MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

JUNE 22-23, 2022
SUMMARY MINUTES

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MEETING PURPOSE

The United States (US) Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC) convened a meeting of the Advisory Committee on Immunization Practices (ACIP) on June 22-23, 2022. The meeting took place remotely via Zoom, teleconference, and live webcast. This document provides a summary of the meeting, which focused on Influenza; Pneumococcal; Measles, Mumps, Rubella (MMR); Human Papillomavirus (HPV); Coronavirus Disease 2019 (COVID-19); Respiratory Syncytial Virus (RSV); and Monkeypox Vaccines. Please note that while public comments were provided each day prior to votes and votes were made at the end of each day, votes are included in this document with their respective topical sessions for ease of reading what transpired with each topic area.

WEDNESDAY: JUNE 22, 2022

WELCOME AND INTRODUCTIONS

Call to Order/Roll Call

Dr. Grace Lee (ACIP Chair) called to order and presided over the first day of the June 22-23, 2022 ACIP meeting. She conducted a roll call, which established that a quorum was present. A list of Members, *Ex Officios*, and Liaison Representatives is included in the appendixes at the end of this summary document. The following conflicts of interest (COIs) were declared:

- ❑ Dr. Kevin Ault declared a COI with the HPV discussion, given that he acted as a consultant for PANHPVAX, which is in the process of developing an HPV vaccine.

Announcements

Dr. Melinda Wharton (ACIP Executive Secretary, CDC) welcomed everyone and noted that copies of the slides for the day were available on the ACIP website and were made available through a ShareLink™ file for voting ACIP Voting Members, *Ex Officios*, and Liaisons. She indicated that there would be two (2) oral public comment sessions, the first on June 22, 2022 at approximately 3:00 PM Eastern Time (ET) and the second on June 23, 2022 at approximately 1:10 PM ET. To create a fair and more efficient process for requesting to make an oral comment, people interested in making a comment were asked to submit a request online in advance of the meeting. Priority is given to these advanced requests. Given that more individuals registered to make oral public comments than could be accommodated, selection was made randomly via a lottery. Speakers selected in the lottery for this meeting were notified in advance of the meeting. Individuals who were not selected and other individuals wishing to make written public comments may submit them through https://www.regulations.gov using Docket Number CDC-2022-0062. Further information on the written public comment process 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, CDC has issued limited COI waivers. Members who conduct vaccine clinical trials or serve on data safety monitoring

boards (DSMBs) may present to the committee on matters related to those vaccines, but are prohibited from participating in committee votes. Regarding other vaccines of the concerned company, a member may participate in discussions with the provision that he/she abstains on all votes related to that company. ACIP members state any COIs at the beginning of each meeting.

Dr. Wharton also announced that applications and nominations were being solicited for candidates to fill upcoming vacancies on the ACIP. Detailed instructions for submission of names of potential candidates to serve as ACIP members are available on the ACIP website. Applications for ACIP membership are due no later than August 15, 2022, for the 4-year term beginning July 2023. ACIP will be filling 6 positions at this time, including the Consumer Representative position.

INFLUENZA VACCINE

Session Introduction

H. Keipp Talbot, MD (Chair, Influenza WG) introduced this session on behalf of the Influenza Workgroup (WG). She reported that recent WG discussion have focused on elements of the EtR Framework for influenza vaccination of persons ≥65 years of age and development of proposed recommendations for 2022-2023. The agenda for this session included preliminary estimates of 2021-2022 seasonal influenza VE against medically attended influenza, the EtR Framework for influenza vaccination of persons ≥65 years of age, and proposed recommendations, and a vote.

Preliminary Estimates of 2021–2022 Seasonal Influenza VE against Medically Attended Influenza

Jessie Chung, MPH (CDC/NCIRD) presented preliminary estimates of 2021–2022 seasonal influenza VE against medically attended influenza. As a reminder, these are the 4 components of the 2021-2022 US influenza vaccines:

A(H1N1)pdm09	A/Victoria/2570/2019
A(H3N2)	A/Cambodia/e0826360/2020*
B Victoria	B/Washington/02/2019
B Yamagata	B/Phuket/3073/2013

*Reference virus from A(H3N2) genetic clade 3C.2a1b, subclade 2a.1.

The results Ms. Chung shared came from the US Flu VE Network, which is comprised of the following 7 research sites: Kaiser Permanente Washington, Kaiser Permanente Southern California, Baylor Scott & White Health, Marshfield Clinic Research Institute, Vanderbilt University, University of Michigan, and University of Pittsburgh. These sites conduct active enrollment of patients seeking outpatient medical care for an acute respiratory illness (ARI) that includes a cough and/or fever.

This analysis was restricted to ambulatory patients >6 months of age with acute respiratory illness (ARI) with fever or cough ≤7 days in duration. Patients were enrolled October 4, 2021–April 30, 2022. A test-neglect case-control study design was used that compared vaccination

odds among influenza reverse transcriptase polymerase chain reaction (RT-PCR) positive cases and influenza RT-PCR negative controls. Persons who tested positive for SARS-CoV-2 were excluded from this analysis. Vaccination status was defined as "receipt of at least one dose of any 2021–22 seasonal flu vaccine according to medical records, immunization registries, and/or self-report." VE was calculated from logistic regression models adjusted for study site, age, self-rated general health status, race/ethnicity, and month of illness onset.

The Flu VE Network enrolled over 6,000 persons in this timeframe, including 502 (7%) who tested positive for influenza and 2,046 (30%) who tested positive for SARS-CoV-2. There were 15 flu/SARS-CoV-2 co-infections detected. Among the influenza positives, 94% were A/H3N2 viruses. All of the genetically characterized viruses belonged to Clade 3C.2a1b, Subclade 2a.2 and no influenza B viruses were detected among these participants.

Overall, VE against influenza A viruses was 34%, with a statistically significant 95% confidence interval that ranged from 19% to 46%. VE against influenza A/H3N2 was 35%, with a 95% confidence interval that ranged from 19% to 47%. When broken down into 3 age groups (6 months – 17 years, 18 – 49 years, ≥ 50 years), VE against A/H3N2 was highest in the pediatric age group, including persons 6 months – 17 years for whom VE was 44% (22 to 60) and was statistically significant. VE among adults 18 – 49 years was 27% (-3 to 48). It was not possible to calculate an adjusted VE estimate for adults ≥50 years of age due to the limited number of cases enrolled. Only 67 A/H3N2 cases were enrolled in this age group.

To summarize, the preliminary findings for the 2021-2022 US season indicate that vaccination reduced ARI due to A/H3N2 by 35% (95% CI: 19–47). Almost all viruses sequenced nationally belong to Clade 3C.2a1b, Subclade 2a.2. Very low influenza prevalence was observed among all enrollees this season. The 2022-2023 Northern Hemisphere influenza vaccine will include updated reference virus for A/H3N2 (Clade 3C.2a1b, Subclade 2a.2), as well as an updated B/Victoria component (B/Austria/1359417/2021).

Discussion Summary

Dr. Poehling requested a reminder the percent of persons who were both influenza-positive and COVID-19-positive and asked whether any differences were observed between those who had influenza only versus those who were co-infected.

Ms. Chung indicated that only 15 co-infections were identified. Given that there were so few co-infections, no comparisons were made.

Influenza Vaccines for Persons Aged ≥65 Years: EtR Framework

Lisa Grohskopf, MD, MPH (CDC/NCIRD) summarized the EtR Framework discussion by the Influenza Vaccines WG for the review of influenza vaccines for persons ≥65 years of age, following a brief review the background for this assessment. Persons ≥65 years of age are at increased risk of severe illness, hospitalization, and death due to influenza relative to younger age groups. This age group has been a target population for annual influenza vaccination since the early 1960s. However, influenza vaccines are often less effective for people in this age group compared with younger populations. This table summarizes annual estimates of US influenza VE from the CDC US Flu VE Network for the 2011-2012 through 2019-2020 seasons.

Season	Overall VE, % (all ages, viruses, and vaccine types)	≥65 yrs (all viruses and vaccine types)
2019-20	39 (32, 44)	39 (9, 59)
2018-19	29 (21, 35)	12 (-31, 40)
2017-18	38 (31, 43)	17 (-14, 39)
2016-17	40 (32, 46)	20 (-11, 43)
2015-16	48 (41, 55)	42 (6, 64)
2014-15	19 (10, 27)	32 (3, 52)
2013-14	52 (44, 59)	50 (16, 71)
2012-13	49 (43, 55)	26 (-10, 50)
2011-12	47 (36, 56)	43 (-18, 72)

All of the influenza vaccines currently approved and available in the US with the single exception of the live-attenuated influenza vaccine (LAIV), are approved for persons ≥65 years of age. These include the following:

- ❑ 5 standard-dose, unadjuvanted inactivated influenza vaccines (SD-IIVs)
- ❑ 1 high-dose inactivated influenza vaccine (HD-IIV)
- ❑ 1 adjuvanted inactivated influenza vaccine (aIIV)
- ❑ 1 recombinant influenza vaccine (RIV)

ACIP has previously expressed no preferential recommendation for any specific influenza vaccine or vaccines for this age group. There were 3 influenza vaccines of specific interest for this review. The high-dose inactivated influenza vaccine currently available as Fluzone® High-Dose Quadrivalent (HD-IIV4) was approved as a trivalent in 2009 for persons ≥65 years of age. It contains four times the hemagglutinin (HA) dose per virus compared with SD-IIVs (60 µg vs. 15 µg). Initial approval was under the FDA Accelerated Approval pathway based on superior immunogenicity to SD-IIV3. Subsequent approval under the traditional pathway occurred in 2014, following demonstration of superior efficacy to SD-IIV3 in a 2-season randomized trial among 32,000 participants ≥65 years of age. HD-IIV4, the currently available quadrivalent formulation, was approved in 2019 on the basis of non-inferior immunogenicity to HD-IIV3 and replaced HD-IIV3 for the 2020-2021 season.

