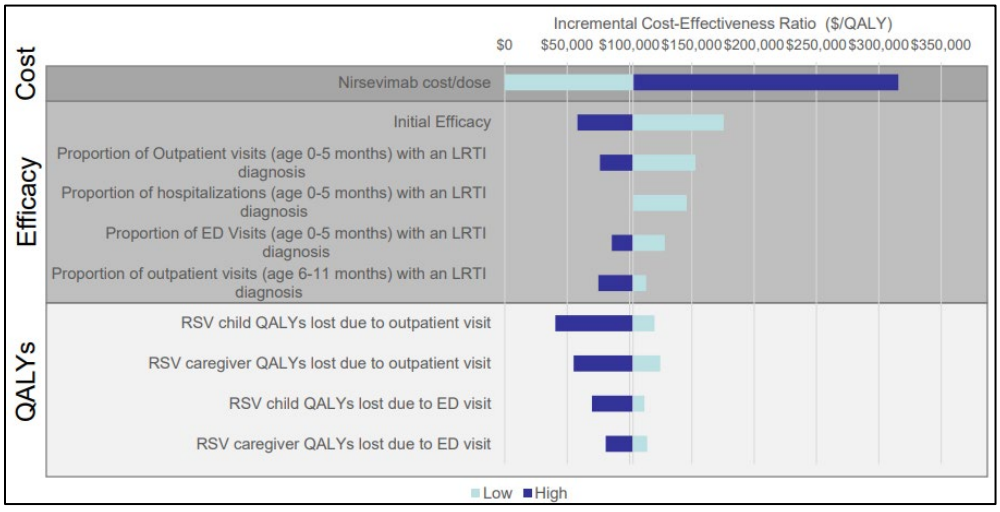
In terms of RSV costs used in the model, disease-specific hospitalization costs were just under $11,500, ED costs a little over $550, and outpatient visits were a little over $80. These estimates came from a systematic review by Bowser published in 2022. Because the analysis was conducted from a societal perspective, productivity costs also were included. Days of productivity lost for caregivers if their child gets sick with a medically-attended case of RSV and productivity lost if the infant child dies were included. This is in addition to QALY years lost. The cost of the intervention also was included. In the base case, $300 per dose was assumed for nirsevimab. That was varied in the sensitivity analysis from $50 to $600. The model also included quality of life lost due to RSV for the child and the caregiver. Different levels of QALY were included for outpatient visits, ED visits, and hospitalizations. QALY of life lost was shown in terms of quality-adjusted life days lost so that it would be more intuitive since RSV typically affects children in time scales of days. As an example, an outpatient visit would lead a child to lose 3.1 quality-adjusted life days and also would cause a caregiver to lose 1.5 quality-adjusted life days. In the end, quality-adjusted life days were converted to QALYs by dividing the values by 365. There is a lot of uncertainty surrounding quality of life losses from RSV. The lower ranges were based on study by Grosse in 2019 and the upper bound was based on an unpublished survey conducted during the pandemic that asked for quality of life lost from outpatient and inpatient RSV events for children and their caregivers. Inputs also related nirsevimab AEs also were included for systemic reactions, injection site reactions, SAEs, medical costs, productivity costs, and QALYs lost associated with those AEs.

In addition to the base case results, many uncertainty analyses were conducted. A one-way sensitivity analysis was conducted varying each parameter one at a time. Some scenario analyses also were run, one of which examined whether nirsevimab also reduced upper respiratory tract infections (URTIs) to the same extent that they reduced LTRIs. Another scenario analysis examined the impact of changing the timing of nirsevimab administration. An additional scenario examined high-risk children entering their second RSV season.

The results start with a base-case that looked at a hypothetical cohort of 1,000 births with the assumption of 100% uptake of nirsevimab. This analysis looked at the first RSV season and assumed a cost of $300 per dose and that nirsevimab only reduces LRTIs. In terms of some of the resulting health outcomes with natural history and nirsevimab, LTRIs were reduced with nirsevimab and the URTIs were not shrinking. Events averted with nirsevimab per 1,000 births included 59 outpatient visits, 20.9 ED visits, 7.8 inpatient visits, 1.7 ICU stays, 42.3 inpatient days, and 5.2 ICU days. Looking at the results in terms of the number needed to prophylax to avoid one of these events also can be assessed. For example, 128 people would need to be prophylaxed to avoid 1 inpatient stay.

Regarding costs, nirsevimab has a little over $300,000 in intervention costs in AEs. The intervention costs are higher for nirsevimab than for natural history. However, in the other cost categories related to RSV disease are lower (e.g., outpatient, ED, inpatient, and deaths). Nirsevimab saves costs associated with RSV disease. However, the healthcare and productivity cost savings from reduced RSV do not quite offset the cost of providing nirsevimab. In the end, nirsevimab is more expensive than natural history. The cost per event averted with nirsevimab is about $2,476 per outpatient visit averted or $18,515 for inpatient visit averted. In terms of the QALYs lost from a population of 1,000 births, with nirsevimab 0.03 QALYs were lost due to AEs. Far fewer QALYs were lost overall with nirsevimab as compared to natural history because of averted RSV outcomes and impacts to the children and their caregivers. Overall, natural history would lose 4.73 QALYs whereas the nirsevimab strategy only lost 3.32 QALYs. Overall, the nirsevimab strategy is $144,926 more expensive than no prophylaxis. But 1.42 QALYs would be saved with nirsevimab. The overall ICER ratio was $102,805 per QALY gained.

Now to look at the sensitivity analysis. Because this is a new product, there were many uncertainties. This graph shows how the top 10 most influential parameter assumptions affect the cost-effectiveness of nirsevimab:



Recall that the base-case ICER was about $100,000 per QALY gained. If the nirsevimab costs were lower at $50 per dose, providing nirsevimab would be cost-saving. However, if nirsevimab costs were higher at $600 per dose, the ICER would increase to $315,613 per QALY year gained. The next section below in nirsevimab cost in the light-gray subsection is parameters related to nirsevimab efficacy. If the nirsevimab efficacy is higher, then the incremental cost-effectiveness ratio drops. The other parameters in that light gray section are related to the fraction of RSV infections that nirsevimab might impact. The section below that in the lightest gray includes parameters related to the QALYs lost from RSV. The dark blue portion of the bars suggest that children and their caregivers would be losing a lot of quality of life from RSV. If that is the case, nirsevimab looks more cost effective.

The first important parameter is cost. The ICER varies as the cost of nirsevimab changes. The initial assumption was $300 per dose, but if it were more expensive, the ICER would rise. If nirsevimab were cheaper, the ICER would drop. If nirsevimab is assumed to affect only LRTIs, only 57 outpatient visits would be averted in the base-case. If nirsevimab is assumed to reduce URTI with the same effectiveness as has been shown to reduced LRTI, infections averted would be 108 outpatient visits and 33.5 ED visits. If nirsevimab also reduces URTIs, it would substantially lower the cost-effectiveness ratio. In this scenario, the ICER would drop to $45,092 per QALY gained if nirsevimab cost $300 per dose.

In terms of how changing the timing of administration of nirsevimab might affect its cost-effectiveness, recall that in the base-case it was assumed that nirsevimab would be given to newborns in October–March. This analysis assessed administration to newborns in October–February or October–April. Those born out of the season would still be given nirsevimab at the beginning of the season in October or November. It also would vary the efficacy in months 6–10 from 0.0% to 50%. In months 6–10, the timing of administration does not have a huge impact on the overall ICER. Whether children born in March or April receive nirsevimab at birth or in the Fall does not make a huge difference in the ICER. There are tradeoffs between providing nirsevimab at birth when the children are most vulnerable and providing nirsevimab in the Fall when protection would be most likely to match the peak of the RSV season. These effects roughly cancel each other out, so the timing does not make a major difference in terms of cost-effectiveness.

Another scenario of interest is whether giving nirsevimab would lead to reduction in palivizumab use being given to high-risk children. In the base-case, palivizumab usage was not changed. This analysis shows what the potential cost impact might be if clinicians chose to give nirsevimab instead of palivizumab to infants who are currently getting palivizumab. A few additional assumptions included about the current use of palivizumab were that 1.6% of infants were high-risk and palivizumab-eligible, uptake was 75% in high-risk infants, 4.1 palivizumab doses per person were administered on average, and palivizumab cost was $1,228 per dose. If nirsevimab replaces palivizumab, the incremental cost of nirsevimab would decrease. It would not be quite as increasingly expensive. With essentially the same health outcomes, the ICER was $59,250 per QALY gained.

In a scenario with higher-risk children entering their second RSV season, it was assumed that immunization was administered in October for those under 19 months of age. To define high-risk, a range of increased incidence of RSV-associated hospitalization and mortality was explored. This analysis looked at 1x, 2x, 4x, 6x, and 10x higher incidence for RSV-associated hospitalization and increases in mortality given hospitalization. It also assessed a $600 cost, which is equivalent to 2 doses at $300 and $1,000 total cost which is two $500 doses. Looking at the cost-effectiveness results for nirsevimab in a second season, with no increased risk not

many events would be averted, but those are older children who have lower risks to start with. However, in a high-risk population at 6 to 10 times the risk of hospitalization or death, the events averted would be much higher. This shows the cost-effectiveness results for nirsevimab in the second season for the $600 and $1,000 total cost of nirsevimab:

	ICER by cost of nirsevimab (product plus administration) ($/QALY)	
Hospitalization and Mortality rate	$600	$1000
1x (base)	$ 815,051	$ 1,410,155
2x	$ 449,238	$ 800,666
4x	$ 145,014	$ 282,945
6x	$ 53,061	$ 122,409
10x	$ 404	$ 27,390

Nirsevimab given in the second season is very expensive if the population is not at much higher risk. However, a population with a much higher risk than the general population, perhaps at 6 to 10 times the base risk of hospitalization and death, giving nirsevimab potentially could be a lot more cost-effective.

There are some limitations to these analyses. The model structure does not contain varying risk groups besides age. The analysis of the first season was done for all children regardless of risk. The model does not include dynamic transmission, so nirsevimab was not reducing population transmission of RSV. Additionally, models like this are a function of the underlying parameter assumptions, and there were many uncertain inputs. There was uncertainty about what the actual nirsevimab costs would be for payers, and there was not great information on quality of life with RSV and data were lacking on long-term efficacy.

In summary, the cost-effectiveness of nirsevimab depends on many factors, particularly the cost per dose that could cause the ICER to vary between being cost-saving to over $300,000 per QALY gained. Nirsevimab efficacy, particularly against URTIs could cause the ICER to vary between roughly $75 and $150,000 per QALY gained. Variations in the QALY with RSV for both children and caregivers could cause the ICER to vary between $40,000 and $125,000 per QALY gained. Under certain conditions, nirsevimab may be cost-effective. Under other conditions, it might be less favorable.

Cost-Effectiveness Analysis for Nirsevimab: Comparison to Manufacturer Model

Ismael R. Ortega-Sanchez, PhD (CDC/NCIRD) compared and summarized key elements and findings of 2 economic models on the use of nirsevimab for the prevention of LRTI caused by RSV among infants in the US. These models have been presented and discussed with the Maternal/Pediatric WG. The first study was conducted by Sanofi and its collaborators. Sanofi manufactures nirsevimab. The second study was the CDC-University of Michigan study presented by Dr. Hutton. For full disclosure, Dr. Ortega-Sanchez indicated that he was part of the team that conducted the CDC model. None of the authors had any COIs for any part of the CDC model.

In terms of the policy questions and considerations, most comparisons in this presentation focused on how the 2 models addressed the first question in the following policy questions, and touch on the second part of the question in a few areas:

Policy Questions:

1) Should one dose of nirsevimab be recommended
    a) at birth for all infants born during October to March ***and***
    b) for all infants born during April through September and <8 months of age when entering their first RSV season?

2) Should nirsevimab be recommended for children <20 months of age entering their second RSV season who remain at increased risk of severe disease?

To consider the economics of the policy question is to consider simultaneously the health benefits and costs of nirsevimab utilization; namely, "Is the use of nirsevimab against RSV LRTI in all infants <8 months entering their first RSV season and in high-risk children <20 months entering the second season cost-effective?" To answer this question, the 2 models used the same standard of care in infants in first season and high-risk children entering the second season. Standard of care assumes palivizumab only for infants eligible as per the American Association of Pediatrics (AAP) recommendation and no immunization for all other pre-term and term infants. The base-case scenario focused on analyzing the cost-effectiveness of giving nirsevimab to infants in the first season and high-risk children in the second season.

Depending on the policy question, key elements of this economic model were defined on: 1) the modelling approach, including targeted population(s), perspective (healthcare vs. societal), and intervention strategies and comparators; 2) the inputs for RSV disease burden, nirsevimab efficacy, and costs, including incidence of RSV disease and rates of outcomes, direct and indirect costs of RSV disease, and the intervention in terms of efficacy, duration of protection, safety, and program costs; and 3) influential assumptions that were compared across the 2 models.

In general, the 2 models followed similar designs. Both used a static analytical decision-making approach, relying on probabilistic simulation sensitivity analyses to manage data uncertainties. Both modeled hypothetical populations of infants <8 months of age and high-risk children 8─19 months of age and used reasonable time frames, analytical horizons, and discount rates. They also accounted for loss of income associated with temporary productivity loss in caregivers or premature death in patients. Once the models were set, they were fed by different types of input data, including clinical, epidemiological, economic, and QALY data including nirsevimab clinical characteristics. Across models, the sources, specific values, and assumptions of these parameters had some overlaps, but there were marked differences as well. Dr. Ortega-Sanchez noted that the full report with these input data and assumptions from these models could be made available to ACIP members.

This table delineates the standard outcomes estimated and reported by the 2 models, ratios of incremental cost per QALY saved, and the number needed to immunize (NNI) to prevent a health outcome:

	Sanofi	UM-CDC
Prevention of: • MA RSV LRTI	✓	✓
• RSV LRTI hospitalizations	✓	✓
• RSV-associated deaths	✓	✓
QALYs saved	✓	✓
$/QALY saved	✓	✓
Number needed to immunize (NNI) to avert an: • MA RSV LRTI	✓	✓
• RSV LRTI hospitalization	✓	✓
• RSV-associated death	✓	✓

In the Sanofi model, the base-case estimate for all infants <7 months in Season 1 with a nirsevimab cost assumed of $500 dose was determined to be about $70,000 per QALY saved. The QALY findings was supported with simulations and sensitivity analysis, most of which were somewhat costly, but there also were some gains in QALYs. For the UM-CDC base-case estimates for all infants <8 months for Season 1 with a nirsevimab cost assumed of $300 per dose was approximately $102,000 per QALY saved. Both models agree that nirsevimab will be costly, but it also will prevent LRTIs, hospitalizations, and saved QALYs among infants and caregivers. This table shows the Sanofi and UM-CDC model comparisons for selected outcome ratios for nirsevimab:

	UM-CDC model Price per dose $300	Sanofi model Price per dose $500
$ / QALY gained		
nirsevimab Season 1, infants	**$102,805**	**$70,430**
nirsevimab Season 2, high risk infants	$842,139[b]	$823,131[a]
nirsevimab Seasons 1 & 2 combined	n/r	$62,589
nirsevimab vs palivizumab, Season 2 PEP[c]	n/r	dominant
$ / hospitalization averted		
nirsevimab Season 1	$18,881	$9,387
nirsevimab Seasons 1 & 2 combined	n/r	$8,316

a. Pre-term infants only
b. High risk <19 months old infants (preterm + PEP) receiving a 2nd dose of nirsevimab in October
c. PEP= palivizumab eligible population
n/r = not reported

It is important to note that even though the CDC model used a lower nirsevimab cost per dose, the costs per QALY saved were higher than those of Sanofi. The same observation could be made for the cost per hospitalization averted.

To understand the discrepancies in these estimates, Dr. Ortega-Sanchez discussed the main sources driving these differences. In the UM-CDC model, nirsevimab cost was the most influential variable, followed by nirsevimab efficacy in hospitalized infants, QALY with RSV LRTI diagnosis, and epidemiological barriers. Sanofi similarly reported one-way sensitivity analysis for key variables. Ranked most influential were epidemiological variables like the risk of RSV, followed treatment cost and efficacy. The price of nirsevimab did not appear in the Sanofi analysis. Aside from the cost per dose, the common most influential barrier identified in the review of this analysis, the following 4 categories of variables were identified that could be influential in the difference of these estimates:

- ❑ RSV-hospitalization rate
  - Sanofi: Age and term-specific hospitalization rates reported in McLaurin (2016)[42]
  - UM-CDC: From RSV-associated hospitalization rates[43] among children aged ≤2 years

- ❑ Unitary medical cost of RSV hospitalization
  - Sanofi: Cost varies by term at birth and by whether Intensive Care Unit or Mechanical Ventilator were needed as reported in McLaurin (2016)[43]
  - UM-CDC: Unit cost was a weighted average by term at birth and age as reported in Bowser (2022)[44]

- ❑ RSV season & intervention period
  - Sanofi: MA RSV season based on Rainisch (2020)[45] but intervention ends in February
  - UM-CDC: RSV-season and intervention period based on CDC surveillance data (2016-2019)[43]

- ❑ Initial efficacy & waning
  - Sanofi: Constant first 5 months as in trials, linear decay from month 6 to month
  - 10 UM-CDC: Sigmoid decay up to 10 months; average residual protection in first 5 months equals constant efficacy from trials

There were marked differences in the rates of hospitalization, medical costs per RSV hospitalization, and medical costs per RSV outpatient visit. The inputs in the Sanofi model were on the high end, while those used in the CDC model were on the lower end. For example, medical costs per RSV hospitalization was $11,487 in the CDC model and $18,790 to $28,812 in the Sanofi model. Particularly influential was the rate of hospitalization, which also was the input data with sizeable uncertainty. Sanofi used the age- and term-specific hospitalization rates in McLaurin published in 2016, while the CDC model used the RSV-associated hospitalization rates among children <3 years of age from the laboratory-confirmed rates in the NVSN. Likewise, data sources of RSV season for the percent of RSV cases by month and how interventions were modelled have some marked difference. Although both intervention seasons began in October, the Sanofi intervention finished in February and the CDC model ran until the end of March. There are a number of other elements regarding the RSV season and intervention that could have impacted the differences between the models.

[42] McLaurin et al. J Perinatol. 2016;36(11):990-996
[43] CDC unpublished data from the New Vaccine Surveillance Network (NVSN) (December 2016 to September 2020)
[44] Bowser et al., J Infect Dis. 2022 Aug 15; 226(Suppl 2): S225–S235
[45] Rainisch et al. Vaccine. 2020;38(2):251-257

Both models used similar initial nirsevimab efficacy and uptake, which was 80.0 (68.5 – 86.1) in the UM-CDC model and 79.0 (68.5 – 86.1) in the Sanofi model. It is important to understand that within the context of duration of protection. The 2 models relied on the available duration of protection data from similar trials that covered approximately 5 to 6 months. However, the residual protection was based on assumptions after this initial period. The Sanofi and CDC models assumed no residual protection after 10 months, although the Sanofi model followed linear decay of efficacy from Month 6 to Month 10 and CDC used a Sigmoid decay up to Month 10 and then 0% afterwards.

An effort was made to use the assumptions made by Sanofi in the CDC model to try to calculate a summary of the estimates. For instance, when the base case and the scenarios used the Sanofi assumption of a nirsevimab cost of $500 per dose in one-year timeframe, the cost per QALY was about 150% higher when using the input data from the CDC model approach. If the intervention period was October–February, the cost per QALY would be approximately 6% higher. If the lower bound medical costs for hospitalization were used, the cost per QALY would be around 10% higher. Conversely, if all medically-attended RSV visits included LRTI and URTI, the cost per QALY would be reduced up to approximately 50%. Similarly, if the nirsevimab price per dose was $200 per dose, the cost per QALY would drop to less than one-third relative to the base-case cost per QALY.

In terms of limitations, there are factors not considered that may result in overestimating the ICER, which means that cost-effectiveness may be underestimated. For instance, in the base-case both models assume no protection against URTI and no protection against asymptomatic/unattended LRTI. In addition, neither model included RSV-related costs incurred after discharge from an RSV-associated hospitalization or ED visit (e.g., productivity losses incurred by caregivers after discharge are not taken into account). Both models assumed no indirect effects of nirsevimab immunization (e.g., no indirect protection against RSV transmission is included).

In conclusion, the differences in key inputs among the Sanofi and CDC models explains the differences in the results. The most significant of these variables include nirsevimab cost per dose, seasonality and intervention period, duration of nirsevimab efficacy, hospitalization rates, and medical costs. In terms of the base case in both models, it can generally be said that nirsevimab would significantly reduce RSV disease burden in infants. Data from clinical trials support impact estimates on disease reduction. However, the economic value of using nirsevimab in infants could be costly or cost-effective. Reasonable nirsevimab price and duration of protection, combined with careful design of seasonal interventions, would determine the cost-effectiveness value of routine prophylaxis among infants ≤7 months of age entering their first RSV season and those born during the RSV season.

EtR Framework for Nirsevimab

Jefferson Jones MD, MPH, FAAP, CDR USPHS (CDC/NCIRD) presented the EtR Framework for nirsevimab, which he noted he would refer to as “immunization” at times because it is a form of passive immunization. Active immunity results from infection or vaccination, which triggers an immune response. Passive immunity is when a person receives antibodies from an external source. One example is antibodies transferred from a mother to baby through the placenta or breast milk. Another example is direct administration of antibodies through intravenous immune globulin (IVIG) or monoclonal antibodies such as nirsevimab.[46]

[46] https://www.cdc.gov/vaccines/vac-gen/immunity -types.htm

During this session, Dr. Jones reviewed the EtR Framework for the following 2 policy questions:

- ❑ Should one dose of nirsevimab be recommended a) at birth for all infants born during October to March and b) when entering the first RSV season and <8 months of age for all infants born during April through September. (PICO Question 1)

- ❑ Should one dose of nirsevimab be recommended for children <20 months of age with increased risk of severe disease entering their second RSV season? (PICO Question 2)

For PICO Question 1, the population was all infants born during April to September who are <8 months of age when entering the first RSV season and infants born during October to March. The intervention was nirsevimab and the comparison was no nirsevimab. The outcomes included medically-attended RSV-associated lower respiratory tract infection (MA-LRTI), RSV-associated LRTI with hospitalization, RSV-associated LRTI with ICU admission, RSV-associated death, all-cause MA-LRTI, all-cause LRTI-associated hospitalization, and SAEs.

The question for the Public Health Problem domain was, "Is RSV-associated disease among infants <8 months of age entering their first RSV season and infants born during the RSV season of public health importance?" Prior to the COVID-19 pandemic, RSV transmission had followed a consistent seasonal pattern. The 2016–2020 seasons consistently peaked during December to February. However, the COVID-19 pandemic interrupted seasonal circulation of RSV and many other respiratory viruses. Following over a year of limited RSV circulation, the US experienced an inter-seasonal RSV wave that peaked in early August 2021. That peak continued throughout the Fall into late December. In summer 2022, limited regional inter-seasonal transmission occurred, largely in the South and South Central US. RSV peaked in October to November 2022 and is decreasing, suggesting that RSV circulation might be transitioning to typical winter seasonality.

It is estimated that each year among US children <5 years of age, RSV is associated with 100 to 300 deaths;[47] approximately 58,000 to 80,000 hospitalizations;[48] 520,000 ED visits;[49] and 1.5 million outpatient visits.[50] Pre-pandemic RSV seasonality is well-defined with limited geographic variability in most of the US. RSV is the most common cause of hospitalization in US infants. The highest hospitalization rates are in the first months of life, and risk declines with increasing age in infancy and during early childhood. Prematurity and other chronic diseases increase the risk of RSV-associated hospitalization, but most hospitalizations are in healthy term infants. The workgroup felt that RSV-associated disease among infants is of public health importance.

For the Benefits and Harms domain question regarding whether the desirable effects outweigh the undesirable affects, the WG used both published data and additional data requested by the WG. The critical outcomes identified by the WG included MA RSV LRTI, RSV LRTI with hospitalization, RSV LRTI with ICU admission, and death due to RSV. Important outcomes were all-cause MA LRTI, all-cause LRTI-associated hospitalization, and SAEs. All outcomes were evaluated using pooled estimates from the Phase 3 and Phase 2b RCTs that were presented during the October 2022 ACIP meeting using the recommended dose. Aggregate data for additional outcomes were provided by the manufacturer to the WG. This differs from the full data submission to the FDA as part of the Biologics License Application (BLA) used for regulatory purposes. Given that no deaths were identified in these trials, this outcome could not

[47] Thompson et al, JAMA, 2003
[48] Hall et al, NEJM, 2009; Rha et al., Peds, 2020; McLaughlin et al, J Infect Dis, 2022
[49] Hall et al, NEJM, 2009
[50] 3Hall et al, NEJM, 2009

be evaluated. Pooled estimates combined the Phase 2b and Phase 3 trials using the recommended dose. The estimated efficacy was 79% for MA RSV LRTI, 80.6% for hospitalization, 90% for ICU admission. The Phase 3 trial was conducted partially during the COVID-19 pandemic, which temporarily led to lower than expected incidence of RSV. This concern applied to all outcomes for indirectness but was deemed not serious. For protection against ICU admission, few ICU admissions were reported, which led to wide confidence intervals. This was rated a serious concern because of fragility or imprecision of the estimates of efficacy for ICU admissions. Because no deaths were recorded, this outcome could not be evaluated. The estimated efficacy against all-cause MA LRTI was 34.8% and against all-cause LRTI hospitalization was 44.9%. The risk ratio comparing SAEs in infants receiving nirsevimab versus receiving placebo was 0.73. Because too few participants were included in the trials to detect rare events like anaphylaxis, which is typical for trials, the WG rated this as a serious concern for imprecision.

In summary, there was high certainty that nirsevimab is effective in preventing MA RSV and RSV hospitalization in addition to preventing all-cause MA LRTI and LRTI hospitalization. There was moderate certainty that nirsevimab was effective in protecting against RSV LRTI with ICU admission and that SAEs were not more common in infants receiving nirsevimab than placebo. It was not possible to evaluate death. Overall, the WG rated the evidence as moderate certainty because of concerns in the precision of protection against ICU admission and ability to detect rare SAEs. The WG felt that the anticipated effect for the main desirable outcomes was large, but some members felt the effects were moderate. The WG felt that the anticipated effect for undesirable outcomes was minimal to small. The WG felt that the balance between the desirable effects relative to the undesirable effects favored nirsevimab more than no intervention.

In terms of the Values domain question regarding whether the target population feel that the desirable effects are large relative to the undesirable effects and if there is important uncertainty in these values, in a survey conducted by the University of Iowa of 523 people who were actively pregnant or pregnant within the last 12 months, about one-third of respondents thought their baby definitely or probably would get an RSV infection within one year after being born. A total of 70% of respondents said they definitely or probably would get an RSV antibody injection for their baby if safe and effective, licensed by FDA, and recommended by CDC. A total of 63% of respondents said they were more worried or equally worried about their baby experiencing side effects from an RSV antibody injection versus symptoms if sick with RSV. A total of 38% of respondents believed that their baby would have no symptoms or mild symptoms if they got sick with RSV, and 24% expressed uncertainty about the disease severity or treatability if their baby got sick with RSV. Despite being unsure if receiving risk to be low, respondents were worried their baby would need to be hospitalized if they got sick with RSV, with a mean response of 4 out of 5, with 5 being most worried. The WG felt that the target population probably feels that the desirable effects are large relative to the undesirable effects. However, the WG varied in whether they felt there was important uncertainty about or variability in how much people valued the main outcomes.

For the Acceptability domain question regarding whether immunization with nirsevimab is acceptable to key stakeholders, in a survey by the Alliance for Patient Access and National Coalition for Infant Health of 175 providers using YouGov to poll US physicians, over 99% of respondents agreed that parents need more information about RSV, 86% reported that they already include RSV education as part of routine care, 97% said immunization could help prevent RSV, and 92% agreed that immunization policy should ensure that all children get access. The AAP has stated that the development of a safe and effective RSV immunization is

a priority. In 2021, the National Foundation for Infectious Disease held a roundtable that agreed on the importance of rapid adoption and deployment of evidence-based RSV prevention. This roundtable included the National Association of County and City Health Officials. The WG felt that immunization with nirsevimab is acceptable to key stakeholders.

In terms of the Feasibility domain question regarding whether nirsevimab is feasible to implement among all infants <8 months of age entering their first RSV season and infants born during the RSV season, nirsevimab is administered as an intramuscular injection using prefilled, single-use syringes available in two different doses for infants born during or entering the first RSV season. The dosages are 50mg (0.5mL) for infants weighing <5 kilograms or 100mg (1.0mL) for infants weighing ≥5 kilograms or more. For high-risk infants and children entering the second RSV season, the dosing is 200mg (or 2 doses of 100mg administered at the same time). Only one dose of nirsevimab is recommended per RSV season. It is stored at refrigerator temperatures (2°C - 8°C) and may be kept at room temperature (20°C - 25°C) when protected from light for a maximum of 8 hours. Nirsevimab would be the first passive immunization product to be independently included in the CDC immunization schedule. Certain immunoglobulin products are already included but are in conjunction with vaccines (e.g., hepatitis B immunoglobulin and the hepatitis B vaccination). One reason for this is that the proposed indication is for all infants. Widespread use of nirsevimab would result in population-level impact. It is unknown at this time if nirsevimab will be included in the VFC program.

FDA has indicated they likely will classify nirsevimab as a drug. Some related WG considerations included that certain types of healthcare workers, particularly medical assistants, can administer vaccines but might not be able to administer a monoclonal antibody under current rules, which may require modification to enable administration of nirsevimab. AE would be reported to the FDA Adverse Event Reporting System (FAERS) rather than VAERS. Many providers are more familiar with VAERS and the methodology is to analyze how these systems differ. Billing and administration codes for nirsevimab have not been finalized and differ for vaccines versus drugs. Some state immunization information systems might not be able to include products that are considered drugs and not vaccines.

The WG felt that nirsevimab is probably feasible to implement. However, some members said this was dependent upon inclusion of VFC and others said they did not know or had concerns until more information on VFC was available.

Pertaining to the Resource Use domain regarding the question about whether nirsevimab immunization among all infants <8 months of age entering their first RSV season and infants born during the RSV season is a reasonable and efficient allocation of resources, the primary source of data was from the cost-effectiveness analyses that were previously presented. There was a brief summary in the base case with nirsevimab for the CDC model at a cost of $300 per infant. The ICER was just over $100,000 per QALY at a cost of $300 per infant and a little under $245,000 per QALY at a cost of $500 per infant. The WG was concerned about the potential cost of nirsevimab, so 2 polls were taken. At a cost of $300 per infant, the majority of the WG said “probably yes” and the minority said “yes” that use of nirsevimab would be a reasonable and efficient allocation of resources. At a cost of $500 per infant, approximately half of the workgroup members said “probably yes” and the remainder said “no,” “probably no,” or “don't know” if use of nirsevimab would be a reasonable and efficient allocation of resources.

For the Equity domain question regarding what the impact of nirsevimab would be on equity, the inclusion of nirsevimab in the VFC program is undetermined. If not included in VFC, state Medicaid, Medicaid expansion, or CHIP and private insurance likely would cover nirsevimab, underinsured, uninsured, and those without Medicaid or Medicaid expansion likely would have reduced access without a VFC option. Multiple studies have shown increased rates of RSV hospitalization among children who are AI/AN compared with the general population. One recent study from RSV Surveillance among Native American Persons (SuNA) highlighted seasonal incidence per 1,000 children among 4 AI/AN communities. Rates in infant were 19 to 112 hospitalizations per 1,000 infants. These rates were frequently 4 to 10 times the rate in the general population. This is thought to be due to social determinants of health (SDOH), such as increased rates of poverty and crowding.[51]

The literature comparing rates of severe disease among non-Hispanic White, non-Hispanic Black, and Hispanic children have shown mixed results. National studies of death certificates have found higher rates among non-Hispanic Black compared with non-Hispanic White children.[52] Hospitalization rates using NVSN surveillance data have shown mixed results.[53] Several NVSN studies have shown no significant differences by race or ethnicity.[54] Other studies have shown differences, but even when they have, the relative risk of hospitalization for non-Hispanic Black and Hispanic children compared with non-Hispanic White children has been mildly increased (e.g., relative risk of 1.2 to 2.2) and has differed by age group.[55]

The WG varied in their opinion of nirsevimab's impact on equity. A large concern was uncertainty about inclusion in VFC. To summarize the overall WG interpretations of all infants receiving nirsevimab in their first RSV season, the WG felt that the desirable consequences probably or clearly outweigh the undesirable consequences in most settings and the WG recommended the intervention.

For PICO Question 2 regarding whether one dose of nirsevimab should be recommended for children <20 months of age with increased risk of severe disease entering their second RSV season, the population was children <20 months of age at increased risk of severe disease with RSV and who are entering their second RSV season. The intervention was nirsevimab of 200mg and the comparison was no nirsevimab. The outcomes were the same as those used for PICO Question 1, including MA-LRTI, RSV-associated LRTI with hospitalization, RSV-associated LRTI with ICU admission, RSV-associated death, all-cause MA-LRTI, all-cause LRTI-associated hospitalization, and SAEs.

For the Public Health Problem domain question regarding whether RSV disease among children who are at high risk of severe disease in their second RSV season is of public health importance, NVSN incidence of RSV-associated hospitalization for the years 2016–2020 were used. The incidence is lower in children 12–23 months of age compared with children 0–5 months and 6–11 months of age. Incidence rate ratios from the NVSN further illustrate these differences. The hospitalization incidence rate ratio for infants 0–2 months of age versus 12–23 months of age was 6.1. For infants 3–5 months versus 12–23 months of age was 3.4. For infants 6–11 months of age versus 12–23 months of age, the rate ratio was 1.9.

[51] Hartman et al, RSV2022 12th International Symposium, Belfast 9/29/2022-10/2/2022; Atwell et al. (manuscript submitted, under peer-review)
[52] Hansen J Infect Dis 2022 Aug 15;226(Suppl 2):S255 -S266
[53] NVSN analyses compared incidence rates of non-Hispanic Black, non-Hispanic White, and Hispanic children
[54] Hall Pediatrics 2013 Aug;132(2):e341; Hall NEJM 2009;360(6):588–598; and IwanePediatrics 2004 Jun;113(6):1758-64, findings differed by age group
[55] IwanePediatrics 2004 Jun;113(6):1758-64, findings differed by age group; and Rha Pediatrics 2020 Jul;146(1):e20193611, findings differed by age group

The manufacturers proposed that some children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season might warrant nirsevimab when entering their second RSV. This includes, but is not limited to, children with the following conditions and perhaps others:

- ❑ Chronic lung disease of prematurity (CLD)
- ❑ Hemodynamically significant congenital heart disease (CHD)
- ❑ Immunocompromised states
- ❑ Down syndrome
- ❑ Cystic fibrosis
- ❑ Neuromuscular disease
- ❑ Congenital airway anomalies

The MEDLEY study, a pharmacokinetics and safety study, included palivizumab-eligible children with hemodynamically significant CHD and CLD for the second season, but no other conditions. Palivizumab is the only product currently licensed for prevention of RSV-associated disease in the US. The AAP has identified groups of children at risk of severe disease from RSV during their second RSV season for the purposes of recommending palivizumab.[56] Palivizumab is recommended for children with CLD if they require medical support within 6 months of the start of the second RSV season, and palivizumab can be considered for children who are profoundly immunocompromised or have cystic fibrosis if there are manifestations of severe lung disease.

After reviewing available evidence, the WG felt that the same children currently eligible for palivizumab when entering their second RSV season per the AAP recommendations could be considered high risk for nirsevimab administration when entering their second RSV season. These group are described more specifically as follows, and other conditions are under review:

- ❑ Children with chronic lung disease of prematurity if require medical support (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the 6-month period before the start of the second RSV season
- ❑ Children who are profoundly immunocompromised
- ❑ Children with cystic fibrosis with manifestations of severe lung disease (previous hospitalization for pulmonary exacerbation in the first year of life or abnormalities on chest XR or CT that persist when stable) or weight for length <10th percentile

For the Benefits and Harms domain question regarding whether the desirable effects outweigh the undesirable effects, the MEDLEY study[57] included CHD and CLD cohorts that for the first season had a 2:1 randomization of nirsevimab to palivizumab. For the second season, the nirsevimab group continued to receive nirsevimab and the palivizumab group was randomized 1:1 to receive nirsevimab or second-season palivizumab. Based on these data, the WG was able to evaluate only 2 outcomes, MA RSV LRTI and SAEs. MEDLEY was a safety and pharmacokinetics (PK) study. It did not evaluate efficacy and efficacy data for children entering their second RSV are not available. The PK data from the trials in infants in their first RSV season were analyzed using modeling. An area under the curve (AUC) was derived using individual estimates as a measure of exposure to nirsevimab and then correlated to efficacy for prevention of the first episode of MA RSV LRTI in infants <12 months of age from the Phase 2b, Phase 3, and MEDLEY trials. Based on these data, an AUC PK threshold of 12.8 day mg/mL

[56] https://publications.aap.org/pediatrics/article/134/2/415/33013/Updated-Guidance-for-Palivizumab-Prophylaxis-Among?autologincheck=redirected

[57] Domachowske et al. https://www.nejm.org/doi/full/10.1056/NEJMc2112186, https://clinicaltrials.gov/ct2/show/NCT03959488

was established. As a surrogate of efficacy, a predetermined threshold was that 80% of MEDLEY participates needed to be above that AUC PK criteria, and 95.8% of infants receiving 200 mg of nirsevimab for their second RSV season were above that AUC criteria. The WG had very serious concerns about the evidence for protection against MA RSV LRTI because of indirectness with PK being used as a surrogate outcome and because the AUC PK threshold was determined in the first season, while the indication is for the second RSV season. In addition, the population was limited to children with CHD and CLD, while other conditions are being considered as proposed indications for nirsevimab dose for children entering their second RSV season. The evidence type was low certainty (type 3).

For safety, no SAEs were reported for the group who received palivizumab in both seasons. Among groups who received nirsevimab in the second season, approximately 9% to 10% experienced an SAE. None of these SAEs were deemed by trial investigators to be related to the product, and no deaths were reported. The relative risk of having an SAE among those who received nirsevimab in their second RSV season compared with those who received palivizumab in their second RSV season was 8.4 (95% CI: 0.52-135.50) but with a wide confidence interval. Serious concerns were raised about indirectness because the comparison group was palivizumab recipients rather than placebo. Additionally, there were serious concerns about imprecision because of the small number of participant in the trial. Combined, there was very low certainty in the evidence (type 4).

In summary of GRADE for a nirsevimab dose for the second season, nirsevimab might be effective in preventing MA RSV LRTI but with low certainty. SAEs may not be more common in recipients of nirsevimab compared with children receiving no nirsevimab, but there is very low certainty. No data were available for other outcomes. Overall, the evidence rating was very low certainty (type 4). The WG felt the desirable anticipated effects were moderate and undesirable anticipated effects were minimal. However, some WG members felt that they did not know or that the undesirable anticipated effects were small to moderate. For palivizumab-eligible children, the WG felt that the desirable effects outweigh the undesirable effects and favors nirsevimab.

In terms of the Values, Acceptability, and Feasibility domains, no additional data were available for values or acceptability specific to high-risk populations. The WG felt that the target population feels that the desirable effects are probably large relative to the undesirable effects and that there is probably not important uncertainty or variability. For palivizumab-eligible children, the WG felt that nirsevimab is acceptable or probably acceptable to key stakeholders. An additional consideration for feasibility is that an additional visit to a provider might be needed for administration of nirsevimab prior to the beginning of a second RSV season, either at a specialist clinic or a primary care provider. The WG felt that it was probably feasible to implement nirsevimab to palivizumab-eligible children <20 months of age entering their second RSV season.

For the Resource Use domain question regarding whether nirsevimab use among all high-risk children aged <20 months of age entering their second RSV season would be a reasonable and efficient allocation of resources, at $600 per child, the WG felt it was probably a reasonable and efficient allocation of resources. However, at $1,000 per child, the WG was split if it probably was or was not a reasonable and efficient allocation of resources.

For the Equity domain, equity issues are different by chronic condition among infants and young children. For example, non-Hispanic Black populations experience higher rates of preterm birth than non-Hispanic white populations.[58] The majority of children with cystic fibrosis are from non-Hispanic white populations.[59] Hispanic populations may have a higher prevalence of Down syndrome than non-Hispanic white populations.[60] Hispanic and non-Hispanic AI/AN populations may have higher prevalence of neuromuscular disorders than non-Hispanic White populations.[61]

There was no consensus on the impact of equity. Many WG members felt that it would have no impact among palivizumab-eligible children, but several felt it could increase or reduce equity or did not know. The primary concern was that it is unknown whether this will be included in VFC.

After reviewing the totality of the data and acknowledging uncertainties around aspects of the data, the WG felt that the desirable consequences probably outweigh the undesirable consequences. The WG proposed to ACIP to recommend the intervention for palivizumab-eligible children as defined by the AAP guidance. However, additional conditions will be reviewed.

In summary for the first RSV season, the WG recommended nirsevimab a) at birth for all infants born during October to March and b) when entering first RSV season and <8 months of age for all infants born during April through September. However, many members expressed concerns about feasibility and equity, particularly because inclusion in VFC is unknown. Some WG members expressed concern that at higher prices, nirsevimab may not be a reasonable and efficient allocation of resources. For the second RSV season, the WG would like more time to consider which infants and children would be sufficiently high-risk to warrant nirsevimab in their second RSV season. There are limited efficacy and safety data available at this time in this population, and there are little data to measure the risk of severe disease in the second RSV season by chronic condition. At this time, the WG recommended nirsevimab for those who are eligible for palivizumab in their second RSV season per AAP guidance. Because nirsevimab is assumed to cost less than palivizumab and to be of noninferior efficacy, this was assumed to be cost-effective. The WG will continue to evaluate other conditions.

If licensed by FDA, the 2 policy questions ACIP will be asked to vote on are as follows:

- ❑ Should one dose of nirsevimab be recommended a) at birth for all infants born during October to March and b) when entering first RSV season and <8 months of age for all infants born during April through September?

- ❑ Should one dose of nirsevimab be recommended for children <20 months of age entering their second RSV season who are eligible for palivizumab in their second RSV season? (Note: the second question may have other conditions added).

[58] https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm
[59] McGarry Pediatr Pulmonol 2021 Jun;56(6):1496-1503
[60] Mai Birth Defects Res 2019 Nov 1;111(18):1420-1435
[61] Mai Birth Defects Res 2019 Nov 1;111(18):1420-1435

Clinical Considerations for Nirsevimab

Jefferson Jones MD, MPH, FAAP, CDR USPHS (CDC/NCIRD) presented draft Interim Clinical Considerations and explained that the goals of the WG were to develop simple, uniform recommendations that apply to most US healthcare providers, and provide flexibility for specific situations. For the first indication for infants born during or entering their first RSV season, there were some important considerations for the WG when developing recommendations. In terms of timing and administration considerations, nirsevimab efficacy against MA RSV LRTI and hospitalization in the RCTs was assessed through 150 days after administration, so the efficacy beyond 150 days is unknown. Only 1 dose of nirsevimab is recommended per season, even if given early in the season. If the nirsevimab dose is given too early before the season such as in May or June during the peak of the RSV season, the infant could be beyond 150 days after the dose and have waning protection. Thus, nirsevimab administration should be timed to maximize protection during the RSV season when infants are most at risk of exposure to RSV. For infants born during October–March before the start of most RSV seasons and during the months with the highest RSV activity, the optimal timing of nirsevimab dosing is at birth. For infants born during April–September in months typically with low RSV circulation, the ideal timing for nirsevimab dosing is just before or near the start of the RSV season. Typically, this is mid-October to early December. The 150-day period after administration includes the months of peak RSV circulation, December–February when the infant is most at risk of exposure to RSV. Therefore, for infants born during October–March, nirsevimab is recommended shortly after birth or as soon as possible afterwards. Administration in the hospital prior to discharge is recommended to ensure protection. If this is not possible, administration at the first visit to the primary care provider, ideally within 1 week of discharge, can be considered. However, not all infants are taken to their provider in the first week after discharge. For infants born April–September, nirsevimab is recommended to be administered during October–November such as during regularly scheduled 2-, 4-, or 6-month well-child visits.

Regarding additional considerations, during the COVID-19 pandemic interseasonal RSV transmission has occurred. The WG has expressed that it is important to allow for flexibility of timing in nirsevimab administration during periods of significant interseasonal RSV transmission. However, for the upcoming 2023-2024 season, nirsevimab may not be available prior to October 2023. As a reminder, the incidence of RSV-associated hospitalization is substantially higher during the first 2 months of life and decreases with each month of life.[62] This needs to be balanced. The recommended timing of administration previously presented should serve as a uniform recommendation. If increased RSV transmission is occurring locally in August or September, nirsevimab could be administered earlier than October if available. The NREVSS data could be used as one factor in decision-making. Census division-level or HHS regional-level data is recommended to be used as some state-level data may not be representative. Specific to NREVSS data, and not local hospital or other data sources, greater than 3% positivity of PCR tests for 2 consecutive weeks can indicate an increased rate of RSV detection.[63] To determine if nirsevimab should continue to be administered to newborns shortly after birth beyond March, local jurisdictions can alter administration schedules based on local transmission conditions with clear evidence of ongoing increased transmission. Local data may be a best indicator, but the WG recommended establishing an evidence-based threshold. As noted earlier, NREVSS data at the Census division-level or HHS regional-level could be used as

[62] 2000-2005: Adapted from Hall et al, Pediatrics 2013; 2016-2020: CDC unpublished data
[63] https://www.cdc.gov/surveillance/nrevss/index.html

one factor in decision-making. For NREVSS data, <5% positivity of PCR tests for 2 consecutive weeks can indicate decreasing transmission.

There are some particular geographic considerations. Tropical climates (e.g., Hawaii, Guam, and the US-affiliated Pacific Islands) may have RSV seasonality that differs from the majority of the continental US or is unpredictable. Providers in these areas are recommended to administer nirsevimab to newborns shortly after birth throughout the year to maximize protection in the first 150 days of life—the age at which infants are at the highest risk of hospitalization with RSV. Some specific jurisdictions such as Puerto Rico are recommending nirsevimab during August–March. Providers can consult with local state or territorial health departments for recommendations. In Alaska, RSV seasonality is less predictable and the duration of RSV activity is often longer than the national average. Similar to palivizumab guidance from the AAP, providers are recommended to use RSV laboratory surveillance data generated by the State of Alaska to assist in determining the appropriate timing of nirsevimab. The Alaska Department of Health will continue to provide clinicians with updated Alaska-specific guidance. Infants residing in remote areas who travel long distances to receive well-child care (e.g., those who require medical evacuation by air for severe disease) can be given nirsevimab outside the normal schedule if there is concern that the infant may not have access to nirsevimab at the recommended time.

For the second RSV season indication, the same groups who are currently eligible for palivizumab when entering their second RSV season per AAP recommendations[64] are recommended for nirsevimab when entering their second RSV season. These groups include the following, with other conditions under review:

- ❑ Children with chronic lung disease of prematurity if require medical support (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the 6-month period before the start of the second RSV season
- ❑ Children who are profoundly immunocompromised
- ❑ Children with cystic fibrosis with manifestations of severe lung disease (previous hospitalization for pulmonary exacerbation in the first year of life or abnormalities on chest XR or CT that persist when stable) or weight for length <10th percentile

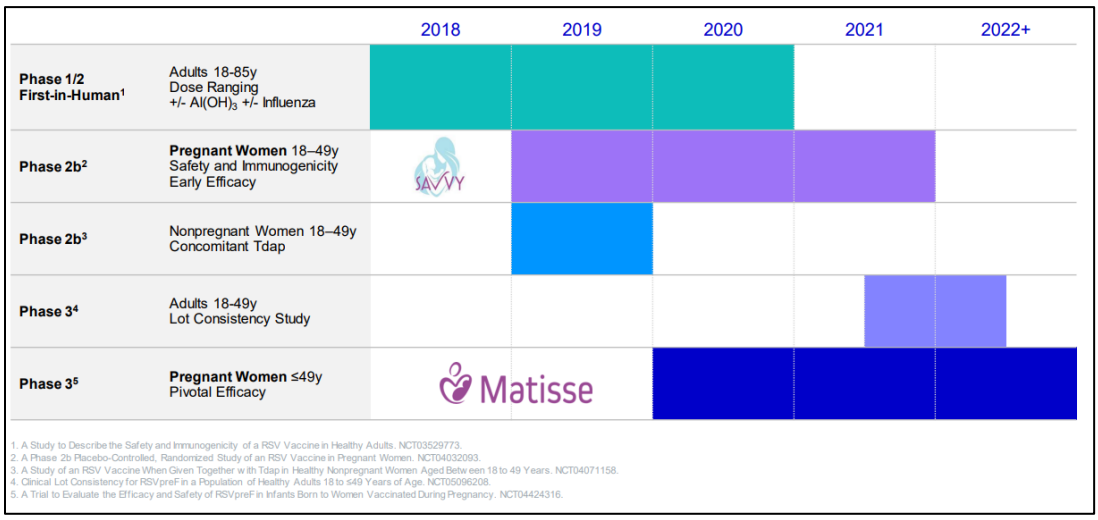
In terms of the timing of nirsevimab administration for the second RSV season, nirsevimab should be administered during October–November when children are normally entering the RSV season. Nirsevimab is not recommended to be used after the second RSV season.

Safety and Efficacy of RSV Bivalent Prefusion F (PreF) Maternal Vaccine

Iona Munjal, MD (Pfizer) presented data from Pfizer's ongoing maternal vaccine program for its bivalent RSVpreF candidate. They believe that this is the first time a maternal vaccine for infant efficacy has been presented in this forum, which brings them great joy regarding the future of maternal vaccines. The proposed indication Pfizer is seeking is the prevention of lower respiratory tract disease (LRTD) and caused by RSV in infants from birth through 6 months of age by active immunization of pregnant individuals. The dose level is 120 µg without an adjuvant. Each dose contains 60 µg of each prefusion protein antigen A and B in a 0.5 mL injection. The presentation is a lyophilized vial with water for injection in a prefilled syringe. The vaccine is to be stored at 2°C to 8°C.

[64] American Academy of Pediatrics Committee on Infectious Diseases and Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics. 2014 A ug;134(2):415-20.

The target of Pfizer's RSVpre-F vaccine is the surface F protein. The F protein is anchored on the surface of the virus. It undergoes a change from its metastable prefusion conformation to a stable post-fusion conformation, causing it to fuse with the host cell membrane and facilitate cell entry. The Pfizer vaccine targets the prefusion form to induce antibodies that are most effective at blocking viral infection. This graphic provides an overview of Pfizer's RSVpreF maternal clinical development program:



During this session, Dr. Munjal focused on 2 maternal studies including the Phase 2b dose-finding and immunogenicity study and the Phase 3 efficacy study. Both studies were conducted in pregnant women who were between 24 and 36 weeks gestation at the time of vaccination.

The Phase 2b study was a proof-of-concept study. In terms of immunogenicity results in a subset of participants who received the 120 µg dose from a total of 562 enrolled maternal participants following vaccination, the neutralizing GMTs were robust at 1 month after vaccination and remained high at delivery and at 6 months postpartum. The RSVpre-F antibodies were found to be efficiently transferred to the infant based on maternal serology at delivery and contemporaneous infant cord blood samples. At the 120 µg unadjuvanted selective dose, transplacental transfer ratios were > 1 overall and were high by geography and in each maternal gestational age category at vaccination.

Looking at the kinetics of the antibody responses following transplacental transfer in infant participants at birth, 1, 2, 4, and 6 months after birth, the RSVpre-F group remained higher than placebo at all time points. Although there is no correlative protection, for comparison, a reference titer of 100 ug/mL palivizumab was demonstrated to be efficacious in preventing infant RSV-associated ICU admission.[65]

[65] Forbes ML, Kumar VR, Yogev R, et al. Hum Vaccin Immunother 2014;10:2789-94

The Phase 3 efficacy study, Maternal Immunization Study for Safety and Efficacy (MATISSE), was conducted in 18 countries globally (3 North American countries, 3 South American countries, 4 countries in Europe, 2 African countries, and 6 countries in the Asia-Pacific region). Women were enrolled if they met qualifying criteria and were less than ≤49 years of age and between ≥24 and ≤36 weeks gestation at the time of enrollment. Over 7,000 vaccinated mothers and their infants were included in this analysis. The study began in June 2020 and follow-up with the cohort is ongoing until the last infant completes the study in the fourth quarter of 2023. This study covered 4 seasons, 2 in the Southern Hemisphere and 2 in the Northern Hemisphere. Women were randomized 1:1 to receive either the study vaccine or placebo. The participants randomized to the RSVpre-F group received a single dose of the 120 µg bivalent vaccine, which contains equal amounts of each prefusion F antigen from RSV subgroups A and B. The vaccine does not contain any adjuvant. Maternal participants were screened, including with an ultrasound, if not already performed, as standard of care prior to vaccination.

Safety was monitored with a self-reported e-diary mobile device soliciting AEs for 7 days following vaccination. All AEs were collected for a month as delivery was a variable time period that may have occurred at any time after vaccination. Most participants' deliveries occurred outside of the AE 1-month period. AESIs, including preterm delivery, and SAEs were collected throughout the study period. In these maternal participants, surveillance for respiratory tract illnesses was conducted through chart reviews, but swabs were not taken. For the infants born to those vaccinated mothers, AEs collected from their first 5 breaths to 1 month after birth. AESIs, SAEs, and newly diagnosed chronic medical conditions were collected throughout the study period. The infants enrolled in the first year of the study were followed for 2 years, which was approximately half the infants. The remaining infants were enrolled for 1 year. Respiratory tract illness surveillance was conducted throughout the study period, with swabs being performed for all MA respiratory events in the first 6 months and for hospitalization and severe illness respiratory events throughout the study period. All cases were adjudicated by an independent event adjudication committee.

In terms of demographics, the maternal characteristics reflected the diverse study population and were similar between the RSVpre-F and placebo groups. The average age at vaccination for maternal participants was 29 years, with participants ranging from 14 to 47 years overall. Data were generated in adolescent participants, and Pfizer will propose to include them in the indication. The average gestational age at vaccination was 30 weeks, with a substantial number of participants vaccinated early in the qualifying 24─36-week gestational window. Infant participants also represented a diverse population. There were approximately equal numbers of male and female participants. Demographics were similar between the RSVpre-F and placebo groups.

The primary objective for the Phase 3 study was to describe the safety profile of RSVpreF in maternal and infant populations. For efficacy, there were 2 equal primary endpoints which were prevention of RSV MA-LRTI within 180 days after birth and prevention of RSV severe MA-LRTI within 180 days after birth. The secondary efficacy endpoints include prevention of RSV MA-LRTIs within 360 days after birth, prevention of RSV hospitalization within 360 days after birth, and prevention of MA-LRTIs due to any cause within 360 days after birth.

Beginning with the safety data for maternal participants and reactogenicity that was solicited in those vaccinated women in their e-diaries, solicited local reactions were mostly mild or moderate and were higher in the vaccinated group. The most commonly reported local reaction was injection site pain. The solicited e-diary systemic events by maximum severity, again from maternal participants following vaccination, were mostly mild or moderate. There were 2 fevers

reported overall and were similar between the vaccine and placebo groups. The most commonly reported event, fatigue, was similar between the vaccine and placebo groups. Headache incidence was slightly higher in the RSVpre-F group compared to the placebo group. Muscle pain was reported more frequently in the RSVpre-F group compared to the placebo group. In terms of AEs by type in the maternal participants within one month after vaccination, overall AEs were common. This was expected from known background rates, and this was a maternal study that included a delivery period. In each category, the events were similar between the RSVpre-F and placebo groups, including the category of SAEs. There have been 5 related SAEs reported in the study to date, all of which were in maternal participants. There were 4 related SAEs in the RSVpre-F group and 1 in the placebo group. All of the events were reported as having been resolved.

Among infant participants, the rates of AEs overall in the first month after birth were higher in the maternal participants. This too was expected from known background rates for a study covering the neonatal period. The events were similar, with no statistically significant differences seen between the RSVpre-F and placebo groups in all categories, including AESIs and in congenital anomalies. Focusing on AESIs include terms of prematurity, low birth weight, and events of developmental delay. These were collected throughout the student period and were similar in the RSVpre-F and placebo groups. Global estimates put infant prematurity at approximately 10% of all births. The rate of prematurity in the study was low, at a little over 5% for all infant participants. This likely reflects the maternal eligibility criteria in the study, including the inclusion of singleton pregnancies only.

With respect to all of the deaths and fetal losses reported in the trial, all events were deemed unrelated by the investigator and sponsor. These data, along with safety information in the ongoing study, are reviewed by an external data monitoring committee. The External Adjudication Committee (EAC) reviews all deaths related to respiratory illnesses of any etiology. Maternal deaths were rare. There was a single maternal death, which occurred in a woman in the Philippines who had an unexpected home birth and died of hypovolemic shock secondary to post-partum hemorrhage approximately 2 months after vaccination. The majority of pregnancies in RSVpre-F vaccinated mothers resulted in live births. Still births and fetal deaths were rare and were reported in no more than 0.3% of participants in each group, or 10 in the RSVpre-F group and 8 in the placebo group. The incidence rate of fetal demises in maternal participants who received RSVpre-F was lower than estimated background rates globally and by country. There were 17 deaths overall at the time of the analysis, 5 in infants born to RSVpre-F vaccinated mothers and 12 in infants born to placebo recipients. There was only 1 infant associated with RSV, which was in an infant from Japan in the placebo group.

The efficacy data in the pivotal Phase 3 MATISSE study were based on an interim analysis conducted in October 2022, which was successful and resulted in a final analysis of all of the infant efficacy data. Infant participants were followed regularly by weekly e-diary response or phone contacts to determine if they had ever sought care in that past week for a respiratory tract illness. Each time they did, a study swab was taken for RSV and vital signs were systematically collected by the study site. All data collected from the study sites, physicians, and hospital visits were collated for a combined review of data by an independent adjudication committee to determine if it was a case. All cases had to have a valid molecular swab positive for RSV. Case definitions used by the adjudication committee are listed here:

Primary Endpoint	Criteria
Medically-Attended RSV LRTI	Medically attended visit and ≥1: • Tachypnea (RR ≥60 (<2 m [60 days]) or ≥50 (≥2 to 12 m) • Peripheral capillary oxygen saturation (SpO2) measured in room air <95% • Chest wall indrawing
Medically Attended Severe RSV LRTI	Medically attended visit and ≥1: • Tachypnea (RR ≥70 (<2 m [60 days]) or ≥60 (≥2 to 12 m) • SpO2 measured in room air <93% • High-flow nasal cannula or mechanical ventilation • ICU admission for >4 hours; unresponsive/ unconscious

Based on the successful interim efficacy analysis at 90 days, the full analysis of infant efficacy endpoints was conducted on the infant available efficacy population. For severe medically attended LRTI, the statistic criterion for success with a lower bound of 20% was met with 39 cases within 90 days after birth. VE of 81.8% was similarly met with 69.4% efficacy at 180 days with 81 total cases. Cases are cumulative at each time point. For medically attended LRTI, the interim analysis results based on 80 cases at 90 days did not meet the statistical criterion for success with the lower bound of 20%. Because that interim analysis required the use of the very stringent 99.5% confidence level, it is notable that the confidence interval for VE at later time points analyzed after the successful interim analysis all had a lower bound greater than 20%, with point estimates comparable to the 90-day result. Medically attended LRTI to 180 days included 174 total cumulative cases of RSV-positive events, with an observed VE of 51.3%.

In terms of the secondary endpoint of the efficacy of RSV-positive medically attended LRTI within 360 days after birth with 240 reported cases, the cumulative VE met the statistical criterion for success of a confidence interval lower bound more than 0% at all timepoints, corresponding to an observed VE between 40% and 45%. For the secondary endpoint of RSV-positive hospitalizations within 360 days after birth, all infants were included who had confirmed RSV that resulted in an admission to a hospital. Although severity criteria were not applied, more than half of these cases also meet the criteria for severe medical attended LRTI. With 63 cases of hospitalization with confirmed RSV, VE was met for the predefined criterion within 180 days.

Regarding the exploratory endpoint of RSV-positive MA-RTIs confirmed by the EAC, there were no prespecified criteria for success on the exploratory endpoint, so a 95% confidence interval was used for presentation purposes. This endpoint looked at all RSV-positive MA-RTI infants who had respiratory tract illness symptoms (e.g., an infant who was taken to the physician or for whom other healthcare was sought who were confirmed to have a valid RSV test within 6 months of birth). Similar to the hospitalization endpoint, severity criteria were not applied. VE was approximately 38% to 39% through the 6-month period, with confidence intervals above zero for all time points, showing that VE was demonstrated across the spectrum of RSV disease even down to milder presentations. With regard to efficacy across MA-LRI by RSV subgroup A or B, for demonstration purposes a 95% confidence interval was used to evaluate the efficacy of A and B as there is no prespecified lower-bound criterion for an exploratory endpoint. Nonetheless, efficacy for RSV A and B was largely consistent with the overall analysis. For RSV

A, there were lower cases overall. Interestingly, this was seen in each year of the study and in each season. This resulted in overlapping but wider confidence intervals.

In summary, the Phase 3 trial demonstrated that the RSVpre-F investigational vaccine was well-tolerated with a favorable benefit-risk profile. The totality of the data demonstrates that efficacy in infants born to mothers vaccinated at 24 to 36 weeks was met for the severe MA-LRTI endpoint through 6 months. Clinically meaningful efficacy was observed for the MA-LRTI endpoint through 6 months. When combined with the secondary endpoint, efficacy was demonstrated through a year.

Workgroup Considerations

Katherine Fleming-Dutra, MD FAAP (CDC/NCIRD) presented the WG's considerations regarding maternal RSV vaccine. The policy question being considered by the WG is:

- ❑ Should the Pfizer RSV bivalent prefusion F vaccine be recommended for all pregnant people as a single dose given at 24─36 weeks gestation?

This maternal vaccine has targeted prevention of RSV disease in infants. Therefore, should this vaccine be licensed by FDA, this recommendation would be considered in the context of the current standard of care for prevention of RSV in infants at the time of ACIP vote.

To highlight a few key considerations regarding this vaccine, including what the data from the trial show regarding the timing of dose within pregnancy, as stated by the manufacturer, the dosing window in the trial was 24─36 weeks gestation. Currently, no data are available on efficacy stratified by gestational age at time of administration. It is important to note that the majority of infants in the Phase 3 trial were born at term, meaning ≥37 weeks gestation, and most doses in the Phase 3 trial were given at ≥28 weeks gestation. This means that the efficacy data from the Phase 3 trial largely reflects doses given in the third trimester. Data regarding efficacy in infants born preterm are limited.

Regarding the number of total lifetime doses, all pregnant people in the trial received their first and only doses of RSV vaccine. Currently, there are no data available on the efficacy of the first lifetime dose during subsequent pregnancies or the safety of additional doses given in subsequent pregnancies.

In terms of the proposed tentative timeline for future ACIP presentations regarding this vaccine, during the June 2023 ACIP meeting, the WG plans to present a summary of the GRADE evidence, a cost-effectiveness analysis, and the EtR framework. An ACIP vote could be held in October 2023 if the product is licensed by that time.

ACIP Discussion Points, Observations, Suggestions on Pediatric/Maternal RSV Vaccines

Following Dr. Hutton's Presentation

- The theoretical uptake assumption of 100% in the base-case seems unlikely. There are parents who refuse vitamin K and hepatitis B vaccine. Dr. Hutton agreed that there probably would not be 100% uptake, but with lower uptake, the ICER would be the same because there would be a lower cost of giving nirsevimab.
- Given that nirsevimab dosing is weight-based, it was not clear what the thinking was behind the $300 assumption. Dr. Hutton clarified that weight was not taken into consideration in the model, but they had to pick some numbers. $300 was thought to be

reasonable, but the sensitivity analysis was run because the manufacturer has a different cost in mind. It also is important to keep in mind that the price the manufacturer sets may not be the price payers pay. The current understanding is that the price will be identical for the lower and higher doses.

- Regarding a question about whether consideration was given to recommending nirsevimab for breast-fed babies who are exclusively human milk-fed and would have significant protection against RSV already, Dr. Hutton indicated that this was not taken into account and it was assumed for the analysis that there would not be a differential for breast-fed versus non-breast fed newborns receiving nirsevimab.
- In terms of whether information would be provided on non-medically-attended RSV infections, Dr. Hutton indicated that the initial model leaned toward making conservative assumptions until additional data become available, at which time adjustments will be made to the model.
- Concern was expressed that high-risk children born outside of an RSV season could be placed at risk of infection for some period of time based on the administration schedule.

Following Dr. Ortega-Sanchez's Presentation

- While the idea of giving nirsevimab to all infants seems to be that this would postpone their first RSV infection until they are older when infections seen in children 2 to 3 years of age are typically reinfections and are milder, clinicians are seeing a lot more RSV in children 2 to 3 years of age who have never had infection and it is more prevalent. It would be beneficial to try to capture additional information through existing surveillance systems to provide more insight on this.
- There is no evidence that this monoclonal antibody will prevent infection, so it may not be putting off infection and instead may be making the first infection less likely to be symptomatic.
- Regarding a question about whether there are second-year data to show that the immune responses post-antibody infusion are not aberrant and are actually helpful, to comment on what the company is doing, rates of RSV MA or LRTI and hospitalization for the second season were presented in October 2022. The Phase 3 trial did not show increased rates among those who received nirsevimab versus placebo. NSVN data will allow for assessment in these age groups.

Following Dr. Jones's Presentations

- While the burden of RSV and its impact on young children and families are huge, there are numerous logistical challenges that ACIP needs to think about carefully (e.g., potential to worsen disparities, timing, cost, billing, who can administer, bundled insurance payments for birth hospitalizations, cost, the need to know what a child has received, coadministration with other vaccines, AE reporting to FAERS and VAERS, et cetera).
- Dr. Jones indicated that in terms of bundled payments, CDC is in discussion with multiple agencies to try to address some of the many challenges so that if nirsevimab is licensed, there will be as smooth as possible a process going into the upcoming RSV season. They have heard that while there may not be initial reimbursement, if ACIP recommends nirsevimab and it is widely used, bundled payments would be updated to reflect the increased cost from its use.
- Dr. Sarah Meyer from CDC's Immunization Services Division (ISD) emphasized that ensuring equitable access is one of the highest priorities. CDC wants to ensure that all children have access if nirsevimab is licensed and recommended. The VFC program has been very effective in helping to reduce disparities for childhood vaccines. There are a

lot of complexities with this being characterized as a therapeutic and not vaccine, many of which have been highlighted in his talk. This is another example of there being a few additional issues that need to be worked through, but those discussions are underway. CDC is working closely with other federal agencies, including CMS, to explore all options to make sure that equitable access of this product can be achieved if it is approved and recommended. Further updates will be shared with the WG and ACIP as soon as possible.

- In terms of coverage, Dr. Romero added that current analyses based on Census data suggest that approximately 5.7% of all children <3 years of age are not covered by private insurance, Medicaid, or CHIP.
- Regarding adverse reporting, Dr. Jones explained that FAERS differs from VAERS. Many providers are familiar with the CDC VAERS platform. Colleagues from FDA's Center for Biologics Evaluation and Research (CBER) have been informing CDC about the system. The current understanding is that AEs following receipt of nirsevimab would be reported to VAERS and reports would be forwarded to FAERS. The hope is to present further information on the FAERS system during a future ACIP meeting.
- Dr. Shimabukuro added that nirsevimab is regulated by CBER as it is a CBER product, so it is monitored by FAERS. There are processes in place for VAERS and FAERS to redirect to reports that are submitted the wrong system. If VAERS receives reports, there will be a process for redirecting those to FAERS and vice versa. Many of the monitoring issues may be related to coordinating with FDA to make sure that CDC is aware of safety findings. CDC also plans to monitor nirsevimab in the VSD, planning for which is underway. While it is challenging to monitor safety when multiple vaccines or products are being administered, CDC will have the data to assess co-administration. CDC also has the Clinical Immunization Safety Assessment (CISA) Project that provides consultations for US healthcare providers of complex AEs associated with a product or when the product is given with other vaccines. In addition, CDC is in the process of developing the next generation v-safe, which also could be used to monitor the safety of this product.
- In terms of coadministration, Dr. Jones conveyed that the consensus of the WG was there is a lack of data but that theoretically, adding passive immunization to regular childhood vaccines poses a low risk.
- CDC's Dr. Melissa Coughlin and Dr. Natalie Thornburg agreed that while there are no data, the theoretic risk that providing an antibody in conjunction with a vaccine for any AE is low. The best source of information is to look at palivizumab administration for safety signals. Palivizumab has been used for a very long time, though in a small population, but no safety signals have been observed thus far. Direct and indirect data could be provided during a future ACIP meeting.
- In terms of the birth dose, many institutions already have infrastructure in place for the hepatitis B dose. It might be beneficial for ACIP to understand that process and how to expand it, as well as birth dose coverage.
- ACIP members expressed concern that nirsevimab may be considered a drug rather than a vaccine. While it is not technically a vaccine, it confers passive immunization in the same way that most other vaccines do that are given to children. If it is not covered under the VFC program, there will be numerous problems. Leaving this up to individual states almost certainly will lead to inequities of delivery. From a feasibility standpoint, it is unclear what would happen in practices if nirsevimab is classified as something other than a vaccine. The bottom line is that if this product is licensed, it should be made available for all children without regard to the ability to pay. It is not clear how that would happen beyond inclusion in the VFC.

- Dr. Rebecca Coyle, Executive Director of the American Immunization Registry Association (AIRA), highlighted some of the known issues that exist with regard to IISs. They are aware that there are going to be challenges implementing nirsevimab using the routine systems in terms of the clinical decision-making perspective, given that forecasting has to account for seasonality and locality. There also are likely to be issues with how data would be submitted to IISs because there are uniform code sets that all EHRs and IISs use, and it could be costly to modify systems because this product is not considered a vaccine. While many partners are working through these challenges, it is unlikely that operationalization would take effect immediately when the product goes live.
- There are lessons learned from Evusheld, which could be used as a model. It would be beneficial for standardization of what products ACIP considers. ACIP did not review Evusheld, nor is that information logged into IISs.
- Dr. Long, WG Chair, emphasized that it will be imperative for the WG and ACIP to better understand the actual cost of nirsevimab, including administration costs. When the WG asked the manufacturer and they presented $500, the WG had assumed a lower cost of $300 and had modeled that. Giving this to a birth cohort could cost a billion dollars, not even considering the administration fee. Given that the VFC's budget is $5 billion, other important vaccines could be dropped. It would be difficult for the WG or ACIP to say that there would be a recommendation regardless of cost. There was a sense in the WG that at a cost of $200 to $300, this could be doable. However, there was considerable trepidation among WG members for anything more than that. The WG also felt that there would have to be a decision about the VFC and how this product would be provided in order to make an ACIP recommendation.
- In the era of vaccine hesitancy, there will need to be considerable education that this medication is not a vaccine per se. There have been horrific issues with palivizumab in terms of conflicting recommendations at the local level and parental acceptance.

Following Dr. Munjal's Presentation

- Data on whether maternal participants were breastfeeding or not would help to differentiate the impact of breastfeeding on the antibody response in the infant. Dr. Munjal indicated that Pfizer studies are collecting data on breastfeeding in terms of exclusivity and duration, which will be analyzed in the future. However, they do not have data on breastmilk composition or antibodies in breastmilk in either of the studies.
- It would be beneficial to have more granular data at some point on maternal outcomes (e.g., mode of delivery, preeclampsia, preterm labor, gestational hypertension, et cetera). Dr. Munjal indicated that Pfizer does have data on pregnancy-related events for which they can provide additional data.
- Regarding coadministration questions, Dr. Munjal reported that Pfizer has 2 published trials. One characterized coadministration with influenza in nonpregnant patients and the other was a noninferiority study assessing Tdap coadministration in women. The influenza coadministration was a descriptive not a noninferiority study. Among the nonpregnant participants in the lower age groups, there was a trend toward lower titers to influenza overall. Therefore, coadministration was not recommended in the Phase 3 study. The 120 µg RSVpre-F vaccine is being studied in the older adult population, and there is a study ongoing that is assessing noninferiority of coadministration in the older adult population. For the maternal population, there would be no additional clinical studies. Pfizer would analyze that in a larger post-marketing cohort.
- Regarding a request for further details about congenital malformations in the vaccine and placebo cohorts, Dr. Munjal indicated that congenital anomalies are collected in all of Pfizer's clinical studies throughout the study period. In order to have the most

complete and consistent reporting, investigators are asked to follow guidance by the CDC's Metropolitan Atlanta Congenital Defects Program (MACDP). A systematic list of congenital anomalies were collected throughout the study. The rates of congenital anomalies were 5.9 in the placebo group and 4.8 in the RSV pre-F group, so there was no difference between the groups. Background rates are complicated because there is variable reporting on congenital anomalies in terms of WHO rates versus US rates. Pfizer anticipated a similar background rate, but that was based on comparable maternal studies not other studies of background rates because this population is quite unique in that it self-selects for women who have had required screening ultrasounds. Those whose infants have congenital defects identified by screening ultrasound are excluded.

Following Dr. Fleming-Dutra's Presentation

- Prior to making a decision, ACIP would appreciate having information on coadministration with influenza, RSV, COVID, and Tdap vaccination that include antibody levels.
- Thinking about the potential for a combined platform of nirsevimab and this vaccine, consideration needs to be given to:
  - Integrating these from a decision-making perspective with regard to benefits and risks
  - Having a monoclonal antibody available to pregnant persons who deliver early and may not have an opportunity to be vaccinated
  - Understanding the biological implications and safety of maternal vaccination followed by passive immunization of the infant
  - Contemplating how to address pregnant persons who receive scant prenatal care
  - Understanding how pregnant people feel about acceptability, values, and preferences with regard to receiving a vaccine after pregnancy or having their infant receive nirsevimab

RSV VACCINES: ADULT

Introduction

Camille Kotton, MD (Chair, Adult RSV WG) introduced the adult RSV vaccines session. She reminded everyone that the October 2022 sessions included a manufacturer safety and efficacy presentation by GSK regarding the adjuvanted candidate RSV vaccine for older adults (RSVpreF3); a manufacturer safety and efficacy presentation by Pfizer regarding bivalent candidate RSV vaccine for older adults (RSV pre-F); and a WG presentation on interim considerations regarding novel RSV vaccines for older adults. Recent WG discussions have focused on cost-effectiveness of RSV vaccination among US older adults, GRADE and EtR for GSK adjuvanted RSVpreF3 and Pfizer bivalent RSVpreF, and CDC vaccine safety surveillance systems. The WG's recent discussions have focused on possible policy recommendations for RSV vaccines of US older adults including whether RSV vaccines should be recommended for US adults ≥65 years of age or if RSV vaccines should be recommended for US adults ≥60 years of age. GSK and Pfizer have submitted BLAs to the FDA for use of these products in adults ≥60 years of age. The FDA's target action for a regulatory decision is in May 2023. ACIP recommendations would be made only if the vaccines are approved and licensed by FDA. This session included presentations on the cost-effectiveness of RSV vaccination among US older adults; a comparison of RSV vaccination economic analyses performed by the University of Michigan/CDC, GSK, and Pfizer; the EtR framework for GSK and Pfizer candidate vaccines; and vaccine policy options.

Cost-Effectiveness of the GSK and Pfizer Vaccines: Main CDC Model

David W. Hutton, PhD, MS (University of Michigan) presented the results of the University of Michigan/CDC (UM-CDC) economic analysis of RSV vaccination in older adults. The overall goal was to evaluate the cost-effectiveness of RSV vaccination in the US population ≥60 years of age. Vaccine policy was evaluated for several age groups (≥60 years, ≥65 years, ≥70 years, and ≥75 years). The outcomes examined included resource utilization, cases, costs, deaths, and QALYs lost from RSV with or without vaccination. The ICER of vaccination was compared to no vaccination and scenario analyses were performed that examined key areas of uncertainty related to these questions. Intervention with GSK and Pfizer vaccines were examined. Each vaccine was individually compared to a no vaccination strategy. The base-case assumed an age-based RSV vaccination recommendation for adults ≥65 years of age. Other potential age groups were examined in the sensitivity analysis. The vaccination intervention was examined over a time period of 1 year, but a lifetime analytic horizon was used to look at outcomes that might last beyond a year, such as years of life lost to deaths.

This analysis used a decision-tree model that incorporated several elements. With no vaccination, individuals can become infected. Infection can lead to hospitalization, ED visits, outpatient visits, or none of these. Individuals who are hospitalized potentially could die. Vaccination may involve AEs such as systemic reactions, injection site reaction, SAEs, or none of these. Individuals could become infected as well. Of course, the RSV outcomes are less likely to happen with vaccination. This decision tree was used to calculate the numbers of events, costs, QALYs, and numbers needed to vaccinate (NNV) for the various outcomes and cost per QALY gained. Because this was a decision tree model, it did not take into account any reductions in RSV transmission. Therefore, the results were not dependent upon vaccine uptake. Infections that were not medically attended were not taken into account. One of the key epidemiological parameters was the incidence of RSV. It is important to keep in mind that reported incidence might be under-reported because of imperfect PCR sensitivity. For the base-case, it was assumed that sensitivity was 95%, and that was adjusted for to estimate the true cases of RSV. A scenario analysis examined what the results would be if the sensitivity was lower, meaning the actual cases of RSV were even higher.

The estimates for RSV hospitalization incidence came from CDC RSV-NET in the season starting in 2015 and ending in 2019. The rates were slightly lower for the younger age groups and were higher for those over 75 years of age. As mentioned earlier, there was considerable uncertainty surrounding these rates. The incidence estimates of ED and outpatient visits related to RSV came from a study by McLaughlin, et al. published in 2022, which was a Pfizer-sponsored meta-analysis.[66] Similar to the hospitalization incidence, the incidence of ED and outpatient RSV visits also increased with age. The UM-CDC model was estimated for RSV mortality linked to hospitalization. These numbers also came from RSV-NET.[67] Notably, the probability of dying from hospitalized RSV increased with age.

The model incorporated seasonality to account for incidence of RSV, timing of RSV vaccination, and waning immunity. In terms of the fraction of annual infections occurring in each month, most infections occurred from November through April. Seasonality data came from NREVSS 2015–2019. The model assumed that vaccine uptake follows a seasonal pattern similar to

[66] McLaughlin JM, Khan F, Begier E, Swerdlow DL, Jodar L, Falsey AR. Rates of Medically Attended RSV Among US Adults: A Systematic Review and Meta-analysis. Open forum infectious diseases 2022 Jul (Vol. 9, No. 7, p. ofac300).

[67] CDC RSVnet data includes the following RSV seasons: 2015-16, 2016-17, 2017-18, and 2018-19. Ranges incorporate a 20% increase/reduction from the base case value

influenza vaccination uptake. It also is important to understand the efficacy of RSV vaccines. This table shows estimates of RSV VE from the GSK and Pfizer Phase 3 trials:

Variable	Value	Range	Source
Vaccine Efficacy (%)			
GSK			
Medically attended RSV LRTI/LRTD (ED, and hospitalization)	87.5%	58.4% – 96.2%	GSK phase 3 trial
Medically attended RSV ARI (outpatient)	79.0%	54.3% – 91.5%	GSK phase 3 trial
Pfizer			
Medically attended RSV LRTI/LRTD (ED, and hospitalization)	80.0%	6.3% – 97.9%	Pfizer phase 3 trial
Medically attended RSV ARI (outpatient)	69.2%	30.0% – 88.0%	Pfizer phase 3 trial

Efficacy was split into 2 components, 1 against ED visits and hospitalizations, and the other against outpatient visits. Efficacy was based on how the trials evaluated RSV LRTI (efficacy against ED visits and hospitalizations) and all ARIs (efficacy against outpatient visits). The efficacy preventing the more severe outcomes was higher than the efficacy preventing outpatient visits.

Given that definitive information was not available on the long-term efficacy of these vaccines, the decision was made to model efficacy with an exponential decay in the efficacy over time. Efficacy over the first 6 months was based on the average efficacy seen in the trials. There was slightly different efficacy against hospitalization compared to outpatient visits.

The estimates for RSV medical costs (e.g., hospitalization, ED visits, outpatient visits) were taken from a variety of sources that have estimated cost of RSV, which all were inflated to 2022 dollars using the Gross Domestic Product (GDP) Price Deflator. The hospitalization cost estimates came from a study by Ackerson in 2020 that studied the cost of inpatient hospitalization but did not include costs of follow-on care that might occur subsequent to hospitalization, such as rehabilitation care. Given that the vaccines are new, the precise vaccine costs were not known. A cost of $100 was used as the base-case for the price per vaccine dose. This may not be the exact number payers ultimately will pay for the vaccines, so a range of $50 to $200 was used in the sensitivity analysis. In addition, $16.96 was included for vaccine administration costs. Productivity costs also were included for an individual's time to go get the vaccine.

Health-related QALY losses from RSV were included for outpatient visits, ED visits, and hospitalization for RSV. These estimates came from a study that surveyed people with QALY lost for medically attended RSV infections. Additional inputs related to RSV illness also were included, such as productivity costs for individuals when they are sick with RSV, productivity costs associated with vaccination, and vaccination AEs and associated quality of life medical and productivity costs associated with them. Several analyses of uncertainty were conducted, including one-way and two-way sensitivity analyses, several potential age-based recommendations for RSV vaccination (≥60 years, ≥65 years, ≥70 years, ≥75 years), a variety

of vaccine costs from $50 to $200, and some scenario analyses examining higher RSV incidence.