The adjuvanted influenza vaccine, also an inactivated vaccine currently available as Fluad® Quadrivalent (aIIV4), was approved in the US as a trivalent aIIV3 in 2016 for persons ≥65 years of age. This product had been in used previously in Europe for many years since as early as 1997. It contains the adjuvant MF59 initially was approved under the Accelerated Approval pathway based upon non-inferior immunogenicity to unadjuvanted SD-IIV3. In a post-marketing efficacy study, the quadrivalent aIIV4 was compared with Tdap in a 2-season randomized trial among 6,700 persons ≥65 years of age. The primary efficacy endpoint for this study, prevention of PCR-confirmed protocol-defined influenza-like illness (ILI) due to any influenza was not met. It was noted that 88% of the antigenically characterized viruses from cases in the active arm were antigenically mismatched. Efficacy was noted against PCR-confirmed CDC- and World Health Organization (WHO)-defined ILI due to any virus. aIIV4 is approved under the Accelerated Approval pathway and replaced aIIV3 for the 2021-22 season.

Flublok® Quadrivalent is somewhat different from the previous 2 vaccines in that it was not initially approved in the US for persons ≥65 years of age. Flublok® Quadrivalent initially was approved as a trivalent Flublok® RIV3 in 2013 for persons 18 through 49 years of age. This vaccine has 3 times the HA dose per virus compared with SD-IIVs. It is a recombinant HA and it has no viruses or eggs used in production. It was initially approved under the traditional pathway based upon efficacy demonstrated in a randomized placebo-controlled study among persons 18 through 49 years of age. Subsequently, it was approved for persons ≥50 years of age in 2014 under the Accelerated Approval pathway on the basis of immunogenicity studies among persons in this age group. RIV4, the quadrivalent formulation, demonstrated efficacy relative to SD-IIV4 in a single-season randomized study conducted among about 8,600 persons ≥50 years of age. RIV3 and RIV4 gained traditional approval for ages 50 and older in 2017. RIV4 replaced RIV3 for the 2018-2019 season. To recap, these 3 vaccines are all currently available as are the rest of the influenza vaccines that are available as quadrivalent formulations. As of this influenza season, trivalent influenza vaccines are no longer available.

The Grading of Recommendation Assessment, Development and Evaluation (GRADE) summary for this review was presented during the February 2022 ACIP meeting. The question of focus was, “Do the relative benefits and harms of HD-IIV, aIIV, and RIIV as compared with one another and with other influenza vaccines favor the use of any one or more of these vaccines over other age-appropriate influenza vaccines for persons ≥65 years of age?” Inherent in this question were 6 relevant comparisons, which included the following:

- ❑ HD-IIV vs. SD-IIV
- ❑ aIIV vs. SD-IIV
- ❑ RIV vs. SD-IIV
- ❑ HD-IIV vs. aIIV
- ❑ HD-IIV vs. RIV
- ❑ aIIV vs. RIV

One thing to note in this presentation going forward is that the terms “higher dose” and “adjuvanted influenza vaccines” replace the collective term previously used in these discussions to define collectively high dose adjuvant and recombinant vaccines, which was “enhanced influenza vaccines.” The reason for this change is that while there is a precedence for the use of the term “enhanced influenza vaccines” in the literature, it does not have a strict definition and might lead to confusion as to what counts as such a vaccine, particularly as new vaccines emerge going forward.

The population, intervention, comparators, outcomes (PICO) for this question were as follows. The population of interest was adults ≥65 years of age. Interventions included higher dose, adjuvanted, or recombinant influenza vaccines (collectively higher dose or adjuvanted vaccines in trivalent or quadrivalent formulations). Comparators included SD-IIVs and higher dose and adjuvanted influenza vaccines, which were included in both the intervention and the comparator boxes because they could be compared with one another. Critical outcomes of interest included influenza illness, influenza-associated outpatient and emergency department (ED) visits, influenza-associated hospitalizations, and influenza-associated deaths—all due to any viral type or subtype and defined by laboratory-confirmation, diagnostic codes, or clinical definitions. Critical safety outcomes included any solicited systemic adverse event (AE) Grade 3 or higher and Guillain-Barré Syndrome (GBS). Important outcomes included any solicited injection-site AE Grade 3 or higher and any serious adverse event (SAE).

With that background, Dr. Grohskopf summarized the WG's discussion and considerations of the EtR Framework domain-by-domain, starting with the first domain of public health importance. In discussing the significance of influenza among persons ≥65 years of age, the WG reviewed influenza hospitalization and surveillance data, as well as an analysis by Rolfes et al[1] that estimated the burden of influenza in the US by age group for the 2010-2011 through 2015-2016 influenza seasons using data from routine influenza surveillance, outbreak investigations, and survey data describing proportions of persons seeking healthcare. The highest burden of influenza hospitalizations and deaths was among persons ≥65 years of age, with estimated ranges of 87,000 to 521,000 hospitalizations, 3,000 to 17,000 excess pneumonia and influenza deaths, and 9,000 to 43,000 excess respiratory and circulatory deaths over this 6-year study. The WG was unanimous in the view that influenza among older adults is a problem of public health importance.

The next domain is benefits and harms. The systematic review and GRADE were previously summarized in some detail in previous meetings. Most recently, GRADE was summarized during the February 2022 ACIP. This presentation focused primarily on the critical outcomes selected by the WG. For benefits those are prevention of influenza illness, influenza-associated outpatient/ED visits, influenza-associated hospitalizations, and influenza-associated deaths. For harms the critical outcomes were any solicited systemic AE of Grade 3 or higher and GBS.

In terms of the comparisons of higher dose and adjuvanted influenza vaccines with one another, there was only 1 randomized study that was relevant for all 3 comparisons (HD-IIV vs. aIIV, HD-IIV vs. RIV, and aIIV vs. RIV). This was a very small study that included all 3 vaccines, with approximately 30 participants per group. This was primarily an immunogenicity study that reported influenza PCR-positive ILI as an exploratory outcome. Given the size and power of the study, no significant differences were observed for any of these outcomes. In each comparison, the quality of evidence was determined to be of very low certainty. The study was downgraded for risk of bias as it was an open-label study, as well as for imprecision. There were no other randomized studies for any of these 3 comparisons or studies that used laboratory-confirmed influenza outcomes.

The remainder of the studies retrieved for these comparisons were retrospective cohort studies, including diagnostic code-defined outcomes. Since the last presentation of these data, following some additional discussion, the certainty results containing these data have been downgraded an additional step for risk of bias due to concerns over potential for residual confounding. Therefore, some of the certainty levels are lower than in the February 2022 presentation. For the high-dose versus adjuvanted comparisons, neither vaccine was favored in retrospective cohort studies for the outcomes of influenza-associated outpatient/ED visits or influenza-associated hospitalizations. Certainty was low. Downgrading for this was due to the outpatient studies, risk of bias, and inconsistency because 2 studies were performed during the same season that had substantially different estimates. For the hospitalization outcome, certainty was downgraded for risk of bias and imprecision. For the high-dose versus adjuvanted comparison that summarizes the retrospective cohort data, in the case of the estimates for high-dose versus recombinant and adjuvanted versus recombinant, there was evidence of benefit for the recombinant vaccine for prevention of influenza-associated hospitalizations. Again, both favored recombinant with low certainty. However, these results came from only 1 study performed over one influenza season.

[1] Rolfes et al. Annual estimates of the burden of seasonal influenza in the United States. Influenza Other Respi Viruses 2018;12:1232-137

Considering together the results among studies affording direct comparisons of benefit outcomes among the higher-dose and adjuvanted vaccines, the WG felt that the evidence is insufficient currently to inform a decision for any one vaccine over the others. In the interest of time, the WG did not re-summarized the safety results that were presented in February 2022. However, it also was reassuring that among studies providing safety data for these comparisons, which included one randomized controlled trial (RCT) comparing high-dose versus adjuvanted vaccine for safety outcomes, there were no results favoring any vaccine. Overall certainty for these outcomes was low, primarily due to imprecision stemming from low event counts and often small sample sizes.

The WG then discussed comparisons of each of the higher dose or adjuvanted vaccines with standard dose unadjuvanted vaccines. For high-dose versus standard dose for influenza illness, there was 1 large, 2-season randomized trial that noted a relative risk of 0.76 translating into a relative VE of about 24%, favoring high-dose compared with standard dose. This was high-certainty evidence. For influenza-associated outpatient and ER visits, there was evidence favoring high-dose with a relative risk of 0.7 from a retrospective of cohort study covering 4 seasons, with low certainty and that was downgraded for risk of bias. For hospitalizations, there was evidence of relative effectiveness favoring high-dose with a relative risk of 0.79 from a cluster-randomized trial conducted within a network of 823 nursing homes during a single season. This was judged to be moderate-quality evidence. Though it is a cluster-randomized trial, it was reassuring that the risk estimate, and by extension, the relative VE was similar to that obtained in the large, randomized efficacy trial. There also was evidence from observational studies favoring high-dose over standard dose for influenza-associated deaths, with an effect estimate of 0.67, which was low-certainty evidence.

Moving to a comparison of adjuvanted versus standard dose for the benefits outcomes of efficacy and effectiveness, no RCTs were retrieved that used laboratory-confirmed influenza outcomes. One RCT, primarily a safety study, examined occurrence of influenza identified strictly by a symptomatic definition that saw no difference. Studies spoke to the outcome of influenza-associated outpatient visits, but evidence here was variable. There were 2 retrospective cohort studies identified that examined code-defined outcomes that were conducted in the same season. No effect was seen in the pooled estimate. This evidence had to be downgraded for risk of bias and inconsistency because the 2 estimates from the same season had substantially different results. There were 2 smaller observational studies that, combined, favored aIIV with a risk estimate of 0.64. For hospitalizations, there was evidence favoring aIIV with a risk ratio of 0.79 and moderate certainty from a cluster-randomized trial using diagnostic code to find pneumonia and influenza outcomes. This trial was of similar design and was conducted in a similar nursing home network to the cluster-randomized trial described earlier for the high-dose vaccine. There also was evidence favoring aIIV from 3 retrospective cohort studies using code-defined hospitalizations and from 2 smaller observational studies. These estimates for hospitalizations were considered to be low-certainty evidence.