In terms of the results, the base-case assessed at a hypothetical cohort of 100,000 individuals. It was assumed that 20% of them would get vaccinated based on the assumption that RSV vaccine uptake would be slightly lower than the influenza vaccination uptake. The base-case assumed vaccination of individuals ≥65 years of age with a $100 vaccine cost over a 1-year time horizon. In terms of resulting health outcomes, vaccination with GSK or Pfizer vaccines would lead to reductions in outpatient visits, ED visits, hospitalizations, ICU stays, deaths, inpatient days, and ICU days. While the reductions might seem small, only 20,000 of the 100,000 people in the cohort were assumed to be getting vaccines in this analysis.

The NNV to avert 1 of these events for the GSK of Pfizer vaccine were typically lower when vaccinating older age groups. The cost would be about $8,000 to $9,000 to avert 1 outpatient visit and about $2 million to avert a death. In terms of the overall cost-effectiveness summary measures, it is anticipated that the GSK vaccine would increase costs by $1.84 million and reduce QALY lost from RSV by 11, leading to an ICER of $180,720 per QALY gained. It is anticipated that the Pfizer vaccine would increase costs by $1.92 million and reduce the QALY lost from RSV by 11, leading to an ICER of $189,407 per QALY gained.

In terms of the sensitivity analyses, recalling that the base-case ICER was about $180,000 per QALY gained, if the vaccine costs for the GSK vaccine were lower at $50 per dose, the ICER would drop to approximately $83,000 per QALY. If the vaccine costs were higher at $200 per dose, the ICER would increase to about $375,000 per QALY. For many of the other parameters, if the value is higher, the ICER would drop. For example, if the incidence of RSV hospitalization was much higher, the ICER would drop to about $32,000 per QALY. The most important parameters are those related to vaccine costs, incidence, VE, and the costs of RSV. For the Pfizer vaccine, the top parameter was VE effectiveness at preventing LRTD. The bar was very wide because the Pfizer VE effectiveness had such a wide confidence interval. Vaccine cost was an important parameter. If the Pfizer vaccine had a cost of $200 per dose, the ICER would be about $384,000 per QALY. If the vaccine costs were only $50 per dose, the ICER would drop to about $92,000 per QALY gained. Similar parameters were important for the Pfizer vaccine as for the GSK vaccine in terms of the ICER. For instance, VE, vaccine cost, and incidence were important parameters.

For the sensitivity analysis looking at how vaccine cost and changing the population vaccinated would affect the cost-effectiveness of the GSK vaccine, vaccinating older age groups would be more cost effective and a lower-cost vaccine would be more cost-effective. The same analysis for the Pfizer vaccine was similar. In terms of the scenario analyses with higher incidence, it is important to recall that there is uncertainty about what the precise incidence of RSV is, particularly given some uncertainty in how precise available tests are at detecting RSV. In the base case, sensitivity was assumed to be 95%, which suggests that not too many cases of RSV are being missed. However, if actual sensitivity were lower as suggested by a 2016 study by Zhang, et al. and a 2022 study by McLaughlin, et al.,[68] more cases of RSV might be being missed than assumed. That is, actual RSV cases might be about 40% to 50% higher than reported. Using higher incidence for the GSK vaccine, if the vaccine were to cost $100 per

[68] Zhang Y, et al. Serology Enhances Molecular Diagnosis of Respiratory Virus Infections Other than Influenza in Children and Adults Hospitalized with Community-Acquired Pneumonia. J Clin Microbiol. 2016 Dec 28;55(1):79-89. doi: 10.1128/JCM.01701-16. PMID: 27795341; PMCID: PMC5228265; and McLaughlin JM, et al. Rates of Medically Attended RSV Among US Adults: A Systematic Review and Meta-analysis. Open Forum Infect Dis. 2022 Jun 17;9(7):ofac300. doi: 10.1093/ofid/ofac300. PMID: 35873302; PMCID: PMC9301578.

dose, the ICER would drop in half to about $91,000 per QALY gained. With higher incidence and $100 cost per vaccine dose for the Pfizer vaccine, the ICER would drop to about $104,000 per QALY gained.

To highlight some limitations of this analysis, the structure did not contain varying risk groups besides age and was for a general older aged population. The model did not include dynamic transmission, so there is no estimate of vaccine impact on population transmission or indirect effects of RSV. No direct post-discharge medical costs were included (e.g., rehabilitation). Additionally, models like this are a function of the underlying parameter assumptions, and this model has many uncertain inputs (e.g., actual vaccine costs for payers, imperfect information about RSV incidence, long-term efficacy).

To summarize, the cost-effectiveness of RSV vaccination depends upon many factors. The vaccine cost could cause the ICER to vary substantially between approximately $80,000 to $385,000 per QALY gained. VE also could cause the ICER to vary between $150,000 and $575,000 per QALY gained. The ages recommended for vaccination also could cause the ICER to vary substantially between about $100,000 to $230,000 per QALY gained. In addition, the incidence of hospitalization could cause the ICER to vary between about $30,000 and $250,000 per QALY gained. Under certain conditions, RSV vaccination may be cost-effective. However, under other conditions it might seem like an expensive intervention.

Comparison of Cost-Effectiveness Results of the Main CDC Model and Each Manufacturer Model (GSK & Pfizer)

Ismael R. Ortega-Sanchez, PhD (CDC/NCIRD) compared and summarized the key elements and findings of the UM-CDC, GSK (RSVpreF3 vaccine), and Pfizer (RSVpreF vaccine) economic studies that were discussed by the WG. The starting point of the 3 economic models was the policy question regarding potential recommendations for the use of RSV vaccine in older adults populations, “Should adults ≥60 years of age (or ≥65 years of age) receive one dose of Respiratory Syncytial Virus (RSV) vaccine (GSK or Pfizer product) for the prevention of RSV disease and its complications?” To consider the policy question, the question also must be answered, “Is vaccinating adults aged ≥65 years (or ≥60 years) against RSV cost-effective?” The 3 models use the same comparator to address this question, unvaccinated older adults ≥65 years of age (or ≥60 years of age).

The policy question also defines key elements in the 3 economic models, including the modeling approach; inputs for RSV disease burden, VE, and costs; and some influential assumptions that need to be defined carefully because of the policy question under consideration. In general, the 3 models followed similar designs. They all used a static analytical decision-making approach, relied on sensitivity analyses and probabilistic simulation to manage various data uncertainties, modeled hypothetical cohorts of US adults ≥60 years of age or ≥65 years of age in order to align with the policy questions, used reasonable timeframe analytical horizons and discount rates, and accounted for loss of income associated with temporary productivity loss and premature RSV-associated deaths. Once the models were set, they were fed by various types of input data (e.g., clinical, epidemiological, economic, quality of life, candidate vaccine characteristics, et cetera. Across models, the source of specific values and assumptions of the parameters have some overlaps, but there were marked differences. This table delineates the standard outcomes estimated and reported by the 3 models, ratios of incremental cost per QALY saved, and the NNI to prevent a health outcome:

	GSK	*Pfizer*	UM-CDC
Prevention of:			
• Outpatient visits for RSV	✓	✓	✓
• RSV hospitalizations	✓	✓	✓
• RSV-associated deaths	✓	✓	✓
QALYs saved	✓	✓	✓
$/QALY saved	✓	✓	✓
Number needed to vaccinate (NNV) to avert an:			
• Outpatient visit for RSV	✓	✓	✓
• RSV hospitalization	✓	✓	✓
• RSV-associated death	✓	✓	✓

The CDC model reported cost per QALY saved estimates for GSK and Pfizer vaccines differentiated by age at which the vaccination program would begin. Although the cost per QALY saved were slightly higher for Pfizer relative to GSK, they were basically in the same ballpark for each age at which the potential vaccine program would be recommended to start. However, the main outcomes of the manufacturers' models compared to those of the CDC model show significant discrepancies. Even though the CDC model assumes a lower vaccine cost per dose for both vaccines, the resulting cost per QALY are much higher than those of GSK and Pfizer. Specifically, the CDC estimates are about 3 times higher than those of GSK and 4 times higher than those of Pfizer for either the adults ≥60 years of age or adults ≥65 years of age strategies.

To understand these discrepancies, an effort was made to try to identify and present the key differences. The CDC model provided a one-way sensitivity analysis for each vaccine with a base-case of age ≥65 years and $180,720/QALY (GSK) and $189,407/QALY (Pfizer). The most influential input variables in the GSK model were vaccine cost, incidence of RSV hospitalization, and outpatient QALYs lost. In the Pfizer model they were VE against LRTD, vaccine cost, and incidence of RSV hospitalization. In a similar fashion, the GSK model reported the most influential variables in a tornado diagram. While cost was the first or second most influential in the CDC model, it ranked 6th in the GSK model. The base-case for the GSK model was age ≥60 years and $ 78,971 /QALY saved. Pfizer also reported one-way sensitivity analysis identifying the most influential variables. Again, medical costs were in 6th place. Aside from the cost of the vaccine dose, the common influential variables identified could group this into these 3 categories:

- ❑ RSV-hospitalization rate
  - GSK: Proportion of MA RSV hospitalized cases identified by PCR, differentiated by age (Belongia, 2018)
  - Pfizer: Differentiated by age and comorbidity profile (Pfizer data on file)
  - CDC: Differentiated by age (four RSV seasons in CDC RSV-NET data)

- ❑ Unitary medical cost of RSV outcomes
  - GSK: Age- and outcome-specific cost for symptomatic RSV LRTD & URTI cases (MA and non-MA) (CMS)
  - Pfizer: Age-, outcome-, and comorbidity-specific cost for MA RSV

- CDC: Age- and outcome-specific cost for MA RSV

❑ Initial VE & waning over time
- GSK: Phase 3, monthly waning: ARI (5.36%), LRTD (2.63%) until 12 months, then to 0%
- Pfizer: Phase 3, flat 7 months, then linear decay to 0% at 24 months
- CDC: GSK's & Pfizer's Phase 3, flat 6 months, exponential decay until 12 months, then to 0%

There were marked difference in the rates of hospitalization, outpatient illness, and unitary medical cost of hospitalization as shown in this table:

	UM-CDC	GSK	*Pfizer*
Incidence of RSV outpatient illness (per 100,000 persons per year)	1,519 (base-case for adults ≥65 years)[a]	1,348 (for adults ≥65 years)[b]	2,430 (base case for adults ≥65 years)[c]
Incidence of RSV hospitalization (per 100,000 persons per year)	**108** (base-case for adults ≥65 years)[d]	**256** (for adults ≥65 years)[b,e]	**300** (base-case for adults ≥65 years)[c]
Direct medical costs per RSV hospitalization	$20,330 – $21,339 (age-dependent)[f]	$13,112 – $26,224 (age-dependent)[g,h]	$12,048 – $38,380 (age- and comorbidity-dependent)[h,i]

a McLaughlin et al. Open Forum Infect Dis (2022): https://doi.org/10.1093/ofid/ofac300; unadjusted for under-detection of RT-PCR testing
b Adapted from Belongia et al. Open Forum Infect Dis (2018): https://doi.org/10.1093/ofid/ofy316
c McLaughlin et al. Open Forum Infect Dis (2022): https://doi.org/10.1093/ofid/ofac300; Ramirez et al. (under review)
d RSV-NET, CDC unpublished data
e Adapted from Falsey et al. NEJM (2005): https://doi.org/10.1056/nejmoa043951; Herring et al. Vaccine (2022): https://doi.org/10.1016/j.vaccine.2021.12.002
f Ackerson et al. J Infect Dis (2020): https://doi.org/10.1093/infdis/jiaa183
g CMS Medicare Inpatient Hospitals (DRG Average Payments from 2019 dataset)
h Kaiser Family Foundation (How much more than Medicare do private insurers pay? 2020): https://www.kff.org/medicare/issue-brief/how-much-more-than-medicare-do-private-insurers-pay-a-review-of-the-literature/
i Merative MarketScan Commercial Claims and Encounters (CCAE) and Medicare Supplemental Coordination of Benefits (MDCR) Databases (2016-2019)

The hospitalization rates and medical costs as input data points using the Pfizer model were on the high end while those using the CDC model were on the lower end, with GSK input values somewhere in the middle. The committee should bear in mind that the higher these input values are in the models, the lower the ICERs or the incremental cost per QALY would be. Particularly influential was the rate of hospitalization, which also was the input parameter with more uncertainty recognized by the manufacturing models. The GSK model showed an inverse relation between the cost per QALY and RSV hospitalization rates. The GSK base-case fell somewhere in the middle within most scenarios. GSK's base-case parameters were mostly from peer-review publications in the last 10 years, while others relied on secondary sources that were used as inputs in some cost-effectiveness analyses as well. It could be argued that considering these uncertainties, the quality of data may be higher for the peer-reviewed publication input.

Likewise, Pfizer reported a similar correlation between the incidence rate of hospitalization and the cost per QALY. However, all of the alternative scenarios were based on similar published sources used by GSK and were high compared to the base-case scenario. An important detail is that the data source of the base-case scenario in Pfizer model relied upon an ongoing, unvetted, and published prospective study with adjusted RSV detection rates. The source was reported as "Pfizer Inc. data on file." The Pfizer data were not available yet for independent review. The input value of 300 per 100,000 population rate of RSV hospitalization was selected for their base-case.

In an analogous way, the CDC model also reported this correlation. For adults ≥65 years of age, the cost per QALY saved for each vaccine was reported as approximately $180,000 for GSK and approximately $189,000 for Pfizer for $1,000 per QALY saved. To consider the uncertainty about the rate of hospitalization in the CDC model, the range in the model relied on those reported in the peer-review sources.

The 3 models showed similar, if not equal, input values for initial or early peak of VE variables are shown in this table:

	UM-CDC		GSK	*Pfizer*
	GSK vaccine	**Pfizer vaccine**		
Vaccine efficacy (VE) against RSV outpatient illness[a]	79.0 (54.3–91.5)[b]	69.2 (30.0–88.0)[b]	71.7 (56.7–82.3)[c]	69.2 (30.0–88.0)[b]
VE against RSV hospitalization and emergency department visit[a]	87.5 (58.4–96.2)[d]	80.0 (6.3–97.9)[d]	82.6 (57.9–94.1)[e]	85.7 (37.9–98.4)[e]

a VE over mean 6–7 months of follow up in phase 3 clinical trials
b Manufacturer phase 3 trial data; VE against medically attended acute respiratory illness
c GSK phase 3 trial data; IDWeek abstract; VE against acute respiratory illness, regardless of whether medically attended
d Manufacturer phase 3 trial data; GSK: VE against medically attended lower respiratory tract disease; Pfizer: VE against medically attended lower respiratory tract illness with ≥3 lower respiratory symptoms
e Manufacturer phase 3 trial data; GSK: IDWeek abstract VE against lower respiratory tract disease, regardless of whether medically attended; Pfizer: IDWeek abstract VE against lower respiratory tract illness with ≥3 lower respiratory symptoms, regardless of whether medically attended (95% CI applied)

This will help to understand where to start and what comes next, which is duration of protection. Although it is important how well the VE starts at the beginning of the RSV season, it is much more significant how it performs during the whole season. The 3 models relied on duration of protection data from both vaccines trials that covered the first 6 to 7 months. However, after this initial period, the residual protection was basically an assumption. Both the GSK and CDC models assumed no residual protection after month 12. Although the GSK model used an initial peak and linear decay, the CDC used an exponential decay to fit the initial VE and the presumed residual after 6 to 7 months to drop later to zero protection after month 12. Unlike the GSK and CDC models, after the initial period, Pfizer model assumed a linear decay to 0% effectiveness at 24 months after vaccination.

Looking at Pfizer's different scenarios for duration of protection and data sources for RSV-associated disease outcomes, if waned to 0% at 12 months, the cost per QALY would increase from $44,000 per QALY to more than $106,000 per QALY. Moreover, with different data sources for the RSV-associated disease outcome rates (e.g., the data from CDC inflated to 1.4), the cost per QALY would increase to $171,000 per QALY. This is very close to what the CDC model calculated, although other caveats need to be considered.

Comparison of GSK and Pfizer vaccines base-case and scenario cost per QALY results using UM-CDC using only the CDC model, if the vaccine costs $200 per dose, with only one-year timeframe, the cost per QALY for GSK would be almost 100% higher than the base-case scenario. Basically, the same happens in the Pfizer scenario. Compared to the base-case, the cost per QALY would be 15% higher in vaccinated adults start at age 60 instead of 65. If the lower bound of medical cost for hospitalization is used, the increase would be only 10% higher. On the other hand, RSV incidence adjusted outward for increased diagnostic yield reveal that a year from testing in addition to RT-PCR on a respiratory specimen will decrease the cost per QALY to approximately 50% of the value that is considered in the base-case scenario. Similarly, when reducing the vaccine price per dose to $50 per dose, the cost per QALY would be reduced considerably to less than 50% compared to the base-case scenario.

There are a number of limitations to this analysis. Factors not considered in the model may result in underestimating the cost-effectiveness of vaccination or over-estimate the ICERs. None of the 3 models included RSV-related medical costs incurred after discharge from an RSV-associated hospitalization or ED visit (e.g., stay in long-term care or rehabilitation facility, assisted living at home, productivity losses incurred by caregivers whose support is needed post-discharge). All 3 of the models assumed no indirect effects of vaccination (i.e., no protection against RSV transmission). VE beyond clinical trial follow-up time (6–7 months) is unknown. All 3 models assumed non-zero declining efficacy beyond 6–7 months (UM-CDC: 12 months, GSK: 12 months, Pfizer: 24 months).

In conclusion, differences in key inputs among the GSK, Pfizer, and UM-CDC models explain differences in the results. The 4 variables to be more influential were incidence of hospitalization, duration of VE, medical costs, and vaccine costs. The GSK and Pfizer models used less conservative estimates and the CDC model used more conservative estimates. Assumptions and selection of input data were crucial in difference in ICERs as well (e.g., adjustment approach of incidence rates of hospitalization, ED, and outpatient) and the selection of medical costs sources and data extraction approach. Yet in general, in general, the base-case in the 3 models suggested that vaccination would reduce the RSV disease burden significantly in older adults. VE clinical trials data and assumptions supported the impact on disease reduction. However, the economic value of RSV vaccines appears to be costly and could be cost-effective. Factors such as RSV incidence, related healthcare costs, initial VE, and duration, combined with reasonable vaccine price, would determine the cost-effectiveness value of RSV vaccination.

EtR/GRADE for 2 Vaccines (GSK & Pfizer)

Michael Melgar, MD (CDC/NCIRD) presented the EtR frameworks for the 2 candidate RSV vaccines for use in older adults manufactured by GSK and Pfizer. The 2 policy questions considered by the WG for each vaccine were as follows:

- ❑ Should vaccination with **GSK RSVpreF3 vaccine** (120µg antigen + AS01E adjuvant, 1 dose IM), rather than no vaccine, be recommended in persons aged ≥65 years?

- ❑ Should vaccination with **GSK RSVpreF3 vaccine** (120µg antigen + AS01E adjuvant, 1 dose IM), rather than no vaccine, be recommended in persons aged ≥60 years?

- ❑ Should vaccination with **Pfizer bivalent RSVpreF vaccine** (120µg antigen, 1 dose IM), rather than no vaccine, be recommended in persons aged ≥65 years?

- ❑ Should vaccination with **Pfizer bivalent RSVpreF vaccine** (120µg antigen, 1 dose IM), rather than no vaccine, be recommended in persons aged ≥60 years?

For simplicity, Dr. Melgar explained that he would present the EtR framework from the perspective of vaccination policy for adults ≥65 years of age and at the end of the presentation would summarize the WG's thoughts regarding the pros and cons of selecting a ≥60 years of age versus a ≥65 years of age threshold. In terms of the EtR framework used by ACIP to make policy decisions within 7 domains, he noted that as he described the WG's interpretations, some components would be the same for both manufacturers and would be presented once while others would be manufacturer-specific. The Public Health Problem domain focused on RSV in older adults broadly. The Values, Acceptability, and Equity domains focused on RSV vaccines

broadly. Manufacturer-specific data were presented for Benefits and Harms, Feasibility, and Resource Use domains.

For the Public Health Problem domain regarding whether RSV among older adults is of public health concern, RSV is recognized by pediatricians but there is a lower awareness of RSV in adults among HCP and the public. Even though it is not often recognized as a cause of illness in adults, and there is substantial uncertainty in RSV epidemiology and the burden of disease in older adults is significant. Among adults ≥65 years of age in the US, RSV is estimated to cause approximately 1 million medical encounters;[69] 60,000 to 160,000 hospitalizations,[70] and 6,000 to 10,000 deaths per year.[71]

CDC's RSV-NET provides active population-based surveillance of laboratory-confirmed RSV-associated hospitalizations at sites in 12 US states. The combined catchment area is estimated to account for almost 9% of the US population. Looking at seasonal rates of RSV-associated hospitalizations among adults stratified by age, hospitalization rates were substantially higher among adults 70—79 and ≥80 years of age compared with younger age groups. Focusing on the potential age thresholds of interest, adults 60—64 and 65—69 years of age experienced intermediate rates of hospitalization.[72]

Among adults hospitalized with RSV, a large proportion are severely ill as measured by the proportion admitted to ICU and the proportion who died. In RSV-NET data from 3 seasons, mortality was highest in those ≥65 years at 5%. However, the proportion admitted to the ICU was over 20% even in younger patients 18—49 and 50—64 years of age. This likely reflects the fact that younger patients hospitalized with RSV have underlying medical conditions that make them more vulnerable to severe outcomes. RSV-NET data reflect only patients hospitalized with laboratory-confirmed RSV and more severely ill patients are probably more likely to be tested for RSV. Therefore, these data may overestimate the proposition with severe illness. Regardless, it is clear that RSV can cause severe disease in hospitalized adults of any age.

Turning back to the published literature, there is evidence that adults with certain underlying medical conditions are at higher risk of RSV illness, particularly hospitalization.[73] The list of medical risk factors has not been as well-documented as that for influenza, but adults with immune compromise, especially those with hematopoietic stem cell transplant (HSCT) or solid organ transplant (particularly lung transplant) and those with cardiovascular disease (CVD), diabetes, chronic obstructive pulmonary disease (COPD), and asthma have been shown to have higher risk of RSV hospitalization than adults without those conditions.

[69] McLaughlin et al, Open Forum Infect Dis (2022): https://doi.org/10.1093/ofid/ofac300

[70] Widmer et al, JAMA Network Open (2012): https://doi.org/10.1093/infdis/jis309; McLaughlin et al, Open Forum Infect Dis (2022): https://doi.org/10.1093/ofid/ofac300; Zheng et al, Pneumonia (2022): https://doi.org/10.1186/s41479-022-00098-x; Branche et al, Clinical Infect Dis (2022): https://doi.org/10.1093/cid/ciab595; and CDC RSV-NET data 2016–2020 (unpublished)

[71] Thompson et al, JAMA (2003): https://doi.org/10.1001/jama.289.2.179; Matias et al, Influenza Other Respi Viruses (2014): https://doi.org/10.1111/irv.12258; and Hansen et al, JAMA Network Open (2022): https://doi.org/10.1001/jamanetworkopen.2022.0527

[72] RSV-NET: unpublished data; https://www.cdc.gov/rsv/research/rsv-net/overview-methods.html. Rates are adjusted for the frequency of RSV testing during recent prior seasons and the sensitivity of RSV diagnostic tests

[73] Anderson et al, Diagn Microbiol Infect Dis (2016): https://doi.org/10.1016/j.diagmicrobio.2016.02.025; Prasad et al, Clin Infect Dis (2020): https://doi.org/10.1093/cid/ciaa730; Kujawski et al, Plos One (2022): https://doi.org/10.1371/journal.pone.0264890; and Branche et al, Clin Infect Dis (2022): https://doi.org/10.1093/cid/ciab595

In summary, RSV is a frequent and often unrecognized cause of severe respiratory illness in older adults. A high proposition of adults across the age spectrum who are hospitalized with RSV are admitted to the ICU. Death is more common with increasing age. The WG felt that RSV disease was indeed of public health importance among adults ≥65 years.

Dr. Melgar approached the Benefits and Harms domain one candidate vaccine at a time starting with GSK's adjuvanted RSVpreF3 vaccine. He presented the GRADE summary reviewed by the WG followed by a NNV analysis. He then presented the same for the Pfizer bivalent RSVpreF vaccine. For the PICO question and outcomes, both manufacturers enrolled adults ≥60 years of age in their large Phase 3 trials. Data from all participants in this age group were included in the GRADE analysis. The intervention was either of the 2 vaccines under consideration. The comparison was no RSV vaccine and the outcomes included RSV LRTI or LRTD, MA LRTI or LRTD, hospitalization for RSV respiratory illness, severe RSV respiratory illness requiring supplemental oxygen or other respiratory support, death due to RSV respiratory illness, SAEs, inflammatory neuropathy (e.g., GBS), and severe reactogenicity (e.g., Grade ≥3).

Beginning with the GSK RSVpreF3 candidate vaccine, the CDC calculated VE estimates over 1 RSV season of follow-up for the outcomes can be considered benefits of vaccination. GSK's pivotal Phase 3 trial was the source of data for all outcomes. The efficacy against RSV LRTD, a critical outcome, was 82.5%. However, the WG was concerned about indirectness because adults ≥80 years of age who are at greatest risk of severe RSV disease were underrepresented in the trial relative to the US population of adults ≥60 years of age. Additionally, persons with immune compromise were excluded all together. The efficacy against MA RSV LRTD was 87.5%. The WG was concerned about indirectness for the same reasons. Efficacies against hospitalization, severe RSV respiratory illness, and death were not calculated due to no or few events recorded in the trial. These outcomes were considered important but not critical by the WG.

In terms of the outcomes that are potential harms of vaccination, in additional to the pivotal Phase 3 trial, an early phase dose selection study also reported these outcomes. The pooled relative risk of SAEs of critical outcome was 1.03. The WG had no serious concerns in the certainty assessment. The pooled relative risk for severe reactogenicity events was 4.1, with a confidence interval that did not include 1.0. The WG had no serious concerns in the certainty assessment either. The outcome of inflammatory neuropathy was not formally evaluated in GRADE because there were no events in the included studies. However, 1 case of GBS was recorded in a recipient of the investigational vaccine in an open-label trial without a placebo arm. This trial was not included in GRADE due to lack of an unvaccinated comparator group. Across all trials, there was a total of 1 case of inflammatory neuropathy among approximately 15,000 investigational vaccine recipients.

In summary, the GSK RSV vaccine likely reduces RSV LRTD with moderate evidence. The GSK vaccine also likely reduces MA RSV LRTD with moderate evidence. The investigational vaccine results in little to no difference in SAEs when all organ classes and types of SAEs are considered. The vaccine increases severe reactogenicity events with high certainty. There were insufficient data to evaluate the outcomes of RSV hospitalization, severe illness requiring respiratory support, death due to RSV respiratory illness, and inflammatory neuropathy. The overall certainty of evidence was considered moderate.

In terms of the NNV analysis performed by CDC colleagues at the University of Michigan as part of the cost-effectiveness analysis, 84 adults ≥65 years of age would need to be vaccinated to prevent 1 outpatient visit over a single year. Over 1,000 would need to be vaccinated to prevent 1 hospitalization, and over 21,000 would need to be vaccinated to prevent 1 death due to RSV. The numbers are larger for adults ≥60 years of age. That is primarily because there is less existing RSV disease in that group at baseline for the vaccine to prevent. Notably, the time horizon matters here. If the vaccine is assumed to have non-zero efficacy during the second year, even if it waned substantially, the NNV could be smaller if the analysis were extended for a second year.

In terms of how substantial the desirable anticipated effects of GSK's candidate are among adults ≥65 years of age, the WG determined that they were moderate or large. Regarding undesirable effects, the WG's majority opinion was that they were minimal or small. However, a minority opinion was that the magnitude of these effects was unknown. These WG members were concerned about the case of Guillain-Barre syndrome (GBS) in the cross-trial safety dataset. It is difficult to know from a single case if this was a true safety signal or a random event. Regarding the balance of desirable and undesirable effects, the WG's majority opinion was that the comparison favors the intervention. There was a minority opinion that the balance was unclear in light of the single observed case of inflammatory neuropathy.

Turning now to the Pfizer investigational vaccine, the CDC calculated VE estimates for the outcomes that could be considered benefits of vaccination. Pfizer's pivotal Phase 3 trial was the source of data for all outcomes. The efficacy against RSV LRTI, a critical outcome, was 85.7%. However, as was the case for the other candidate vaccine, the WG was concerned about indirectness because of under-representation of adults ≥80 years of age and because persons with immune compromise were excluded. The efficacy against MA RSV LRTI was 80%. Again, the WG was concerned about indirectness for the same reasons. Counts of RSV-associated hospitalization and severe RSV respiratory illness were not provided by the manufacturer, so efficacy was not calculated. There were no RSV-associated deaths reported in the trial. Again, these outcomes were considered important but not critical.

In terms of the outcomes that are potential harms of vaccination. In addition to the pivotal Phase 3 trial, an early-phase formulation selection study also reported these outcomes. The pooled relative risk of SAEs of critical outcome was 1.01, and the WG had no serious concerns in the certainty assessment. The pooled relative risk for severe reactogenicity events was 1.47. The WG had concerns about imprecision because the confidence interval for a measure of absolute risk included the potential for both benefit and harm. Two events of GBS or a variant thereof occurred among recipients of the investigational vaccine compared with no events among placebo recipients. Due to the small number of events, measures of relative and absolute risk were not calculated. In total, these were the only 2 cases of inflammatory neuropathy that occurred among approximately 26,000 recipients of the investigational vaccine across all clinical trials.

In summary, the Pfizer RSV vaccine likely reduces RSV LRTI with moderate evidence. The Pfizer vaccine also likely reduces MA RSV LRTI with moderate evidence. The investigational vaccine results in little to no difference in serious adverse events when all organ classes and types of SAEs are considered, and the vaccine likely increases severe reactogenicity events with moderate certainty. There was insufficient data to formally evaluate the outcomes of RSV hospitalization, severe illness requiring respiratory support, death due to RSV respiratory illness, and inflammatory neuropathy. The overall certainty of evidence was considered moderate.

In terms of the NNV analysis for the Pfizer vaccine, 95 adults ≥65 years of age would need to be vaccinated to prevent 1 outpatient visit over a single year. Almost 1,300 would need to be vaccinated to prevent 1 hospitalization. Almost 25,000 would need to be vaccinated to prevent 1 death due to RSV. Again, the numbers are larger for adults ≥60 years of age because there is less baseline RSV disease in that group for the vaccine to prevent.

When asked how substantial the desirable anticipated effects of Pfizer candidate vaccine are among adults ≥65 years of age, the WG responded that they were moderate or large. Regarding the undesirable effects, the WG's majority opinion was that they were minimal or small. However, the minority opinion again was that the magnitude of these effects was unknown. These WG members were concerned about the 2 cases of inflammatory neuropathy observed in the main Phase 3 trial as it is hard to know from 2 cases if this is a true safety signal or random events. When asked about the balance of desirable and undesirable effects, the WG majority opinion was that the comparison favors the intervention. There was a minority opinion that the balance was unclear in light of the 2 observed cases of inflammatory neuropathy.

Data for the Values domain drew upon unpublished results from an online survey developed by CDC in collaboration with the University of Iowa and the Rand Corporation. The survey was designed to assess vaccination intentions for a hypothetical RSV vaccine among US adults ≥60 years of age. The final sample consisted of 586 respondents. Overall, 68% of respondents said they definitely or probably would choose to get vaccinated if a safe and effective FDA-approved RSV vaccine was available. That proportion increased to 77% if it was recommended by a HCP. Among those expressing hesitancy to accept the vaccine, the most common reasons included lack of knowledge about RSV and long- and short-term safety concerns about the vaccine. The WG consensus was that older adults do or probably do feel that the desirable effects of RSV vaccination are large relative to the undesirable effects. However, the WG also believed that there was or probably was important uncertainty or variability in how much older adults value these main desirable and undesirable outcomes of vaccination.

Data informing the Acceptability domain related to whether an RSV vaccine recommendation would be acceptable to stakeholders came from a survey of physicians conducted in February–March of 2017.[74] Surveys were administered to a national network of 930 primary care physicians who agreed to participate in surveys about vaccine policy and who spent at least half of their time practicing primary care. Two-thirds (620; 67%) completed the survey. Among those respondents, 317 (51%) reported taking care of an adult patient who they thought had RSV in the last 12 months, and they were included in the final analysis. A majority (57%) of physicians believed that RSV was a very important pathogen in adults of any age with an immune-compromising condition and in adults ≥65 years of age with cardiopulmonary disease. By comparison, approximately one-third (56%) of physicians believed that RSV was a very important pathogen in adults 50–64 years of age with cardiopulmonary disease and in adults ≥65 years of age without cardiopulmonary disease.

The WG felt that generally recommending RSV vaccines for adults ≥65 years of age would or probably would be acceptable to stakeholders. However, some WG members noted that a limitation of these published results was that only physicians were surveyed. Other clinicians, including pharmacists, who order or administer vaccines may have responded differently.

[74] Hurley LP, Allison MA, Kim L, et al. Primary care physicians' perspectives on respiratory syncytial virus (RSV) disease in adults and a potential RSV vaccine for adults. 2019 Vaccine 37(4): 565-570. ISSN 0264-410X. https://doi.org/10.1016/j.vaccine.2018.12.031.

Regarding the Feasibility domain, feasibility barriers might arise from vaccine storage and handling requirements, the increasing complexity of the adult immunization schedule (including coadministration) and from financial barriers. In terms of the storage and handling requirements for the 2 products under consideration, both vaccines require reconstitution of powder and liquid components, both of which will come supplied in the purchased kit. Both vaccines require refrigeration at 2°C–8°C in the original container and with protection from light. Both vaccines should be administered within 4 hours and otherwise discarded.

To illustrate that the older adult routine schedule is becoming more complex, here is CDC's older adult routine immunization schedule with the potential addition of a regularly scheduled COVID-19 vaccine as discussed at VRBPAC in January:

	50-64 years	≥65 years
Influenza inactivated (IIV4) or Influenza recombinant (RIV4)	1 dose annually	
Tetanus, diphtheria, pertussis (Tdap or Td)	1 dose Tdap, then Td or Tdap booster every 10 years	
Zoster recombinant (RZV)	2 doses	
Pneumococcal (PCV15, PCV20, PPSV23)	1 dose PCV15 followed by PPSV23 OR 1 dose PCV20 (see notes)	1 dose PCV15 followed by PPSV23 OR 1 dose PCV20

The immunization schedule is becoming more complex, and vaccination is not the only age- and risk-based preventive healthcare that adult clinicians must provide. If an RSV vaccine is added, clinicians likely will face competing priorities at each patient appointment. Different age cutoffs may also add to the complexity. Harmonizing age recommendations with those of other older adult vaccines may improve feasibility and may increase uptake. At age 65, all adults are recommended to receive pneumococcal vaccination, and there are specific influenza vaccine formulations licensed for adults ≥65 of age. Finally, recipient feasible barriers include time and financial consideration. Older adults without health insurance coverage may experience financial hardship obtaining an RSV vaccine. Financial hardship also may arise if vaccine recipients need to take off from work to be vaccinated or due to post-vaccination reactogenicity events.

The WG felt that overall, both the GSK and Pfizer candidate RSV vaccines are feasible to implement among adults ≥65 years of age.

For the Resource Use domain, rather than repeating the content presented by Drs. Hutton and Ortega-Sanchez, Dr. Melgar presented the WG's interpretation of the cost-effectiveness analyses. The WG felt that RSV vaccination for older adults could be a cost-effective intervention, but that the cost-effectiveness would depend on several factors around which there is substantial uncertainty. WG members felt that the uncertainty is chiefly driven by uncertainty in the annual incidence of severe RSV illness (particularly hospitalization), uncertainty in vaccine acquisition cost, and duration of protection resulting from RSV vaccination in this population. The WG was concerned about the net societal costs resulting from scenarios in which the vaccine acquisition costs were those assumed by the manufacturers. On the other hand, although the net societal costs in some modeling results were high, the WG noted that none of the 3 models incorporated medical costs resulting from longer-term sequelae of RSV

infection. For instance, inclusion of costs of admission to skilled nursing facilities (SNF) among adults discharged from RSV hospitalizations might lower the net societal costs estimated in the analyses. The WG also noted that vaccination of older age groups would be more cost-effective than vaccination of younger age groups. All evidence taken into account, the WG responded that yes or probably yes both candidate vaccines could be reasonable and efficient allocations of societal resources if recommended for adults ≥65 years of age compared with no RSV vaccine.

With respect to the Equity domain, it is known that RSV disease does not impact all US adults equally. Incidence rates of RSV hospitalization published in 2022 from 3 US states[75] showed that at every age group beginning at ≥45 years of age, incidence was highest among adults living in low-income zip codes and lowest among those living in high-income zip codes. In addition to differences by income level, RSV has differing impact by race and ethnicity. Data on median age of adults hospitalized with RSV reported in CDC's RSV-NET stratified by race and ethnicity over the seasons spanning 2015–2020, Black, Hispanic, AI/AN, and Alaska Native adults hospitalized with RSV were younger than adults overall. In fact, at least 50% of adults in these age groups would not have qualified for RSV vaccination if there had been a recommendation for adults ≥65 years of age. As discussed in the Public Health Problem domain, certain chronic medical conditions increase the risk of severe RSV illness. Adults who are Black, AI/AN, and Hispanic have higher prevalence of many of these conditions, including CVD, diabetes, and asthma when compared with non-Hispanic White adults. The same is true of adults with lower income or socioeconomic status (SES). In these demographic groups, these conditions are also diagnosed at earlier ages, often before age 60, increasing the risk of severe RSV disease earlier in life.

Like most medical interventions, access to a new RSV vaccine may be determined by health insurance coverage. It is known that lack of health insurance is more common among adults younger than 65 years of age.[76] However, even this disparity is not evenly distributed in the US population. AI/AN and Hispanic persons 55–64 years of age are substantially more likely to be uninsured than their same age peers in other racial and ethnic groups. Depending upon the age at which an RSV vaccine is recommended, this may exacerbate existing health inequities among older adults. Similar to the relationship between race, ethnicity, and health insurance coverage, insurance coverage also differs by household income. Especially below age 65, the proportion of adults without health insurance is much higher among those with a household income that is below 3 times the poverty threshold than it is among those above that threshold. Depending upon the age at which and RSV vaccine recommendation is made, this may exacerbate health inequities among adults.

Overall, the WG felt that recommendation for RSV vaccination among adults ≥65 years of age would or probably would increase health equity.

In summary of the WG's overall interpretation, both candidate vaccines demonstrated significant efficacy against LRTI caused by RSV among older adults. However, the trials were underpowered to show efficacy against RSV hospitalization and demographic groups at highest risk of severe illness with RSV, including adults ≥80 years of age, were under-represented in the trials. At least 1 case of inflammatory neuropathy has been observed among recipients of each investigational vaccine. The WG felt that if either vaccine is licensed, post-licensure surveillance

[75] Zheng Z, et al. Estimated incidence of respiratory hospitalizations attributable to RSV infections across age and socioeconomic groups. Pneumonia (Nathan). 2022 Oct 25;14(1):6. doi: 10.1186/s41479-022-00098-x
[76] U.S. Census Bureau, 2021 American Community Survey 1-year estimates: https://data.census.gov/table

for both safety and effectiveness will be critical. The WG identified the pros and cons to the choice of age cut-off for an age-based recommendation, which are summarized in this table:

	Pros	Cons
Age ≥65 years	• Greater risk of RSV disease and therefore more favorable population-wide balance of risks and benefits of vaccination (in light of 1–2 cases of inflammatory neuropathy observed) • Aligns with licensure for adjuvanted and high-dose influenza vaccines and age-based pneumococcal vaccination	• Lost opportunity to prevent additional disease in the 60–64 age group, who are disproportionately from racial and ethnic groups impacted by RSV at earlier ages
Age ≥60 years	• Potential to prevent a greater total burden of disease (e.g., number of hospitalizations) • Increases access to adults 60–64 with medical risk factors for severe RSV disease (disproportionately in racial and ethnic groups impacted by RSV at earlier ages)	• Uninsured adults would have difficulty obtaining vaccination (disproportionately aged 60–64 in racial, ethnic and socioeconomic groups at greater risk) • May experience more difficulty achieving clinician adoption of the recommendation among patients 60–64 • Less efficient allocation of societal resources

If a recommendation is made for adults ≥65 years of age, the target population would be at greater risk of severe RSV disease. Therefore, the balance of risks and benefits of vaccination would be more favorable. The WG was concerned about the possible risk of inflammatory neuropathy, particularly in light of the low observed RSV hospitalization rates and the trials impacting that balance. It also would align with the age-based cutoff for certain influenza vaccines and pneumococcal vaccination. On the other hand, this selection would exclude adults 60—64 years of age among whom certain racial and ethnic groups are impacted by RSV at earlier ages. If a recommendation is made for adults ≥60 of age, there is the potential to prevent a greater total burden of RSV disease and it would increase access to persons 60—64 years of age with medical risk factors for severe RSV illness. Conversely, persons 60—64 years of age who are uninsured would have more difficulty obtaining vaccination, counteracting some of these potential gains in equity. Clinicians also may be less willing to adopt a recommendation among adults younger than 65 years of age. Such a recommendation would be a less efficient allocation of collective societal resources.