For recombinant versus standard dose. For this comparison, and for recombinant vaccine data in general, there are fewer studies. For influenza illness, there were 2 RCTs, a smaller one dating from about 2010 comparing RIV3 with SD-IIV3 and a more recent larger trial comparing RIV4 and SD-IIV4. This was high-certainty evidence, but the risk estimate was equivocal. Of note, the more recent larger study drives most of the results in the meta-analysis for this particular comparison and the total study population was ≥50 years of age. For the study population as a whole, there was a reduction in PCR-confirmed influenza with RIV4 compared with SD-IIV4 for a relative risk of about 0.7. PCR-confirmed influenza was the primary outcome

defined by the study. However, no reduction in risk was seen for persons ≥65 years of age in a sub-analysis. However, the WG, felt that this work was nonetheless important because of the reduction seen for persons ≥50 years of age and because a reduction in risk for some other outcomes, including culture-confirmed influenza, was seen in the subset of persons ≥65 years of age. There also was evidence of benefit against hospitalization from a large retrospective cohort study among Medicare beneficiaries using diagnostic code of defined outcomes, which yielded a risk estimate of 0.83. While this favored recombinant vaccine, it was judged low-certainty evidence.

To summarize the harms outcomes for each vaccine of interest versus standard dose unadjuvanted vaccine, neither vaccine was favored for any of the 2 critical safety outcomes across any of the 3 comparisons. The overall quality of these estimates was low to very low. This primarily was due to small event counts and often small sample sizes in these studies, as well as the relative rarity of GBS.

In terms of the WG's considerations, it was recognized that among the 3 higher dose and adjuvanted vaccines, the most data are available to support high-dose, which had some evidence favoring its benefits for all 4 of the selected critical efficacy and effectiveness outcomes. This includes the very large 2-season randomized trial that noted a relative VE of 24% for high-dose versus standard dose vaccine. However, considering data for the various outcomes across the vaccine comparisons, it also was noted that the most data were available across the board for hospitalizations. While all of the efficacy outcomes were regarded as critical, hospitalizations are of particular interest for being a relatively common and also severe outcome for this age group. For this outcome, there is evidence supporting each of the 3 higher dose or adjuvanted influenza vaccines over standard dose vaccines. These estimates were considered moderate certainty for high-dose and adjuvanted vaccines. In each case, this was driven by findings from large cluster-randomized trials. Evidence was of low certainty for hospitalization outcomes for the recombinant vaccine. In the discussions of these factors in looking over these findings, the WG also noted that relative VE varies from season-to-season. Therefore, the benefits of one vaccine compared with one another are not necessarily static. Relative benefit might not be seen for any given vaccine combination or one vaccine over another being better in every season. For some seasons in multi-season studies, no benefit was seen for the higher dose or adjuvanted vaccine over standard dose vaccines. It seems that what performs better in one season might not in another.

With regard to safety, no concerns were identified in the findings for the critical safety outcomes from the WG's review. There was discussion concerning the overall level of certainty for these outcomes, which was low to very low depending upon the comparison and the outcome. The WG was concerned that it is important to emphasize that this is due to a low level of certainty in the evidence, largely due to imprecision of the effect estimates. This is not uncommon with safety studies in general due to small event counts and small sample sizes for some studies. The WG felt strongly that it should be emphasized that this is not to be interpreted as a safety concern.

In terms of the overall certainty of the evidence for the critical outcomes, the level of certainty was low for each vaccine comparison for benefits overall. For harms overall, certainty was low for high-dose versus standard dose and adjuvanted versus standard dose and very low for recombinant versus standard dose. Approximately half of the WG indicated that the desired anticipated effects are they are moderate, but a substantial minority thought that this varies due to the variability of influenza VE from season-to-season. The majority of the WG thought that the desirable anticipated effects are minimal. Considering all of these findings and factors, the

sentiment of the majority of the WG was that the balance of benefits and harms favors the intervention.

Moving to the domain of values, the WG found no published evidence reflecting values of US seniors concerning higher dose and adjuvanted vaccine specifically or the relative importance of the selected outcomes. However, 1 analysis was identified that might speak to values. There was a recent Centers for Medicare and Medicaid (CMS) analysis of their data for Medicare beneficiaries that suggests that the majority of community-dwelling Medicare beneficiaries ≥65 of age already have received 1 of these 3 vaccines in recent seasons. This suggests that some seek out these vaccines specifically. However, it also was noted that provider choices and recommendations also are important in determining what vaccines are received. The impressions of the WG regarding the questions for this domain reflected some degree of uncertainty. The majority of WG members indicated that they thought the target population probably feels that the desirable effects of a new recommendation are large relative to the undesirable effects, and that there probably is not important uncertainty or variability in how people value the main outcomes evaluated.

Regarding the domain of acceptability, no literature was found reflecting the acceptability of the vaccines of interest among US seniors. A number of studies and papers were found that reflected questions, such as willingness to pay for specific vaccines over others. However, most of these were not US papers and do not reflect US payment for influenza vaccines or the US population. However, the WG felt that some indirect evidence of the acceptability of high-dose, adjuvanted, and recombinant influenza vaccines among persons ≥65 years of age can be seen in recent analyses of VE among Medicare beneficiaries, which suggests that most people ≥65 years of age already have received a higher dose or an adjuvanted vaccine in recent seasons.[2] of them are reflected, are in the tables that you saw earlier. There were some exclusions in the study population. For example, one of the more significant ones is that persons residing in nursing homes at the time of vaccine administration were excluded. In addition, not all vaccinations are recorded in the Medicare database. Therefore, it cannot be said that the study populations for these papers includes the entire universe of Medicare beneficiaries. The analytic datasets contained 12 to 13 million people each season. For each season, the majority of individuals in this dataset had received 1 of 3 vaccines (HD-IIV3, aIIV3, or RIV4), with approximately 81% having received one of these vaccines in the 2019-2020 data. While this is not direct evidence of acceptability to all key stakeholders, the current degree of uptake suggests at least some current level of acceptability to vaccine providers and recipients. The majority of WG members felt that the intervention is acceptable to key stakeholders.

In terms of the domain of resource use, there are multiple published economic evaluations of high-dose and adjuvanted vaccines compared with standard vaccines. Given the possibility of a recommendation for more than 1 of these vaccines over SD-IIV, an economic analysis was conducted. For this section, Dr. Grohskopf presented an analysis by Dr. Fangjun Zhou of the CDC Immunization Services Division (ISD). The objective of this work was to conduct a cost-effectiveness analysis of use of higher dose and adjuvanted influenza vaccines (HD-IIV, RIV, and aIIV) among adults ≥65 years of age in the US compared with standard dose unadjuvanted influenza vaccines from the societal perspective. The assumptions for the base case were drawn from the averages of the 2017-2018 through 2019-2020 influenza seasons for

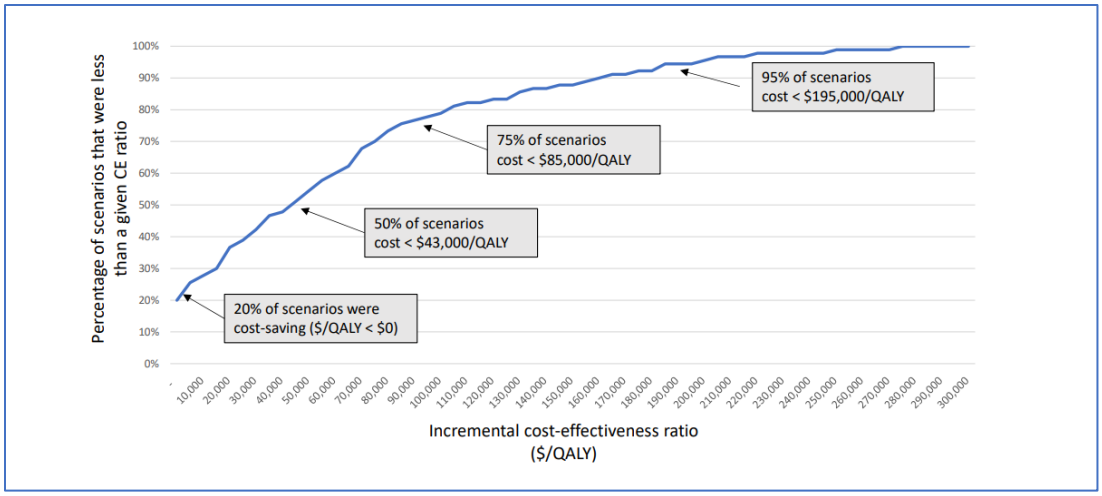
[2] a) Izurieta HS, et al. Relative Effectiveness of Cell-Cultured and Egg-Based Influenza Vaccines Among Elderly Persons in the United States, 2017-2018. J Infect Dis. 2019 Sep 13;220(8):1255-64; b) Izurieta HS, et al. Relative Effectiveness of Influenza Vaccines Among the United States Elderly, 2018-2019. J Infect Dis. 2020 Jun 29;222(2):278-87; and c) Izurieta HS, et al. Comparative Effectiveness of Influenza Vaccines Among US Medicare Beneficiaries Ages 65 Years and Older During the 2019-2020 Season. Clin Infect Dis. 2021 Dec 6;73(11):e4251-e9.

disease burden, vaccination coverage, and VE. The basis for the selection of these 3 seasons was that they were some of the few seasons in which there were relative VE estimates for all relevant vaccine comparisons that are available within the context of the same study. These estimates came from the Izurieta et al studies, which estimated relative VE of the various vaccine comparisons against pneumonia and influenza diagnostic-coded hospital encounters. That is, inpatient stays and ED visits combined. These particular estimates from these papers were used for these assumptions. Using the base-case assumptions, the incremental cost-effectiveness ratios in dollars per quality-adjusted life year (QALY) were $52,000 for high-dose versus standard dose, $60,100 for adjuvanted versus standard dose, and were cost-saving for recombinant versus standard dose. Average cost-effectiveness ratios were $6,600 for high-,dose versus no vaccine, $7,600 for adjuvanted versus no vaccine, and were cost-saving for both the recombinant versus no vaccine and standard dose versus no vaccine.