To summarize the WG summary interpretation regarding GSK's candidate vaccine, for an age threshold of ≥65 years of age and one of ≥60 years, the WG felt that the desirable consequences of a vaccine recommendation probably outweigh the undesirable consequences in most settings. However, when considering a recommendation at ≥60 years of age, there were substantial minority opinions that the desirable and undesirable consequences were closely balanced or that there was insufficient evidence to make a determination. The majority opinion was in favor of recommending that GSK candidate vaccine for adults ≥65 years of age, but was not in favor of a broader recommendation for adults ≥60 years of age. There was a substantial minority opinion not to recommend this product based on currently available evidence. These WG members were concerned about the balance of risks and benefits considering the single case of inflammatory neuropathy observed in a recipient of the investigational vaccine and the under-representation in the clinical trials of adults older than 80 who are at greatest risk of severe RSV illness. They felt that it is imperative to demonstrate efficacy in this age group prior to making a recommendation. Further, they felt that a post-implementation safety signal for inflammatory neuropathy, even if caught early, could undermine confidence in RSV vaccines and in vaccines more generally. Among WG members who did support a recommendation among adults ≥65 years of age, there also was a minority opinion to include a recommendation

for individual adults 60–64 years of age based on shared clinical decision-making intended to facilitate access to the vaccine among adults with medical conditions placing them at high risk of severe RSV disease.

To summarize the WG summary interpretation regarding the Pfizer candidate vaccine, for an age threshold of ≥65 years of age and one of ≥60 years of age, the WG felt that the desirable consequences of a vaccine recommendation probably outweigh the undesirable consequences in most settings. However, when considering a recommendation at age 60, there were substantial minority opinions that the desirable and undesirable consequences were closely balanced or that there was insufficient evidence to make a determination. The majority opinion was in favor of recommending the Pfizer candidate vaccine for adults ≥65 years of age but was not in favor of a broader recommendation for adults ≥60 years and older. However, as with the other candidate vaccine, there was a substantial minority opinion among WG members not to recommend this vaccine based on currently available evidence. Similar to the considerations for the other candidate vaccine, these WG members were concerned about the balance of risks and benefits considering the 2 observed cases of inflammatory neuropathy and the underrepresentation of the very oldest adults in the clinical trials. Among WG members who did support a recommendation among adults ≥65 years of age, there was a minority opinion to include a recommendation for adults 60–64 years of age based on shared clinical decision-making intended to facilitate access to the vaccine among adults with medical conditions that place them at high risk of severe RSV disease.

GSK Statement

Leonard Friedland, MD (GSK) thanked the members of the ACIP for giving GSK the opportunity to make a brief statement. He said that he and his GSK colleagues are proud to have developed the GSK RSV candidate vaccine for older adults being discussed by the ACIP. He focused his remarks on the policy consideration regarding whether adults 60–64 years of age should be included in routine RSV vaccine recommendations. RSV results in considerable clinical and economic burden among all adults ≥60 years of age, including adults 60–64 years of age. GSK's cost-effectiveness model, which uses burden of disease estimates that align to the current body of published scientific evidence, estimates that vaccinating adults 60–64 years of age would result in roughly 260,000 fewer symptomatic RSV cases in adults 60–64 years of age, including over 100,000 fewer output visits and around 7,400 fewer hospitalizations each year. The model found that GSK's RSV vaccine is cost-effective across a range of price points, indicating that the vaccine would be considered a good public health value for adults ≥60 years of age. In addition to reducing the burden of RSV, including adults 60–64 years of age in RSV vaccine recommendations would have health equity benefits. Studies have demonstrated that certain racial and ethnic minority groups are more likely to have underlying risk factors for severe RSV outcomes, are more likely to be diagnosed with risk factors for severe RSV at younger ages, and are more likely to have undiagnosed risk factors—particularly at younger ages before they are eligible for Medicare. Studies also have found that certain racial and ethnic minorities are more likely to have severe RSV-related outcomes, including a study being presented by the CDC at the ReSViNET Conference that demonstrates that a higher proportion of younger adults hospitalized for RSV were Black, Hispanic, or AI/AN. Excluding adults 60–64 years of age from age-based routine recommendations would be detrimental to the racial and ethnic groups who develop risk factors for severe RSV at younger ages. Additionally, shared clinical decision-making recommendations at any age would be detrimental to racial and ethnic groups who have undiagnosed risk factors. Age-based RSV vaccine recommendations for adults ≥60 years of age would ensure equitable access across all older adults. To spend a moment on GSK's candidate vaccine, the vaccine is highly efficacious in adults with one or

more underlying comorbidities of interest. Data on co-administration with high-dose influenza, adjuvanted influenza vaccines, and VE through 2 RSV seasons will become available in the second to third quarter of 2023. GSK appreciates all of the work that CDC and ACIP are doing to improve the lives of older adults and to improve health equity and looks forward to continuing collaborative discussions.

Pfizer Statement

Dr. Alejandro D. Cané (Pfizer) thanked the ACIP for the opportunity to provide Pfizer's comments, emphasizing that Pfizer was very proud to share its vaccine. The RSVpreF vaccine represents Pfizer's commitment to developing a targeted prevention measure to address an important amendment for RSV illness, which has been largely unrecognized and under diagnosed. Pfizer recognizes that there are many unanswered questions such as duration of protection, need for future revaccination, and underdiagnosis of RSV. As such, economic modeling is necessary based on uncertain inputs and assumptions. While vaccine price plays a role in the evaluation, it also is important to know that the burden of disease is a critical aspect to be considered. In fact, the University of Michigan/CDC model that was presented earlier in the day used a hospitalization incidence rate of 108 per 100,000 persons per year among adults ≥65. This is the main input difference in the vastly disparate cost-effectiveness results for the CDC model versus either the Pfizer or GSK models. Pfizer used a base-case incidence of 300 and 256 cases per 100 adults per year, respectively. That is fully aligned with recent CDC published data that reports on hospitalizations incidence rates among adults ≥65 years of age of 240 to 356 cases per 100 persons per year. Pfizer remains committed to developing vaccines as a public health strategy and has a goal of eliminating barriers to vaccine access and uptake. Pfizer looks forward to working with the CDC in the coming months to continue to collect data and inform this important question to further support policy discussion on RSV vaccine use in the adult population.

ACIP Discussion Points, Observations, Suggestions on Adult RSV Vaccines

Following Dr. Hutton's Presentation

- Regarding a question about scenarios in which such a vaccine would be cost-neutral or cost-saving, Dr. Hutton indicated that they did not find many scenarios in which the vaccine would be cost-saving. There would have to be a scenario in which several things were occurring simultaneously. Higher incidence or much lower vaccine cost could get closer to cost-savings. They did look at a scenario with a 3-year time horizon, assuming that the VE decays at an exponential rate and found that with higher incidence over a longer time period, potentially this scenario could be cost-saving.
- In terms of a question regarding standard cost-effectiveness thresholds per QALY gained, Dr. Hutton said there is not necessarily a clear threshold in the US. Anything less than $50,000 per QALY is typically seen as highly cost-effective in the US, but a lot of people would argue that there should be a willingness to spend $100,000 to $150,000 or more per QALY gained. There is not necessarily a right answer in the US, unlike in the UK where there are very specific thresholds.
- Dr. Ortega-Sanchez added that there have been many discussions about what constitutes a good threshold. For many years, $50,000 per QALY has been used, but that proved not to be substantiated by theoretical principles/concepts or data. It was then raised to $100,000 per QALY that was corrected to address inflation. Other thresholds have been suggested by international organizations, such as the WHO, which said it should be 3 times the GDP per capita. In the case of the US, that would be

approximately $180,000 per QALY at 3 times the $60,000 GDP per capita. That is only a suggestion and CDC usually does not adopt that kind of threshold.

Following Dr. Ortega-Sanchez's Presentation

- Regarding the models seeming to vary depending upon the RSV hospitalization rate and the hospitalization rates seeming to vary depending upon the study, Dr. Melgar acknowledged that surveillance for RSV disease has not been as robust as surveillance for influenza over the last 10 to 20 years, for example. In all 3 of the models by Dr. Ortega-Sanchez, the incidence of RSV hospitalization happens to be one of the most influential parameters that determines how cost-effective it would be to vaccinate against RSV in this age group. As Dr. Ortega-Sanchez showed, even within CDC-derived estimates of RSV epidemiology, there is a tremendous amount of uncertainty in the per population incidence of RSV hospitalization. That is reflected in the charts showing the sensitivity of the ICER by the model input of the number of RSV hospitalizations year-to-year. While CDC continues to work on its surveillance systems to update these estimates, the uncertainty interval continues to be very wide.
- It would be beneficial to know what proportion of the study population in the Phase 3 trials were 70 and older, 75 and older, and 80 and older. Dr. Melgar noted that he would discuss this further during the EtR framework presentation, but one of the key factors and considerations the WG discussed was the fact that adults ≥80 years of age were substantially under-represented in the clinical trials.

Following Dr. Melgar's Presentations

- Concern was expressed about GBS being observed in 1 out of 15,000 in the GSK open-label trial in 2 of the RSV recipients out of 26,000 in the Pfizer clinical trial, meaning that there is a possibility that this could be a side effect in 1 in 13,000 to 1 in 15,000. More information was requested about this and specifics about the cases. Dr. Melgar noted that the distinction may be somewhat subtle in terms of the trials in which these cases occurred. The GSK case occurred in a Phase 3 open-label trial. While this trial was randomized but did not include a placebo arm, which is why it was not included in the GRADE evaluation. The intent of that trial was to evaluate different revaccination schedules, which is where the randomization took place. There were 1,650 adults ≥60 years of age enrolled. Among them, around 4% reported at least 1 SAEs and 2 of those was a case of GBS that occurred 9 days after vaccination. That case was in a 78-year-old female in Japan. The level of certainty of the diagnosis of GBS was a Brighton Collaboration Level 3. It led to hospitalization lasting 179 days, and the patient recovered. This was the only case of inflammatory neuropathy that occurred in GSK's safety database that spans all of their clinical trials in which there were a total of approximately 15,000 RSV vaccine recipients. The Pfizer cases of GBS both occurred in the Pfizer pivotal Phase 3 trial in which there was a placebo arm. Both occurred in adults in their 60s, a male in the US and a female in Japan. The patient in the US initially suffered a Non-ST-Elevation Myocardial Infarction (NSTEMI) 7 days after vaccination with the investigational vaccine and developed new-onset weakness the next day. A nerve conduction study diagnosed Acute Inflammatory Demyelinating Polyneuropathy (AIDP) in the lower extremities. This was diagnosed as Brighton Collaboration Level 1 as GBS. The other case was diagnosed retrospectively as the Miller Fisher syndrome (MFS) variant. The onset was 11 days after vaccination with the RSVpreF vaccination and certainty was Brighton Collaboration Level 4. This was the level of detail that was provided by the manufacturers. Summed across all of Pfizer's clinical trials, there were approximately 26,000 RSVpreF vaccine recipients and a total of 2 cases of inflammatory neuropathy. While the summary of 1 in 13,000 to 15,000 is correct for both

investigational vaccines, it is important to realize that 1 or 2 is very sparse to actually calculate a rate, which is why this was not done.
- Data are needed on: prevention of hospitalization for RSV, coadministration with other vaccines (especially COVID and influenza), VE and safety in nursing home patients where morbidity and mortality are highest from RSV disease, VE and safety in adults ≥75 years of age who have the highest morbidity and mortality behind those in nursing homes, longer-term outcomes, and GBS and other inflammatory neuropathies that result from infection with RSV (particularly because natural baseline incidence of inflammatory neuropathy increases with age).
- In the cost-effectiveness modeling, it would be helpful to see explicit incorporation of hospitalization for outcomes other than RSV and costs associated with post-discharge, as well as modeling with the actual cost of the vaccine.
- Clarification is needed about whether this vaccine would be covered under Medicare Part D. It is possible for physicians to implement Medicare Part D vaccines and be reimbursed, but it is difficult. CMS has made some changes that has made this easier in 2023.
- There is concern about risk-based vaccination because many patients will not perceive themselves as being at risk. Shared clinical decision-making would make implementation more complicated for physicians, which may result in missed opportunities to vaccinate at-risk patients who do not see themselves as being at risk.
- The survey conducted among physicians was done in 2017, but physicians may be more knowledgeable now about RSV.
- Equity could be better addressed.
- A recurring theme about this and all adult vaccines is that a VFA program like the VFC is needed.

CHIKUNGUNYA VACCINE

Introduction

Beth Bell, MD, MPH (Chair, ACIP Chikungunya Vaccines WG) introduced the chikungunya vaccine session. By way of background, the FDA recently accepted Valneva's BLA application for their chikungunya vaccine and granted priority review with licensure possible as early as August 2023. No Chikungunya vaccine has ever been licensed in the US or globally, and there are no existing ACIP chikungunya vaccine recommendations. To address this, the Chikungunya Vaccine WG was formed in May 2022 to develop policy options for ACIP's consideration for use of chikungunya vaccine among US persons at risk of chikungunya, including travelers; residents of US territories and states with, or at risk of, transmission; and laboratory workers.

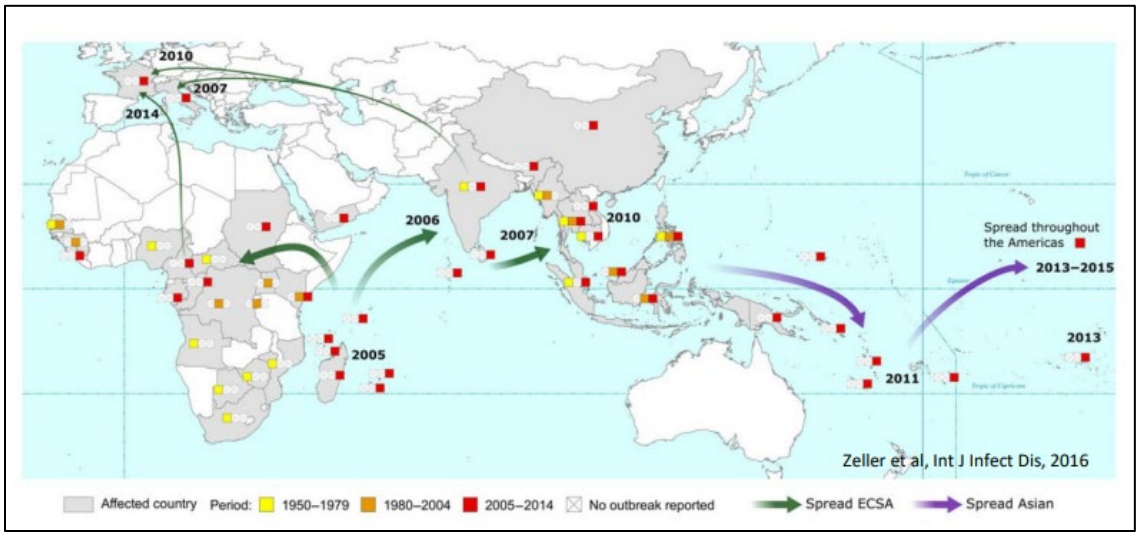
The Terms of Reference (TOR) for the Chikungunya Vaccines WG are to: 1) review information on chikungunya disease, including outcomes; 2) review data on chikungunya epidemiology and burden among US residents, including travelers and persons living in areas at risk for local transmission; 3) review data on safety, immunogenicity, and effectiveness of chikungunya vaccines; 4) provide evidence-based recommendation options for ACIP; 5) identify areas in need of further research for informing potential future vaccine recommendations; and 6) publish a chikungunya vaccine *MMWR Recommendations and Reports* document.

As a reminder, previous WG presentations to ACIP on this topic provided during the October 2022 meeting included an overview of chikungunya virus disease and vaccines and a discussion about the immunogenicity and safety of Valneva's chikungunya vaccine. Building upon that, presentations during this session focused on the global epidemiology of chikungunya, chikungunya in US travelers, persistent arthralgia following chikungunya, and WG considerations.

Global Epidemiology of Chikungunya

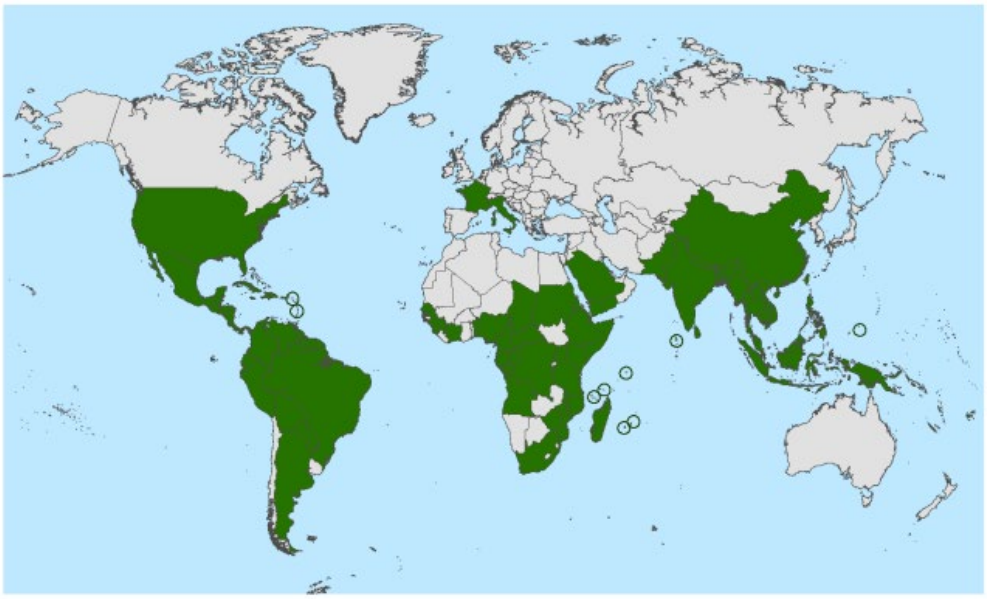
Susan Hills, MBBS, MTH (CDC/NCEZID) presented some information on chikungunya virus transmission to provide some background on the overall global patterns and the risk of the disease. As a reminder, chikungunya is a mosquito-borne disease with the virus primarily transmitted in an ongoing cycle between humans and mosquitos. The main mosquitos involved are *Aedes* aegypti and *Aedes albopictus*, which are the same mosquitos that transmit some other arboviruses such as dengue virus (DENV) and Zika virus (ZIKV). Chikungunya disease is clinically characterized by the acute onset of fever and often severe polyarthralgia. Groups at risk for more severe disease include adults ≥ 65 years of age, people with underlying medical conditions (e.g., hypertension, diabetes, and heart disease), and neonates infected through intrapartum transmission.

This map is useful to illustrate the dramatic spread of chikungunya virus that began in 2004 and lasted for about 12 years:



After chikungunya virus was first detected in Tanzania in the 1950s, for about 5 decades it caused sporadic cases and occasional outbreaks in parts of Africa and Asia. In 2004, the epidemiology changed dramatically, beginning with a large outbreak in Kenya followed by rapid spread of the virus to Indian Ocean islands and beyond, causing numerous outbreaks as it expanded across the globe. Ultimately in late 2013, the virus was introduced into the region of the Americas, initially spreading throughout the Caribbean and then broadly throughout South and Central America. Because the populations in the Americas were largely immunologically naïve to chikungunya virus (CHIKV), there was a very large outbreak. More than 2.4 million suspected or confirmed cases were reported during the outbreak period. Subsequently, the outbreak subsided.

During the last 6 years, while there has been some variability in case numbers reported from year-to-year, typically fewer than about 200,000 cases have been reported annually from the Americas. This map[77] shows all countries and territories with past or current transmission of Chikungunya virus:



Transmission is known to have occurred in the past, albeit occurring currently in over 110 countries worldwide. This map is readily available and is often referenced, but it is sometimes misinterpreted because it just shows countries and territories that have ever had chikungunya virus transmission, but these locations did not necessarily have any current transmission. In fact, understanding the current patterns of chikungunya virus transmission can be challenging. There are some sources of data such as Ministry of Health websites, WHO websites, and data on traveler cases that are collected by national authorities or published in journal articles. However, the available information on chikungunya virus transmission is usually incomplete and typically not available in a timely manner.

When considering the current patterns of chikungunya virus transmission, there are some general overall features of note. The disease occurs in tropical and subtropical regions with very rare outbreaks reported in temperate areas. It is often seen in the same locations where similar *Aedes* mosquito-borne diseases are found such as dengue and Zika. Transmission can be impacted by several factors, including weather, environmental conditions, pre-existing population immunity, population density, and the type of *Aedes* vectors present.

Patterns of chikungunya virus transmission vary in different locations. In Africa, Asia, and Central and South America, the general pattern is ongoing 1-level transmission with periodic outbreak activity. This reflects a cycle where immunologically susceptible individuals continue to acquire infection and propagate human-mosquito-human transmission cycles. Outbreaks are unpredictable in terms of timing and size. Typically, after high incidence outbreaks, low-level transmission continues for many years. Complete cessation of transmission after outbreaks is common in island nations because they are geographically isolated and often have small populations that develop herd immunity during outbreaks. It is more feasible for interruption of

[77] https://www.cdc.gov/chikungunya/geo/index.html

transmission to occur compared with large countries with contiguous borders. Currently, there is no evidence of chikungunya virus transmission in most Pacific Island and Caribbean countries and territories. Nonetheless, there is ongoing potential for reintroduction of virus in island settings without transmission. The risk increases over time as population immunity wanes. Once there is low population immunity, the possibility of reemergence and then an explosive outbreak is high.

Periodic outbreaks are a key feature of chikungunya virus transmission. In terms of location, outbreaks are more likely in regions with no or mild outbreaks in the recent past. However, this is unlikely to accurately predict the location of any future outbreaks as other factors also contribute. Sometimes outbreaks are localized and sometimes they are widespread. Once an outbreak begins, it can increase rapidly in size. About 30% to 60% of the susceptible population can be infected within a few months. Huge outbreaks like those that occurred in the immunologically naïve population in the Americas from 2014–2016 are unlikely in future. However, there is likely to be continued reporting of large outbreaks on an ongoing basis. For example, there is currently an ongoing outbreak in Paraguay with over 50,000 suspect cases. In regard to the timing of outbreaks, most occur during the rainy season and abate during the dry season, but outbreaks can occur in the dry season. In terms of duration, the period of intense transmission is typically short, often only about 3 to 6 months.

The interval between outbreaks is unpredictable and variable. There can be 20 years or more between outbreaks in any particular location. Various factors likely impact the interval between outbreaks, including pre-existing population immunity, build-up of non-immune population over time, environmental conditions, and other factors. Some countries regularly report outbreaks, but these are typically in different locations of the country.

In summary, the key points of the global epidemiology of chikungunya are that the disease mainly occurs in tropical and subtropical areas. Currently, most countries with chikungunya virus activity have low-level ongoing transmission. However, chikungunya is an outbreak-prone disease. The impact of outbreaks when they occur is important because they often can result in intense transmission. In general, the duration of any outbreak is short.

Chikungunya in US Travelers

Nicole Lindsey, MS (CDC/NCEZID) noted that as mentioned earlier, the WG will be considering recommendation options for chikungunya vaccine use among various groups. The first group the WG will be considering is travelers to areas at risk. Therefore, she summarized the data on chikungunya in US travelers based on data from national surveillance for US travelers, including confirmed and probable cases in residents of US states reported to CDC. All of these cases have laboratory evidence of infection based on either molecular or serologic testing. Cases reported from US territories and associated states were excluded due to difficulties in differentiating travel-associated and locally-acquired cases. Prior to 2006, chikungunya was very rarely reported in US travelers, so the data included here are for cases reported for 2006–2021. Overall, 4,590 traveler cases were reported during this timeframe. Because chikungunya was not a notifiable disease until 2015, we expect that reporting may have been more incomplete during the earlier years.

From 2006–2013, cases were rare with an average of 7 cases reported annually. All of these cases reported travel to areas in Asia, Africa, or the Indian Ocean that were known to have chikungunya activity. There was a large increase in reported cases concurrent with explosive outbreaks in the Americas, with more than 3,700 cases reported in 2014 and 2015 together. Annual numbers of cases have declined steadily since the Americas abated. Overall, 35% of reported cases were male and 65% were female. This predominance of female cases was consistent by year and by age group. A predominance of female cases has been reported in the literature fairly consistently. Some authors have hypothesized that the difference could be due to greater healthcare-seeking behaviors among women, as most seroprevalence studies have not shown a significant difference in infection rates by sex. The majority of cases occurred in persons 40–59 years of age. There were relatively few cases in the very young and older age groups. This age distribution is likely reflective of the age of the traveler population, given that infection rates are not expected to different by age. The age distribution was consistent over time.

Although cases occurred in all months of the year, 61% occurred during June through September. This likely reflects popular times of travel as well as the timing of seasonal outbreaks and locations of travel. Because 2014 accounted for such a high proportion of the total cases, the WG wanted to see if there was any difference in seasonality for that year compared to other years. When the 2014 cases are removed, there is still a peak in the summer months, but the curve is flatter. There is more of a discernable peak in January.

In terms of clinical outcomes, about 18% were hospitalized. In the literature, the reported frequency of hospitalization of chikungunya-infected patients ranges from about 0.5% to 11% and may be affected by access to medical care, local clinical practices, reporting and testing practices, and frequency of comorbidities and coinfections in the population. The hospitalization rate among cases reported to CDC is high and is likely artificially inflated due to biases of identification and reporting of more severe disease cases in travelers. There were 4 reported deaths. While causes of death were not available, these deaths were among older adults with a mean age of 77 years. No deaths occurred during the acute illness. The mean time from illness onset to death was about 2 months. Hospitalization rates were highest among young children and adults ≥60 years of age. Infants were most likely to be hospitalized. Of the 17 cases reported, 7 were in children under 2 years of age who were hospitalized.

More than half of the cases (~54%), were reported to have been infected in locations in the Caribbean. More than 80% were reported to have acquired infection in one of the Americas regions. Because this was heavily influenced by the 2014-2015 outbreak in the Americas, the WG looked at region of infection just in the past 5 years. Among the 532 cases reported during that time, 60% were infected in locations in Asia. About 27% were infected in 1 of the 4 Americas regions, and about 8% were infected in Africa. The 10 most common countries or territories of infection for cases reported since 2006 were in the Americas with the exception of India, which accounted for approximately 9% of cases overall. By far the highest number of cases, over 1,000, originated from the Dominican Republic. Looking at trends in more recent years without the influence of the Americas outbreaks, the most common location of infection in the last 5 years was India, which accounted for about 37% of cases. Most cases originated from Asian countries, although a fair number are still being identified related to travel in the Americas locations.

There are several limitations of national surveillance data. Reported cases are likely an underestimate of the true incidence of disease among US travelers. More severe cases are more likely to be identified and reported, leading to an inflated proportion of severe outcomes such as hospitalization and death. The data provided through national surveillance are often incomplete, particularly for travel history. There is no information available on duration of travel or activities during travel that might be associated with an increased risk of infection. Additionally, there is no information on the duration of specific symptoms or long-term sequelae.

In summary, outside of the time of the unprecedented outbreaks in the Americas, relatively few chikungunya disease cases in US travelers are reported annually. Reported cases likely underestimate the true incidence of disease and overestimate the proportions of severe outcomes. Very young children and older adults have the highest hospitalization rates. Cases have occurred among travelers to all regions with chikungunya risk and can occur year-round, with case numbers reflecting levels of chikungunya virus activity in and numbers of travelers to destinations with risk.

Persistent Arthralgia Following Chikungunya

Nicole Lindsey, MS (CDC/NCEZID) next discussed chronic arthralgia, an important sequela of chikungunya infection. It often is reported that the acute symptoms of chikungunya typically resolve in 7 to 10 days and that mortality is rare. However, a significant proportion of patients have continued to recurrent arthralgia in the months and years following their acute illness. Other long-term complications have been reported less frequently (e.g., fatigue, depression, alopecia, impaired memory, sleep disorders, and lowered quality of life). Although other sequela have been reported, chronic arthralgia is clearly the most significant of these. Therefore, understanding disease burden in relation to this outcome is very important in understanding the potential benefits of vaccination.

Multiple studies that have been published reported on chronic joint symptoms following chikungunya infection. There is variability in these studies in terms of methodology, symptoms assessed, definitions and ascertainment of symptoms, self-report versus assessment by a clinician, duration of follow-up, and characteristics of the cohort of patients. Meta-analyses have been published, but these also varied in the specific outcomes analyzed and the criteria used to evaluate studies for inclusion. After reviewing the published meta-analyses, the WG determined that none used the outcome and inclusion criteria that would be most useful in guiding the vaccination recommendation process and therefore decided to perform its own review and meta-analysis.

The primary objective of the WG's review and analysis was to estimate the percentage of patients with chronic arthralgia defined as ≥3 months following chikungunya infection. A literature search was conducted in Medline for articles describing primary data on arthralgia following chikungunya infection published from January 1, 2000─October 24, 2022. Articles were excluded if the investigators did not confirm all chikungunya infections by serologic or molecular testing. Studies where only a clinical diagnosis was made were not included. Studies also were excluded in which cases were from specific subgroups that might affect disease severity or duration or duration of symptoms (e.g., children, people with coinfections, abnormally large proportion of cases hospitalized for acute disease). Non-English language articles also were excluded. These accounted for less than 5% of all articles identified in the original search.

The original search identified 1,167 publications and all titles and abstracts were reviewed. Of those, only 80 required a full text review to determine whether they met the WG's criteria. Of those, 27 met the inclusion criteria and a data extraction was completed using a standardized spreadsheet tool. The 27 included articles accounted for a total of 4,079 chikungunya infected persons. Most of the studies were clustered in 1 of 2 time periods, 2005–2006 during the outbreaks in the Indian Ocean and 2014–2015 during the initial outbreaks in the Americas. Overall, 23 studies were conducted among local populations during outbreaks. Of these, 4 studies were among travelers to outbreak locations, 14 included patients infected in countries in the Americas, 8 were in countries in the Indian Ocean, 4 were in Asia, and 1 was in Europe. Only 4 of the 27 studies included a control group of non-infected persons. There was a range of severity of illness among populations included in the studies (0%–33% hospitalized) and varied demographics of included participants.

There were more than 27 datapoints because some studies reported estimates from multiple timepoints. The WG chose 3 timepoints to generate summary estimates at 3, 6, and 12 months. There were 7 studies that evaluated arthralgia at 3 months after acute infection, accounting for 733 patients. All studies included patients who sought healthcare for their acute symptoms. There were 2 studies among travelers, 1 among travelers to locations in the Indian Ocean and 1 with travelers to locations in the Americas. There were 5 cohorts from communities with outbreaks in Brazil, French Guinea, Martinique, St. Maarten, and Thailand. In all studies, there was a predominance of females. The studies included patients of varying ages. The mean or median ages ranged from a low of 35 years to a high of 51 years. There also was a range of disease severity from no hospitalizations to 17%. Among the 7 studies, the reported proportion of patients with chronic arthralgia at 3 months ranged from 42% to 86%. The summary estimate for this timepoint was 51%, with a 95% confidence interval from 44% to 58%.

There were 9 studies that evaluated arthralgia at 6 months, accounting for 961 patients. All studies included patients who sought healthcare for their acute symptoms. There were 3 studies among travelers, all among Indian Ocean travelers, and 6 in communities with outbreaks in Bangladesh, French Guinea, Martinique, Mexico, Suriname, and Thailand. Again, there was a predominance of females in a range of ages. The mean ages ranged from a low of 32 years to a high of 60. Hospitalization rates ranged from 0% to 33%. The reported proportion of patients with chronic arthralgia at 6 months ranged quite widely from 13% to 70%. The summary estimate for this timepoint was 35%, with a confidence interval from 24% to 47%.

There were 10 studies that evaluated arthralgia at 12 months, accounting for 1,539 patients. Of these studies, 9 included patients who sought healthcare for acute symptoms and 1 was a population-sample obtained from persons testing positive during a serosurvey who were asked about symptoms at the time of the blood draw. All studies were conducted in communities with outbreaks occurring, including Aruba, Bangladesh, Brazil, Grenada, Italy, Malaysia, Martinique, Reunion Island, and the US Virgin Islands). Again, there was a predominance of females and a range of ages and hospitalization rates. The reported proportion of patients with chronic arthralgia at 12 months also ranged widely from a low of the 19% to a high of 61%. The summary estimate for this timepoint was 38%, a 95% confidence interval from 29% to 46%. Among the 9 studies that assessed arthralgia at multiple timepoints, in general there was a decrease in the proportion over time.

As noted earlier, the first task of the WG is to develop recommendations for travelers. This table presents results of the 4 studies that were among travelers specifically:

Reference	Location, Year	N	Population description	3m	6m	24m
Simon 2007	Indian Ocean, 2005-2006	47	French travelers treated at Lavaren Hospital in Marseilles	86%	48%	
Larrieu 2010	Indian Ocean, 2005-2006	29	French travelers treated at University Hospital in Bordeaux			59%
Taubitz 2007	Indian Ocean, 2006	16	German travelers treated at Institute of Trop Med in Hamburg		13%	
Bocanegra 2016	Americas, 2014-2015	34	Spanish travelers who presented to public health	50%		

These 4 studies had relatively small sample sizes. Due to the methods of patient identification, they tended to include more older person and skew toward those with more severe acute disease. The Simon study included 47 French travelers who acquired illness in locations in the Indian Ocean. A very high percentage, 85%, reported arthralgia at 3 months and 48% had arthralgia at 6 months. Another study of French travelers identify from a different facility reported almost 60% with arthralgia at 2 years. Notably different results were reported by a small study of 16 German travelers from the same general outbreak location and time period. Only 13% of cases had arthralgia at 6 months. There was 1 study of Spanish travelers from the outbreak in the Americas. In that group, 50% reported arthralgia at 3 months.

To highlight some limitations of this work, there is substantial variability among the studies the WG included in terms of case definitions, populations included, and the findings. Almost all of the studies that have been completed are among persons who sought healthcare for their disease symptoms and are not representative of all infected persons. There are only a few studies that included a control group to account for background rates of arthralgia in the population. For the meta-analysis, the crude estimates were used from all studies to calculate the summary estimates.

To summarize the 4 studies that did include a control group of uninfected persons, the first 2 were conducted following the Reunion Island outbreak. The Soumahoro 2009 study (Reunion 2005-2006) included 199 cases and 199 controls. At 17 months after onset, the chikungunya cases reported significantly more joint pain than was reported in the control group at 53% compared to 28%. It was estimated that 47% of pain in the cases was attributed to chikungunya infection. The Gerardin 2011 (Reunion 2005-2006) study was larger, with 512 cases and 582 controls. At 16 months, cases were more likely to report musculoskeletal pain than controls at 43% compared to 17%. It was estimated that 60% of pain in the cases was attributed to chikungunya infection.

The 2 studies with controls were conducted following the outbreak in the US Virgin Islands. The Feldstein 2017 (USVI 2014-2015) study included 165 cases and 167 controls. At 6 months, the difference in arthralgia between case patients and controls was 32% after adjusting for age, sex, and history of arthritis. At 12 months, the adjusted difference was 19%. The Hennessey 2018 (USVI 2014-2015) study included 171 cases and 338 controls. At 12 months, 31% of case

patients and 26% of controls reported joint pain. The study estimated that only 23% of joint pain in the case patients was attributed to chikungunya infection.

To review the key points, this meta-analysis that included patients who almost universally sought healthcare during their acute infection showed that a substantial proportion had chronic arthralgia following infection. There was variability among studies at all timepoints, but it is estimated that about half of patients have arthralgia at 3 months after illness onset. The proportion with arthralgia decreased over time, and just over a third were estimated to have arthralgia after a year. It is very important to understand that these proportions of persons with chronic arthralgia are likely over-estimates when the broader population is considered. First, they reflect almost exclusively the healthcare-seeking population who are likely to have more severe disease compared to those who do not seek healthcare. Among the population as a whole, rates almost certainly would be lower. Second, the rates do not account for underlying rates of arthralgia in the population. The small number of studies that did include a control group provided variable results, but overall suggested when this background rate of arthralgia was taken into consideration, 20% to 60% of reported arthralgia after chikungunya might be attributable to the prior chikungunya virus infection.

In summary, it is difficult to provide a precise estimate of incidence of long-term joint pain after chikungunya. In addition, the percentages of patients with long-term joint pain are likely variable based on several factors, including the severity of acute illness and patient age, sex, and comorbid conditions, particularly pre-existing joint conditions. However, long-term joint pain after infection is an important complication of chikungunya that could be prevented by vaccination.

Workgroup Considerations

Nicole Lindsey, MS (CDC/NCEZID) concluded the session by briefly reviewing the WG plans and timelines. As Dr. Bell mentioned earlier, FDA recently accepted Valneva's BLA for chikungunya vaccine and granted priority review. Therefore, licensure is possible as early as August 2023. The WG is initially focusing on developing recommendations for ACIP's consideration for travelers and laboratory workers and plans to present the EtR Framework during the October 2023 ACIP meeting. A vote on these recommendations would follow at the February 2024 meeting. The WG then plans to continue its discussions to consider recommendations for adults living in US territories and states at risk for outbreaks. During the next few months, the WG plans to comprehensively review the vaccine immunogenicity and safety data as a part of the GRADE assessment. The WG anticipates making further presentations to ACIP on topics relevant to consideration of vaccine use in territories and US states with risk of transmission in the future. Additionally, the WG anticipates that over time there will be additional data on the use of Valneva's vaccine among younger age groups. Additional chikungunya vaccines may be submitted for licensure in the US, and those data will be presented to the ACIP as they become available.

ACIP Discussion Points, Observations, Suggestions on Chikungunya Vaccines

Following Dr. Hill's Presentation

- Regarding an inquiry about whether there are any data on acquisition of chikungunya infection among residents of the US who have not left the country, Dr. Hills indicated that there has been limited evidence of transmission in the US in just 2 states, Florida and Texas in 2014. There were 12 cases of local transmission in Florida and there was 1 case of local transmission in Texas. There was a large outbreak of chikungunya in Puerto Rico that began in 2014. The last clear evidence of transmission in Puerto Rico

was in mid-2017. One of the questions that the WG is going to consider is the use of chikungunya vaccine in US territories and affiliated states with risk of transmission and in states in the US with evidence of transmission. The first questions the WG plans to tackle relate to US travelers and laboratory workers. The WG does plan to present some additional data in the future in relation to US states and territories.

Following Dr. Lindsey's Presentation (Travelers)

- No questions or comments.

Following Dr. Lindsey's Presentation (Arthralgia)

- No questions or comments.

Following Dr. Lindsey's Presentation (WG Considerations)

- Regarding an inquiry about whether there will be any consideration of pregnant and lactating women, Ms. Lindsey indicated that pregnancy will be a contraindication since this is a live-attenuated vaccine. Discussions have not yet started in the WG, but various factors will be considered over the next couple of months. The WG would be happy to discuss lactating women in the future.
- Regarding how confident the WG is that climate change will impact the dynamics of the epidemiology in the coming years, Ms. Lindsey indicated that the WG is struggling with the availability of surveillance data. While some Ministry of Health websites post data, they are often not complete or timely. There are various sources of data such as WHO and traveler data, but overall the data tend to be incomplete and not timely. The WG will discuss a variety of issues in depth over the next couple of months, including considerations about how to make recommendations in the context of limited and potentially untimely data.

DENGUE VACCINE

Introduction

Wilbur Chen, MD, MSc (ACIP Member and WG Chair) emphasized that DENV infections are so extensive, they put approximately half of the global population at risk. There are 4 genetically distinct DENV serotypes: DENV-1, 2, 3, 4. Infection with 1 serotype provides life-long type-specific immunity, but only short-term cross-protection of approximately 1 to 2 years against the other 3 serotypes. Importantly, it is with the second dengue infection that there is increased risk of severe dengue illness. This is due to a phenomenon called antibody-dependent enhancement (ADE).

ACIP already discussed and voted on Dengvaxia™. Clinical trials found different outcomes with Dengvaxia™ vaccination among children with and without previous dengue infection. Children without previous dengue infection had a higher risk of hospitalization and severe dengue if they were vaccinated and subsequently had a natural DENV infection, which basically mimics the second dengue infection. Children with previous dengue infection were protected from hospitalization and severe dengue when they were vaccinated with Dengvaxia™.

Dengvaxia™ was recommended by the ACIP during the June 2021 meeting. Three doses of Dengvaxia™ are indicated for the prevention of dengue disease caused by serotypes 1, 2, 3, and 4 in children 9–16 years of age with the provisions that they should have laboratory confirmation of prior dengue virus infection and be living in endemic areas.

Since the June 2021 ACIP meeting, the WG took a hiatus and then reconvened in August 2022 when the WG restarted its meetings to discuss the Takeda product, TAK003, the focus of this session in terms of efficacy, immunogenicity, and safety from Takeda and the WG's interpretation. During the June 2023 ACIP meeting, the WG plans to present the GRADE and cost-effectiveness analysis. During the October 2023 ACIP meeting, the WG plans to present the EtR framework and draft recommendations and hopes to have a vote ready for the ACIP at that time. The WG will continue to review efficacy, immunogenicity, and safety data through the GRADE process; review the EtR domains and cost-effectiveness analysis; and develop policy options to present for an ACIP vote.

This session included presentations on the efficacy, safety, and immunogenicity of TAK-003; and the WG's summary and interpretation of the TAK-003 efficacy, safety, and immunogenicity data.

Takeda Dengue Vaccine (TAK-003) Safety and Efficacy

Shibadas Biswal, MD (Takeda Vaccines) noted that TAK-003 is an investigational compound that has not been approved by the US FDA for use in the US. Currently, this vaccine is approved for use in UK, Europe, and Indonesia for use regardless of prior dengue exposure status. That is, it can be used in both dengue-naïve and pre-exposed individuals. Takeda is seeking an indication for this vaccine in the US for prevention of dengue in individuals 4–60 years of age regardless of prior dengue exposure. This presentation focused on the construct of the vaccine, its immune response profile, the clinical development process, efficacy profile from the pivotal efficacy trial, safety profile from an integrated analysis of placebo-controlled trials, and immunogenicity data from the pivotal efficacy trial.

To describe the construct of this vaccine, TAK-003 is a live, attenuated tetravalent vaccine constructed using DENV-2 as the backbone. A dengue-based vaccine was expected to have a better chance of protection against the disease. The serotype 2 component has a TDV-2 attenuated structure. In constructing the other 3 components, the pre-membrane and envelope protein genes from DENV-2 are replaced with those from the other 3 serotypes, DENV-1, 3, and 4. That leads to 4 virus components corresponding to each of the 4 Dengue serotypes. The primary mechanism of action is to replicate locally and induce immune response against all 4 serotypes. This includes humoral-mediated immunity, cell-mediated, and innate immunity. For Dengue, an immune correlate of protection has not been established. The broad spectrum of immune responses are likely to contribute to protection against infection, virus clearance, and prevention of severe disease.[78]

Turning to an overview of the clinical development of this vaccine, the vaccine has been evaluated in 19 completed or ongoing clinical trials in 13 dengue-endemic and non-endemic countries. Over 28,000 children and adults 1.5–60 years of age participated in Phase 1–3 clinical studies. Clinical development included both baseline seronegative and seropositive participants. Approximately 20,000 participants received at least 1 dose of TAK-003 in clinical development programs.

[78] Biswal S, et al. Lancet 2020;395:1423–1433; Tricou V, et al. Lancet 2020;395:1434–1443; Sharma M, et al. J Infect Dis 2020;221:867–877; Michlmayr D, et al. J Infect Dis 2021;233:247–257; Tricou V, et al. Vaccine 2022;40:1143–1151

The pivotal efficacy trial was a randomized double-blind placebo-controlled trial that was designed in accordance with WHO guidelines and was conducted in 8 dengue-endemic countries. The trial included more than 20,000 participants 4—16 years of age. This age range was selected to ensure inclusion of both seronegative and seropositive individuals. Also importantly, dengue incidences tend to be higher in this age group in endemic areas. Participants received either TAK-003 or placebo by subcutaneous injection into the upper arm. Two-thirds received vaccine and one-third received placebo in a 2:1 randomization ratio. Baseline samples were collected from all participants to assess baseline serostatus. Active surveillance with weekly contact was in place throughout the study to detect all symptomatic dengue cases. Dengue cases were confirmed through RT-PCR. After 2 doses 3 months apart, the trial had a follow-up period of approximately 4.5 years. Toward the end of this follow-up period, a booster dose was administered to a subset of participants and is currently ongoing. In this presentation, Dr. Biswal described only data from the pre-booster part of the trial.

Overall demographics were similar between placebo and vaccine groups. Nearly 28% were dengue seronegative at baseline. The mean age at enrollment was 9.6 years. Slightly more participants were enrolled in Latin America than in Asia. The trial was conducted in a wide geographic area to maximize chances of detecting all 4 dengue serotypes. At the Asian site, all 4 serotypes were reported with DENV-2 being the most common. At the Latin American sites, the serotypes were mostly DENV-1 and DENV-2, with DENV-1 being the most common. DENV-4 was generally infrequently reported in the trial, which is also in line with known dengue epidemiology.

In terms the key efficacy data starting with the primary and secondary efficacy endpoints, the trial metrics primary endpoint demonstrated 80% efficacy in the symptomatic dengue at the end of the past 12 months after vaccination. It also met the key secondary endpoint demonstrating efficacy against dengue leading to hospitalization at the end of 18 months after vaccination. The trial met all additional secondary efficacy endpoints for which there were sufficient cases to evaluate. This includes efficacy in baseline seropositive and baseline seronegative participants, efficacy by each serotype, Dengue Case Adjudication Committee (DCAC)-defined virologically confirmed dengue (VCD). Two endpoints were not met due to low numbers of cases. Those were efficacy against DENV-4 serotype and efficacy against severe VCD.

Looking at the exploratory analysis beginning with the long-term VE by baseline dengue serostatus, TAK-003 continued to reduce incidence of dengue fever during the 57 months of surveillance. TAK-003 was efficacious soon after the first dose with early separation of placebo on maximum curves and it remained efficacious through the whole 57 months in both seronegative and seropositive participants. The cumulative efficacy during this time from the first dose was 61% overall, 54% in seronegative participants, and 64% in seropositive participants. Looking at the similar curves for dengue hospitalizations, TAK-003 also reduced hospitalizations over 57 months. The cumulative efficacy during this timeframe was 84% overall, 79% in seronegative participants, and 86% in seropositive participants. Overall, the vaccine demonstrated protection against symptomatic dengue and those leading to hospitalization, irrespective of prior exposure to dengue over 57 months of follow-up.

Turning to further exploratory analysis looking at the profile of the vaccine stratified by baseline serostatus at each serotype level for all symptomatic cases, efficacy was clear for 6 out of 8 of the subgroups in this analysis. In seropositive participants, efficacy was seen against all 4 serotypes. In seronegative participants, efficacy was shown against DENV-1 and DENV-2. The data for DENV-3 in seronegative participants suggested a lack of efficacy with a marginally negative point estimate. For DENV-4. there are too few cases in seronegative participants to

assess the efficacy profile. Looking at similar data for hospitalized cases, the first thing notable is that the efficacy was consistently higher against hospitalizations than it was against any dengue. Again, the efficacy profile was clear for the 4 serotypes in seropositives and for DENV-1 and DENV-2 in seronegatives. Looking specifically at DENV-4 in seronegatives, the only case of hospitalization was in a placebo recipient. For DENV-3 hospitalizations in seronegatives, the case counts were small so VE was inconclusive, but the point estimate was negative.

Looking deeper into data in a country-by-country analysis, it is important to know that the surveillance methodology was the same across sites and clinical management of febrile illnesses was according to local standards of care. In other words, rates for hospitalizations were not defined in the drug protocol and trial centers were able to hospitalize according to local standards. As a result, there were considerable barriers in hospitalization rates looking specifically at the placebo group. Cases were proactively hospitalized based on local dengue testing regardless of clinical condition. In all countries other than Sri Lanka, hospitalization was due to clinical need. As a result, 68% of cases in Sri Lanka were hospitalized compared to an average of 16% across all other countries.

In terms of the sensitivity analysis, excluding the data from Sri Lanka, seropositive participants had high efficacy against hospitalized dengue across all 4 serotypes. That is not affected by hospitalization practices in Sri Lanka. In seronegative participants, DENV-1, 2, and 4 results also were not impacted by hospitalization practices in Sri Lanka. Only DENV-3 was the exception, and therefore requires further interpretation. There were numerically more hospitalized cases in the vaccine group compared to placebo group, although case counts were small. Excluding the Sri Lanka data, the case counts were proportionate and there was no difference between the 2 groups. These data must be considered in the context of a number of factors. While detections were the same across all sides, the hospitalization approach was unique in Sri Lanka. More than 85% of all DENV-3 cases in seronegative participants appeared outside Sri Lanka, but there was no evidence of increased hospitalization. DENV-3 cases in seronegative participants in Sri Lanka were reported from one site during Year 3. In summary, there is little evidence that vaccination increases the risk of hospitalization in seronegative recipients infected by DENV-3. This will be further monitored and studied in the post-marketing setting.

Now to review safety data from an integrated analysis of placebo-controlled trials. Solicited reactions occurred more frequently in the vaccine group than the placebo group. Unsolicited AE had similar incidence in both the vaccine and placebo groups. The most frequent vaccine-related unsolicited AE were injection site pruritus, bruising, and pyrexia. In an integrated analysis of SAEs in the placebo-controlled trials, the rates of SAEs were 8% in the vaccine group and 9.6% in the placebo group. None of the deaths reported were related to the investigational vaccine. There were also no deaths caused by dengue in the development program.

In terms of immunogenicity, the primary immunological endpoint of all studies in the program was based on neutralizing antibodies. In the pivotal efficacy trial, TIDES, seropositivity rates in seronegative participants were used to measure the proportion of responders to the vaccine. The vaccine was found to be immunogenic against each of DENV-1, 2,3, and 4 serotypes. This was based on achieving the lowest detectable level of antibody response. To clarify, this is not synonymous with correlate of protection. Seropositivity rates after 1 dose of TAK-003 were greater than 90% for each serotype, with 85% of vaccines having a tetravalent response. After the second dose, nearly 100% of the participants had a tetravalent response among those who were seronegative. Regarding the GMTs of antibody response over time, titers increased after

the first dose for all serotypes, with highest levels against DENV-2. Titers against Dengue-1, 3, and 4 were similar. Persistence of antibody titers were seen out to 51 months after the first vaccination in the seronegative participants.

To summarize, TAK-003 has been evaluated in 19 clinical course trials in 13 countries. Data from the pivotal trial showed long-term efficacy in both baseline seronegative and seropositive participants. TAK-003 is immunogenic against all 4 serotypes. Data from the pivotal trial suggested varying efficacy profiles by serotype. It was efficacious against all 4 serotypes in seropositive participants. In seronegative participants, it was efficacious against Dengue-1 and Dengue-2, the serotypes most commonly seen in the trial. In baseline seronegative participants, the data suggested lack of efficacy against Dengue-3 and did not allow assessment of Dengue-4 due to low incidence. However, the long-term follow-up did not conclude a high risk of hospitalized or severe forms of Dengue associated with TAK-003. The totality of the data did not indicate harm. Safety data from the integrated analysis of placebo-controlled trials showed that TAK-003 had an acceptable safety profile. To conclude, TAK-003 represents a new tool that can have a critical role in reducing dengue burden globally and in the US.

Workgroup Considerations

Gabriela Paz-Bailey, MD, PhD, MSc (CDC/NCEZID) presented a summary of the WG's interpretation of TAK-003 efficacy, safety, and immunogenicity data. Takeda's trial was a double-blinded placebo control study. Participants were enrolled and randomized to vaccine or placebo at a 2:1 ratio. The study included children 4─16 years of age. The study was conducted across 5 countries in Latin America and 3 countries in Asia. It has a follow-up time of 57 months after the first dose. The safety set included about 20,000 participants of whom 28% were seronegative at baseline. The primary endpoint was virologically confirmed dengue or VCD due to any serotype measured at 1 year after the second dose in the series. The secondary endpoints were stratified by the participants' serostatus and by dengue serotype. The secondary outcomes included the outcome VCD, hospitalizations for dengue, dengue hemorrhagic fever (DHF), and a trial-specific severe dengue definition.

Dr. Paz-Bailey summarized the data for the follow-up time of 57 months and included data from all the trial sites, including VE for the outcome of VCD for all serotypes and serostatus combined and then stratified by serostatus and then stratified by serotype. Starting with an overall vaccine efficacy for all serotypes and all serostatuses combined for VCD of 61%, stratified by serostatus VE was 64% in seropositives and 54% in seronegatives. When stratified by individual serotype, there was efficacy against all serotypes in seropositives. However, VE for seronegatives was negative with 95% confidence interval crossing zero for DENV-3 and DENV-4. The WG's interpretation for the outcome of VCD was that there is evidence of protection against all 4 serotypes for seropositives. For seronegatives, there is significant protection against DENV-1 and DENV-2 but not for DENV-3 or DENV-4. There are insufficient data to rule out an increased risk of VCD for these 2 serotypes.

Similar trends were observed for the outcome of hospitalizations. There was VE of 84% against hospitalizations for serostatuses and serotypes combined. Stratified by serostatus, there was significant protection in both seropositives and seronegatives. Stratified by serotype, there was significant protection for seropositives against serotypes 1, 2, and 3 and a calculated VE of 100% against DENV-4. However, there were only 3 events for these serotypes and they were all in the placebo arm. For seronegatives, there was significant protection for DENV-1 and DENV-2 and a negative VE for DENV-3 of 88% with confidence intervals crossing zero. There was only 1 hospitalization event for DENV-4 in the placebo arm. While the negative VE for

DENV-3 among seronegatives suggested a higher rate of hospitalization in the vaccinated participants compared to placebos. It is important to emphasize that the hospitalization rate for the serotype was overall low for both the vaccine and the placebo arms in the trial. For DENV-3, there were 3 hospitalizations in the placebo arm and 11 in the vaccine arm, which had twice as many participants as the placebo arm. That equals a hospitalization rate of 0.04 per 100 person years for the placebo and 0.07 for 100 person years for vaccinated participants. For DENV-4, there was only 1 case in the placebo arm.

The WG interpretation of these data was that in seropositives, there is protection against all serotypes, although there were very few hospitalizations for DENV-4. For seronegatives, there was protection for DENV-1 and DENV-2. Once again, there were few hospitalizations for DENV-4. There was no efficacy for DENV-3 against hospitalization and there were insufficient data to rule out the possibility of an increased risk of hospitalization among vaccinated children.

Looking at the outcome of severe dengue for the outcomes of DHF based on the 1997 WHO definition and the trial-specific definition for severe dengue, Dr. Paz-Bailey showed VE by serostatus but not by serotype since there were very few events. There was VE of 70% overall against DHF for serostatuses and serotypes combined. When stratified by serostatus, there was VE of 81% in seropositives and −3.4 in seronegatives. There are only 5 DHF cases in the vaccine arm and 13 cases in the placebo arm for seropositives. In seronegatives in the placebo arm, which had half as many participants as the vaccine arm, there were only 2 diastolic heart failure cases,1 due to DENV-1 and 1 due to DENV-3. There were 4 DHS cases in the vaccine arm, and they were all due to DENV-3. For the trial-specific definition of severe dengue, VE was 70% for serostatuses combined, with a confidence interval ranging from -24.7 to 92.9%. When stratified by serostatus, the VE was 90% in seropositives. For seronegatives, there were only 2 cases, both of which occurred in the vaccine arm and were due to DENV-3.

The WG interpretation of these data was that overall, it is difficult to draw conclusions, particularly stratifying by serotype, due to the small number of events. For seropositives, there was protection against DHF and trial-defined severe dengue. For seronegatives, there was no efficacy for either outcome.

The immunogenicity data for the vaccine was evaluated in a subset of participants. Among seronegative vaccine recipients, the GMTs (calculated using $PRNT_{50}$) were highest for DENV-2. GMTs were stable over 51 months after the first dose for DENV-1, 3, and 4 and decreased over time for DENV-2. However, DENV-2 titers remained higher than the other serotypes at 51 months. Solicited AEs were higher among recipients of the vaccine compared to placebo, and unsolicited AE were similar between the vaccine and placebo. SAEs were similar among the vaccine and placebo arms. Only 1 of the SAEs was deemed to be related to the vaccine and 4 were related to the placebo. The most common SAEs were dengue fever and DHF, which were both higher in the placebo group compared to the vaccine group. There were 16 deaths in the vaccine arm and 10 in the placebo arm, none which were related to the vaccine.

In summary, the WG had 5 conclusions they believed to be clear based on the data presented. TAK-003 protects seropositive recipients against VCD and hospitalization due to any serotype. Additionally, TAK-003 protects seronegative recipients against VCD and hospitalization for DENV-1 and DENV-2. However, the vaccine does not protect seronegative recipients against VCD and hospitalizations for DENV-3. DENV-4 efficacy assessment is limited by a low number of events. The data suggests that there is no protection against VCD for DENV-4, and there was only 1 DENV-4 hospitalization. Finally unsolicited, SAEs and deaths were similar in the vaccine and placebo arms.

The WG identified 3 observations that they are still working through. First, the WG is discussing the implications for the unknown VE against DENV-4 hospitalization among seronegative. Second, there is no efficacy against VCD or hospitalization for DENV-3 among seronegative recipient in the vaccine compared to placebo groups. The data are insufficient to rule out an increased risk among those who are vaccinated. Finally, the WG is still debating the significance of the immunogenicity data because there is no clearly defined correlate of immune protection for the dengue vaccine.

ACIP Discussion Points, Observations, Suggestions on Dengue Vaccines

Following Dr. Biswal's Presentation

- Regarding an inquiry about why efficacy was not observed in seronegatives, Dr. Biswal indicated that they have looked into a number of factors sch as immunological basis and genotype, but still do not have a definitive answer.
- In terms of a question about whether there were other discrepancies between the immunologic response and clinical efficacy in the hospitalization data, Dr. Biswal explained that there was a negative point estimate for DENV-3 hospitalizations. After the Sri Lanka data were removed, this negative point estimate was not seen.
- Given what has been learned about dengue disease and dengue vaccination, continuing evidence of absence of harm is going to be important. While it is understood that there were differences in hospitalization rates in Sri Lanka, that did not necessarily mean that the data are invalid. More information is needed about whether the data should or should not be included from Sri Lanka, because otherwise it seemed like the data should be included as intended in the WG's interpretation of whether there is absence of harm or no absence of harm. Dr. Biswal emphasized that the sensitivity analysis had a negative point estimate when Sri Lanka was included that was not there when Sri Lanka was removed. The intent was not to remove the data, but to understand what was occurring. Sri Lanka had 6 cases in 1 site in the vaccine group and none in the placebo group. The cases were not adjudicated as severe, so in the investigators' view, they do not represent an increase in the severity of cases in the vaccine group. This is mostly likely by chance due to the varying hospitalization practices.

Following Dr. Paz-Bailey's Presentation

- ACIP expressed gratitude for the excellent summation of a considerable amount of confusing information.

VARICELLA

Public Health Impact of 25 Years of Varicella Vaccination in the United States

Mona Marin, MD (CDC/NCIRD) presented on the public health impact of 25 years of the varicella vaccination program in the US. Historically, varicella was considered a disease of little consequence, of rite of passage during childhood, too mild to warrant prevention. That misconception started to change after the first cases of fatal varicella were reported in mid-1950s in children treated with newly introduced immunosuppressive therapy that cured several serious diseases but unmasked the lethal potential of the varicella-zoster virus (VZV).[79]

[79] Cheatham et al. Am J Pathol 1956; 32:1015-35

In the late 1960s through early 1970s, immunosuppressive treatment was increasingly used as systemic steroid therapy for organ transplantation or childhood cancers. Leukemia, previously almost always fatal, was cured in about 80% of children only to have many of them die of varicella before immune reconstitution. Varicella no longer seems too inconsequential to justify the development of a vaccine. In 1974, research from Japan announced the varicella vaccine that contained an attenuated strain of VZV after studies showed impressive results on small numbers of healthy children and adults and children with leukemia in remission.[80] In the US, there initially was controversy about the use of a varicella vaccine, with important concerns being the risk for latency and persistence of immunity.

However, fear of varicella in leukemic and other immunocompromised children led to trials in the US in the early 1980s in children with leukemia that demonstrated VE and safety.[81] Subsequent studies in healthy people also showed that the vaccine was safe and effective in children and adults. In 1995, the varicella vaccine was licensed and recommended in the US. The US became the first country with a routine varicella vaccination program. ACIP made a scientifically informed, yet bold decision in recommending varicella vaccination. There was debate around the time of the vaccine recommendations about whether the health burden of varicella justified a vaccination program, whether the vaccine would be accepted by parents and providers, whether the varicella program would shift the burden of varicella from children who had milder disease to adults who had more severe presentations, whether there was a risk during pregnancy, and whether the program would increase herpes zoster (HZ) incidence.

Before vaccine, varicella represented a significant medical and societal health burden in the US that assumed more importance once other preventable causes of health burden and mortality, such as polio and measles had been controlled. In the US, approximately 4 million cases of varicella occurred every year pre-vaccine, approximating the birth cohort and resulting in 11,000 to 13,000 hospitalizations and 100 to 150 deaths. The greatest health burden occurred in children, with more than 90% of cases, 70% of hospitalizations, and about half the deaths from varicella.[82]

As mentioned, the US varicella program started in 1995 when 1 dose was recommended for routine vaccination of children 12─18 months of age and catch-up vaccination for older children and other susceptible persons. In 2007,[83] the policy was changed to a routine 2-dose childhood program with the first dose at 12─15 months of age and the second at 4─6 years of age, catch-up vaccination of persons who had received 1 dose, and vaccination of all eligible susceptible persons. The main rationale for the policy change was continuing low-level community transmission, with outbreaks in highly 1-dose vaccinated elementary school populations although these were smaller and less frequent than pre-vaccine.

Regarding acceptability, varicella program implementation was highly successful.[84] High coverage was attained among young children of 89% by the end of the 1-dose program in 2006 and has remained around 91% since then, with coverage levels similar to those of MMR, a more mature program. There was rapid uptake of the second dose after the 2-dose recommendation in 2007, with coverage reaching a median of 93% by 2020 in 6 states—again approaching the coverage of 2-dose MMR. The second vaccine characteristic that influences vaccine impact is

[80] Takahashi et al. Lancet 1974
[81] Gershon at al. JID 2021
[82] Wharton et al. 1996; Galil et al. 2001; Davis et al 2004; Meyer et al. 2000; Nguyen et al. 2005; Enders and Miller. 2000
[83] MMWR 2007;56(RR-4):1–39 . Available at www.cdc.gov
[84] Elam-Evans et al. JID 2022

the performance of the vaccine.[85] One dose of varicella vaccine is moderately effective in preventing varicella of any severity at 82% and highly effective in preventing moderate or severe varicella at more than 97%. The second dose adds 10% or more improved protection against varicella of any severity.

In terms of the impact of the program on varicella, in 4 states that consistently reported varicella cases to the NNDSS since before vaccine introduction, incidence declined by more than 97% from the pre-vaccine period through 2018.[86] The decline was impressive during the 1-dose program at more than 86%. During the 2-dose program from 2007─2019, incidence declined further by 90% from the end of the 1-dose program. Incidence declined in all age groups during the 2-dose program, indicating additional control added by the second dose and no increase in disease in other ages. The greatest decline was in children 5─9 and 10─14 years of age, who were the primary recipients of the second dose. Additionally, in 7 states with consistent outbreak reporting, the number of outbreaks declined by 82%.[87]

Moving to varicella hospitalizations,[88] varicella hospitalization rates declined 90% by 2019 compared with the pre-vaccine period. Hospitalization rates continued to decline during the 2-dose program. Absolute numbers are instructive to define the burden in a population. Dramatic declines were observed in hospitalization rates of over 94% in all age groups younger than 50 years of age, with the greatest declines in children and adolescents. More than 10,500 varicella hospitalizations are now prevented annually, including more than 1,250 among infants and more than 4,200 among children 1─4 years of age.

Large declines occurred for deaths as well. The overall varicella mortality rate declined 89% from the pre-vaccine period to 2017─2019. Most of this decline occurred during the 1-dose program. Similar to hospitalizations, the mortality rates declined in all age groups in persons younger than 50 years of age. Deaths declined from an annual average of 84 deaths pre-vaccine with varicella as the underlying cause to 3 deaths in 2018─2019 with deaths practically eliminated among those younger than 20 years of age with a 99.4% reduction.[89] In 5 of the last 9 years, no underlying or contributing deaths were reported in this age group.[90]

To summarize HZ trends during the US varicella vaccination program, before the routine varicella vaccination program was adopted, some experts were concerned that decreased circulation of VZV and therefore implicit bias boosting would lead to an increase in HZ in adults. In persons aged ≥30 years, HZ incidence increased during the earlier study years, with decelerations in later years. There was no acceleration following introduction of the varicella vaccine and deceleration in later years starting in 2007 with the oldest age groups. Among children and young adults, age-specific HZ incidence declined in a step-wise pattern once each age group was comprised mostly of persons born during the varicella program and therefore likely vaccinated. Incidence among children 1─14 year of age is converging at the lowest levels.[91]

[85] Marin et al. Pediatrics 2016 and Son et al. JID 2010.
[86] Marin et al. JID, 2022
[87] 29 states and the District of Columbia reported age data during 2005–2006 (end of 1-dose program) and 38 during 2018–2019 (mature 2-dose program); National Notifiable Diseases Surveillance System data; Marin et al. JID 2022. §Outbreak: ≥5 varicella cases; Leung et al. JID 2022.
[88] Marin et al. JID 2022. Data: HCUP National Inpatient Sample (NIS).
[89] Marin et al. JID 2022.
[90] 2011, 2013, 2014, 2017, 2018. Data: National Center for Health Statistics
[91] Leung et al. JID 2022. MarketScan 1998–2019.

To conclude, the US varicella vaccination program has been successfully implemented, resulting in substantial disease prevention and societal savings over the last 25 years. The varicella vaccine has shown good effectiveness that has been maintained to date and has a favorable safety profile. High vaccine coverage was reached and maintained. The program prevented morbidity and mortality with large declines. Approximately 91 million varicella cases; 238,000 hospitalizations; and 1,900─ to 2,400 deaths have been prevented over the 25 years of the program. The program is highly cost-savings with $23.4 billion net societal savings to date. US data do not support prior predictions that the varicella vaccination program would increase HZ incidence among adults and documented reduced herpes zoster incidence among children and adolescents born in the vaccine era, with reduction due to the varicella program likely to extend to the entire population over time. Details of the program can be found in the article titled, "The Varicella Vaccination Program in the United States: 25 Years of Saving Lives and Preventing Illness" was included in a *Journal of Infectious Diseases* (*JID*) supplement released on November 1, 2022.[92]

ACIP Discussion Points, Observations, Suggestions on Varicella Vaccines

Following Dr. Marin's Presentation

- ACIP members, ex officios, and liaisons applauded the tremendous work the Varicella Vaccine Program has done over the last few decades, emphasizing the importance of highlighting what is not seen, given that what is not seen can be forgotten. It is important to demonstrate the profound impact of this program and all those involved in it.
- It also is important to recognize all of the states that got varicella vaccine included in school immunization laws. These laws have been very important in establishing high immunization rates and maintaining them over the years. This has been true not only for varicella, but also for many other vaccinations.

FRIDAY: FEBRUARY 24, 2023

COVID-19 VACCINES

Introduction

Matthew F. Daley, MD (WG Chair) introduced the COVID-19 vaccines session on behalf of the ACIP COVID-19 Vaccine WG. Bivalent booster authorization was extended to children 6 months of age and older. On December 8, 2022, the FDA granted Emergency Use Authorization (EUA) for use of Moderna bivalent COVID-19 booster in children 6 months─5 years of age and use of Pfizer BioNTech bivalent COVID-19 vaccine as a third primary series dose for children 6 months─4 years of age.[93] The following day, CDC expanded the use of updated bivalent COVID-19 vaccines for children 6 months─5 years of age.[94]

[92] https://academic.oup.com/jid/issue/226/Supplement_4
[93] https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-updated-bivalent-covid-19-vaccines-children-down-6-months
[94] https://www.cdc.gov/media/releases/2022/s1209-covid-vaccine.htm

Since the last ACIP meeting, the WG has been very active reviewing and discussing numerous topic areas, including the following:

- ❑ Epidemiology of COVID-19, including multisystem inflammatory syndrome in children (MIS-C) and hospitalization data
- ❑ VE updates
- ❑ COVID-19 among persons with immunocompromise, including VE and Evusheld
- ❑ Inputs for cost-effectiveness analyses
- ❑ COVID-19 vaccine safety updates
- ❑ Updated benefit/risk analyses
- ❑ Updates to COVID-19 vaccine use in children 6 months through 5 years of age, including Moderna COVID-19 vaccine booster doses
- ❑ Ongoing work to increase uptake of bivalent COVID-19 vaccines
- ❑ Considerations for the transition to a bivalent primary series
- ❑ Future directions for the COVID-19 vaccination program overall

The agenda for this session including presentations on the following:

- ❑ Plan to End the COVID-19 Public Health Emergency (PHE) on May 11, 2023
- ❑ COVID-19 vaccine safety updates from CDC
- ❑ COVID-19 vaccine safety updates from FDA
- ❑ VaST summary
- ❑ WG interpretation and summary
- ❑ Updates on COVID-19 hospitalizations in the US
- ❑ Updates on COVID-19 VE in the US
- ❑ Considerations for transitioning to a bivalent primary series
- ❑ NCIRD Director's Remarks
- ❑ WG interpretation and summary
- ❑ Updated benefit-risk analysis for COVID-19 vaccines
- ❑ COVID-19 vaccines in terms of future directions for the program

Plan to End the COVID-19 Public Health Emergency (PHE) on May 11, 2023

Sarah A. Meyer, MD, MPH (CDC/NCIRD) provide information about the federal government's plans to end the COVID-19 PHE on May 11, 2023. CDC has been receiving many questions about what this means and does not mean for the vaccination program. CDC remains dedicated to preventing severe illness and death from COVID-19, with particular concern for populations who are at higher risk of adverse outcomes. CDC is actively working with other federal agencies and offices to maintain access to vaccines, testing, and therapeutics to the extent possible. Much of the current COVID-19 vaccine program will remain unchanged after the PHE ends in May. The primary impact of the PHE ending on the vaccination program is the possibility of reduced submission of vaccine administration data from some jurisdictions. This is because the Data Use Agreements (DUAs) for COVID-19 vaccine administration were established with termination provisions that referenced the PHE. However, state and territorial public health jurisdictions have been asked to extend this DUA through the end of 2023. Thus far, the majority of jurisdictions have done so. It is important to note that the end of the PHE does not equate to the end of the current national vaccine distribution program or the transition to commercialization. This has been one of the biggest points of confusion CDC has heard about. The end of the PHE does not mean the end of the federal vaccine program. CDC also has received many questions regarding commercializing COVID-19 vaccines and continues to work with HHS on this process. CDC is collecting questions to help ensure the agency addresses the

needs of jurisdictions and partners moving toward commercialization in the future. Further information will be shared with the ACIP as soon as possible.

COVID-19 Vaccine Safety Updates: CDC

Tom T. Shimabukuro, MD, MPH, MBA (CDC/NCEZID) described: 1) CDC's VSD Rapid Cycle Analysis (RCA) monitoring methods and assessment processes for statistical signals; 2) VSD RCA signal detection and signal assessment for ischemic stroke after Pfizer-BioNTech COVID-19 mRNA bivalent booster dose vaccination in the age group 65 years and older; and 3) rates of myocarditis and pericarditis following COVID-19 mRNA vaccination.

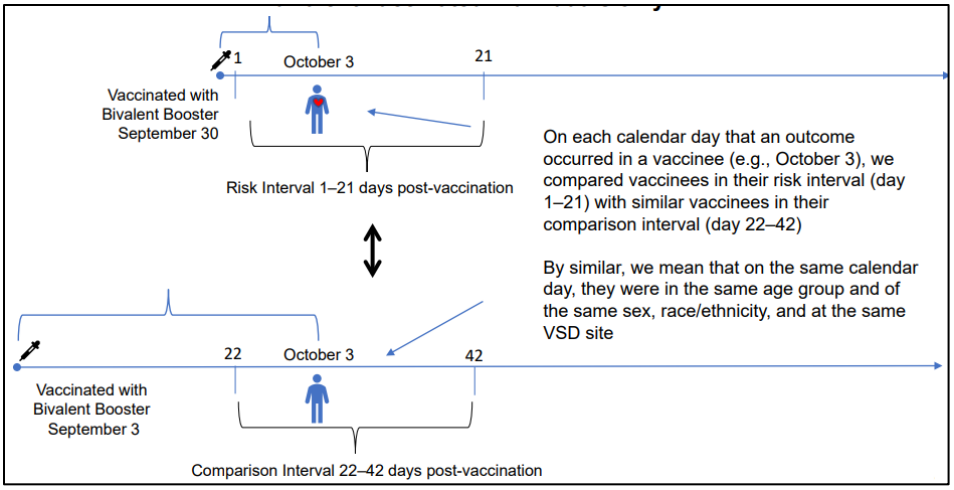
By way of background, bivalent COVID-19 mRNA booster vaccinations first became available in the US in September 2022. As of February 2023, 52.5 million bivalent booster doses have been administered to people ages 5 years and older in the US. This includes 22.3 million doses in people ≥65 years of age. CDC and partners monitor the safety of licensed and authorized US vaccines using multiple complementary systems.[95] Safety data support CDC recommendations that everyone eligible for a COVID-19 mRNA bivalent booster get vaccinated.

As a reminder, the VSD was established in 1990. It is a collaboration between CDC and 9 integrated healthcare organizations throughout the US and includes EHRs on approximately 12.5 million individuals. The strengths of VSD rapid cycle analysis include its population of 12.5 million people, which is about 4% of the US population across the VSD data sites. The VSD data sites are geographically, racially, and ethnically diverse. The VSD RCA uses near real-time data, with analyses updated weekly. The VSD RCA has access to comprehensive medical records, including exposures of vaccinations and outcomes. This allows rapid chart reviews to obtain additional clinical information as needed. The VSD employs innovative methods for RCA. The vaccinated concurrent comparative method is the primary analysis. Recent vaccinees as comparators are expected to be more similar to current vaccinees than unvaccinated individuals, with the advantages that the potential biases associated with calendar time, site, and demographic factors can be adjusted for carefully. In addition, these analyses can begin sooner than alternative methods. Supplemental analyses are conducted weekly. Unvaccinated or un-boosted comparators also would be available to provide context in real-time. Using vaccinated concurrent comparators with supplemental analyses offers substantial benefits compared to either unvaccinated or historical comparators.

The primary methodology for RCA for the primary analysis is the vaccinated concurrent comparator method. This has been used for bivalent boosters and the primary series and for the primary series and monovalent boosters. Pre-specified outcomes were assessed during weekly sequential monitoring after bivalent vaccination. The risk of pre-specified outcomes 1–21 days following a bivalent vaccination is compared with bivalent vaccinated individuals who were 22–42 days following the bivalent dose. That is the comparison interval. All analyses are adjusted for age, sex, race, ethnicity, VSD site, calendar time in days, and seasonality. The signaling thresholds is a 1-sided p-value <0.01.[96] To illustrate, this schematic depicts a hypothetical vaccinee with the outcome in the risk interval and a concurrent comparator "bivalent vaccinated individuals only:"

[95] https://www.cdc.gov/vaccinesafety/index.html

[96] Rapid Cycle Analysis (RCA) to monitor the safety of COVID-19 vaccines in near real-time within the Vaccine Safety Datalink. Available at: Rapid Cycle Analysis (RCA) to monitor the safety of COVID-19 vaccines in near real-time within the Vaccine Safety Datalink (cdc.gov)



Using the methods described, the VSD conducted RCA for the prespecified outcomes shown here:

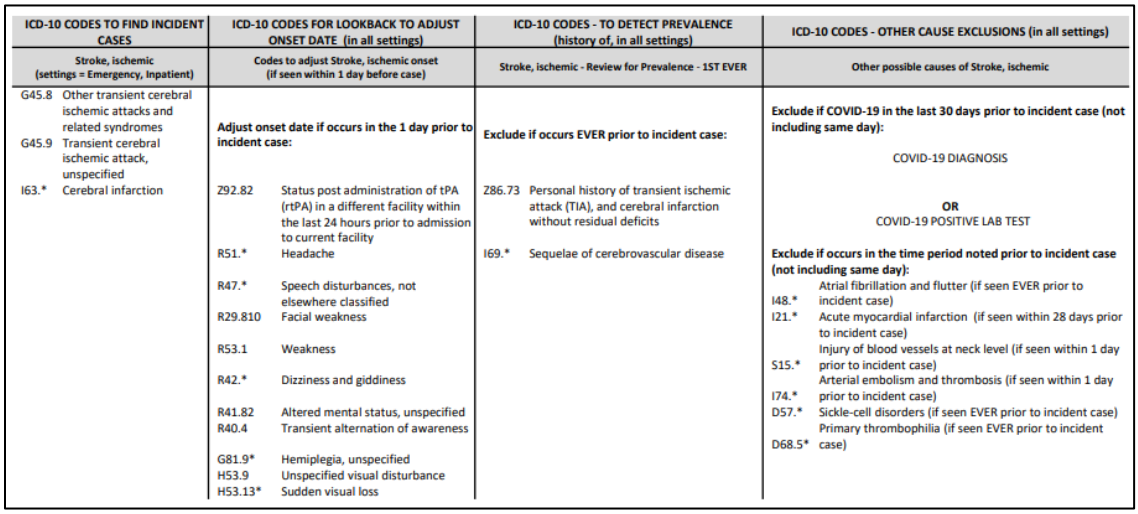
Prespecified outcomes	Settings
Acute disseminated encephalomyelitis	Emergency dept, Inpatient
Acute myocardial infarction	Emergency dept, Inpatient
Acute respiratory distress syndrome	Emergency dept, Inpatient
Anaphylaxis*	Emergency dept, Inpatient
Appendicitis	Emergency dept, Inpatient
Bell's palsy	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 COVID-19 bivalent booster vaccine monitoring for these pre-specified outcomes, VSD RCA detected a statistical signal for ischemic stroke after Pfizer-BioNTech bivalent booster vaccination in the age group ≥65 years. No other VSD RCA pre-specified surveillance outcomes have signaled in any age groups for either of the mRNA COVID-19 bivalent booster vaccines or when data for the 2 mRNA vaccine types are combined/pooled.

To look in more detail at the VSD COVID-19 RCA preliminary analyses for the ischemic stroke signal after Pfizer-BioNTech bivalent booster among people ≥65 years of age to assess whether it reflects a real effect of vaccination on an outcome, substantially more Pfizer bivalent boosters (580,000) were administered in the VSD compared to Moderna boosters (309,000). Then there were substantially more Pfizer bivalent boosters administered in this age group early in the bivalent booster program. The peak of bivalent booster vaccination, most of which was Pfizer in this age group, was occurring at the same time as peak influenza vaccination.

This is the VSD RCA ischemic stroke definition with inclusion/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	**Adjust onset date if occurs in the 1 day prior to incident case:**		**Exclude if occurs EVER prior to incident case:**		**Exclude if COVID-19 in the last 30 days prior to incident case (not including same day):**	
G45.9	Transient cerebral ischemic attack, unspecified					COVID-19 DIAGNOSIS	
I63.*	Cerebral infarction					**OR**	
		Z92.82	Status post administration of tPA (rtPA) in a different facility within the last 24 hours prior to admission to current facility	Z86.73	Personal history of transient ischemic attack (TIA), and cerebral infarction without residual deficits	COVID-19 POSITIVE LAB TEST	
		R51.*	Headache	I69.*	Sequelae of cerebrovascular disease	**Exclude if occurs in the time period noted prior to incident case (not including same day):**	
		R47.*	Speech disturbances, not elsewhere classified			I48.*	Atrial fibrillation and flutter (if seen EVER prior to incident case)
		R29.810	Facial weakness			I21.*	Acute myocardial infarction (if seen within 28 days prior to incident case)
		R53.1	Weakness			S15.*	Injury of blood vessels at neck level (if seen within 1 day prior to incident case)
		R42.*	Dizziness and giddiness			I74.*	Arterial embolism and thrombosis (if seen within 1 day prior to incident case)
		R41.82	Altered mental status, unspecified			D57.*	Sickle-cell disorders (if seen EVER prior to incident case)
		R40.4	Transient alternation of awareness			D68.5*	Primary thrombophilia (if seen EVER prior to incident case)
		G81.9*	Hemiplegia, unspecified				
		H53.9	Unspecified visual disturbance				
		H53.13*	Sudden visual loss				

In terms of the main findings for the bivalent RCA concurrent comparator analysis of ischemic strokes during the risk interval versus the comparison interval, Pfizer bivalent booster met the threshold for a statistical signal in the sequential analysis. Since then, it has attenuated for an adjusted rate ratio of 1.36, with a nominal confidence interval of 1.05 to 1.76, which did not meet the sequential statistical threshold for a statistical signal. More specifically, the signal for ischemic stroke following Pfizer bivalent occurred on November 27, 2022 in persons ≥65 years of age. At that point, the rate ratio was 1.92. The statistical signal persisted for 8t weeks, although it attenuated slightly. In the past several weeks, it has intermittently met the signaling criteria. At this time, the rate ratio was 1.36 and did not meet the signaling criteria. The caveat is that in VSD RCA, once there is a signal, it always signals. Weekly sequential analyses are continued because they are informative and shows when a signal drops below the signaling threshold.