In terms of the estimated numbers of health outcomes for each vaccine type under the base case set of assumptions, each vaccine (HD-IIV, aIIV, and RIV) was estimated to result in fewer illnesses, hospitalizations, and deaths. Looking across the 3 vaccines, approximately 2,000 additional deaths would be prevented with enhanced influenza vaccines. This assumes current use of higher dose and adjuvanted vaccines of 80% in the population ≥65 years of age. It was further estimated that an additional approximately 400 deaths might be prevented if 100% of these vaccinated adults received one of the higher dose or adjuvanted vaccines. To get an idea of the potential impact of different scenarios of relative VE and influenza burden on the incremental cost-effectiveness ratios, the 2017-2018, 2018-2019, and 2019-2020 estimates for VE were applied to the disease burden data from 10 consecutive influenza seasons from 2010-2011 through 2019-2020, with the results shown in this table:

	2017/18 VE			2018/19 VE			2019/20 VE		
Season	HD vs SD-IIV	aIIV vs SD-IIV	RIV vs SD-IIV	HD vs SD-IIV	aIIV vs SD-IIV	RIV vs SD-IIV	HD vs SD-IIV	aIIV vs SD-IIV	RIV vs SD-IIV
2010/11	18,300	99,100	cs	65,700	26,000	cs	68,400	50,500	13,700
2011/12	90,200	271,200	45,400	196,400	107,500	1,700	202,400	162,300	79,900
2012/13	4,600	79,900	cs	48,800	11,800	cs	51,200	34,600	300
2013/14	20,100	100,600	200	67,300	27,800	cs	70,000	52,100	15,600
2014/15	1,800	69,600	cs	41,500	8,300	cs	43,800	28,700	cs
2015/16	67,200	215,900	30,500	154,400	81,400	cs	159,300	126,400	58,800
2016/17	21,400	116,700	cs	77,300	30,500	cs	80,400	59,300	16,000
2017/18	cs	37,600	cs	16,900	cs	cs	18,500	7,400	cs
2018/19	48,400	181,300	15,500	126,400	61,100	cs	130,700	101,300	40,800
2019/20	73,100	246,500	30,300	174,800	89,700	cs	180,500	142,100	63,300

To summarize the results from this table into a more visual format, the following incremental cost-effectiveness curve was constructed:



This illustrates that 20% of the scenarios were cost-saving, 50% cost less than $43,000 per QALY gained, 75% of scenarios cost less than $85,000 per QALY gained, and 95% cost less than $195,000 per QALY gained. Incremental cost-effectiveness ratios for higher dose and adjuvanted vaccines versus standard vaccines vary considerably based upon underlying VE and influenza season severity.

This analysis has some limitations. This modeling work indicates substantial uncertainly in estimates of value due to multiple product comparisons and the inherent variability of influenza burden and VE from season-to-season. As noted earlier, the VE assumptions were derived from estimates obtained in a retrospective cohort study of vaccine for the prevention of influenza-associated hospital encounters. These estimates are not from randomized trials, in part because randomized trials are too few in number to be able to find sufficient assumptions for this model. In addition, it is difficult to find estimates for all of the relevant outcomes during the same influenza season. It should also be noted that VE might differ for different outcomes, even for the same vaccine comparison within the same season. That is to say, VE for hospitalizations/hospital encounters and ED visits will not necessarily be the same as VE for clinical illness or other outcomes. On the question of whether the intervention is a reasonable and efficient allocation of resources, the WG acknowledged that given the variabilities associated with influenza burden and VE, cost-effectiveness of higher dose or adjuvanted vaccines will vary from season-to-season. However, a majority of the WG felt overall that a recommendation to use higher dose and adjuvanted influenza vaccines over standard dose vaccine would be a reasonable and efficient allocation of resources. A minority of the WG voiced that it probably would be a reasonable and efficient allocation of resources and a smaller minority indicated that this would vary.

In terms of the domain of equity, racial and ethnic disparities in overall influenza vaccine coverage and in rates of severe influenza illness have been documented in several studies. Mahmud et al (2021) examined receipt of high-dose vaccine versus all other seasonal influenza vaccines combined as a group among Medicare beneficiaries ≥65 years of age during the 2015-2016 influenza season. In addition to disparities in receipt of any seasonal influenza vaccine, a finding that has borne out in many other papers, the authors noted disparities in the use of high-dose vaccine compared with standard-dose vaccine by race and ethnicity. Compared with White recipients, those of Black or Asian race and those of Hispanic ethnicity were significantly less like to receive the higher-dose vaccine. In discussing the potential impact of a new recommendation on equity, the WG recognized that impact depends upon underlying causes of

the differences in receipt of these vaccines. Potential factors include (but are not limited to) cost, differences in practice settings, and differences in linkage to care. It also was noted that the Mahmud study occurred during the 2015-2016 season at which time, aIIV had not yet been introduced in the US, RIV was relatively new to the market, and there were somewhat fewer options for this age group. Nonetheless, given what is known about persisting disparities in influenza vaccination coverage in the population as a whole, inequities in this age group remain a concern. While it is not possible to know whether a recommendation for higher dose or adjuvanted vaccines would positively impact equity, the WG's sense was that there is not a basis to predict negative impact. On the question of equity, the majority of the WG expressed the view that a new recommendation probably would increase equity. A smaller proportion expressed that the intervention would increase equity or that it would probably have no impact. None indicated that equity would be reduced or probably reduced.

In the WG's discussion of the domain of feasibility a point that was thought to speak to the issue of feasibility was, it was observed that the analyses of CMS data suggest most community-dwelling CMS beneficiaries ≥65 years of age already have received a higher dose or adjuvanted influenza vaccine during recent seasons (2017-2018 through 2019-2020). While there were differences in the proportions who received high-dose versus adjuvanted versus recombinant relative to one another and there was some shifting in those proportions over the 3 seasons examined, these vaccines already appear to be in established use in this population. From a reimbursement perspective, CMS already reimburses for all influenza vaccines that are approved for this age group. There are some differences in the reimbursement rates. HD-IIV, RIV, and aIIV are reimbursed at a higher rate than SD-IIVs as of 2021-2022 at approximately $65 to $67 per dose for the higher dose and adjuvanted vaccines versus approximately $20 to $28 for single dose presentations of SD-IIVs. There is somewhat more spread in the figure for the standard dose vaccines primarily because the reimbursement for Flucelvax® Quadrivalent, the cell-based vaccine, is somewhat higher than the remaining vaccines that are egg-based. Higher dose and adjuvanted influenza vaccines are also similar in administration and storage to other intramuscular influenza vaccines. Overall, the WG felt that an intervention recommending higher dose or adjuvanted influenza vaccines would be feasible to implement.

To summarize the WG's overall conclusion in considering all of the EtR domains and with the intervention being higher dose or adjuvanted vaccines over SD-IIVs for persons ≥65 years of age, the breakdown for the domains follows. The WG agreed that influenza among older adults is a problem of public health importance. The substantiality of desirable and anticipated effects of an intervention was felt to be moderate on average, but variable. The substantiality of the undesirable anticipated effects was felt to be minimal. The balance of the desirable and undesirable effects was felt to favor the intervention. Overall, the certainly of the evidence for the higher dose and adjuvanted vaccines versus the standard vaccines was low for the critical efficacy and effective outcomes. The breakdown for the critical safety outcomes was low for high-dose and adjuvanted and very low for recombinant. The low to very low assignments of certainty were primarily due to low precession of the estimates gathered from studies that often had small event counts and small sample sizes. The WG reinforced that overall, these vaccines have been demonstrated to be safe. While there were few specific data to discuss relevant to values, the WG felt that the target population probably feels that the desirable effects outweigh the undesirable effects and that there is probably no important uncertainty or variability in how people value the main outcomes. The WG felt that the intervention is likely to be acceptable to key stakeholders and a reasonable and efficient use of resources. With regard to equity, most felt that the intervention probably would increase equity, and no one responded that it would decrease equity. The intervention was felt to be feasible to implement.

In considering the elements of the EtR previously discussed with regard to overall balance of consequences inherent in a new recommendation, the majority of the WG felt that desirable consequences clearly outweigh undesirable consequences in most settings. A somewhat lesser proportion responded that they thought that desirable consequences probably outweigh undesirable consequences in most settings. None of the other options were selected. On the question of whether there is sufficient evidence to move forward with the recommendation, the majority of WG members responded "yes." The WG discussed several potential recommendations. The first option was to make no change in the recommendation. That is to say that any age-appropriate influenza vaccine is recommended for persons ≥65 years of age. The second option was that that high-dose vaccine is recommended when available and that, if not, any age-appropriate vaccine can be used. The third option was that high-dose vaccine is recommended when available. If not, then either adjuvanted or recombinant vaccine may be used, if available. If none of these 3 options is available, then any age-appropriate vaccine may be used. The fourth option was that that high-dose adjuvanted or recombinant vaccines are recommended when available. If none of these 3 vaccines is available, any age-appropriate vaccine may be used. The majority of the WG opted for the fourth option.