Looking at a temporal scan analysis of ischemic stroke by day after the Pfizer bivalent boosters in people ≥65 years of age, and older, a statistically significant cluster of cases was detected on days 13–22 following vaccination. As a reminder, the pre-specified risk interval was Days 1–22. This clustering is more subtle and not as well-defined compared to the prominent clustering observed for myocarditis several days after vaccination. Nonetheless, it was statistically significant clustering. Comparing the rate preceding the statistical clustering for ischemic stroke on Days 13–22, the rate appeared to be lower. This implies that there may be lower than expected counts in the comparison interval.

CDC's colleagues at the Kaiser Permanente Northern California Vaccine Study Center conducted a chart review of a subset of 24 cases from the initial cluster, which was slightly different at 11–21 days. Of these, 22 were incident stroke or transient ischemic attack (TIA) cases for a positive predictive value (PPV) of 92%. None had any history of stroke or TIA. The median age was 77.5 years. Symptom onset rarely shifted from the electronic date. Of the 22, 5 (23%) had a known history of SARS-CoV-2 infection, only 1 of which within the last 6 months. None had a mention of recent exposure to SARS-CoV-2 in the chart notes. A total of 14 (64%) of these cases had influenza vaccine co-administered on the same day. Of those 14, 13 were high-dose influenza vaccines and 1 was adjuvanted. In terms of outcomes among the 22 verified cases, 13 (59%) were discharged home, 18 were discharged home with home health, 9% were discharged to a SNF, and 3 (14%) died. One death was in a male 75–79 years of age

approximately 1 month after the stroke, and the death was likely related to the stroke. Another was in a female 65─69 years of age noted after craniotomy, although the relationship to surgery was unclear. This death was due to cardiac arrest about 2.5 months later. The last case was in a male 70─74 years of age during hospitalization for metastatic cancer, with subsequent death due to cancer-related complications during hospitalization. A random sample of risk and comparison interval cases across VSD sites are currently being reviewed.

One of the supplemental analyses focused on ischemic strokes during the 1─21 day interval comparing bivalent booster versus un-boosted concurrent comparators (but eligible for a bivalent booster). This is essentially a vaccinated versus unvaccinated analysis, but the unvaccinated individuals are likely to be fairly similar to boosted individuals because they are highly vaccinated and are eligible for a booster. In this analysis, the adjusted rate ratio was 1.07 0.89–1.28 and was not statistically significant. The supplemental analysis did not signal for ischemic stroke. An additional supplemental analysis focused on ischemic strokes during the 22─42 day interval comparing bivalent boosted versus un-boosted concurrent comparators (but eligible for booster). The investigators essentially performed the same analysis using a different interval. They found an adjusted rate ratio of 0.76 (0.6 to 0.95), which suggested a protective effect or reduced rate of stroke in the comparison interval.

Given that a fairly high percentage of the cases in the chart review noted simultaneous high-dose or adjuvanted influenza vaccines, an additional post-signal analysis was performed to assess simultaneous vaccination. Among those ≥65 years of age who received bivalent Pfizer + same-day high-dose or adjuvanted influenza vaccine, there were 43 cases in the risk interval of 1─21 days and 26 cases in the comparison interval of 22–42 days. The adjusted rate ratio was 1.65 (1.02 – 2.72), which just met statistical significance for the lower bound of the 95% confidence interval. Among those ≥65 years of age who received a bivalent Pfizer booster without any same-day influenza vaccine, the adjusted rate ratio was 1.19 (0.87 – 1.62), which was not statistically significant.

A follow-on to that analysis was done to assess expected cases after bivalent booster + high-dose or adjuvanted influenza vaccine based on ischemic stroke incidence in un-boosted people eligible for a booster among the older age groups in 5-year increments. The total expected was 38.7 cases in a 3-week interval. Observed cases in the 1─21-day risk interval was 43. Observed cases in the comparison interval was 26, substantially below the expected background of 38.7. Again, these findings suggest a reduced rate of stroke in the comparison interval.

To summarize the statistical signal for ischemic stroke following bivalent Pfizer-BioNTech COVID-19 mRNA booster vaccination in people ≥65 years of age, the statistical signal persisted for 8 weeks. The rate ratio has slowly attenuated from 1.92 to 1.36 and intermittently met signaling criteria. Temporal clustering evaluation found a significant cluster 13─22 days after vaccination. Supplemental analyses using un-boosted concurrent comparators showed a rate ratio of 1.07(95% CI 0.89–1.28), which was non-statistically significant. Of the small subset of charts reviewed, most confirmed cases had co-administered high-dose or adjuvanted influenza vaccine. Analyses evaluated simultaneous high-dose or adjuvanted influenza vaccine showed a rate ratio of 1.65 (95% CI 1.02–2.72, which was statistically significant. Separate analyses did not detect an elevated rate ratio for stroke after influenza vaccine alone, and supplemental analyses suggests the comparison interval rates were lower than expected.

Some additional considerations include a small number of strokes and precise rate ratios limit some analyses. There was reduced follow-up time after Moderna booster doses due to distribution delays. Simultaneous influenza vaccine analyses were limited by small numbers. It is difficult to interpret temporal clustering during risk and comparison intervals. There is possible unmeasured confounding. The results may be influenced from confounders that vary over time. There is a question regarding whether early adopters of bivalent booster vaccination have greater risk of near-term cardiovascular events, although the same trend has not been observed for acute myocardial infarctions. There is a potential impact of differential vaccine availability after the EUA. There are simply more Pfizer doses available and administered in VSD than Moderna doses. There is also the possible role of SARS-CoV-2 infection before the booster. Background incidence of SARS-CoV-2 infection was rapidly changing during bivalent booster uptake. The analyses excluded cases with COVID-19 diagnosis or positive laboratory tests in the prior 30 days, although asymptomatic infections and home antigen tests are not consistently documented in EHRs. However, chart reviews did not find recent SARS-CoV-2 infection or exposure.

In terms of further evaluation and key next steps, weekly monitoring will continue along with exploration of potential data-related explanations for this statistical signal in VSD. Chart review of a random sample of 100 cases across VSD sites is in process. CDC will consult with other surveillance systems to better understand the possible role of simultaneous high-dose or adjuvanted influenza vaccination with COVID-19 vaccination and the possible decreased rate of stroke in the 3─6 weeks following vaccination.

To touch on some data from other systems and programs, there have been no unusual or unexpected reporting patterns observed and no evidence of a safety concern detected for ischemic stroke with either bivalent booster in VAERS. FDA monitoring in CMS data and VA monitoring in the VA system have not detected any safety signals using the historical comparator designs. Surveillance conducted by international regulatory and public health partners has not detected a safety concern for ischemic stroke following bivalent booster vaccination. There has been no evidence of a safety signal for ischemic stroke in Pfizer's global monitoring, nor were any safety signals detected for ischemic stroke for the primary series or monovalent boosters for Pfizer or Moderna vaccines in the US and global monitoring. Notably, these surveillance activities did not include analyses to evaluate the effect of simultaneous influenza vaccination. 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 co-administration of bivalent booster and influenza vaccines.

Regarding myocarditis and pericarditis following COVID-19 mRNA vaccination in the VSD, approximately 135,000 Moderna and 431,000 bivalent boosters have been administered for a total of approximately 566,000 booster doses administered. Based on VSD incidence rates of verified myocarditis or pericarditis in the 0–7 days after Pfizer-BioNTech vaccination in people 12–39 years of age, there have been no new or unusual findings. There has been only 1 case in a male in the 18─29 years of age group.[97] The highest incidence rates have been among adolescent and young adult males after Dose 2 of the primary series. Rates were somewhat lower after the monovalent booster dose and lowest after the bivalent booster, with a caveat that the bivalent booster dose data are sparse. Little difference has been seen across Dose 2 and the first monovalent dose for females, particularly in females 30─39 years of age.

[97] Primary series and 1st monovalent booster data through August 20, 2022, bivalent booster data through January 29, 2023; Source: Goddard K, et al. Incidence of Myocarditis/Pericarditis Following mRNA COVID-19 Vaccination Among Children and Younger Adults in the United States. Ann Intern Med. 2022;175:1169-1771

VSD incidence rates of verified myocarditis or pericarditis in the 0–7 days after Moderna vaccination was assessed in people 18–39 years of age. Given that such few doses were administered among those 12–17 years of age, it was not informative and not included. The data among those 18–29 years of age and 30–39 years of age showed the same general trend. The highest incidence rates were in males after Dose 2, although there were wide confidence intervals on these point estimates. There were lower incidence rates after the monovalent booster dose, with the lowest rates after bivalent boosters with the caveat that the number of doses was limited. There was not much difference in the incidence for the females 18–29 years of age, with no substantial differences across the monovalent and bivalent booster doses in those 30–39 years of age.

COVID-19 Vaccine Safety Updates: FDA

Richard Forshee, PhD (FDA/CBER/OBPV) presented COVID-19 vaccine safety updates based on FDA's active surveillance on bivalent COVID-19 vaccines. The following data sources are available to the FDA CBER Biologics Effectiveness and Safety (BEST) System from multiple research partners with whom the FDA is working as part of this initiative, which includes data on hundreds of millions of patients:

Data Source*	Database Type	No. Patients Covered (Millions)	Time Period Covered
CMS- Medicare	Claims	105	2005 - present
MarketScan Commercial and Medicare Supplemental	Claims	254	1999 - 2019
MarketScan Medicaid	Claims	48	1999 - 2019
MarketScan Commercial (IBM)	Claims	65	2016 - present
Blue Health Intelligence	Claims	93	2016 - present
Optum - Adjudicated	Claims	66	1993 - present
Optum - Pre adjudicated	Claims	31	2017 - present
HealthCore	Claims	70	2010 - present
CVS Health	Claims	41	2018 - present
OneFlorida Clinical Research Consortium - Medicaid	Claims	6.7	2012 - present
OneFlorida Clinical Research Consortium - EHR	EHR	5.6	2012 – present
Optum EHR	EHR	102	2007 - 2020
MedStar Health Research Institute	EHR	6	2009 - present
PEDSnet	EHR	6.2	2009 - present
IBM CED	Linked EHR Claims	5.4	2000 - present
Optum Integrated Claims - EHR	Linked EHR Claims	25	2007 – 2020

*Data lag varies based on data source, ranges from a few days to a few months.

For this sequential analysis of the COVID-19 bivalent vaccines, the FDA worked with 3 of its commercial research partners and the CMS Medicare data to determine the various age ranges that were included in the analysis. Given the finding that was discussed by Dr. Shimabukuro, Dr. Forshee noted that he would focus on FDA's Medicare analysis with persons ≥65 plus of whom 36 million were enrolled in the Medicare private fee-for-service (PFFS) system. One of the concerns that everyone working in COVID-19 safety surveillance has had is that the claims data, and in some cases the EHR data, have not always reliably captured all the COVID-19 vaccinations, especially early in the pandemic when the vaccines were first rolling out. Many vaccinations were delivered in mass vaccination clinics and not all of that vaccination data made its way back into the healthcare claims systems.

In order to try to address the concern of under-capture of COVID-19 vaccines, extensive efforts have been made to reach out to IISs. These are confidential population-based, computerized databases that report immunization doses administered by participating providers to persons in US public health jurisdictions. This had to be done jurisdiction-by-jurisdiction and data source-by-data source. This resulted in the ability to obtain substantially more information about the COVID-19 vaccination status of individuals.

As discussed in the previous presentation, there are different phases of vaccination active surveillance. The earliest stage is descriptive monitoring in which descriptive statistics of vaccine doses and selective AEs are provided while waiting for sufficient doses to accumulate in order to move to more statistically rigorous approaches. The next approach is the signal detection phase during which sequential testing is being performed while vaccine doses accumulate in order to identify potential safety risks early. It is important to note that this approach does not prove a causal relationship. The current approach is moving into a signal evaluation phase in which more robust study designs are used to evaluate any potential safety signals that have been identified.

In terms of the BEST Initiative specifically, this table summarizes the vaccinations that have been observed in the systems the FDA is using:

Age Groups (years)	BNT162b2 (# vaccinations)	mRNA-1273 (# vaccinations)	Total (# vaccinations)
5/6-17[1]	196,992	13,016	210,008
18-35[1]	442,870	211,694	654,564
36-64[1]	1,248,430	654,220	1,902,650
65+[2]	4,265,244	3,042,074	7,307,318

1. Data cuts: CVS data through 10/2022, HealthCore data through 11/2022, Optum data through 12/2022
2. Data cuts: CMS data through 12/2022

The red box at the bottom of the table highlights that most of the vaccinations observed have been among the population ≥65 of age, with more than 7 million total vaccinations (over 4 million Pfizer and over 3 million Moderna). The numbers are smaller for the younger age groups.

For the FDA sequential analysis, near real-time surveillance was used. Again, this design cannot establish a causal association. The study population included several age ranges: 6 months—4/5 years, 5/6—17 years, 18—64 years, and ≥65 years. For the myocarditis/pericarditis outcome, the study population was additionally split into 18—35 years of age and 36—64 years of age. The exposure was either the Moderna (mRNA-1273.222) or Pfizer (BNT162b2) COVID-19 bivalent boosters containing the original SARS-CoV-2 virus and Omicron variants BA.4 and BA.5. The statistical method used was MaxSPRT, which is a sequential probability ratio test. The comparator was historic rates. The FDA is monitoring a number of AEs in adult and pediatric populations. Among these, the closest for the particular analysis of ischemic stroke was non-hemorrhagic stroke. The difference between the definitions is that the FDA's non-hemorrhagic stroke definition does not include transient ischemic attack or TIA, whereas the ischemic stroke that Dr. Shimabukuro discussed did include TIA.

The only signal the FDA has detected thus far was for myocarditis/pericarditis in the young adult population 18–35 years of age that was detected for the Pfizer BioNTech bivalent vaccine. This is consistent with what was seen with the earlier mRNA COVID-19 vaccines. Relevant to the discussion in this session, the FDA has not seen a signal for non-hemorrhagic stroke in any of the populations, including the Medicare population ≥65 years of age. Several of FDA's AEs have completed their surveillance period at this point. Most relevant to this discussion is that non-hemorrhagic stroke is that the maximum length of the pre-defined surveillance has been reached without a signal. As of the last observation period in 2019 comparing non-hemorrhagic stroke for Pfizer bivalent vaccine compared to historical rates, the risk ratio was 0.76. This means that the rate that observed after the Pfizer COVID-19 bivalent vaccine is less than what would be expected based on the historic rate.

There was some discussion in the earlier presentation about concomitant influenza vaccination. Among the 4.25 million doses of Pfizer BioNTech bivalent vaccine in the CMS database, 38% of those Medicare recipients who received the Pfizer bivalent booster also received a seasonal influenza vaccination on the same day, 78% received a seasonal influenza vaccine within +/- 42 days. More than 90% of the concomitant and influenza vaccines were either high-dose or adjuvanted vaccines. No signal has been seen to date for non-hemorrhagic stroke, even though a large number of individuals received the influenza vaccine at the same time or at close to the same time as their bivalent COVID-19 vaccine.

In summary, this was a large-scale signal detection study of the 2 COVID-19 mRNA bivalent vaccines conducted in multiple claims databases. RCA surveillance detected a signal for myocarditis/pericarditis following the Pfizer BNT162b2 bivalent vaccine among adults 18–35 years of age. Among adults ≥65 years of age, several AEs already have completed the surveillance period without a signal. It is important to emphasize again that signal detection studies do not establish a causal relationship, and further evaluation of signals is required in more robust studies. Surveillance is ongoing and will be expanded to children <5 years of age as more doses accumulate in younger age groups.

As Dr. Shimabukuro discussed in his presentation, it is important to consider the totality of evidence about the potential safety risk of ischemic stroke or non-hemorrhagic stroke. No excess reports of stroke have been seen in VAERS. The CMS database did not show any increase in non-hemorrhagic stroke or hemorrhagic stroke among approximately 4.25 million doses administered. The VA database has not shown an increase in stroke in their preliminary analyses. Various countries in Europe and Israel have not identified an increased risk of stroke reported in their surveillance systems. Pfizer notes no increase in the signal in their global safety database or when comparing the monovalent to bivalent vaccines. However, the FDA is launching a formal epidemiologic study in order to prepare for potential vaccine coadministration in 2023-2024. This will be a self-controlled study in which the individual beneficiary serves as his or her own control and will assess the occurrence of non-hemorrhagic stroke in different time periods of risk in a control window. Specific analyses will examine coadministration of adjuvanted or high-dose influenza vaccines as part of this more formal epidemiological study. Work is underway on the protocol for that analysis.

VaST Summary

H. Keipp Talbot, MD MPH (VaST Chair) reminded everyone that the objectives of VaST are to: 1) review, evaluate, and interpret post-authorization and approval of COVID-19 vaccination safety and data; 2) serve as the central hub for technical subject matter expertise from federal agencies conducting post-authorization and approval safety monitoring; 3) advise on analyses, interpretation, and presentation of vaccine safety data; and 4) provide updates to the ACIP COVID-19 Vaccines WG and the entire ACIP on COVID-19 vaccine safety. Between December 21, 2020 through February 24, 2023, VaST has had 71 independent meetings to review vaccine safety data and 17 joint meetings with the ACIP COVID-19 Vaccines WG. In addition, VaST has presented or given reports during 22 ACIP meetings. During this session, Dr. Talbot described the VaST assessment of the statistical signal for ischemic stroke in the VSD following the bivalent COVID-19 booster vaccination and myocarditis pericarditis following mRNA COVID-19 vaccination.

The statistical signal among persons ≥65 years of age for ischemic stroke/TIA following bivalent Pfizer, BioNTech COVID-19 booster vaccination is based on limited data and has been attenuating over time. A signal has not been observed in 2 other US active vaccine safety monitoring systems[98] or in data from other countries.[99] The US systems differ from each other. The VSD and VA analyses included TIA with ischemic stroke, while the FDA CMS analyses did not. VSD is the only US system that uses concurrent comparator groups. The VA and FDA CMS analyses have not evaluated simultaneous administration with influenza vaccination.

There is no increased rate ratio for ischemic stroke/TIA following bivalent Moderna COVID-19 booster vaccination. Previous surveillance in VSD and other US systems found no evidence of increased risk of ischemic stroke/TIA after the primary series or monovalent COVID-19 booster vaccination for either Pfizer-BioNTech or Moderna products. The cause of the increased rate ratio is unclear. Potential contributing factors include simultaneous administration of bivalent COVID-19 booster and influenza vaccines or unmeasured confounding or bias. Most VSD participants ≥ 65 years of age received high-dose influenza vaccine in 2022-2023 season. VaST would like to review additional data on simultaneous administration of bivalent COVID-19 booster and influenza vaccination. VaST highlighted the following areas for further exploration, which are to: 1) assess the impact of recent respiratory viral illness on the risk of ischemic stroke and TIA; and 2) analyze in VSD the potential reasons for the lower rate of ischemic stroke/TIA in the vaccinated comparator group that could be contributing to the increased rate ratio.

VaST also has reviewed data on myocarditis and pericarditis following COVID-19 vaccination since April 2021 and has provided several assessments during ACIP meetings. Rates after the monovalent primary series, monovalent booster series, and bivalent booster doses have been assessed. Rates have been highest in adolescent and young adult males following primary series Dose 2 and the first monovalent booster dose. Outcomes after the monovalent primary series and monovalent booster doses also have been assessed. Data on rates after bivalent COVID-19 booster vaccinations are limited, primarily due to the limited use of the bivalent COVID-19 booster. Current data in the VSD do not raise additional concerns about myocarditis following the bivalent COVID-19 booster vaccination.

[98] FDA analysis of Centers for Medicare and Medicaid Services (CMS) data, and Department of Veterans Affairs (VA) rapid cycle analyses
[99] Israel and European countries

In terms of future plans, VaST is preparing to transition review of vaccine safety data to the ACIP COVID-19 Vaccines WG.

WG Interpretation and Summary

Evelyn Twentyman, MD, MPH (CDC/NCIRD) discussed the WG's interpretation of the data on ischemic stroke, COVID-19, and influenza in adults ≥65 years of age in terms of the statistical signal reviewed in-depth earlier in the session; important new and published contextual evidence regarding ischemic stroke, COVID-19, and influenza in adults ≥65 years of age; the WG's interpretation and next steps.

To briefly review the statistical signal for ischemic stroke identified in the highly sensitive VSD RCA system following Pfizer COVID-19 mRNA bivalent booster vaccination, the rate ratio has attenuated over time based on comparison rates of ischemic stroke in an early interval after a booster receipt with rates in a later interval. The supplemental analysis, which compared rates after booster among boosted people with rates over the same period with un-boosted people, did not show an elevated rate ratio. As Dr. Shimabukuro mentioned earlier, there were fewer cases of stroke among the bivalent boosted than the eligible but un-boosted in the later interval. Additionally, while stratified analysis evaluating people with co-administration of high-dose or adjuvanted influenza showed a rate ratio of 1.65, the rate ratio was not elevated. People who received Pfizer bivalent mRNA booster without simultaneous influenza vaccine and a separate analysis did not detect an elevated rate ratio for ischemic stroke after influenza vaccine alone. Moreover, the statistical signal has not been identified in any other age groups following other vaccines or combination of vaccines in the VSD RCA or in any other vaccine safety monitoring systems in the US (VAERS, CMS, VA, VA EHR) or around the world (Canada, EU. Israel). While it is important to note that these other systems generally did not have the ability to investigate co-administration with influenza vaccine, such analyses are planned.

The put this information in the context of what is known and what has been learned recently from new data regarding relationships of ischemic stroke, COVID-19, influenza, it is known that COVID-19 disease is associated with increased risk of acute ischemic stroke (AIS). Among Medicare beneficiaries ≥65 years of age, incidence of AIS hospitalizations was 10 times higher during the 3 days post-COVID diagnosis compared with control periods.[100] COVID cohort estimated incidence of AIS is 2.10% (1.97—2.23) within 6 months after COVID diagnosis,[101] though stroke and COVID symptoms present concomitantly in >80% of cases.[102] A recently completed analysis on COVID identified an incidence of stroke of 2.2% overall among patients ≥65 years of age who were hospitalized with COVID-19 between March 2020 and October 2022. COVID-19 patients who develop stroke are more likely to be of older age, have more severe COVID-19 disease, and are more likely to have hypertension, diabetes, and coronary artery disease than those who do not.[103] In terms of who may be at greater risk, it is known that those who develop stroke are more likely to be of older age, have more severe COVID-19 disease, and more likely to have hypertension, diabetes, and coronary artery disease than those who do not develop stroke. In terms of who may be at lower risk, it has been observed that COVID-19 vaccination is associated with a reduced risk of ischemic stroke after COVID-19, including for those ages ≥65 years of age.

[100] Yang Q et al. Neurology 2022; 98(8): e778-789
[101] Taquet M et al. Lancet Psychiatry 2021; 8(5): 416-427
[102] Nannoni S et al. International Journal of Stroke 2021;16(2): 137-149
[103] Nannoni S et al. International Journal of Stroke 2021;16(2):137-149

In terms of influenza, influenza vaccination, and stroke, an association between recent respiratory infection and increased stroke has been noted in some observational studies.[104] While 2 small randomized studies did not note a significant effect of influenza vaccination on stroke risk,[105] decreased risk of stroke with influenza vaccination has been reported in several observational studies.[106] Additionally, a benefit of influenza vaccination has been noted in some studies examining major cardiovascular outcomes, some including stroke within composite outcomes.[107] The hope is to learn more about COVID-19 and influenza and their relationship to stroke and to better understand potential protective effects of vaccination given the limitations that potential reduction in stroke risk varies and is not seen in all studies; populations, study designs, outcome definitions, and analytic methods vary across studies; observational data are more subject to bias; and overall data are limited concerning specific influenza vaccines and stroke-specific risk.

In the collective effort to interpret the ischemic stroke safety signal, there was a particular interest in these outcomes within the population of people ≥65 years of age. CDC was able to initiate pursuit of these questions through 2 large healthcare data sources, the National Patient-Centered Clinical Research Network (PCORnet©) and HealthVerity. PCORnet© is comprised of EHR data from ambulatory, ED, and inpatient settings. It covers all patients with and without insurance in participating health systems, or about 10% of the US population including those ≥65 years of age. There is almost no lag in these data because it comes directly from participating PCORnet© sites following structured inquiries and does not have external dependencies, such as processing of claims. CDC used these data to rapidly assess incidents of stroke across this diverse population among those with recent COVID-19 or influenza and incidence overall in this population.

HealthVerity is a massive healthcare data source that includes medical claims from closed payor systems related to ambulatory, ED, and inpatient settings. These data are linked to vaccination data from the Federal Retail Pharmacy Program (FRPP) using health verities prior to say preserving record linkage technology. It covers patients insured through Medicare Advantage or about 25% of the US population ≥65 years of age. There is an approximate 3-month lag in data when using closed claims. These data were to assess incidence of stroke across the insured US population with recent COVID-19 or influenza vaccination and incidence overall in this population.

Methods used in each of these datasets were designed to capture incident strokes. Patients with a history of stroke were intentionally excluded to avoid over-estimation of incidence but may have resulted in under-capture of history of stroke and TIA associated with risk of stroke. ICD-10 codes were generally chosen to align with the definitions of stroke used in the VSD. It is known that stroke and COVID symptoms often present simultaneously, as do stroke and influenza symptoms. Stroke is frequently an early complication of respiratory disease. While healthcare data can identify the exact date and time of the administration of a vaccine, that is not true for the onset of COVID or influenza infection or their symptoms. Use of the interval of -3 to 28 days around diagnosis allows for the identification of patients who were admitted with acute stroke, get tested for COVID-19, and have a positive test that results on Day 1 or 2 of their hospital stay.

[104] Smeeth L et al, N Engl J Med 2004; 351: 2611-8; Zurrú MC et al, Stroke 2009; 40:1986-90
[105] Loeb M et al, Lancet Global Health 12 2022; 10: e1835-e1844; Phrommintikul A et al, Eur Heart J 2011; 32: 1730–1735
[106] Holodinsky JK et al, Lancet Resp Health 2022; 7: e914-e922; Rodriguez-Martin S et al, Neurology 2022; 00: e2199-e2160; Asghar Z et al, Vaccine 2015; 33: 5458-5463; and Chiang MH et al, Am Heart J 2017;193:1-7
[107] Phrommintikul A et al, Eur Heart J 2011; 32: 1730–1735; Chiang MH et al, Am Heart J 2017;193:1-7

There was a high incidence of stroke following COVID-19 or influenza diagnosis in the PCORnet© data over the late Omicron period of 2022. In the -3 days prior to COVID diagnosis to 28 days post-diagnosis, there was an incidence of approximately 8,800 incident strokes per million over these days. Although there is not a current estimate of incident strokes in the US, it is possible to calculate an average incidence of stroke in this population using this healthcare data. Incidence within -3 to 7 days of COVID-19 disease was 93.5% per million among adults ≥65 years of age with COVID-19 (N=77,981) and 90.9% in adults ≥65 of age with influenza (N=11,396). Average stroke incidence among adults ≥65 years of age in the HealthVerity population over 28 days was slightly less than 1,400 strokes per million over this time period. In contrast, a very low incidence of stroke was observed in the recently vaccinated population. Notably, the groups in this analysis for both PCORnet© and HealthVerity are of the same age category and adjusted time at risk. Crude incidence within these groups is not otherwise adjusted for underlying medical conditions or older age groups. While attributable risk was not presented and causality was not assessed in any way, these are helpful observations.

With regard to the WG's interpretation and next steps, the WG believes that the review of safety data is reassuring and must continue. The priorities identified by the WG are to: 1) continue to closely follow the intermittently statistically significant signal and VSD, with continued review by VaST and colleagues; 2) continue performing supplementary analyses to clarify the relationship between the signal and any specific vaccine, co-administration of vaccines, and/or confounding; and 3) continue the most intensive vaccine safety surveillance in US history. While the data pertaining to vaccine safety is reassuring, in contrast, the data pertaining to COVID-19 disease and influenza were not so reassuring. Based on the review of healthcare data demonstrating high incidence of stroke with COVID-19 or influenza, the priorities include increasing awareness of the risk of stroke with COVID-19 disease and influenza and continuing to encourage uptake of the bivalent COVID-19 boosters.

In summary, the COVID-19 ACIP WG remains confident in current COVID-19 vaccine recommendations and does not recommend any changes to the current recommendations, including those regarding coadministration of vaccines. CDC and partners anticipate the opportunity to review and consider upcoming analyses prior to the 2023-2024 influenza season.

Updates on COVID-19 Hospitalizations: COVID-NET

Christopher A. Taylor, PhD (CDC/NCIRD) provided updates on population-based rates of COVID-19-associated hospitalizations from COVID-NET. All hospitalizations captured in COVID-NET from March 2020–February 2023 had a positive SARS-CoV-2 test during hospitalization or within 14 days prior to admission. Rates of older adults 65–74 years of age and ≥75 years of age respectively have been highest throughout the pandemic. For both the Delta and early Omicron peaks in January 2021 and January 2022, rates among adults ≥75 years of age were about 2 times as high as those in the next youngest age group of adults 65–74 years of age. For the 6 months from August 2022–February 2023, rates among adults ≥75 years of age were 3 times as high relative to adults 65–74 years of age. Rates among children <6 months of age remained elevated relative to older children and adolescents.

From March 2020–February 2023, the proportion of hospitalizations comprised of adults ≥75 years of age increased steadily since Summer 2021. For the 6 months from August 2022–February 2023, about 40% of all adult COVID-19 hospitalizations were among adults ≥75 years of age. In terms of hospitalizations among pediatric age groups from March 2020–February 2023, hospitalizations comprised of infants <6 months of age increased steadily and in the most recent 6 months from August 2022–February 2023 showed that infants <6 months of age

comprised more hospitalizations than all other pediatric age groups, with 25% to 30% of all COVID-19-associated hospitalizations in this age group.

To assess the proportion of hospitalizations for which COVID-19 was a likely reason for admission by age group and period of COVID variant predominance for June 2020─November 2022, trained COVID-NET surveillance officers used an established algorithm. As a reminder, all COVID-NET hospitalizations have a laboratory-confirmed positive SARS-CoV-2 test during hospitalization or within 14 days before hospital admission. Hospitalizations for which admission was noted as likely due to trauma, obstetrics, labor and delivery, psychiatric admissions requiring acute medical care, and inpatient surgery or procedures were categorized as such. Hospitalizations for which the chief complaint included fever, respiratory illness, COVID-like illness (CLI), or suspicion for COVID-19 were classified as having COVID-19 as the likely reason for admission. Hospitalizations for which the medical chart specifically indicated that COVID-19 was an incidental finding but that the admission was likely not COVID-related were categorized as such. For hospitalizations for which another reason for admission was specified in free text, COVID-NET clinicians examined the specified reasons and further classified.

For the period June 2020─November 2022, about 80% to 90% of COVID-19-associated hospitalizations among children ≤4 years of age had COVID-19 as a likely reason for admission across all variant periods. For older children 5─11 years of age, the range was between 70%─95%. Adolescents 12─17 years of age had the lowest proportion of hospitalizations with COVID-19 as a likely reason for admission at 50%─60% for the Omicron-predominant period beginning in December 2021. Among this group, many admissions were psychiatric admissions requiring acute medical care, with more than 25%─35% of hospitalizations in some months. Adults 18─49 years of age had a similarly low proportion of hospitalizations with COVID as a likely reason for admission at 50%─70% during the Omicron period. Among this group, many admissions were due to labor and delivery, with more than 25%─30% of hospitalizations attributed to that in some months. Among adults ≥50 years of age, between 80%─90% of hospitalizations included COVID as a likely reason for admission across all variant periods examined.

Looking at underlying medical conditions among non-pregnant adults ≥18 years of age in COVID-NET from June 2022–November 2022 in which COVID-19 was a likely reason for admission, the most common underlying medical conditions were chronic lung disease, cardiovascular disease, obesity, diabetes, and neurologic disorders. Chronic lung disease was prevalent and more than two-thirds of all adult COVID-19-associated hospitalizations. Cardiovascular disease present in more than half; diabetes, obesity, and neurologic disorders in about one-third; and renal disease in about one-quarter. A total of 96% of hospitalized adults had at ≥1 underlying medical condition.

Regarding the prevalence of underlying medical conditions in COVID-19-associated hospitalizations among children and adolescents ≤17 years of age from June 2022─November 2022, the most recent 6 months for which complete data were available, the data were limited to hospitalizations for which COVID-19 was the likely primary reason for admission. The most common underlying medical conditions are asthma, prematurity, feeding tube dependence, and obesity. It is important to note that asthma and prematurity were underlying medical conditions in more than 10% of these pediatric cases. In contrast to adults, 49% of COVID-19-associated hospitalizations among children and adolescents had no recorded of underlying medical conditions. There were some notable differences between younger and older pediatric age groups. Among children <2 years of age, prematurity was by far the most common underlying condition recorded in nearly 20% of all hospitalizations. The next most common was feeding

tube dependence at 5%. Among the 3 older pediatric age groups, the most common underlying medical conditions differed. While the order of these most common conditions varied by age group, the most common are asthma, feeding tube dependence, obesity, immunocompromising conditions, and chronic lung disease not including asthma and not related to prematurity.

With regard to vaccination status by age group among non-pregnant adults ≥18 years of age and older in COVID-NET from October 2022–November 2022, the 2 months of data available after the updated bivalent booster dose was approved, more than half of hospitalized children 5–17 years were unvaccinated. One-third of adults 18–49 years of age remain unvaccinated, with less than 25% for adults ≥50 years of age. Very small proportions of hospitalizations occurred among persons vaccinated with the updated bivalent booster. Looking at age-adjusted rates of COVID-19-associated hospitalizations by vaccination status for adults ≥18 years of age from January 2021–December 2022, in December 2022, compared to adults who received an updated bivalent booster dose, the monthly rates of hospitalization were 16 times higher among unvaccinated adults and 2.6 times higher among vaccinated adults who had not received an updated bivalent booster dose.

Updates to COVID-19 Vaccine Effectiveness in the United States

Amadea Britton, MD, SM (CDC/NCIRD) presented a summary of VE data available from CDC studies, including VE of the original monovalent vaccines against symptomatic infection in children aged 6 months–4 years (Pfizer-BioNTech) and 6 months–5 years (Moderna); VE of bivalent vaccines against symptomatic infection in children and adolescents aged 5-17 years and adults aged ≥18 years; and bivalent vaccines against severe disease in adults, with a focus on adults ≥65 years of age.

Beginning with data on VE against symptomatic infection in young children 6 months–5 years of age for Moderna and 6 months–4 years of age for Pfizer-BioNTech as presented in the previous week's *MMWR*. For children 6 months–5 years receiving Moderna, the recommended primary series is 2 doses given 4 to 8 weeks apart. Given that dosing interval and the initial authorization date of June 18, 2022, August 1, 2022 was the earliest date that a child could have been included in analysis for the complete series. In other words, the earliest a child receiving the vaccine could have been at least 2 weeks out from completion of their second dose. For children 6 months–4 years of age receiving the Pfizer-BioNTech vaccine, the recommended primary series is 3 doses, with the first and second doses separated by 3 to 8 weeks and the second and third doses separated by at least 8 weeks. Since this series required an extra dose, the earliest date a child could have been included in analyses of the complete primary series was September 19, 2022. For Pfizer-BioNTech, the recommended third dose was changed from a monovalent to a bivalent dose on December 9, 2022, but this analysis was restricted to VE of monovalent doses because uptake of the bivalent dose in his age group remains too low at this time to estimate VE.

For background, national coverage estimates from CDC's COVID Data Tracker show that young children 2–4 years of age have the lowest coverage for either a single dose or a completed primary series, with just over 10% for 1 dose and just over 5% for the complete primary series. Coverage is even lower among children <2 years of age. Children vaccinated early may be meaningfully different from those who remain unvaccinated, which may impact VE estimates. These estimates should therefore be considered preliminary.[108]

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

The Increasing Community Access to Testing (ICATT) Program 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 this analysis, only children whose caregivers reported symptoms and who were between 3–5 years of age for the Moderna analysis and 3–4 years of age for the Pfizer-BioNTech analysis were included. Children with immunocompromising conditions were excluded. These data are for tests from July 4, 2022–February 5, 2023, although the analysis start date varied depending on dose analyzed. This was a period when the Omicron BA.4 and BA.5 sub-lineages predominated, but included some time when XBB and related sub-lineages were circulating.

Looking at preliminary estimates of VE for primary series monovalent Moderna vaccine among children 3–5 years of age against symptomatic infection from July 4, 2022 – February 5, 2023, VE was 40% for 1 dose or a partial series during the interval between the first and second dose. VE for the complete 2-dose primary series of Moderna, VE was 60% during the 2 weeks to 2 months after the second dose. This decreased to 36% after 3 to 4 months, though the confidence interval was wide and had some overlap with the earlier estimate.[109] Looking at the same data for the Pfizer BioNTech among children 3–4 years of age, VE for a 1-dose partial series was 19%, with a confidence interval that just crossed the null. For 2 doses, which for Pfizer is also a partial series, VE was 48% in the interval between Doses 2 and 3. For 3 doses, the complete Pfizer primary series, VE was 31% in the 2 weeks to 4 months after the dose.

There are a number of limitations for this analysis. First, as noted earlier, vaccine coverage is low in children <5 years of age. When coverage is low, vaccinated children may be meaningfully different than unvaccinated children, potentially biasing early VE estimates and making the estimates less stable over time. Second, the prevalence of prior infection among children is high. Based on CDC's seroprevalence data through December 2022, more than 87% of children 6 months–4 years of age have had a prior infection.[110] If unvaccinated children have protection from prior infection, it may lead to underestimation of VE. However, as the prevalence of prior infection is so high, these estimates are likely to represent the current situation among young children in the US. Lastly, while the goal of the US COVID-19 vaccination program is to prevent severe disease and hospitalization, the ICATT platform estimates VE for symptomatic infection only. Low vaccination coverage in this age group has, to date, prevented estimation of VE against more severe disease in other platforms and may impact future ability to estimate VE in this age group, including against severe outcomes. Given this context, VE against symptomatic infection can provide important insight into vaccine protection.

In summary, a complete monovalent primary vaccination series helped provide protection for children 3–5 years of age against symptomatic SARS-CoV-2 infection for at least the first 4 months after vaccination. Some waning of the monovalent Moderna primary series might occur by 3 to 4 months after the second dose based on point estimates, although confidence intervals overlapped. This is similar to patterns observed in older children and adults in the first months after vaccination. Waning of monovalent Pfizer-BioNTech VE against symptomatic infection could not be assessed, but it is also likely based on analyses in older children and adults. CDC recommends that children should stay up to date with COVID-19 vaccines, including completing the primary series. Those who are eligible should receive a bivalent vaccine dose. CDC will continue to monitor VE in this age group, including against severe disease and for recently authorized bivalent doses.

[109] Fleming-Dutra, Ciesla, Roper, et al. MMWR February 16, 2023
[110] https://covid.cdc.gov/covid-data-tracker/#pediatric-seroprevalence

Moving to updated estimates of VE against symptomatic infection among children and adolescents 5–17 years of age and adults ≥18 years of age for a bivalent booster dose against symptomatic infection, Dr. Britton first reviewed the concepts of “absolute” and “relative” VE. Absolute VE compares the frequency of health outcomes in vaccinated and unvaccinated people, such as comparing outcomes in people who received an updated bivalent booster versus no vaccine at all. Relative VE compares the frequency of health outcomes in people who received one type of vaccine to people who received a different vaccine or by comparing people who received more vaccine doses to those who received fewer doses, such as comparing outcomes and people vaccinated with an updated bivalent booster versus monovalent vaccine only. In this analysis, relative VE can be interpreted as the additional protection provided by an updated bivalent booster among people who already received monovalent COVID-19 vaccines.

This analysis again used the FRPP data through ICATT. Looking at children and adolescents 5—17 years of age and adults ≥18 years of age with CLI, individuals with the last monovalent dose less than 4 months previously were excluded. Persons with immunocompromising conditions also were excluded. Tests in this analysis were completed between December 1, 2022 and February 13, 2023. This includes periods of both BA5-related sub-lineage predominance and XBB/XBB.1.5 related sub-lineage predominance. Because previously published work from this platform demonstrated that VE against symptomatic disease for these 2 groups was similar, these time periods were combined.

In terms of the results for relative VE for children and adolescents 5—17 years of age. Relative VE in the month after vaccination was 65% for children 5—11 years of age and 68% for adolescents 12—17 years of age. An early indication of slight waning as was observed with the monovalent vaccine. Notably, a Pfizer BioNTech bivalent booster was first authorized for adolescents ≥12 years of age on September 1, 2022 and for children 5—11 on October 12, 2022. Moderna was authorized for children and adolescents 6—17 on October 12th as well. This means that there is less follow-up time for children 5—11 years of age, so it was not possible to estimate VE 4 to 5 months after the bivalent dose in children 5—11 years of age.

Looking at the same analysis adult age groups with individuals who received a bivalent booster compared to individuals who received only 2 to 4 doses of monovalent vaccine, similar waning patterns were observed across age groups. Estimates of waning among adults ≥65 years of age appeared to be slightly lower than in younger individuals. The pattern of waning against symptomatic infection was very similar to what was observed after monovalent booster doses, with VE against symptomatic infection decreasing to minimal protection by around 5 to 6 months.

Now moving to updated estimates of VE against ED/UC encounters and hospitalizations among adults ≥18 years of age in the VISION Network, the VISION Network is a multistate network based on EHRs. Like ICATT, it uses a test-negative design with cases having CLI and a positive PCR and controls having CLI with a negative PCR. For this analysis, VE was adjusted for age, sex, race, ethnicity, geographic region, calendar time, and local rates of SARS-CoV-2 circulation. Vaccination was determined via EHRs and state and city registries.

In terms of absolute VE of ≥2 monovalent doses against ED/UC encounters and hospitalizations among adults ≥18 years of age and adults ≥65 years of age from September 2022 – January 2023, it is important to note that the median time since last monovalent dose was almost a full year for both age groups. What was observed was that residual protection against ED/UC encounters was minimal for both age groups. However, it remained somewhat higher against hospitalization, with residual protection of 19% for adults 18—64 years of age and 28% for those

≥65 years of age. Understanding that there is likely some residual protection from monovalent vaccines against hospitalization is important context to understand the relative contributions of bivalent vaccines. Also observed was that protection appeared to be slightly higher for both outcomes in adults ≥65 years of age, which may be due to behavioral differences and lower infection-induced immunity among older individuals.

Preliminary estimates of VE against hospitalizations among adults aged ≥65 years show relative VE of the bivalent booster against ED-UC visits and hospitalizations. The reference groups in this analysis were the individuals from the VISION Network analysis who received only monovalent doses, with their last dose at least 2 months previously. Note again that most individuals in this group were almost a full year from their last dose. Among these individuals, a bivalent booster offered an additional 50% protection against ED-UC visits in the first 7─59 days after boosting, which declined to 36% after 60 days. The median time since the last dose was 76 days. Relative VE against hospitalization was similar at 52% and 31% at 7─59 and 60─119 days, respectively. Although the relative trends were similar for both outcomes, residual protection prior to the booster was higher against hospitalization than for ED-UC visits, so it is likely that total protection against hospitalization also was higher. There also may have been some hospitalizations captured by the VISION Network platform that represent less severe COVID-19 disease comparable to that of an ED or UC visit.

To provide an update 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 IVY Network, the IVY Network is a multistate VE platform that uses a prospective test-negative design. For this analysis, participants were from 24 hospitals in 19 states with hospitalization between September 8, 2022 and January 30, 2023. This analysis included data beyond what was published in the *MMWR* in December. Participants included in this analysis were adults ≥65 years of age who were hospitalized with CLI. Cases had a SARS-CoV-2 positive PCR or antigen test, and controls were negative for SARS-CoV-2 and influenza by PCR. Models were adjusted for age, sex, race and ethnicity, admission date, and HHS Region. Looking at the updated IVY results among adults ≥65 years of age, comparing people with at least 2 monovalent doses but no bivalent dose, to unvaccinated people, VE was 17% with a confidence interval crossing the null. This is consistent with limited to no residual protection. The relative VE of a bivalent booster, comparing individuals who received a bivalent booster with individuals with at least 2 monovalent doses but no booster, the additional protection offered by a bivalent booster was 52%. Note that the median time since last dose was almost a year at 352 days. In terms of absolute bivalent VE, comparing individuals who received a bivalent booster to unvaccinated individuals who never received even monovalent vaccine, the estimate is almost identical to the relative VE of the bivalent booster. This is consistent with the finding that the monovalent vaccine is providing limited to no protection after 1 year.

To share some information on the COVID-19 hospitalizations included in this analysis, all cases included in the analysis met the CLI definition. Patients with incidentally detected SARS-CoV-2 infections with no CLI were not included. However, of all included hospitalized cases, 59% had hypoxemia (e.g., low oxygen levels) and 16% required ICU-level care. This suggests that, as with VISION, there may have been some cases included that, while a result of COVID-19 disease, did not represent severe COVID-19 disease. Inclusion of less severe cases may result in lower estimates of VE against hospitalization, as VE tends to be higher against more severe outcomes.

There are several limitations for the data on older children, adolescents, and adults. First, for estimates of absolute VE, if unvaccinated individuals are meaningfully different than vaccinated individuals, these estimates may be biased. Second, for interpretation of estimates of relative VE, residual protection from prior doses is an important consideration. This is likely to be particularly important for severe disease, for which residual protection from prior doses may be higher than protection for symptomatic infection. In addition, interpreting waning relative VE for bivalent doses is challenging because relative estimates also are dependent on the underlying patterns of waning protection of prior monovalent doses. This means that if relative VE decreases, it does not necessarily mean the total protection on individual experiences has decreased by that same amount. Third, there is limited information on prior infection. Although, just as with young children, it is known that rates of prior infection in adults and older children are high. VE estimates presented during this session are therefore a snapshot of how well the vaccine is working under current conditions. Lastly, VE against COVID-19-associated hospitalization from the platforms presented represents COVID-19 disease requiring hospitalization but may underestimate protection against more severe disease, such as that requiring respiratory support and ICU level care.

In summary, current data from CDC VE platforms demonstrate that bivalent booster doses provide added protection compared to earlier monovalent doses against symptomatic infection in children and adolescents 5─17 years of age and in adults ≥18 years of age. However, there may be early evidence of waning consistent with patterns previously observed from monovalent vaccines against symptomatic disease. Updates to VE of bivalent booster doses against ED/UC visits and hospitalization in adults confirm that the bivalent vaccines are providing protection against ED/UC visits and hospitalization compared to people who received 2, 3, or 4 doses of the monovalent vaccine and no bivalent dose. For most people who received monovalent doses and are eligible for a bivalent booster, more than a year has elapsed since their last monovalent dose and they may have limited remaining protection. All eligible people should stay up to date on COVID-19 vaccinations, including receiving a primary series and a bivalent dose if eligible.

Considerations for Transitioning to Bivalent Primary Series

Sara Oliver, MD, MSPH (CDC/NCIRD) discussed considerations for a bivalent primary series for which ACIP thoughts were being requested on harmonizing the vaccine strain composition for mRNA COVID-19 vaccines across both primary series and booster doses. At this point, logistically that would mean changing the primary series from the monovalent vaccine (original/ancestral strain) to bivalent (original/ancestral plus Omicron BA.4/5 strains) for all ages. The current recommendation is for people ≥6 months of age to receive a 2-dose monovalent vaccine and a bivalent booster dose. The proposal for future recommendations would be for people ≥6 months of age to receive a 2-dose bivalent primary series and a bivalent booster dose in most ages. While a later presentation would discussion simplifying the primary series and booster approach for some ages, this presentation focused specifically on using the existing vaccine framework, but potentially using a bivalent vaccine for all recommended doses. Policy on any bivalent primary series will be coordinated with FDA for regulatory action and CDC for recommendations for use. Therefore, Dr. Oliver noted that these discussions were pre-decisional and there would not be a vote specifically on this.

The summarize the public health problem for the primary series, the eligible persons would be those who are unvaccinated currently, which predominantly is a pediatric population.[111] Looking at weekly population-based rates of COVID-19-associated hospitalizations among children and adolescents ≤17 years of ages in COVID-NET from March 2020–February 2023, the highest rates are among children ≤6 months of age. Hospitalization rates have varied over the last several years, with an increase during the larger BA.1 Omicron surge in early 2022, especially among children 6 months—2 years of age. Half of hospitalized children had no underlying medical conditions. Looking at COVID-19 hospitalizations by vaccination status, across all ages of children 5—11 years of age and adolescents 12—1 years of age between December 2021 - December 2022, hospitalization rates were higher for unvaccinated children and adolescents.[112] Given low uptake of the bivalent boosters in the pediatric population, it is not yet possible to estimate hospitalization rates for children and adolescent with a bivalent booster. The lowest hospitalization rates are among the vaccinated individuals, so hopefully data in coming months will be able to include the bivalent population.

In terms of COVID-19 deaths in children and adolescents by year of age over the course of the pandemic, over 1,500 children have died from COVID since early 2020. The highest numbers of death have been in the youngest children and in older adolescents. While analyses on death rates by vaccination status cannot be limited to just the pediatric population at this time, the lowest rates of death have been among those with the updated or bivalent booster.[113]

To summarize, children and adolescents can develop severe COVID. While the rates in children are lower than adults, nearly 1,500 children and adolescents have died from COVID since the beginning of the pandemic, and it is not possible to predict which children will have severe disease. Half of the hospitalized children and adolescents had no underlying medical condition. During all time periods, COVID hospitalizations and mortality were consistently higher among unvaccinated persons than among persons who had completed a primary series and/or an updated booster. In spite of this, many children remain unvaccinated for COVID.

In terms of the data on benefits and harms, data are available to evaluate a bivalent vaccine as a primary series for Moderna using their BA.1 bivalent vaccine given as a primary series to children 6 months—5 years of age. These data were presented during the VRBPAC meeting in January 2023. There were 179 children who received a 25 ug bivalent vaccine who were compared to nearly 5,000 children who received a monovalent ancestral vaccine previously. The median follow-up time for the 2 groups varied slightly. For the original ancestral vaccine, the follow-up time was just over 100 days, whereas for the bivalent vaccine, it was 85 days. An important note is that the 2 studies were conducted during different timeframes, so the seropositivity of the participants was different. For the study with the original vaccine, 8% of children were baseline SARS-CoV-2 seropositive. Among children who received a bivalent primary series, over 60% were baseline seropositive. This likely reflected the impact of Omicron infections over the past year.

[111] Source: https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends Updated February 10, 2023
[112] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination Accessed February 10, 2023
[113] Source: https://data.cdc.gov/NCHS/Provisional-COVID-19-Deaths-Counts-by-Age-in-Years/3apk-4u4f/data. Accessed February 16, 2023

Comparing the immunogenicity of the original monovalent vaccine and the BA.1 bivalent vaccine, the GMT for the BA.1 neutralizing antibodies for the bivalent compared to the monovalent had a GMR of 25.42 (20.14, 32.07). This clearly met the prespecified superiority criteria. The BA1 bivalent vaccine provided a boost, but the ratio was below 1.0. However, the ratio of 0.83 (0.67, 1.02) did meet the prespecified noninferiority criteria with a lower bound of the confidence interval of 0.67.

For the available safety data of a bivalent primary series, there were 142 children who received both doses and were included in the safety analysis. Overall, the percentage of patients reporting a solicited local or systemic event was similar to or less than percentages seen after the original vaccine. However, this may be a result of the larger seropositive participants in that bivalent group. The AEs seen after a bivalent primary series were similar to what was reported after the original vaccine in this age group. No Grade 4 solicited AE were reported. There was 1 SAE of asthma exacerbation after the first dose that was assessed as unrelated to vaccination by the investigator. In terms of local reactions for the BA.1 bivalent vaccine compared to the original vaccine, rates were the same or lower in the bivalent group. Injection site pain was the most common local reaction. Regarding systemic reactions among children 6─36 months of age 37 months─5 years of age, similar patterns were seen overall. Irritability was most common in the younger children and fatigue in the older children.[114]

Thinking through other considerations for a bivalent primary series, Dr. Oliver addressed some concerns pertaining to imprinting. As a reminder, imprinting is the concern that the initial exposure to 1 virus strain may prime the B-cell memory and limit the development of memory B cells and neutralizing antibodies against new strains. As there are now 3 years of experience with this virus, it is known that prior infection and/or vaccination history likely have some impact on the subsequent immune response and that the risk of reinfection can vary by somebody's previous infection or exposure.[115] This can be impacted by a variety of factors (e.g., continued virus evolution of SARS-CoV-2, time since last vaccination, prior infection, imprinting). Affinity maturation that can occur. This is the ability of memory B cells to mature over time, especially when exposed to newer strains.[116] Affinity maturation also is likely improved with more time between doses. While somewhat limited, several studies have shown that variant-specific vaccines can not only boost, but also initiate new variant-specific immune responses. However, most of these studies are focused on laboratory-based assays.[117] The clinical impact of different immune responses by prior exposure or how it may differ by vaccination and infection, requires additional research. What is known is that vaccines continue to be able to provide a broad boost in antibody response and continue to provide important protection against severe COVID. It also is important to note that imprinting concerns relate to the incremental benefit of updated variant-specific vaccine.

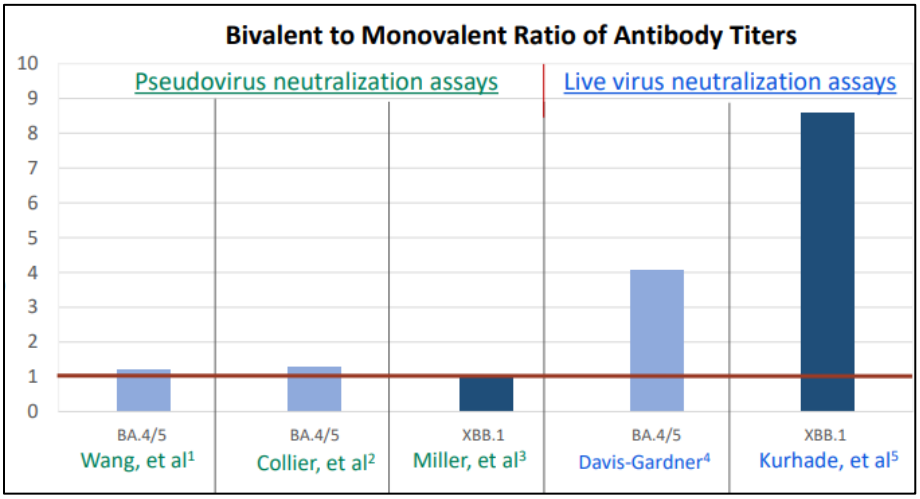
[114] From Jan 26, 2022 VRBPAC meeting: https://www.fda.gov/media/164810/download

[115] Immune boosting by B.1.1.529 (Omicron) depends on previous SARS-CoV-2 exposure | Science; Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution (nature.com); and Protective Effect of Previous SARS-CoV-2 Infection against Omicron BA.4 and BA.5 Subvariants | NEJM

[116] Affinity maturation of SARS-CoV-2 neutralizing antibodies confers potency, breadth, and resilience to viral escape mutations – ScienceDirect; and The germinal centre B cell response to SARS-CoV-2 | Nature Reviews Immunology

[117] SARS-CoV-2 Omicron boosting induces de novo B cell response in humans | bioRxiv; and Molecular fate-mapping of serum antibody responses to repeat immunization (nature.com)

To review the available data that compare monovalent and bivalent vaccines, the only available data for a primary series already have been reviewed. Several studies compared antibody titers with recent Omicron sub-lineages for both the bivalent and monovalent vaccines. Studies ranged from approximately 21–42 days after the bivalent vaccine. For this interpretation, assays differed by laboratory and the exact level of titers could not be compared across different laboratories. The most meaningful outcome for this is the ratio of antibody titers from bivalent to monovalent vaccines, which is depicted in this figure:



1. https://www.biorxiv.org/content/10.1101/2022.10.22.513349v1.full.pdf
2. https://www.nejm.org/doi/full/10.1056/NEJMc2213948
3. https://www.nejm.org/doi/full/10.1056/NEJMc2214314
4. https://www.biorxiv.org/content/10.1101/2022.10.31.514636v1
5. https://www.nature.com/articles/s41591-022-02162-x

In the figure, a ratio of 1, highlighted with a red line, would mean the 2 vaccines are equal. A ratio of over 1 would mean an improvement with a bivalent vaccine, and a ratio of less than 1 would be better titers in the monovalent vaccine. The figure also differentiates by type of assay done. The studies done with a pseudo-virus neutralizing assay have green text and the live virus neutralization assays have blue text. The bars are also slightly different shades of blue based on which Omicron sub-lineage was tested. BA.4/5 is in the lighter blue and the XBB is shown in a darker blue. Overall, most studies show an improvement in neutralizing antibodies for Omicron sub-lineages with a BA.4/5 bivalent vaccine, where that ratio would be over 1. There are differences noted in the ratios of type of assays where the improvement in the bivalent vaccines seemed to be more noted when the assay was the live virus assay. However, the clinical impact is unknown for any specific ratio or antibody level. Notably, neutralizing antibodies at a single point in time cannot convey the entirety of the immune response.

To highlight the clinical data, the outcomes for monovalent and bivalent vaccines must be compared. It was not possible to do head-to-head comparison of studies comparing clinical outcomes directly in the US due to timing of the authorizations. However, these data were shown during the VRBPAC January 2023 and are published in a preprint.[118] A study in the UK found an approximately 10% increase in relative VE for the prevention of COVID infections for a bivalent BA.1 vaccine. However, no COVID hospitalizations were noted at the time, so it was not possible to estimate the differential impact for the prevention of severe COVID.

[118] https://www.fda.gov/media/164810/download A Randomized Trial Comparing Omicron-Containing Boosters with the Original Covid-19 Vaccine mRNA-1273 | medRxiv

Overall, bivalent COVID-19 vaccines are able to induce an immune response when given either as a primary series or as a booster. There are limited data to directly compare COVID-19 outcomes after receipt of a monovalent or bivalent vaccine, especially against the prevention of severe disease. COVID-19 vaccines have a high degree of safety. Initial safety data from a bivalent primary series trial are encouraging, but the study was not powered to assess rare AEs.

To highlight some feasibility and implementation considerations with a transition to a bivalent primary series, there are currently 11 total mRNA COVID-19 vaccine products (5 Moderna and 6 Pfizer-BioNTech) between monovalent, bivalent, and different doses and formulations by age. While the final number of products ultimately will depend upon what is authorized in transitioning from primary series to bivalent, it is possible to reduce from 11 to 5 total products (2 Moderna and 3 Pfizer-BioNTech). Importantly, this would eliminate look-alike vials for Pfizer and Moderna. In terms of feasibility and implementation, a transition to a bivalent primary series could improve storage space. Providers have limited storage space. In addition to monovalent and bivalent products, the VFC program stock is required to be duplicate and separate. It also reduce errors, by eliminating look-alike vials. Currently, one of the most common administration errors reported is providers giving a bivalent vaccine as a primary series dose in error. It also would allow for continued access to primary series. While the dates vary by product and age group, the majority of current monovalent vaccine stock in the US expires within the next few months. There would be a possibility that access to primary series could be more limited without transitioning to a bivalent option. Regarding resource use, work is ongoing to evaluate cost-effectiveness in preparation for transition to commercialization of COVID-19 vaccines. For this particular question, vaccines are already purchased, delivered, and available. Transition of a primary series recommendation for monovalent to bivalent is unlikely to have a significant impact on resource use.

In summary, receiving a COVID-19 vaccine primary series continues to be important for the prevention of COVID-19 severe disease, hospitalization, and death. In spite of this, many children and adolescents remain unvaccinated for COVID-19. COVID-19 vaccine recommendations that are simple to implement may remove some barriers to uptake. Harmonizing the primary series and booster doses could simplify the presentation, reduce administration errors, and allow for continued access to primary series for unvaccinated populations. Overall, the WG was supportive of this transition of the mRNA COVID-19 vaccine primary series from monovalent (original) to bivalent (original plus Omicron BA.4/5).

In closing, Dr. Oliver requested feedback from the ACIP on the following:

- ❑ Transition to bivalent primary series can occur only after FDA regulatory action and updates to CDC recommendations. There is no vote. It is pre-decisional, but ACIP's discussions can help inform actions for the future.

- ❑ What are ACIP's thoughts on a transition of the mRNA COVID-19 vaccine primary series from monovalent (original) to bivalent (original plus Omicron BA.4/5)?

Notably, "monovalent" and "bivalent" designations are based on the currently authorized products. For future vaccines, the focus would be on harmonization of products across primary series and booster doses.

NCIRD Director Remarks

José R. Romero, MD (CDC, Director NCIRD) indicated that before the committee began the next series of presentations, he wanted to take a moment to reinforce the importance of the ACIP's input as plans are made for the future use of COVID-19 vaccines and potential updates to the nation's COVID-19 vaccination efforts. These initial discussions by the ACIP voting members, ex officious, and liaisons, were occurring at a time when there are still limited data and several unanswered questions. However, it is essential that ACIP's discussions are not paralyzed by these uncertainties and limitations. The information previously and to be presented to the ACIP would allow them to assess what is now several years of viral and vaccine data. Nevertheless, it is important to acknowledge multiple uncertainties and unknowns that exist. Hopefully, the information presented will begin to help ACIP plan for the best path forward in terms of the use of available COVID-19 vaccines. CDC is encouraged to hear of ACIP's support for tentative plans to harmonize COVID-19 vaccine efforts and shift from the original monovalent primary vaccine formulation to a formulation used for updated bivalent boosters. While this would not happen until the appropriate FDA authorizations, it is clear that concurrence on a single vaccine composition for primary and booster doses would help streamline and simplify CDC's recommendations, reduce complexity, and allow for clearer communication and guidance to HCP and to the public. CDC recognizes that the previous 3 years have been very difficult for the ACIP as they have crafted their recommendations. Dr. Romero emphasized that he knew this firsthand, having occupied a seat at the inner-table during the initial 18 months of the SARS-CoV-2 pandemic. He and ACIP have often been asked to make difficult decisions without all of the information desired in order to quickly respond to this evolving, unprecedented global pandemic and public health emergency. This has led to the crafting of incremental vaccine policies that have at times added complexity to COVID-19 vaccinations and schedules. Despite the previously mentioned challenges, the ACIP has helped shape vaccine policies that ultimately have helped protect millions of people across the US and save millions of lives. CDC and the American public are grateful for the ACIP's contributions and leadership. CDC remains committed to the efforts to ensure optimal vaccine recommendations moving forward. CDC will continue to monitor the SARS-CoV-2 evolution, COVID-19 disease levels, and vaccine safety and effectiveness in the months ahead and looks forward to hearing the ACIP's thoughts and insights as they discuss the future direction of the COVID-19 vaccine program.

Benefit-Risk for COVID-19 Vaccines

Megan Wallace, DrPH, MPH (CDC/NCIRD) further discussed the benefit and risk assessment for COVID-19 vaccine with respect to benefits of COVID-19 vaccine by age for the primary series; the incremental benefits of COVID-19 vaccine by age and time since the last dose for a bivalent booster dose, with sensitivity analyses modeling high and low points in the pandemic; and the benefit-risk assessment for the bivalent booster dose focused on individuals 12–17 years of age and 18–49 years of age.

To review the methods used, an assessment was performed for both primary series and bivalent booster doses with the results presented in per million primary series or per million bivalent booster doses. The COVID-NET COVID-19-associated hospitalization rates were used from December 2022, which were the most recently available rates by vaccination status.[119] Sensitivity analyses were used to model high and low points in the pandemic. The time horizon, the period over which benefits of vaccination were allowed to accrue, was 6 months. VE

[119] https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination. Rates among unvaccinated used for primary series assessment. Rates among those vaccinated with monovalent doses only used for bivalent booster dose assessment.

estimates were used from VISION,[120] with the assumption of waning by 10% each month starting after Month 2. VE for the primary series assessment was based on the absolute VE for a bivalent dose.[121] The VE for the bivalent booster assessment was based on the relative VE by interval from last monovalent dose to bivalent dose.[122]

These are the monthly rates of COVID-19-associated hospitalization by vaccination status from COVID-NET (main driver of these assessments), rate among the unvaccinated (basis of the primary series assessment), and rate among the vaccinated (basis of the bivalent booster assessment), there were considerable differences in the hospitalization rates by age group:[123]

December 2022 hospitalization rates per 100,000 vaccinated persons with no bivalent booster by age group, COVID-NET

Age group	Rate per 100,000 persons
5-11 Years	2.13
12-17 Years	2.66
18-49 Years	12.89
50-64 Years	27.48
≥ 65 Years	121.10

In terms of estimated COVID-19-associated hospitalizations prevented for every million mRNA COVID-19 primary series over a 6-month period, there are still significant benefits to primary series vaccination. The benefits are the most striking in the older adults, with nearly 16,000 hospitalizations prevented per million doses given. Even for children, nearly 250 hospitalizations were prevented per million doses given. For those age groups for which there were sufficient data, the benefits of the bivalent booster were added. These were the additional benefits one would expect from a bivalent booster beyond the benefits they already are receiving from any previous monovalent doses. Not surprisingly, the expected benefits were smaller for the bivalent booster than the primary series but were still substantial in the older adults, with nearly 2,500 hospitalizations prevented per million doses. For adolescents, these numbers were smaller than seen in the past, with an estimated 53 hospitalizations prevented among adolescents 12–17 years of age per million doses over 6 months.

Dosing interval refers to the time between the most recent monovalent dose and a bivalent dose. Dosing interval has a noticeable impact on the benefits, with longer intervals showing greater benefit. Because benefits of a bivalent booster dose were smallest in adolescents 12–17 years of age and because the benefit assessment is so strongly impacted by hospitalization rates, sensitivity analyses were used to explore what the benefits would look like in this age group under different epidemiologic scenarios. Focusing on the time since the Omicron surge and hospitalization rates in adolescents 12–17 years of age by vaccination

[120] https://www.cdc.gov/mmwr/volumes/71/wr/mm715152e1.htm?s_cid=mm715152e1_w.
[121] Absolute VE of bivalent booster dose (57%) used as the estimated primary series VE. Absolute VE from the bivalent booster was used as an estimate of primary series VE because current VE of monovalent primary series is unknown.
[122] Relative VE of bivalent booster dose used in booster dose assessment (5-7 month interval: 38%; 8-10 month interval: 42%; 11+ month interval 45%). Relative VE for ED/UC visit was used for 2-4 month interval (31%) because VE against hospitalization was not available
[123] https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination

status, benefits were calculated from a low hospitalization rate scenario from March 2022 and a high hospitalization rate scenario from July 2022. For both the low and high scenario, the rate was steady for the 6-month time horizon.[124] The benefits were driven strongly by hospitalization rates. In the high incident setting, approximately 120 hospitalizations would be prevented per million doses over 6 months depending on the dosing interval. The dosing intervals have been different from monovalent and bivalent booster doses. Among adolescents who received a monovalent booster, nearly half received the monovalent booster at an interval less than 8 months after their primary series. Among adolescents who received a bivalent booster dose, over 90% received a bivalent booster ≥8 months after their previous dose.[125]

In terms of the potential myocarditis risk following the bivalent booster dose in this age group, there are limited data to inform the myocarditis risk following a bivalent booster dose. Preliminary VSD myocarditis rates following bivalent booster dose in adolescent and young adult males are lower than first monovalent boosters, but this is limited by small numbers of doses administered. Myocarditis risk is lower with longer time between doses. Rates of myocarditis were lower with an extended interval between Dose 1 and Dose 2 for the primary series.[126] A longer interval between doses for bivalent boosters compared to monovalent boosters also may impact myocarditis rates. Most individuals with myocarditis or pericarditis have fully recovered at follow-up.[127] In previously published analyses, the risk of adverse cardiac outcomes were 1.8 to 5.6 times higher after SARS-CoV-2 infection than after mRNA COVID-19 vaccination among males 12–17 years of age.[128]

Looking at myocarditis rates from the VSD shown in Dr. Shimabukuro earlier by age and sex for Pfizer-BioNTech for Dose 2 of the primary series, the monovalent booster dose, and the preliminary data for the bivalent booster dose, few bivalent doses have been captured in the VSD. However, there has been only 1 myocarditis case reported in any of these age groups. Looking at the incidence rates by dose, the risk might be trending downward, with bivalent boosters having the lowest risk. Again, these are small numbers and wide confidence intervals.[129] In terms of Moderna myocarditis rates from the VSD, no myocarditis cases have been reported. Again, there have been few bivalent booster doses captured.[130]

With regard to estimated COVID-19 hospitalizations prevented versus potential myocarditis cases for every million bivalent mRNA COVID-19 booster doses among adolescents 12–17 years of age, it would be expected that 31–136 hospitalizations, 9–40 ICU admissions, and 1 death would be prevented. Based on the preliminary data on myocarditis following bivalent booster in VSD, zero myocarditis cases have been observed in nearly 50,000 males who have received a bivalent booster dose and no cases in females with a similar number of doses.[131] Applying a correction to account for the potential incidental SARS-CoV-2 infections among hospitalized patients that Dr. Taylor discussed in the COVID-NET presentation, it was estimated

[124] https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination
[125] IZ Data Lake: Accessed 2/7/2023
[126] https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-02-04/11-COVID-Moulia-508.pdf
[127] https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-02-04/04-COVID-Kracalic-508.pdf
[128] https://www.cdc.gov/mmwr/volumes/71/wr/mm7114e1.htm?s_cid=mm7114e1_w
[129] Primary series and 1st monovalent booster data through August 20, 2022, bivalent booster data through January 29, 2023; Source: Kristin Goddard, Kayla E. Hanson, Ned Lewis, et al. Incidence of Myocarditis/Pericarditis Following mRNA COVID-19 Vaccination Among Children and Younger Adults in the United States. Ann Intern Med. [Epub 4 October 2022]. doi:10.7326/M22-2274
[130] Primary series and 1st monovalent booster data through August 20, 2022, bivalent booster data through January 29, 2023; source: Goddard K, et al. Incidence of Myocarditis/Pericarditis Following mRNA COVID-19 Vaccination Among Children and Younger Adults in the United States. Ann Intern Med. 2022;175:1169-1771.
[131] Based on preliminary Pfizer-BioNTech bivalent booster safety data from VSD (incident rate/million doses): 0 (95% CI: 0-62) in males and 0 (95% CI: 0-60) in females

that among adolescents 12–17 years of age,[132] it would be expected that 17–75 hospitalizations, 5–22 ICU admissions, and 0–1 death would be prevented. Again, zero myocarditis cases have been observed in nearly 50,000 males who have received a bivalent booster dose and no cases in females with a similar number of doses.[133]

Looking at the benefit risk assessment for adults 18–49 years of age per million doses over 6 months, it would be expected that 117–376 hospitalizations, 21–69 ICU admissions, and 4–11 deaths would be prevented. Among adults 18–39 years of age in the VSD, 1 myocarditis case was identified in a male with over 180,000 bivalent booster doses given. No cases have been reported in females who over 270,000 doses recorded.[134] While 18–49 is a fairly wide age group for benefits, it was not possible to stratify it further for rates by vaccine status. However, looking at hospitalization rates overall, adults 18–29 years of age had lower rates than adults 30–49 years of age, but higher rates than the adolescents. Adults 18–29 years of age likely would have lower numbers for benefits, but probably still somewhat higher that what was observed for adolescents. If the correction for potential incidental SARS-CoV-2 infections among hospitalized patients is applied, it would be expected that 81–259 hospitalizations, 15–48 ICU admissions, and 3–8 deaths would be prevented.

There are several important limitations to the benefit risk assessment that should be noted. The benefits of vaccination may continue to accrue beyond the time horizon used. Stable hospitalization rates were assumed for the duration of the time horizon, which may not represent what will happen in the future. The underlying complexity of vaccine histories and previous infections could not be accounted for. COVID-NET hospitalization rates included hospitalizations for which COVID-19 was not a primary reason for admission. The extent to which COVID-19 hospitalization rates include incidental findings is the extent to which benefits may be overestimated. Current COVID-19 epidemiology reflects the impact of both prior vaccination and prior infection. It is not possible to account for possible future increases in COVID-19 hospitalization rates or a new variant. Myocarditis rates following bivalent booster doses are uncertain. Studies are underway to assess the long-term impact of vaccine-associated myocarditis.

In summary, significant benefits continue to outweigh risks for primary series vaccination in all age groups. The benefits of a bivalent booster dose vary by age, time since last dose, and COVID-19 incidence. The risk of myocarditis after COVID-19 vaccines is likely reduced by a longer interval since last dose. Additional data can better define risk after bivalent vaccines, but current data are encouraging. Changes in COVID-19 hospitalization rates would impact the benefit assessment. There are additional benefits of COVID-19 vaccines unable to be quantified in the benefit risk assessment, including likely prevention of post-COVID conditions, possible reduction in transmission, and increased confidence in social interaction. The benefit-risk assessment will continue to be monitored as new data are available. Receipt of primary series continues to be important in all ages and boosters remain an important option to improve protection against severe COVID-19, especially for higher risk populations.

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[132] Results were adjusted to account for potential incidental findings of SARS-CoV-2 infection by multiplying the estimated hospitalizations, ICU admissions, and deaths prevented by the estimated percent of COVID-NET hospitalizations that are likely due to COVID-19 among 12 – 17-year-olds during on Omicron BA.5 predominant period (55%)

[133] Based on preliminary Pfizer-BioNTech bivalent booster safety data from VSD (incident rate/million doses): 0 (95% CI: 0-62) in males and 0 (95% CI: 0-60) in females

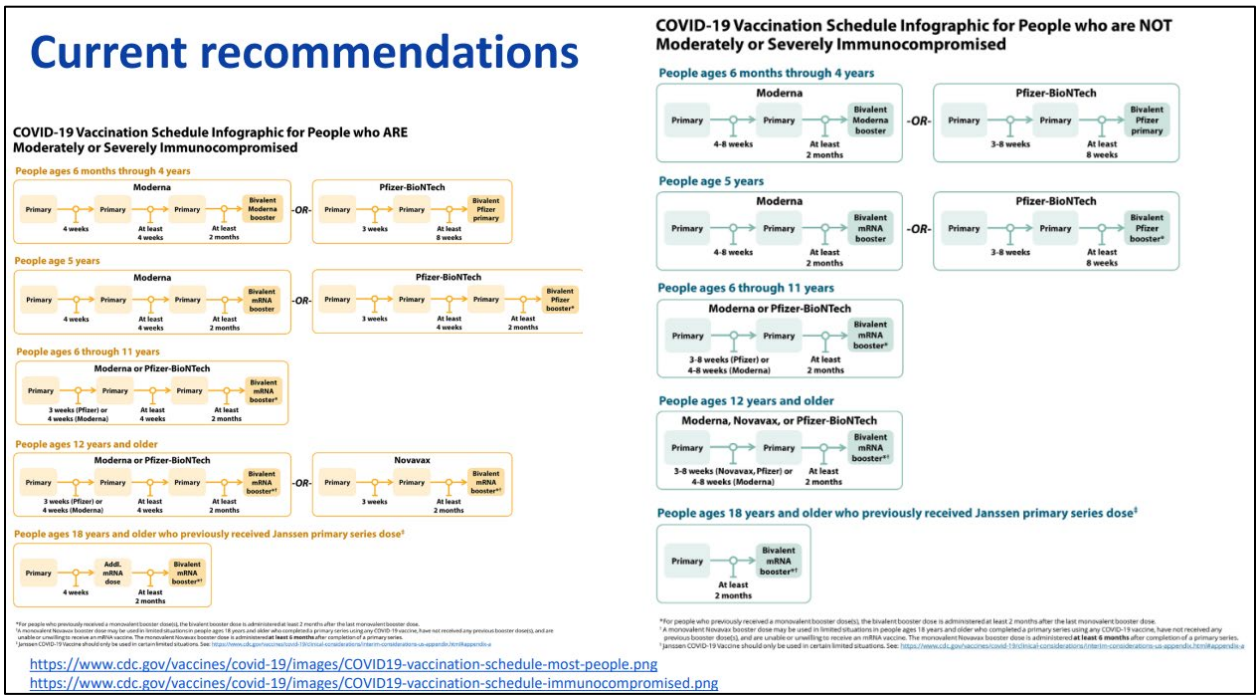
[134] 2Based on preliminary bivalent booster safety data from VSD among persons ages 18-39 years. Among Pfizer-BioNTech recipients, rates per million doses were: 20 (95% CI: 1–53) in males ages 18–29 years; 0 (95% CI: 0– 37) in females ages 18–29 years; 0 (95% CI: 0–36) in males ages 30–39 years and 0 (95% CI: 0–26) in females ages 30–39 years. Among Moderna recipients, rates per million doses were: 0 (95% CI: 0–162) in males ages 18–29 years; 0 (95% CI: 0– 101) in females ages 18–29 years; 0 (95% CI: 0– 85) in males ages 30–39 years and 0 (95% CI: 0–63) in females ages 30–39 years.

COVID-19 Vaccines: Future Directions

Sara Oliver, MD, MSPH (CDC/NCIRD) presented COVID-19 considerations for future planning for COVID vaccines. For planning purposes, it is important to aware of and evaluate the current status of COVID-19 vaccine, where there are going, and how to get there. To flesh that out, Dr. Oliver reviewed the current recommendation, vaccination rates, and hospitalization rates for the program at large. The ultimately goal is clear, simple recommendations. In thinking through how to get there, ACIP was asked to focus on the following questions:

- ❑ How frequently should people get a COVID-19 vaccine?
- ❑ Are there groups/populations who should have >1 vaccine per year?

This graphic of the current recommendations for COVID-19 vaccines illustrates the complexity of the recommendations:



https://www.cdc.gov/vaccines/covid-19/images/COVID19-vaccination-schedule-most-people.png
https://www.cdc.gov/vaccines/covid-19/images/COVID19-vaccination-schedule-immunocompromised.png

COVID-19 vaccine uptake is higher with older ages. However, uptake for bivalent boosters is only about 40% for adults ≥65 years of age.[135] While in general uptake has declined as the number of doses recommended have progressed, people tend to get vaccinated in waves shortly after recommendations.[136] In terms of why vaccine coverage is lower than desired, recent studies reflect profound COVID-19 vaccine message fatigue,[137] a desire to end the use of mitigation measures,[138] and a common perception that immunity is sufficient without future vaccine doses.[139] There are other reasons as well. Barriers to vaccine access still persist for

[135] https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends Updated February 10, 2023
[136] IZ Data Lake
[137] Guan et al. Health Communication 2022: COVID-19 Message Fatigue: How Does It Predict Preventive Behavioral Intentions and What Types of Information are People Tired of Hearing About? - PubMed (nih.gov)
[138] CDC's State of Vaccine Confidence Insights Reports, Jan 26 2023: CDC's State of Vaccine Confidence Insights Report
[139] Sinclair et al. MMWR Jan 20 2023: MMWR, Reasons for Receiving or Not Receiving Bivalent COVID-19 Booster Vaccinations Among Adults — United States, November 1–December 10, 2022 (cdc.gov)

some populations, including but not limited to people who live in rural areas,[140] people experiencing homelessness,[141] and people with disabilities.[142] Despite improvements in vaccine equity after primary series vaccination observed with the incredible efforts in 2021 to get people vaccinated with the primary series, disparities in booster coverage have emerged.[143]

In addition, the virus continues to evolve. Looking at trends in weighted variant proportion estimates and Nowcast for the period November 6, 2022–February 11, 2023, nearly three-fourths of isolates were projected to be XBB.1.5.[144] It also is important to look at the estimated number of reported COVID-19 cases by variant.[145] Even with newer variants, massive increases have not been seen as those that occurred in the winter of 2021 and 2022. Most adults have now had SARS-CoV-2 infection, vaccine, or both. Looking at seroprevalence by vaccine and infection history among adult US blood donors between January–June 2022, only 6% had neither infection nor vaccine.[146]

Looking at weekly population-based rates of COVID-19-associated hospitalizations by age group in COVID-NET for the period March 2020–February 2023, the highest hospitalization rates continue to be among older adults. However, hospitalization rates among those <65 years of age have not mirrored the similar increases recently as they did earlier in the pandemic. Based on monthly age-adjusted rates of laboratory-confirmed hospitalizations by vaccination status among adults ≥18 years of age in COVID-NET for the timeframe January 2021–December 2022, hospitalization rates are the lowest among those who have received a bivalent vaccine. In December 2022, compared to adults who received an updated bivalent booster dose, the monthly rates of hospitalization were 16 time higher among unvaccinated and 2.6 times higher in vaccinated adults without an updated booster dose.

To summarize the present status, current COVID-19 vaccine recommendations are complex. Uptake of current bivalent vaccine is low. The SARS-CoV-2 virus continues to evolve, but recent virus evolution has not led to large population-level surges and cases or hospitalizations. Most adults have prior infection, prior vaccination, or both. Hospitalization rates are highest in older adults but remain low among people who have received a bivalent booster.