A number of points emerged during the WG's discussion of the EtR and of the potential recommendation language just summarized, some of which concern the evidence base. It was acknowledged that randomized trials, ideally against laboratory-confirmed outcomes, are the most desirable evidence. However, such trials are few in number, are very resource-intensive to implement, and are not easily executed over repeated seasons. Given the variability of influenza seasons and of VE, it is difficult to assume that findings from a few seasons will generalize to all or most seasons. In this case, there are only 2 randomized efficacy trials comparing higher-dose and adjuvanted vaccines versus-standard dose vaccines with laboratory-confirmed outcomes—the 2-season trial for high-dose versus standard dose and the 1-season trial for recombinant versus standard dose. There were no comparable randomized trials comparing adjuvanted standard dose. The trial mentioned at the start of this presentation of aIIV versus Tdap was not part of the GRADE analysis in this review because the primary focus was on studies providing estimates of relative VE of influenza vaccines compared with one another. As noted, this study did not demonstrate efficacy for its primary outcome. However, the majority of antigenically characterized viruses from that study were due to antigenically drifted viruses. This demonstrates another difficulty with randomized trials of influenza vaccines. If the study is performed in what turns out it be a season of meaningful mismatch between vaccines and the predominant viruses in circulation, it might be difficult or impossible to draw conclusions either way about efficacy from the work of that season. An analogous, although more extreme example of this, occurred with an earlier trial of high-dose vaccine versus standard-dose vaccine, which occurred during what would become the 2009 H1N1 pandemic. In this study, no cases occurred to viruses antigenically matched with vaccine viruses due to the widespread circulation of the pandemic virus, which essentially replaced the other viruses in circulation for that season.

While randomized trials are critical from a practical standpoint, decisions regarding potential preferential recommendations for influenza vaccines might need to draw from observational studies and not be restricted to RCTs, while acknowledging the limitations of the observational studies in order to gain perspective on performance across seasons. It was acknowledged that the most data for the most outcomes are available to support the high-dose vaccine. However, it also was noted that while a single randomized trial of RIV4 versus IIV4 did not demonstrate benefit for the primary outcome for persons ≥65 years of age, it did demonstrate benefit for some other outcomes in this age subgroup of interest and also for the population as a whole for persons ≥50 years of age. It also was noted that there is evidence to support adjuvanted

vaccine from a cluster-randomized study and several observational studies. Another point was raised that a recommendation for a single vaccine over all others might lead to confusion if that vaccine does not demonstrate consistent benefit across future seasons. Conversely, it was felt that a recommendation for any of the 3 vaccines provides a balance of science and practicality given what is known about the variability of influenza seasons and VE.

As noted earlier, there are fewer data comparing HD-IIV, aIIV, and RIV with one another. Among the available studies, the most provided data for the high-dose vaccine versus adjuvanted vaccine comparison. In these 3 comparisons as a whole, the only relative benefit was seen for the recombinant vaccine versus adjuvanted vaccine and the recombinant vaccine versus high-dose vaccine. However, these 2 outcomes were based on a single study from a single influenza season. Overall, current evidence was felt to be insufficient to recommend one vaccine over the others. However, it also is likely that there will be more comparative data to examine in the near-term, possibly with the current quadrivalent formulations of the high-dose and the adjuvanted vaccines for which the WG did not have any data to use in this review. Other points spoke to feasibility and acceptability issues. For example, a recommendation for 1 of 3 vaccines, when available, provides flexibility for providers. For example, for those who care for adults across an age spectrum, stocking RIV might be more practical since it is approved for persons ≥18 years of age and not only for persons ≥65 years of age. Another point raised was that this approach minimizes some of the risk associated with the recommendation for 1 vaccine above all others. For example, if there are unexpected delays in vaccine availability or manufacturing problems.

Discussion Summary

Referring to Slide 18, Dr. Poehling requested additional details about what was meant by saying that they “favor the high-dose” and “favor aIIV” and “favor RIV.”

Dr. Grohskopf indicated that one of the issues the WG noticed in looking across studies, since they had a sizable amount of retrospective cohort data in this canon they retrieved through the literature search, was that the estimates for outpatient and ED visits were somewhat more inconsistent than hospitalizations. It is difficult to know exactly where that is coming from. One hypothesis the WG discussed is the possibility that since these are diagnostic code-based outcome definitions, the majority of them used ICD-9 pneumonia and influenza codes. Some of them were more restrictive and used only influenza codes. Someone might be more likely to get assigned that diagnosis on their coding sheet if they had been admitted to the hospital and gotten the test as opposed to being seen as an outpatient or in the ED. The WG did not always see benefit in outpatient versus ED studies. In the particular case for the 4 retrospective cohort studies combined, the WG noted that there are a lot of differences in the US Flu VE Network data in terms of VE versus in this kind of data from a retrospective cohort study of CMS data. The US Flu VE data have laboratory confirmation whereas the retrospective cohort data are by and large all code-based outcome definitions. The sample sizes for the US Flu VE Network are far smaller, in the thousands, as opposed to in the millions with the CMS analyses. Even if looking at data from the same season, it might not be possible to draw a lot of parallels. Another thing to consider with the Flu VE Network data, which has occurred over time, is that the proportion of people who are receiving the high-dose vaccine in that network has increased since high-dose was introduced. This has increased considerably since the 2014-2015 season, along with a lower proportion of recombinant and adjuvanted use. Therefore, it is difficult to draw parallels between them. The end goal is to assess the same thing, which is VE, but the studies are measuring in different ways on different populations than the US Flu VE Network

population, particularly with the number of persons ≥65 years of age being much smaller than in a Medicare database.

Dr. Poehling requested additional information regarding aIIV and RIV comparison.

Dr. Grohskopf responded that there were fewer studies overall for this comparison. There was some variability with outpatient and ED depending on the study type. It was interesting that the 2 retrospective cohort studies for adjuvanted versus standard dose. Looking at each of them individually, they had results suggesting efficacy, but one favored one vaccine and not the other. While there was some variability, there were relatively tight intervals. One of the reasons there are fewer data for outpatients than hospitalizations is that in the Izurieta group's large 3-season analyses, the outpatient outcome were assessed for the first season, 2017-2018, and not for the 2018-2019 and 2019-2020 seasons.

Dr. Daley asked how many of these studies were industry-funded and whether that was discussed during the WG's consideration of the body of the evidence.

Dr. Grohskopf said that while she did not recall the exact number, the large 2-season RCT for the high-dose versus standard dose that had 32,000 people was an industry study. The comparison study for the recombinant versus standard dose, the single-season study, also was an industry study. She thought the RCT for adjuvanted versus standard dose was an industry study, which was not as helpful from an efficacy point of view because the outcome used was just a symptom-based influenza definition and it was mostly a safety study. Among the observational studies, the large CMS database studies were US Government (USG) work. Some of the large retrospective cohort studies were funded either by manufacturers or had industry authors.

Dr. Daley asked what could be done to ensure that health inequality is not exacerbated by this recommendation. Perhaps there are settings in communities of color or in disadvantaged geographic areas in which only standard dose is offered. There also may be awareness issues among persons ≥65 years of age who are seeking vaccine but do not know that there is a high-dose or adjuvanted vaccine recommended for them.

Dr. Grohskopf acknowledged the importance of ensuring that health inequity is not exacerbated. An effort is being made to get a better sense of what makes these situations different from other situations and why these things are happening. No having good linkage to care or a stable relationship with a healthcare provider (HCP) or a group of providers could be a factor. One of the strongest determining factors for getting an influenza vaccine is a trusted provider making a recommendation for it. There probably also are logistical issues. For instance, some clinical settings may not be sufficiently staffed or may not have good connections with other clinical groups to be able to efficiently handle multiple types of influenza vaccines—particularly if they serve smaller populations and need to stock vaccine that can be used for a broader range of the patients under their care. It is important to get a better sense of the root causes, which may be multiple.

Dr. Sanchez agree with the fourth possible recommendation that was made by the WG favoring HD-IIV4, aIIV4, or RIV4. He emphasized the importance of education for the public and providers.

Dr. Long said that it was amazing that there is a vaccine that is recommended for the entire US population, but for which the efficacy for influenza-like disease is quite low. These are mucosal infections with the inflammatory signatures. Because the virus changes so much, better efficacy would be beneficial. But maybe in future they should give up what they cannot have, a lot of control of simple disease, and focus more on hospitalizations and death. This intervention would be estimated to save an additional 2,000 deaths per year for persons ≥65 years of age, which is truly remarkable and cost-saving. She thinks a recommendation is very important because even in healthcare organizations, healthcare workers are aging. A recommendation would help to ensure that the most potent vaccines are available for this age group.

Dr. Talbot noted that it is much easier for practices to stock 1 vaccine product and give it to everyone, so many clinics probably have done that because it is much easier. This also has created a disparity. Moving to a recommendation that an older adult should get a relatively better vaccine would change that. It would then become a priority to identify patients ≥65 years of age and give them the correct vaccine. She thinks such a recommendation would help to reduce current disparities.

Dr. Goldman (ACP) asked whether in the 2015 study that looked at equity, the data were subdivided for Medicare Advantage plans (Part C) versus straight Medicare. One of the quirks of vaccine reimbursement is that certain vaccines like influenza, pneumonia, and hepatitis B are covered under Medicare Part B. Others are covered under the drug plan, which in some cases, especially with the full-risk plans, may prevent physicians from being able to vaccinate in their office. This may further decrease access, availability, and equity. He asked if the WG considered this in the nuances of how to increase equity, especially allowing physicians to be able to administer certain vaccines in their offices.

Dr. Grohskopf indicated that the Izurieta analyses and the other analyses from that group that is out of FDA excluded Medicare Advantage, Part C, from the analyses.

Dr. Long said she was getting more confused as they went along with so many recommendations. While the recommendation was straightforward, it also had embedded in it that if one of these vaccines is not available, the standard vaccine should be given. She would rather say that high-dose or adjuvanted vaccines should be made available for people ≥65 years of age. If they want to save those extra 2,000 lives, they want to be sure that all doctors understand that they should be giving these vaccines preferentially. The way the recommendation read seemed too passive.

Dr. Lee requested that Dr. Long raise this question again during the vote session.

Dr. Fryhofer (AMA) said that speaking as a practicing physician who administers influenza vaccines in her office and orders influenza vaccines for her office generally in February each year, they need to make sure that they do not keep people in the current influenza season from being vaccinated. If the ACIP decided to vote on this recommendation, it likely would affect the supplies physicians have in their offices. She requested that the committee consider this in terms of making this recommendation.

Dr. Poehling asked whether the percentage is known of persons ≥65 years of age who are vaccinated in a pharmacy versus a physician office. She also emphasized that as they are thinking about adult recommendations, it would be helpful to make sure there is a universal registry so that there is clear communication between practices and pharmacies.

Dr. Grohskopf said that while she was not certain of the exact answer to that, vaccination in pharmacies has been increasing over the last number of years and is fairly commonplace. Before the vote, they can seek additional information about the exact proportion to report back to the ACIP. Related to that is that it does seem that these vaccines are readily available in retail vaccination settings.

Dr. Lee commended and expressed appreciation for the WG, under the leadership of Drs. Talbot and Grohskopf, for synthesizing this tremendous amount of data so succinctly and efficiently. The literature is vast and variable, and it takes a lot of work to get it into a form that makes it easier for ACIP to deliberate on. As they learned from the COVID-19 pandemic, pharmacy partners have been incredibly helpful in ensuring that they are a key part of the delivery system. That has been longstanding for influenza vaccines in addition to physician offices who have done a huge amount of vaccine delivery. She agreed that it would be incredibly helpful to have information about what proportion of individuals, by age group, receive vaccines in pharmacies versus offices more broadly and specific to influenza vaccine and what products are available where. In terms of whether regional or local variability and availability could impact some communities more adversely than others, if pharmacies are a predominant delivery system in certain communities for receiving influenza vaccine, that would be very helpful. As they look ahead about what can be done to reduce disparities, having that information would be helpful. She imagined that at the state and local levels, partner with their colleagues in the community could help to ensure that the gap is being closed from an implementation standpoint. She emphasized that education, community outreach, and sustaining the relationships built over the course of COVID-19 continue to be key. Resources are dwindling again and all of the efforts made to engage community partners have been critical for the COVID-19 response and in reducing disparities. She worries that as attention and funding fade, there will be important missed opportunities to continue to address disparities in health equity. While Dr. Lee recognized that this is not necessarily an ACIP- or CDC-only issue, federal funding is important to all vaccines in terms of preventive health issues. The recommendation proposed made sense in the context of the cost-effectiveness analysis, but she asked about the difference in the actual cost per dose of these vaccines. In terms of additional information, it would be helpful to understand what the vaccine safety monitoring plans would be going forward.

Dr. Grohskopf indicated that finding out the average retail price of these vaccines is generally fairly tricky. The WG was not successful in determining the wholesale price. Their understanding was that the prices for vaccines can vary somewhat depending upon the purchasing power of the purchaser, how much they are buying, and what price can be negotiated. The analysis that she summarized used the CMS reimbursement rates cost assumptions. For the 3 vaccines in question, this was fairly similar at approximately $65 to $66 each versus a single-dose presentation of the standard vaccines. They used single-dose presentation for comparison mainly because there are no multi-dose presentations for the higher dose and adjuvanted vaccines. They are all prefilled syringes and are roughly $20 to $21 except the cell-culture vaccine, which is a little more expensive. There was some discussion about this with CDC’s economics group, and they typically used those numbers rather than a wholesale price for these analyses. For the second question regarding future safety monitoring, certain safety events are routinely monitored for in the VSD. She would anticipate that to continue, but deferred to colleagues in the Immunization Safety Office (ISO) for more details.

Dr. Goldman (ACP) pointed out as a private practice physician who gives all vaccines in his office, including influenza vaccines, that they make sure not to neglect or forget about the physicians who patients trust the most to advise them and how the system is being shifted to take vaccines out of physicians' offices. Reimbursement issues, keeping the door open, and systems are making it increasingly difficult for practicing physicians to administer vaccines. He stressed that he meant no disparagement to his colleagues in the pharmacy sector who have been incredibly helpful during the COVID-19 pandemic and in their assistance with getting outreach to various patients, but they cannot forget the physicians who also are vaccinating. He has patients get 2 or 3 doses of influenza vaccine at a pharmacy within the same 2-month period because they are not using the registry and communicating with the physician offices. The importance of partnership collaboration must be emphasized. Physicians are the leaders of the healthcare team and need to be included in the vaccination efforts.

Dr. Lett pointed out that some of the other QIV vaccines are less expensive than the 3 preferred vaccines being discussed. She has heard from some AIM colleagues that they are concerned that some systems may not be making the higher-priced vaccines available. She wondered what kind of language could be used in terms of the vote and final recommendation to ensure that systems make the preferential vaccines available as well.

Dr. Grohskopf indicated that there was some discussion among the WG members about that. On the one hand, all of these vaccines are reimbursable under Medicare for those who are eligible. It does require spending more on the front end to purchase the vaccines and she imagined that being reimbursed for them requires actually having administered them. Every year, many doses of influenza vaccine are discarded in general. The hope is that if there is a recommendation and there is more public awareness, these vaccines would be recommended more to patients and potentially would be more beneficial in terms of leading to more people getting vaccinated. Even though persons ≥65 years of age is one of the higher coverage groups in the US, there still are about 25% to 30% percent of those folks who do not get vaccinated. There could be some uninsured individuals.

Dr. Talbot added that the last part of the recommendation about getting whatever vaccine is available was something the WG was very concerned about. There was concern that if someone went to a pharmacy that did not have one of the newer vaccines, that they would not get vaccinated at all. The idea was to allow them to get a standard dose vaccine if nothing else was available so that there would not be a missed vaccination opportunity. Perhaps the language could be worded more clearly to close the loop.

Dr. Lee stressed that one of the ways that disparities in children have been reduced is through the Vaccines For Children (VFC) program. To Dr. Goldman's discussion points, frontline providers already are doing a huge amount of counseling, preventive care, and healthcare for their patients. In addition, they are asked to bear the burden of the upfront cost of delivering vaccines. Vaccines are unlike any other intervention physicians provide. A Vaccines for Adults (VFA) program could be incredibly impactful and powerful in reducing these disparities, particularly as there are increasing numbers of vaccines available for adults. Being able to help provider communities deliver these vaccines without financial risk to the providers would go a long way in making sure that the care that is needed is being provided in the moment that providers are caring for their patients. There are many providers who do not carry vaccines because it is a financial cost upfront that they are not sure is going to get fully reimbursed. This is an important service for the public good and is one that ACIP should emphasize and support going forward.

Influenza WG: Summary/Proposed Recommendations for the 2022-2023 Influenza Season

Lisa Grohskopf, MD, MPH (CDC/NCIRD) next presented a brief summary of influenza vaccine safety and an overview of the proposed recommendations for the 2022-2023 influenza season. For the 2021-2022 season, approximately 175 million doses of influenza vaccine were administered in the US. No new safety concerns were identified in VAERS. Within the VSD, approximately 5.5 million doses of vaccine were administered. No new safety concerns were identified in this system either. Within the ISO's Clinical Immunization Safety Assessment project (CISA), 2 ongoing studies have been enrolling this season. These are both co-administration studies and they are not currently enrolling since vaccination for the season has essentially ended or is close to ending. However, they will resume enrollment during the 2022-2023 influenza season. The first is, "Safety of Simultaneous versus Sequential Administration of mRNA COVID-19 Vaccines and Quadrivalent Inactivated Influenza (IIV4) (Registered on ClinicalTrials.gov: NCT05028361). This study enrolled 73 participants ≥12 years of age during the 2021-2022 season. There was a safety panel assessment that noted no safety concerns. The second is, "Safety of Simultaneous Vaccination with Zoster Vaccine Recombinant (RZV) and Quadrivalent Adjuvanted Inactivated Influenza Vaccine (aIIV4) (Registered on ClinicalTrials.gov: NCT05007041). This study 102 participants ≥65 years of age during the 2021-2022 season. There was a safety panel assessment of this study, which also identified no safety concerns.

To summarize the proposed recommendations for the 2022-2023 influenza season, the draft 2022-2023 ACIP Influenza Statement contains many recommendations that are similar to previous seasons. The core recommendation that annual vaccination is recommended for persons ≥6 months of age who do not have contraindications stands, with the hope that this is reaffirmed during the vote. There are 3 main updates. One is the US influenza composition for the 2022-2023 season. There is a section on the change in the approved age indication for Flucelvax® Quadrivalent, which is the cell-culture-based inactivated vaccine(ccIIV4). This change in age indication occurred in the Fall after the publication of the last statement. The main topic of discussion during this session was the proposed new recommendation of language for influenza vaccinations of persons ≥65 years of age.

This table lists the influenza compositions for 2022-2023 compared with the 2021-2022 influenza season:

2021-22	2022-23
Egg-based IIV4s and LAIV4:	***Egg-based IIV4s and LAIV4:***
A/Victoria/2570/2019 (H1N1)pdm09-like	A/Victoria/2570/2019 (H1N1)pdm09-like
A/Cambodia/e0826360/2020 (H3N2)-like	A/Darwin/9/2021 (H3N2)-like
B/Washington/02/2019 (Victoria lineage)-like	B/Austria/1359417/2021 (Victoria lineage)-like
B/Phuket/3073/2013 (Yamagata lineage)-like	B/Phuket/3073/2013 (Yamagata lineage)-like
Cell-culture-based IIV4 and RIV4:	***Cell-culture-based IIV4 and RIV4:***
A/Wisconsin/588/2019 (H1N1)pdm09-like	A/Wisconsin/588/2019 (H1N1)pdm09-like
A/Cambodia/e0826360/2020 (H3N2)-like	A/Darwin/6/2021 (H3N2)-like
B/Washington/02/2019 (Victoria lineage)-like	B/Austria/1359417/2021 (Victoria lineage)-like
B/Phuket/3073/2013 (Yamagata lineage)-like	B/Phuket/3073/2013 (Yamagata lineage)-like

Red type denotes change compared 2021-22.
https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-march-3-2022-meeting-announcement#event-materials

For the 2022-2023 influenza season, all vaccines will be quadrivalent as there are no longer any trivalent vaccines. In addition, the influenza A(H3N2) and influenza B/Victoria components have been updated.