In terms of future planning, the question of how frequently people should get a COVID-19 vaccine needs to be considered. While the ability to capture COVID cases has changed over time with increasing utilization of the home antigen test, CDC continues to be able to closely monitor COVID hospitalizations. Increases in COVID-19 cases and hospitalizations have occurred during the winter months, due to the development of a new immune escape variant, and/or both as occurred during the BA.1 winter surge when both occurred. However, the most recent winter did not have the increases seen in either of the previous 2 winters.[147]

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[140] Assessing barriers to access and equity for COVID-19 vaccination in the US - PMC (nih.gov)
[141] McCosker et al. Vaccine May 2022: Strategies to improve vaccination rates in people who are homeless
[142] Griffin-Blake et al. Barriers and facilitators of COVID-19 vaccine uptake among people with disabilities. Presentation to the COVID-19 Vaccine Innovation Team: Feb 8 2023
[143] COVID-19 Vaccination Coverage, by Race and Ethnicity — National Immunization Survey Adult COVID Module, United States, December 2020–November 2021 | MMWR (cdc.gov)
[144] https://covid.cdc.gov/covid-data-tracker/#variant-proportions Accessed Jan 20, 2023
[145] Data sources: https://covid.cdc.gov/covid-data-tracker/#variant-proportions and https://covid.cdc.gov/covid-data-tracker/#trends_newtestresultsreported_7daytestingpositive_00
[146] https://covid.cdc.gov/covid-data-tracker/#nationwide-blood-donor-seroprevalence-2022
[147] Cases from October 2021-February 2023 https://covid.cdc.gov/covid-data-tracker/#trends_weeklycases_select_00; and Admissions from October 2021 – February 2023 https://covid.cdc.gov/covid-data-tracker/#new-hospital-admissions

Looking at trends over time and number of doses for monovalent vaccines and VE against hospitalizations for the first part of 2022,[148] declines were seen over time with monovalent COVID-19 vaccines. This is likely impacted by both time since vaccine dose and continued virus evolution. Additional vaccine doses restored protection lost over time. While it is too soon to know the impact of waning and virus evolution on the VE of the bivalent vaccines over time, CDC continues to closely monitor the impact of waning and virus evolution on VE for bivalent doses and will present updates to ACIP when available. It is known that time since last dose impacts COVID-19 VE. Relative VE of bivalent boosters, meaning the additional benefits of a bivalent booster, are higher the longer it has been since the last monovalent dose. Safety also is likely improved with longer time between doses, with myocarditis risk appearing to be lower with longer time between doses.[149]

To summarize the data pertaining to how frequently people should get a COVID-19 vaccine, winter months and immune escape variants have impacted COVID-19 epidemiology. This past winter did not see the same level of increases in cases and hospitalizations as previous winters. Time since last COVID-19 vaccine dose may increase the incremental benefits of a COVID-19 vaccine and decrease the risk of myocarditis. Vaccine protection likely declines over time. A plan for a fall booster dose could provide added protection, at a time when many would be approximately 1 year out from their last dose. Future epidemiology and SARS-CoV-2 virus evolution could help determine the need for continued annual boosters.

In terms of the question regarding whether there are populations who still need a primary series, most adults have completed a primary series. However, most children 6 months—4 years of age remain unvaccinated (92.4% of children <2 years of age and 89.7% of children 2—4 years of age). For most older children, adolescents, and adults, future doses will be an additional boost after prior infection, prior vaccination, or both. In addition, young children will continue to age into the vaccine recommendation at 6 months and could be SARS-CoV-2 naïve. Because of this, some population of young children likely still will need a prime and a boost to optimize immunity.

Data from a CDC/University of Iowa/RAND survey show that among parents with an unvaccinated or under-vaccinated child 6–23 months of age, 38% intended to get their child vaccinated in the next month, 39.4% said they “definitely” or “probably” will not vaccinate their child, and 23% said they were unsure. Additionally, 38% of parents of children 2–4 years of age said they “definitely” or “probably” would get their child vaccinated in the next month, 43.2% said they “definitely” or “probably” would not, and 18.4% were unsure. Doctor’s offices and clinics were the most trusted place for parents to have their child receive a COVID-19 vaccine, as reported by 51.1% of parents of children 6–23 months of age and 52.5% of parents of children 2– 4 years of age. Therefore, thinking through optimal strategies for primary series vaccination in this young pediatric population continues to be important.

Looking at weekly population-based rates of COVID-19-associated hospitalizations among children 6 months—4 years of age in COVID-NET for the period March 2020–February 2023, pediatric hospitalization rates were higher among children 6 months to <2 years of age. Based on pediatric SARS-CoV-2 infection-induced and combined seroprevalence from US commercial laboratories for the time period March–December 2022, the youngest children 6—11 months of

[148] BA.2/BA.2.12.1 estimates: Link-Gelles et al. MMWR: https://www.cdc.gov/mmwr/volumes/71/wr/mm7129e1.htm BA.4/BA.5 estimates: Link-Gelles et al. medRxiv: https://www.medrxiv.org/content/10.1101/2022.10.04.22280459v1. Individuals with prior infections excluded. Adjusted for calendar time, geographic region, age, sex, race, ethnicity, local virus circulation, respiratory or non-respiratory underlying medical conditions, and propensity to be vaccinated.

[149] Tenforde et al. MMWR December 16, 2022: https://www.cdc.gov/mmwr/volumes/71/wr/mm715152e1.htm

age have the lowest both infection and combined immunity and it increases with age of the child.[150]

To summarize whether there are populations who may still need a primary series, children <2 years of age have higher COVID hospitalization rates than older children. Children <4 years of age are less likely to have both prior infection and prior vaccination. Children have frequent visits to HCP. According to the AAP's recommended schedule for well-child visits, prior to 3 years of age, children are recommended to go to the pediatrician at least every 6 months or more. The WG discussed continued primary series recommendations for young children 6 months—2 years of age and 6 months—4 years of age.[151] There was not a clear consensus from the WG for either age cut-off. Without a clear-cut off from the data, the WG thought feasibility also could be considered in thinking this through.

The next population of interest is older adults. Based on weekly population-based rates of COVID-19 hospitalization among all ages from COVID-NET from March 2022—February 2023, the highest hospitalization rates were among adults ≤75 years of age followed by adults 65—74 years of age. Based on age-adjusted rates of COVID-19-associated hospitalization by vaccination status and receipt of booster dose in adults ≥65 years of age in COVID-NET from January 2021–December 2022,[152] in December 2022, adults ≥65 years of age who received a bivalent booster had a 12.8 times lower risk of hospitalization for COVID-19 compared to unvaccinated people and a 2.5 times lower risk of hospitalization compared to those vaccinated without a bivalent booster. Data from ICATT[153] on relative VE of bivalent booster against symptomatic infection in adults ≥18 years of age from December 1, 2022–February 13, 2023 demonstrate that immunity and vaccine response are different in older adults and patterns of VE, including waning, may be different in older adults. Waning for bivalent VE against hospitalization, including among older adults, is not yet known.

To summarize whether older adults should be recommended for >1 vaccine annually, older adults have higher rates of hospitalization than younger adults, but the rates of vaccination among older adults who already have received their bivalent booster remain low. The WG emphasized the importance of older adults being up to date on current recommendations, including receiving a bivalent booster. The WG discussed more frequent COVID-19 vaccine doses for older adults and at this time felt that the data were insufficient to determine a conclusion on a need for frequent vaccines, and there was concern that it may not be feasible to implement a vaccine program in all adults ≥65 years of age. However, there was much discussion that these recommendations can be updated based on closely monitoring data in older adults, including hospitalization rates of older adults who have received a bivalent booster, bivalent VE and patterns of waning in older adults, and SARS-CoV-2 virus evolution and the possibility of future immune escape variants.

[150] https://covid.cdc.gov/covid-data-tracker/#pediatric-seroprevalence and unpublished data from CDC
[151] https://www.healthychildren.org/English/family-life/health-management/Pages/Well-Child-Care-A-Check-Up-for-Success.aspx
[152] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination Accessed Feb 17, 2023
[153] Unpublished CDC data. From ACIP presentation February 24, 2022

In terms of whether people with immunocompromising conditions should be recommended for more frequent vaccines, numerous studies[154] have demonstrated that mRNA COVID-19 VE among immunocompromised persons is lower than that of immunocompetent persons, including within the period of Omicron. This has been demonstrated across a range of immunocompromising conditions and is particularly notable for organ or stem cell transplant recipients. Among people with immunocompromise, recommendations prior to the bivalent booster allowed for up to 5 monovalent doses of COVID-19 vaccine. VE studies are not yet sufficiently powered to evaluate the effectiveness of a bivalent booster among persons with immunocompromise.

Looking at what is known, a published paper by Ferdinands, et al. compared VE among persons with an immunocompromising condition to people without immunocompromising conditions.[155] VE among immunocompromised persons is lower than that of immunocompetent persons at comparable time points after Dose 2 and Dose 3. VE wanes in both immunocompetent and immunocompromised people.[156]

In summary for this population, immunocompromised adults can have a less robust immune response to COVID vaccines. While not necessarily the scope of ACIP's work for now, it is important to note that there is not currently any authorized prophylactic monoclonal antibody products for populations at higher risk of COVID-19. The WG discussed more frequent COVID-19 vaccine doses for people with immunocompromising conditions and felt that the data were insufficient at this time to determine a conclusion for definitive recommendations moving forward. However, the WG acknowledged that this population may continue to be more vulnerable to severe COVID and is likely to need flexibility with future COVID-19 vaccine recommendations.

With respect to the future goal for simple recommendations, COVID-19 vaccines continue to be the most effective tool available to prevent serious illness, hospitalization, and death from COVID-19. While the goal of the COVID-19 vaccine program continues to be prevention of severe disease, prevention of post-COVID conditions, increased confidence in social interactions, and even a temporary protection against symptomatic disease can be important as well. As discussed throughout the day, the benefits of additional COVID-19 vaccine booster doses vary by age, time since last dose, and COVID incidence. A simplified annual recommendation could help reduce vaccine and message fatigue. A COVID vaccine framework that is similar to a well-understood influenza vaccine framework could be easy for COVID-19 vaccine providers to implement and for the public to understand.

[154] Britton A, Embi PJ, Levy ME, et al. Effectiveness of COVID-19 mRNA Vaccines Against COVID-19–Associated Hospitalizations Among Immunocompromised Adults During SARS-CoV-2 Omicron Predominance — VISION Network, 10 States, December 2021—August 2022. MMWR Morb Mortal Wkly Rep 2022;71:1335–1342. Embi PJ, Levy ME, and Patel P, et al. Effectiveness of COVID-19 Vaccines at Preventing Emergency Department or Urgent Care Encounters and Hospitalizations Among Immunocompromised Adults: an Observational Study of Real-World Data Across 10 US States from August—December 2021. Preprint. *Effectiveness of COVID-19 Vaccines at Preventing Emergency Department or Urgent Care Encounters and Hospitalizations Among Immunocompromised Adults: An Observational Study of RealWorld Data Across 10 US States from August-December 2021 (medrxiv.org) Ferdinands J M, Rao S, Dixon B E, Mitchell P K, DeSilva M B, Irving S A et al. Waning of vaccine effectiveness against moderate and severe covid-19 among adults in the US from the VISION network: test negative, case-control study BMJ 2022; 379 :e072141 doi:10.1136/bmj-2022-072141

[155] Figure: Ferdinands J M, Rao S, Dixon B E, Mitchell P K, DeSilva M B, Irving S A et al. Waning of vaccine effectiveness against moderate and severe covid-19 among adults in the US from the VISION network: test negative, case-control study BMJ 2022

[156] VISION: mRNA COVID-19 VE for hospitalizations among immunocompetent versus immunocompromised adults during Omicron predominance (mid-Dec. 2021—Jul. 2022)

In terms of the WG's interpretation of considerations for future planning, simple recommendations are easier to communicate, which also may improve uptake. The WG was very supportive of simplified recommendations and planning for the future of COVID-19 vaccines, which also could include additional updates to COVID-19 vaccines in the future. However, uncertainties remain for the ideal timing and populations for future booster doses, especially if new immune escape variants develop. The WG was supportive of a Fall or annual COVID-19 vaccine program, with the flexibility to adjust based on new data, especially for populations at higher risk. The WG will continue to review data to inform future deliberations including data on VE of bivalent vaccines over time; safety data of the bivalent vaccines, especially in terms of monitoring myocarditis rates as more doses are administered; cost-effectiveness analyses; COVID-19 epidemiology, including hospitalization rates among the vaccinated and boosted people; SARS-Cov-2 genomic surveillance and virus evolution; and data from vaccine manufacturers as they continue to study these vaccines. As a reminder, discussions about future COVID-19 vaccine recommendations are pre-decisional and intended to inform planning and additional analyses.

In conclusion, Dr. Oliver posed the following questions for the ACIP's consideration and deliberation:

- ❑ What are ACIP's thoughts on a simplified framework for future COVID-19 vaccine recommendations?
- ❑ What does ACIP think about children who may still need a primary series?
- ❑ What does ACIP think about future recommendations for older adults?
- ❑ What does ACIP think about future recommendations for people with immunocompromising conditions?

ACIP Discussion Points, Observations, Suggestions on COVID-19 Vaccines

Following Dr. Shimabukuro's Presentation

- Regarding an inquiry about whether there is specific surveillance in nursing homes, Dr. Shimabukuro said that while he was not aware of specific surveillance in nursing homes, the VSD analyses may include nursing homes. In addition, Dr. Forshee may be able to provide additional insight on nursing home residents from the CMS data. Dr. Forshee added that the Medicare sequential analyses did not include nursing home residents. They have performed some separate analyses on nursing home residents, but specifically for the outcome of ischemic stroke.
- In terms of a question about the point at which these data would be widely publicized, Dr. Shimabukuro indicated that this information has been posted on the CDC website, presented during the last VRBPAC meeting, were presented to the ACIP during this session, and presumably would soon be published. He emphasized that the data he presented during this session were not sufficient to conclude that there is a safety problem with the Pfizer bivalent booster and ischemic stroke in adults ≥65 years of age or a safety problem with the Pfizer bivalent booster and co-administration with high-dose or adjuvanted influenza vaccines. There are other factors that could be the reason for the statistical signal, such unmeasured confounding or chance alone. Monitoring will continue and the recommendations for bivalent booster vaccination and influenza vaccination have not changed.
- As a reminder for the public, Dr. Lee stressed that no safety signals were detected for ischemic stroke for the primary series or monovalent boosters for Pfizer-BioNTech or Moderna COVID-19 vaccines in US and global monitoring.

Following Dr. Forshee's Presentation

- With respect to a question about whether there is an opportunity to for the FDA to partner with CMS to assess nursing home data, Dr. Forshee emphasized that the FDA has done some work already on safety and effectiveness data among nursing home populations, but have not specifically looked at the ischemic stroke. He emphasized that he and Dr. Shimabukuro talk on a regular basis and their teams meet regularly, so they can continue this discussion as part of their ongoing conversations.
- It would be beneficial to have data on how much coadministration of influenza vaccine occurs in other systems. Dr. Forshee indicated that he could speak only to what was observed in their CMS analysis.

Following Dr. Talbot's Presentation

- Dr. Lee took a moment to express gratitude to Drs. Talbot, Hopkins, Wharton, and Markowitz for leading the very focused and specialized VaST WG. Because of the intensity and need for real-time safety surveillance and the need to coordinate and collaborate across federal agencies and with global colleagues, this particular WG has been highly impactful in response to the COVID-19 pandemic by focusing attention on safety. She thanked the VaST WG for its contributions as its activities transitions back to the COVID Vaccines WG. As evidenced by the 71 additional meetings of the VaST WG, it was possible to look closely at the data to ensure that the vaccines and the vaccination program were indeed considered safe and effective for the public. She emphasized that it is important to recognize that this was the phenomenal work behind the scenes of many unsung heroes including individuals, public and private partners, federal agencies, academia, health systems, and others. Behind the 71 meetings and under extremely difficult circumstances, this was a tremendous effort of too many colleagues to name who have brought information to the public as quickly as possible.
- Dr. Poehling emphasized that the deliberate transfer of the VaST WG activities to the COVID Vaccines WG would ensure that due diligence would continue.

Following Dr. Twentyman's Presentation

- It is clear that there is a risk of stroke following infections such as COVID-19 and influenza infections and a protective effect of vaccines has been observed against some of the complications of infections such as stroke. Balancing the risk of vaccination versus the risk of infection and the totality of the data, it is not convincing that the VSD signal was a true signal. Nevertheless, it deserves further investigation over time.
- Some patients remain concerned about the potential long-term safety of COVID vaccines.
- In terms of encouraging vaccine uptake among the public, it would be extremely beneficial to have some simple numbers to convey that one's risk of stroke at ≥65 years of age is X times higher than having a stroke after getting vaccinated.

Following Dr. Taylor's Presentation

- Regarding whether monthly age-adjusted rates of laboratory-confirmed hospitalizations by vaccination status were available for the pediatric population, Dr. Taylor indicated that the data for adults ≥18 years of age are posted publicly and were age-adjusted. He showed those data because they included data on the bivalent booster dose. There is a quality standard for the COVID-NET data that requires that a certain proportion of the underlying COVID-NET catchment population has to reach a certain level of vaccination in order for the rates to be considered stable. The most recent data analyzed for the pediatric groups had not yet reached the standard to be able to include them.

- These data highlight the importance of continuing to think about how to encourage vaccine acceptance. Given that the CICP working well is an important part of vaccine acceptance, expeditious review of claims are crucial as related to vaccination and the continued development of an Injury Table.
- Given the 16-fold higher hospitalization rate among the unvaccinated in the context of the current transmissibility of COVID-19, it would be helpful to know the prevalence of natural infection rates among adults. Dr. Taylor noted that while there is immunity provided by infection, it is not possible to adjust for that because they do not have a variety of other data sources such as prior infection, home testing results, et cetera. As more people become vaccinated, perhaps this could be assessed in a seasonal manner similar to what is done for influenza.
- Assuming that the bulk of the unvaccinated have been infected, these data suggest that prior infection does not confer much immunity and that what is conferred may be only against the variant to which one is exposed. If the data support that, it is important to send a clear message that prior infection is not adequate for protection against future hospitalization from COVID.
- For the monthly age-adjusted rates of laboratory-confirmed hospitalizations by vaccination status and underlying condition, it would be beneficial to have a breakdown by race and age group. For instance, some chronic conditions are higher among African Americans, AI/AN, and Latinos. Dr. Taylor indicated that while there is not sufficient power to show the vaccination rates by race and ethnicity, they do see patterns of differences within groups. A publication has been submitted looking further at COVID-NET data by race and ethnicity because it is so important. Differences have been observed since the beginning of the pandemic, so it is clearly important to continue to describe them in the ways that are possible.

Following Dr. Britton's Presentation

- Hopefully in the future when there are sufficient data, ACIP could see the ED/UC and hospitalizations among children, recognizing that their vaccination recommendations came later and those data probably are going to lag. Dr. Britton emphasized that this is a high priority and they are checking every available avenue.
- It will be interesting to know whether these data may have implications for the future in terms of whether an additional booster dose might be added or might be given annually similar to influenza vaccines.

Following Dr. Oliver's Presentation #1

- ACIP expressed appreciation for the systematic approach that was taken to share all of the available data.
- Vaccine acceptance is critical, so processing CICP claims expeditiously is imperative and encourages vaccine acceptance. An update on the Vaccine Injury Table and an explanation to the public about why it takes time to develop that table is very important. Dr. Grimes acknowledged that HRSA wholeheartedly agrees that expeditious processing of claims is of paramount importance. A large volume of claims have been submitted to the CICP of over 11,000 alleged COVID-19 countermeasures injuries. Over 8,000 of those are COVID-19 vaccine-related. HRSA has been processing claims as expeditiously as possible and that effort will continue moving forward. For the CICP, HRSA promulgates Countermeasures Injury Tables. For a serious physical injury to be added to the Countermeasures Injury Tables, it must meet compelling, reliable, and valid medical and scientific evidence. To be promulgated, the alleged injuries must go through

the Federal Rulemaking process, which takes time. The Vaccine Injury table specific to the VICP is a separate process that currently does not cover COVID-19 vaccines.

- There is major support from pediatricians, family medicine practitioners, and other vaccinators for harmonization of the number and look of the products. Look-alike products are a major source of safety concerns. Simplification will improve the logistics, feasibility, and confidence of families in receiving the vaccine.
- Families are having a difficult time understanding why a bivalent vaccine is recommended for adults, but their young child is recommended to have 2 doses of monovalent before they can receive a bivalent. Given that this has been a very confusing message, moving to a bivalent would be easier to communicate.
- Clarity is needed on what a transition to bivalents will mean for immunocompromised and immunosuppressed patients, given that it has become increasingly difficult for people to find monovalent vaccine.
- In terms of the 2 options in front of the ACIP to continue to modify the authorizations for special cases or allow clinicians to have the ability to prescribe as they think it makes clinical sense to do so, Dr. Kaslow indicated that the FDA is working diligently on this topic as quickly as possible, but that this was all he could say at this time.
- In addition to SARS-CoV-2's miraculous ability to change and escape immune protection, the age groups affected and clinical disease observed also change. Given this, it is critical for the newer strain bivalents to be available for the primary series in individuals down to 6 months of age.
- The CMS requirement for HCW/HCP to receive at least the primary series is causing some consternation and delay in bringing on new staff because of difficulty in finding vaccine. Flexibility in allowing the bivalent vaccine serve as the primary series could help to alleviate this issue.
- It will be beneficial in terms of harmonizing to understand whether the primary series with Pfizer will continue to be 3 doses or both Pfizer and Moderna might eventually both be 2 doses. Pfizer indicated that as discussed in the recent VRPBAC meeting, Pfizer is currently enrolling for its dose-finding portion of a primary bivalent series with the bivalent Omicron BA.4/5. These data are anticipated to be available later in the fall. This trial has experienced the issue with low uptake in terms of enrollment in the clinical trial. As per the currently authorized vaccine, Pfizer is working on a 3-dose primary series. Phase 1 includes children 6 months to <2 years of age and 2─5 years of age, with 90 participants in of those groups for a total of 180.
- ACIP put forth a strong plea for simplification and more data to support confidence in the safety and the effectiveness of these vaccines that will help the ACIP and CDC translate this to the broader population.

Following Dr. Wallace's Presentation

- It would be beneficial to better understand how much the risk for MIS-C, MIS-A, and long-COVID is decreased with vaccination. Dr. Wallace indicated that an *MMWR* was published about a year ago that looked at VE of the primary series in children and adolescents against MIS-C, which showed a high protective effect of primary series monovalent vaccination. An article in August 2022 in *Clinical Infectious Disease* (*CID*) that looked at a reduced likelihood of MISC in children 5─18 years of age showing that primary series vaccination was associated with reduced likelihood of MISC in children 5─18 years of age.
- It is important to better understand the full spectrum and burden of post-COVID conditions in general and to incorporate them into the information on the benefits and

risks of COVID-19 vaccination and the decision-making for the full spectrum of COVID-19 prevention.

- Dr. Lee recognized that there are multiple federal efforts in this space and the ACIP appreciates the continued collaboration across federal agencies to engage in information sharing to ensure that the understanding of the benefit-risk balance is optimized. She emphasized how much the ACIP appreciated the overall summary and summative statements demonstrating that the benefits continue to outweigh the risks for the primary series in all age groups. The committee will continue to think through what else can be done to mitigate risk via the schedule and how to simplify it over time and longer intervals as an important intervention that can be implemented in the context of individual risk, immunocompromised persons, et cetera.

Following Dr. Oliver's Presentation #2

- There was extremely strong support for as much simplification as possible moving forward.
- While there is a population of younger children who will continue to age in who have never had a primary series, this also could be true for someone 11 years of age, 23 years of age, or some other age who has not had the primary series but wants to get it—even if they likely have had natural infection. Part of the conversation about who needs an annual booster regards what to do about people who never received the primary series and where they fit in. At this pivotal point, the idea that someone 18 years of age who has never gotten the primary series but has been infected and then gets a single dose in the Fall probably would have decent protection. While there is not a lot of data at this point and this is not known as an established fact, an assumption underlying this is that a recommendation might be that this individual who is 18 years of age might not get the 2 doses and would just get the annual dose to be considered "up to date."
- It seems like there should be enough data to say that someone who has a documented SARS-CoV-2 infection just needs a booster, although that might be more complicated than saying every child <5 years of age should get a primary series. Dr Oliver noted that they have heard from some of their implementation-minded colleagues that have vaccine recommendations that differ based on prior SARS-CoV-2 testing potentially would be difficult to implement.
- There was no mention of pregnancy or pregnant women. For instance, should every pregnant woman receive a booster dose during each pregnancy to prevent infection in herself and her infant ≥6 months of age? This question should be raised in the WG. Dr. Oliver indicated that the WG looks forward to outlining the available data to answer this question and bring it to ACIP. It was not included here because it is a separate issue that needs a deeper dive. It is on the docket of items the WG will be tackling next.
- There was no mention of the scheme of things with Novavax in all of this. Dr. Oliver responded that the WG was very intentional, especially in the last presentation when talking about the transition from monovalent to bivalent, that the primary series discussions focused on the mRNA vaccines. No changes are anticipated at this time. The primary series that is currently authorized and recommended for Novavax is monovalent. The understanding is that Novavax will continue to be available and recommended as is. She called on Novavax colleagues to speak to their planning for the future. Dr. Denny Kim from Novavax reported that they are in discussions with the FDA and anticipate that within the next 2 to 3 months, they will have more clarity on the future direction going forward for the 2023 Fall and Winter campaign and future vaccination regimens. While he was not at liberty to say more about their discussions with FDA, in the context of the ACIP discussions, the Novavax primary series regimen for individuals

≥12 years of age is already approved as a booster dose in the same dose and presentation. They are working on a bivalent formulation as well and will be prepared to deliver that based on what the FDA advises for the Fall and Winter campaign. They also have a de-escalation clinical trial that utilizes the same dose as the primary series for individuals ≥12 years of age.

- Practitioners have heard from families that it would be beneficial to have one message across all age groups of children. A study showing the benefit and duration of 1 bivalent vaccine would enhance the confidence in making a change versus making inferences.
- While very low rates of far less than 5% are being seen among well-vaccinated people who are immunocompromised and receive standard antiviral treatments, many immunocompromised individuals have not taken the opportunity to get the bivalent vaccine. Based on feedback from patients, this is primarily due to vaccine fatigue or not being fully aware of the opportunity. Moving forward, it is important to get the message out to people who are immunocompromised to get their bivalent dose.
- It would be beneficial if the FDA would permit enhanced flexibility of recommendations, which would allow providers to give additional doses to individuals who are immunocompromised, and to be responsive to upcoming increases in disease activity or variants, et cetera.
- Regarding an inquiry about whether the WG has discussed a role for shared clinical decision-making for the older adult population or people with immunocompromising conditions, Dr. Oliver indicated that the WG has talked about populations who may benefit from a more permissive recommendation for whom population-level recommendations for everyone would not be sufficient. For instance, timing of immunocompromising might be a factor. The WG did not feel like the epidemiology and duration data were sufficient to propose a structure for shared clinical decision-making at this point.
- In terms of whether the WG had any concerns that inequities would result if certain groups or populations were recommended to have more than 1 dose per year, Dr. Oliver emphasized that the WG has reviewed the inequities that currently exist with the bivalent vaccines and is considering ways to address those such as simple recommendations that everyone can understand and removal of barriers. They have heard that sometimes people are identified as being vaccine-hesitant when in fact they simply face barriers to getting vaccinated. Dr. Twentyman added that whenever the complexity of recommendations increase to the point of compromising delivery in any way (e.g., through clinician frustration, public COVID-19 message fatigue, et cetera) those who have less strong access to the healthcare system who will be affected, regardless of whether they want to get the vaccine or not.
- In terms of minoritized communities, equity is a particularly major concern in the pharmacy community. It is known that up to this point, Hispanic and Latino individuals in particular are more likely to get immunized in a pharmacy than in other points of care based upon recent data.
- Concern was expressed regarding the influx of undocumented immigrant populations who have never received a vaccination. There was a presentation earlier in the session showing that 50% of children who are hospitalized have no known underlying medical conditions but are sick enough to be hospitalized. This raised questions about whether there could be issues other than lack of vaccination and underlying conditions that might impact immunity and contribute to more severe disease a (e.g., food insecurity, poor nutrition, living environment, post-traumatic stress, et cetera). Dr. Oliver did not know whether they had that level of data on social factors for children, but thought it was compelling.

- It seems that if children get the bivalent primary series, a bivalent booster may not be necessary and perhaps the number of vaccines provided to children could be reduced. Dr. Jones indicated that there are relatively little data in children compared with adults. Because many VE platforms can have difficulty identifying previous infection, particularly asymptomatic infection, a lot of the data come from laboratory studies looking at those who had a known previous infection and were subsequently vaccinated or had a breakthrough infection. At least among those studies, many of which were early in the pandemic, showed that 1 dose of a vaccine led to neutralizing and binding antibodies that were at least as high as or higher than those who received a primary series. Based on those laboratory studies among those who previously were infected,1 dose of a vaccine appears to give at least as robust a response as a primary series. VE studies, the majority of which are in adults, have shown that hybrid immunity does give superior protection compared to just infection-induced immunity. Although infection induced immunity does appear to give robust protection, particularly against severe disease, and there is limited waning over a long amount of time. There is less information available about 1 dose versus 2, but the vaccination appears to increase or restore immunity.
- ACIP members pointed out how amazed they were with the work that CDC's staff, professionals, and scientists perform, emphasized that they do not get enough credit for that, and wanted to make sure they were recognized appropriately during this forum.
- There was a lot of support for a regular recommendation that everyone get an annual booster and a shared clinical decision-making recommendation for certain categories of people (immunocompromised, persons ≥65 years of age, et cetera) so they could decide with their provider about when and how many doses to get.
- Heretofore, studies have been in healthy populations. While it is understood that studies occur in a stepwise manner, it seems prudent at this juncture to move forward quickly toward studying particularly vulnerable pediatric and adult populations.
- If ethical, perhaps some RCTs could be conducted with co-administration of COVID vaccine and influenza vaccine in one arm and separate administration in the other arm.
- Practically speaking, there is support for single dose presentations—preferably prefilled syringes. That would allow practices to purchase vaccine in small quantities and potentially could expand the number of locations across the country where vaccine would be available. There is a certain reluctance to go into a multi-dose vial if there is only one patient who needs the vaccine. On a related note, current supplies of bivalent vaccines are about to expire in some locations, so it would be beneficial to know whether there is going to be a recommendation for additional vaccine before those doses expire.
- In closing, Dr. Lee recapped some of the important considerations that arose throughout this session:
  - Simplified messaging for the broader population would be beneficial because messaging has gotten so complex it can be barrier for people to understand how to best protect themselves. The challenge is that oversimplification of the message may not be helpful.
  - Flexibility for individual clinicians to work with their clients makes sense because there are always going to be various situations or circumstances.
  - Strong and continued updating of clinical considerations is important to ensure that the benefit-risk balance is retained over time.
  - It is clear from the data that hybrid immunity is both the strongest and the longest, but all immunity wanes over time. Dr. Lee noted that she was personally struggling with the need to acknowledge that immunity is a combination of both infection and vaccination, but that would not make messaging simple in any way.

- The least likely to be immune are going to be the youngest children 6 months–2 years of age as a starting point. A simple recommendation for that age group, that they should get a primary series because they are less protected and have higher hospitalizations rates at this point, would be much more straightforward. Although some members respectfully disagreed and thought that with documentation of COVID-19, the fairly simple message would be that a primary series is not needed no matter what the age. More information about antibody levels could perhaps guide recommendations about who needs a booster when.
- The oldest and immunocompromised persons are more likely to get very sick, even with full vaccination and/or prior infection. The gap in immunity needs to be addressed for these populations.
- ACIP needs to be able to speak confidently about vaccines so that the public can have confidence. There are still many uncertainties that are going to make it difficult to develop a straightforward message, given all of the caveats that need to be explained. There are specific scientific questions in front of the ACIP, but there also is the balance of ensuring that the public's confidence in vaccines is maintained. Realizing that these 2 are not always the same, it is time to start incorporating that thinking going forward.
- There are challenges for which the data are uncertain (e.g., pregnant women, the youngest children, immunocompromised persons, the older adult population, et cetera).
- Transparency about what plans are in place to address particular issues is crucial, especially with confidence issues as one of the end goals. If certain studies are going to be conducted or not, it is important to be transparent about the rationale.
- It is important to reiterate that the goal of vaccines is to prevent severe disease and death.
- There is a misconception that children get mild disease. While deaths among children are infrequent, they do occur.
- There is an opportunity for tremendous disease prevention through COVID-19 vaccination if people get vaccinated. In transitioning to commercialized products, uninsured or underinsured will not have the opportunity by-and-large to be vaccinated. Consideration should be given to the feasibility of establishing an adult vaccine platform modeled after the VFC. Dr. Meyer reminded everyone that this was included as part of the President's Budget. In order for that to be enacted, it would have to be authorized by Congress. Dr. Romero added that he is actively working to convince the legislature and people in general of the need for such a program. While this would be an incremental program that is not fully funded in the beginning, it would grow over time. CDC is committed to this, believes it is very important, and will continue to champion it.

CERTIFICATION

Upon reviewing the foregoing version of the February 22-24, 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.

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ACRONYMS USED IN THIS DOCUMENT

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ABCs	Active Bacterial Core Surveillance System
ACA	Affordable Care Act
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
ADE	Antibody-Dependent Enhancement
ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
AESI	Adverse Event of Special Interest
AHIP	America's Health Insurance Plans
AI/AN	American Indian/Alaskan Native
AIDP	Acute Inflammatory Demyelinating Polyneuropathy
aIIV	Adjuvanted Influenza Vaccine
AIM	Association of Immunization Managers
AIRA	American Immunization Registry Association
AMA	American Medical Association
AMETHST	American **T**ransformative **H**IV **S**tudy
AMIS	American Men's Internet Survey
AOA	American Osteopathic Association
AOM	Acute Otitis Media
APhA	American Pharmacists Association
AR	Adverse Reaction
ARI	Acute Respiratory Illness
ASPR	Administration for Strategic Preparedness and Response
ASTHO	Association of State and Territorial Health Officers
AUC	Area Under the Curve
BARDA	Biomedical Advanced Research and Development Authority
BEST System	Biologics Effectiveness and Safety System
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CBO	Community-Based Organization
ccIIV4	Cell-Culture Based Vaccine
CDC	Centers for Disease Control and Prevention
CHD	Chronic Heart Disease
CHIKV	Chikungunya Virus
CHIP	Children's Health Insurance Program
CICP	Countermeasures Injury Compensation Program
CISA	Clinical Immunization Safety Assessment Project
CLD	Chronic Lung Disease
CLI	COVID-Like Illness
CMC	Chronic Medical Conditions
CMS	Center for Medicare and Medicaid Services

CMV	Cytomegalovirus
COI	Conflict of Interest
CONUS	Continental United States
COPD	Chronic Obstructive Pulmonary Disease
COVID-NET	Coronavirus Disease 2019 (COVID-19) Hospitalization Surveillance Network
CSF	Cerebrospinal Fluid
CSTE	Council of State and Territorial Epidemiologists
CVD	Cardiovascular Disease
cVDPV2	Circulating Vaccine-Derived Poliovirus Type 2
DCAC	Dengue Case Adjudication Committee
DENV	Dengue Virus
DFO	Designated Federal Official
DM	diabetes mellitus
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DUA	Data Use Agreement
DVA	Department of Veterans Affairs
eCRF	Electronic Case Report Form
ED	Emergency Department
EIND	Emergency Investigational New Drug
EMA	European Medicines Agency
EMDS	Enhanced Meningococcal Disease Surveillance
EMR	Electronic Medical Record
ET	Eastern Time
EtR	Evidence to Recommendation
EU	European Union
EUA	Emergency Use Authorization
FAERS	FDA Adverse Event Reporting System
FAS	Freely Associated States
FDA	Food and Drug Administration
FluSurv-NET	Influenza Hospitalization Surveillance Network
FQHC	Federally Qualified Health Centers
FRN	Federal Register Notice
FRPP	Federal Retail Pharmacy Program
GACVS	Global Advisory Committee on Vaccine Safety
GBS	Guillain-Barré Syndrome
GDP	Gross Domestic Product
GISAID	Global Initiative on Sharing All Influenza Data
GMC	Geometric Mean Concentrations
GMT	Geometric Mean Titers
GPEI	Global Polio Eradication Initiative
GRADE	Grading of Recommendation Assessment, Development and Evaluation
HCP	Healthcare Personnel / Providers
HD-IV	High-Dose Influenza Vaccine
HHS	(Department of) Health and Human Services
HIV	Human Immunodeficiency Virus
HRSA	Health Resources and Services Administration
HSCT	Hematopoietic Stem Cell Transplant
HZ	Herpes Zoster

IC	Immunocompromising Conditions
ICERs	Incremental Cost Effectiveness Ratios
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
IDSA	Infectious Disease Society of America
IHS	Indian Health Service
IIS	Immunization and Infectious Diseases
IIS	Immunization Information System
IIV	Inactivated Influenza Vaccine
ILINet	Influenza-like Illness Surveillance Network
IM	Intramuscular
IMD	Invasive Meningococcal Disease
IPD	Invasive Pneumococcal Disease
IPV	Inactivated Polio Vaccine
IRA	Inflation Reduction Act of 2022
ISD	Immunization Services Division
IV	Intravenous
IVIG	Intravenous Immune Globulin
IVWG	Federal Interagency Vaccine Workgroup
IVY	Investigating Respiratory Viruses in the Acutely Ill
LGBTQ+	Lesbian, Gay, Bisexual, Transgender, Queer or Questioning, or Other
LRTD	Lower Respiratory Tract Disease
LRTI	Lower Respiratory Tract Illness
LTCF	Long-Term Care Facilities
MAAEs	Medically Attended Adverse Events
MACDP	Metropolitan Atlanta Congenital Defects Program
MATISSE	Maternal Immunization Study for Safety and Efficacy
MELODY	Prevention of Medically Attended Lower Respiratory Tract Infection Due to Respiratory Syncytial Virus in Healthy Late Preterm and Term Infants
MFS	Miller Fisher Syndrome
MICH	Maternal, Infant, and Child Health
MIS-C	Multisystem Inflammatory Syndrome in Children
MMWR	*Morbidity and Mortality Weekly Report*
MoH	Ministry of Health
MSM	Men Who Have Sex with Men
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization Canada
NAMCS	National Ambulatory Medical Care Survey
NAPNAP	National Association of Pediatric Nurse Practitioners
NBP	Nonbacteremic Pneumonia
NCCDPHP	National Center for Chronic Disease Prevention and Health Promotion
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHS	National Center of Health Statistics
NCIRD	National Center for Immunization and Respiratory Diseases
NDC	National Drug Code
NDCMC	Newly Diagnosed Chronic Medical Conditions
NFID	National Foundation for Infectious Diseases
NHANES	National Health and Nutrition Examination Survey
NHP	Non-Human Primate

NHSN	National Healthcare Safety Network
NIAID	National Institute of Allergy and Infectious Diseases
NICU	Neonatal Intensive Care Unit
NIH	National Institutes of Health
NIS	National Immunization Survey
NMA	National Medical Association
NNDSS	National Notifiable Diseases Surveillance System
nOPV2	Novel Oral Polio Vaccine, Type 2
NP	Nasopharyngeal
NREVSS	National Respiratory and Enteric Virus Surveillance System
NSSP	National Syndromic Surveillance Program
NSTEMI	Non-ST-Elevation Myocardial Infarction
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
NVSN	New Vaccine Surveillance Network
NVSS	National Vital Statistics System
NYS	New York State
OASH	Office of the Assistant Secretary for Health
ODPHP	Office of Disease Prevention and Health Promotion
OGC	Office of General Council
OIDP	Office of Infectious Disease and HIV/AIDS Policy
OP	Oropharyngeal
OPA	Opsonophagocytic Activity
OPV	Oral Polio Vaccine
PCP	Primary Care Provider/Practitioner
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccines
PEP	Post-Exposure Prophylaxis
PFFS	Private Fee-For-Service
PHAC	Public Health Agency Canada
PHE	Public Health Emergency
PHEIC	Public Health Emergency of International Concern
PICO	Population, Intervention, Comparison, Outcomes
PIDS	Pediatric Infectious Disease Society
PK	Pharmacokinetics
POTS	Postural Orthostatic Tachycardia Syndrome
PPSV23	Pneumococcal Polysaccharide Vaccine
PPV	Positive Predictive Value
PR	Puerto Rico
PrEP	Pre-Exposure Prophylaxis
QALY	Quality-Adjusted Life Year
QIV	Quadrivalent Inactivated Influenza
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RESP-NET	Respiratory Virus Hospitalization Surveillance Network
RSV-NET	Respiratory Syncytial Virus Hospitalization Surveillance Network
SAB	Spontaneous Abortion
SAE	Serious Adverse Event
SAHM	Society for Adolescent Health and Medicine

SD-IIV	Standard-Dose Unadjuvanted Influenza Vaccines
SES	Socioeconomic Status
SHEA	Society for Healthcare Epidemiology of America
SME	Subject Matter Expert
SMFM	Society for Maternal-Fetal Medicine
SNF	Skilled Nursing Facilities
STIs	Sexually Transmitted Infections
SVD	Sudan Virus Disease
TIA	Transient Ischemic Attack
TOR	Terms of Reference
UK	United Kingdom
US	United States
USG	United States Government
USVI	US Virgin Islands
VAERS	Vaccine Adverse Event Reporting System
VDPV	Vaccine-Derived Poliovirus
VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VEPP	Vaccine Equity Pilot Program
VFC	Vaccines For Children
VFIP	*Vaccines Federal Implementation Plan*
VICP	National Vaccine Injury Compensation Program
VNSP	Vaccines National Strategic Plan
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VSD	Vaccine Safety Datalink
VZV	Varicella-Zoster Virus
WG	Work Group
WGS	Whole Genome Sequencing
WHO	World Health Organization
WPV	Wild Poliovirus
ZIKV	Zika Virus