Until recently, Flucelvax® Quadrivalent was approved for persons ≥4 years of age. It was approved in March 2021 for persons ≥2 years of age and in October 2021 for persons ≥6 months of age. With the last change, all standard-dose unadjuvanted IIV4s now approved for persons ≥6 months of age.

In addition to these changes, the WG drafted the following proposed language for consideration for the new recommendation for influenza vaccine for persons ≥65 years of age:

> "ACIP recommends that adults aged ≥65 years should receive one of the following higher dose or adjuvanted influenza vaccines, if available: quadrivalent high-dose inactivated influenza vaccine (HD-IIV4), quadrivalent recombinant influenza vaccine (RIV4), or quadrivalent adjuvanted inactivated influenza vaccine (aIIV4). No preference is expressed for any one of these three vaccines over the other two. If none of these three vaccines is available at an opportunity for vaccine administration, then any other age-appropriate influenza vaccine should be used."

Discussion Summary

Dr. Schmader reported that the American Geriatric Society (AGS) endorses the preferential recommendation for high-dose adjuvanted influenza vaccine as presented. AGS sees this as a long overdue improvement in influenza vaccination policy for older adults. There is a population of older adults who do not receive vaccines at provider offices or retail pharmacies, the estimated 1.4 million residents of long-term care facilities (LTCF) who are vaccinated onsite. This recommendation will provide clarity for that group as well.

Dr. Long suggested editing the first line of the recommendation to state "preferentially should receive," removing "if available" at the beginning, and stating "there is no preference between these vaccines" at the end to ensure that people understand that it is no preference between the 3 high-dose vaccines.

Dr. Poehling liked and agreed with Dr. Long's suggestion. She suggesting stating that "there is no preference among these 3 vaccines."

Dr. Hogue indicated that the American Pharmacists Association (APhA) has identified that the vast majority, if not all of the major national pharmacy chains, have connected their computers servers to the state immunization registries in those states where such connectivity has been allowed. Those pharmacy providers are, in fact, feeding data to the greatest extent that it is possible to send such data. There are approximately 20,000 independent pharmacies in the US. Those independent pharmacies have been making special efforts with their state health departments also to get connected. Funding for registries and getting systems established has been woefully lacking. There is a commitment on the part of the pharmacy community to make sure that immunization registries are complete and that the types of vaccines a patient has received are recorded accurately in the registry.

Dr. Sanchez agreed with Drs. Long and Poehling on their proposed language edits. He emphasized that he wants a preference to be clear for the higher-dose or adjuvanted influenza vaccines over the standard dose instead of a wishy-washy-type of recommendation. He asked whether the language that "if they are not available, any other age-appropriate vaccine can be used," could that be in the communications rather than in the vote.

Dr. Loehr pointed out that as a member of the WG, there was a strong feeling about not missing an opportunity to vaccinate and that was why the working "if available" was in there twice. However, he was intrigued by Dr. Sanchez's idea of taking out the last sentence and emphasizing the preferential aspect in the additional communication.

Dr. Fryhofer (AMA) said that speaking as a practicing physician, she strongly advised not taking out that last sentence. Physicians already have ordered their influenza supply for this year. If the last sentence is removed, she fears some patients may be denied any influenza vaccine whatsoever. Not having the sentence in the recommendation basically saying, "This way or the highway."

Dr. Brooks concurred with Dr. Fryhofer for the same reasons, as well as the potential for missed opportunities. Reflecting on the equity slides showing lower rates of high-dose given to relevant minorities, the way the recommendation was stated seemed appropriate. Also, "prefer" seemed like weaker language than "should receive." Perhaps the words "over the other two" could be removed. Otherwise, he agreed with the language as written.

Ms. Bahta supported changing the language to take out "if available" at the beginning. She emphasized that as Dr. Fryhofer mentioned, vaccine ordering already has occurred, which means that clinicians may not have any of the preferred vaccines. While she understood the desire to make this a strong statement, she pointed out that the available evidence is incredibly varied and evidence certainty was deemed low and very low in several aspects of the evidence. Perhaps they were moving too fast to make this language very strong. From a clinical perspective, perhaps something specific needs to be included about not missing an opportunity.

Dr. Bell pointed out that given the body of evidence and all of the logistical concerns colleagues raised, it is important for ACIP to do everything they can to avoid misconceptions and confusion that somehow the high-dose vaccines are the only vaccines that they think people ≥65 years of age should be given.

Dr. Long disagreed with Dr. Bell. They saw that 80% of people ≥65 years of age already are getting a high-dose vaccine. This is not new information. Many studies have shown that as a high-dose is more effective in this age group and that the standard dose vaccines are not very effective. This will save an additional 2,000 lives and it will play out in a more equitable way for ACIP to that high-dose are better and should be used.

Dr. Schaffner indicated that the National Foundation of Infectious Diseases (NFID) was glad to join others in suggesting that the language should be "aged ≥65 years preferentially should receive one of the following higher dose or adjuvanted vaccines . . ." and that "if available" should be left in some form at the end of that statement. NFID strongly endorses a forceful initial statement.

Dr. Lee agreed with others that there has been no other recommendation with this level of detail for an ACIP vote. Language such as “if none of these three vaccines is available” is typically in the Clinical Considerations. The Clinical Considerations are where the importance of health equity, reducing disparities, pragmatic considerations, and the importance of not missing any opportunities for vaccine should be included and that the vote language should be focused on what the vote actually is. That said, she could live with it for this year since ACIP revisits this recommendation every year. She indicated that ACIP would adjourn for a break during which Dr. Grohskopf would edit the language based on the discussion, which ACIP could revisit after the break.

Regarding a question posed earlier about safety monitoring going forward, Dr. Grohskopf indicated that she checked with the ISO about routine safety monitoring done on a vaccine-specific basis and learned that information is already being collected and summarized in VAERS in terms of the 3 vaccines of interest separately. Specific AEs of interest are routinely followed for these vaccines. Regarding the question about the percent of persons ≥65 years of age who are vaccinated in pharmacies, she was forwarded 1 report for persons ≥18 and older that indicated 39%. She will continue to seek additional information specifically on the proportion for persons ≥65 years of age.

Vote #1: Influenza Vaccines for Persons ≥65 Years of Age

Lisa Grohskopf, MD, MPH (CDC/NCIRD) presented the following revised proposed recommendation for influenza vaccine based on the discussion:

> “ACIP recommends that adults aged ≥65 years preferentially receive one of the following higher dose or adjuvanted influenza vaccines: quadrivalent high-dose inactivated influenza vaccine (HD-IIV4), quadrivalent recombinant influenza vaccine (RIV4), or quadrivalent adjuvanted inactivated influenza vaccine (aIIV4). No preference is expressed for any one of these three vaccines. If none of these three vaccines is available at an opportunity for vaccine administration, then any other age-appropriate influenza vaccine should be used.”

Discussion Summary

Dr. Daley said he was in favor of the changes made but was either confused or concerned that the beginning says “preferentially” these vaccines are recommended, but then later says “no preference is expressed.” That could be interpreted as contradicting. Perhaps “No preference is expressed for any one of these three vaccines” could be removed.

Dr. Brooks agreed with what was stated and thought it seemed like a strong recommendation with “preferentially” at the beginning. He also favored keeping the last sentence for clarity rather than just moving it to the Clinical Considerations.

Dr. Grohskopf noted that the last sentence could remain for clarity but could be removed next year when the recommendation is revisited. The guidance is constructed such that there is not a separate Clinical Considerations document.

Motion/Vote #1: Influenza Vaccines for Persons ≥65 Years of Age

Dr. Talbot made a motion for ACIP to adopt the recommendation stating that, "ACIP recommends that adults aged ≥65 years preferentially receive one of the following higher dose or adjuvanted influenza vaccines: quadrivalent high-dose inactivated influenza vaccine (HD-IIV4), quadrivalent recombinant influenza vaccine (RIV4), or quadrivalent adjuvanted inactivated influenza vaccine (aIIV4). If none of these three vaccines is available at an opportunity for vaccine administration, then any other age-appropriate influenza vaccine should be used." Dr. Poehling seconded the motion. No COIs were declared. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Vote #2: Proposed 2022-2023 Recommendations

Lisa Grohskopf, MD, MPH (CDC/NCIRD) presented the following proposed affirmation for the 2022-2023 Recommendations:

> "Affirm the updated *MMWR* Recommendations and Reports, "Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States, 2022-2023 Influenza Season."

Motion/Vote #2: Proposed 2022-2023 Recommendations

Dr. Sanchez made a motion for ACIP to adopt the recommendation to "Affirm the updated *MMWR* Recommendations and Reports, "Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States, 2022-2023 Influenza Season." Dr. Long seconded the motion. No COIs were declared. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Discussion Summary

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

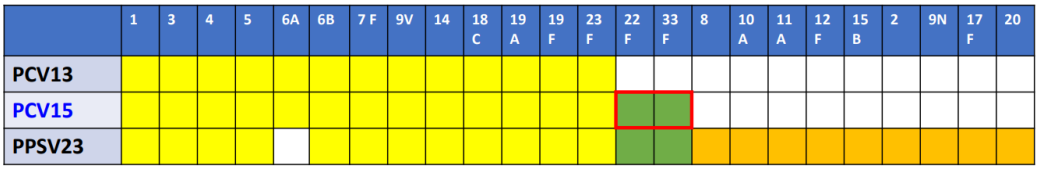
Dr. Talbot said she was super excited that vaccinations are being improved for older adults and to hear so many seniors and senior groups advocating for vaccines. The prevention of hospitalizations, reducing the time on disability, and improving life is incredibly important for US seniors who are a growing population. While these influenza vaccines are better, they are not yet the "homerun" that is needed. She encouraged current vaccine manufacturers to continue to seek the "Holy Grail" of an influenza vaccine that will work every time and will work for older and immunosuppressed patients. She thanked ACIP members for their votes and for looking out for the nation's seniors and encouraged the groups who are advocating for older adults to please continue this work.

Dr. Kotton emphasized how wonderful it is to have this influenza vaccine recommendation for older adults. She highlighted that the immunocompromised patient population still remains very vulnerable to influenza, and although the data for that population are not as robust, hopefully in the near future, ACIP also can make a recommendation for that population to receive these likely improved and better vaccines to provide them with better protection. As it stands, these vaccines are typically not covered by insurance because they are not recommended. Therefore, some of her patients have to pay out-of-pocket. Not only is this expensive, but also it is off-label use. Hopefully, the immunocompromised patient population will be the next frontier.

PNEUMOCOCCAL VACCINES

Session Introduction

Katherine A. Poehling, MD, MPH (ACIP, WG Chair) provide an introduction and overview of the pneumococcal vaccine session on behalf of the Pneumococcal Vaccine WG. This table shows the current 13-valent pneumococcal conjugate (PCV13) and 23-valent pneumococcal polysaccharide (PPSV23) vaccines. The new 15-valent pneumococcal conjugate vaccine (PCV15) includes PCV13 serotypes + 22F and 33F:



The current pneumococcal vaccine recommendations for children are as follows:

- ❑ PCV13 Routine Recommendation
  - 4-dose PCV13 series at 2, 4, 6, and 12–15 months (3+1 schedule)

- ❑ PCV13 Catch-Up Options
  - Healthy children through age 59 months
  - Children with underlying medical conditions through age 71 months

- PCV13 and PPSV23 for Children 24–71 Months of Age with Underlying Medical Conditions
  - Complete recommended PCV13 doses followed by PPSV23 ≥8 weeks later
  - Children who are immunocompromised or with sickle cell disease or asplenia → 2nd dose of PPSV23 recommended 5 years after the 1st dose

- PCV13 and/or PPSV23 for Children 6–18 Years Old with Underlying Medical Conditions
  - One dose of PPSV23 for children with chronic heart/lung disease, or diabetes
  - One dose of PCV13 (if never received) followed by PPSV23 ≥8 weeks for children with immunocompromising conditions, cerebrospinal fluid (CSF) leak, or cochlear implant
    - For children with immunocompromising condition, give a 2nd dose of PPSV23 ≥5 years after the first PPSV23 dose

The general principles addressed during this session were to consider use of PCV15 as an option to PCV13 according to the currently recommended PCV13 dosing and schedules and consider interchangeable use of PCV15 and PCV13. No changes were to be made for the PPSV23 recommendations. The 2 policy questions being considered by the WG include:

- Should PCV15 be routinely recommended for US children <2 years of age as an option for pneumococcal conjugate vaccination according to currently recommended dosing and schedules?

- Should PCV15 be recommended for US children 2–18 years of age with underlying medical conditions as an option for pneumococcal conjugate vaccination according to currently recommended dosing and schedules?

To provide a timeline of what is coming in the future, it is anticipated that a PCV-20 vaccine would be licensed in 2023 and PCV15 was just licensed. In February 2022, the WG presented the pediatric pneumococcal disease epidemiology, the Phase 2/3 PCV15 studies in children and the first part of the EtR Framework and GRADE. The WG received a lot of questions about fever and the potential for febrile seizures and spent a lot of time paying attention to that. The agenda for this session included presentations on PCV15 use in children, a cost-effectiveness analysis, an EtR Framework updates, and a vote if acceptable. During the October 2022 ACIP meeting, the WG will address questions related to PCV15 and PCV-20 use in adults.

PCV15 Pediatric Clinical Development Program Update

Natalie Banniettis, MD, FAAP (Merck) reminded everyone that that she presented an overview of the Phase 3 results of the V114 pediatric clinical development program to ACIP on February 24, 2022. She thanked the ACIP for their post-review of the V114 pediatric clinical data and for the opportunity to present again during this meeting. The first portion of this presentation focused on safety in the Phase 3 pediatric program, including a summary of the pediatric database and an analysis of temperatures ≥104°F. The second portion of the presentation included a brief review of key results of the subgroup analysis requested by the US FDA.

Starting with the Phase 3 safety data, the V114 pediatric clinic program was designed to target pediatric populations in which PCV vaccination is indicated and to generate a robust safety and immunogenicity profile for V114 in children. V114 is approved by the US FDA for immunization

of individuals ≥6 weeks of age for the prevention of invasive disease caused by the 15 pneumococcal serotypes included in the vaccine. The US filing for licensure of V114 in children is supported by 7 clinical trials among children 6 weeks through 17 years of age. In these trials, there were approximately 7,200 participants of whom about 4,800 received V114. Of these, approximately 6,100 were healthy infants 6 through 12 weeks of age of whom approximately 4,300 received V114. Safety data from 3 Phase 2 studies comprised of a total of approximately 4,500 healthy infants, including approximately 3,000 recipients of V114 who were integrated for analysis based on similarities and study design and dosing schedule. This population is referred to as the integrated safety summary in infants (ISS) in this presentation and is considered to be the most robust dataset upon which to assess the safety of V114 in healthy infants who received a 4-dose regimen in alignment with the ACIP recommended schedule.

Previously presented to the ACIP, the ISS population included approximately 3,000 infants in the V114 group and approximately 1,500 in the PCV13 group. The proportions of participants with AEs (e.g., injection site systemic AEs, vaccine-related AEs, and SAEs) were generally comparable between the groups. Notably, there were no discontinuations of the study intervention due to AEs. In both groups, the majority of AEs were mild or moderate in intensity with a duration of 3 days or less. The conclusion of the ISS analysis was that the V114 safety profile is generally comparable to that of PCV13.

In terms of how temperatures are collected and evaluated in the pediatric program, parents are given a digital thermometer and an electronic vaccination report card (eVRC) upon enrollment into the study. Parents are prompted by the eVRC to enter daily maximum body temperatures at approximately the same time each day from Day 1 through Day 7 post-each vaccination and Days 8 through 14 if febrile. The rectal method of temperature measurement was preferred per protocol. On day 15, the investigator reviewed temperature data with the parent and entered new AEs into the database. For example, an unsolicited AE of pyrexia could have been entered or a diagnosis such as upper respiratory tract infection would have been entered if addition signs or symptoms were present. Contemporaneously, the sponsor's clinical team reviewed temperature data and AEs to ensure complete and accurate reporting to the fullest extent possible.

As previously presented, the distribution of solicited daily temperatures in the 7 days post-vaccination was generally comparable between the intervention groups in the ISS analysis with the majority being afebrile in the 7 days post-vaccination. Of those with temperatures ≥100.4°F, the majority were <101.3°F in both groups and the proportion of participants reporting temperatures ≥104.0°F was low in both groups after each vaccination. Turning attention to the daily temperatures following the toddler dose as broached on February 24, 2022 by the ACIP members, at the post-toddler dose timepoint, the sample size included was approximately 2,800 participants in the V114 group, which was more than double the sample size included in the PCV13 group due to the randomization schemes utilized in this study. A subset of 19 participants reported body temperatures of ≥104.0°F with a point estimate of 0.7% and 3 participants in the PCV13 group reported temperatures of ≥104.0°F with a point estimate of 0.2%.

Merck was asked to share additional information about this subset by the ACIP, as members noted a numerical imbalance between the groups. Therefore, an analysis was performed of the aforementioned subset using several statistical methods including weighted and unweighted approaches. Of note, Protocol 31, the large safety study, contributed the majority of participants in the integrated analysis with approximately 2,400 participants randomized 5:1 to receive V114 or PCV13, respectively. Given that the randomization ratio in Protocol 31 differs from that of the

other studies included in the integrated analysis using 1:1 randomization, a weighted approach to pooling the data across studies reduced potential bias in the estimate of the risk differences. Regardless of the statistical method used, the difference between the vaccination groups was small and not statistically significant.

Continuing now with the same subset of participants with maximum body temperatures ≥104.0°F following Dose 4 but focusing only on the 19 recipients of V114, in regard to AEs following the toddler dose, no febrile convulsions or vaccine-related SAEs were reported in these 19 participants. Of the 19 participants, 13 had AEs of pyrexia reported by the investigator with the majority of these pyrexia events resolving within 3 days and all but 1 were non-serious AEs. The single SAE of pyrexia was deemed non-vaccine-related by the study investigator and occurred in a participant who presented with respiratory and gastrointestinal symptoms. Among the 19 participants, 10 reported concurrent AEs that were suggestive of an underlying infectious process along with the reported temperatures of ≥104.0°F. Of the 19 participants, 15 reported these temperatures during the influenza season. Additionally, 9 of the 19 had onset after Day 4 post-vaccination and as such, were less likely to be related to PCV vaccination.

To summarize, in participants with maximum body temperatures ≥104.0°F after the toddler dose in the integrated analysis, the between group differences in incidence were small and not specifically significant based on both weighted and unweighted analyses. No vaccine-related SAEs of febrile convulsion were reported among the V114 recipients. Maximum body temperatures may have been confounded by underlying infection and concomitant vaccination. As for all Merck vaccines, post-marketing safety surveillance of V114 via routine pharmacovigilance activities will be conducted to ensure the safety profile remains adequately characterized.

Transitioning to the second portion of the presentation, Dr. Banniettis briefly highlighted key results of the subgroup analyses performed at the request of the FDA. As background, 2 different pentavalent combination vaccines were used in Protocol 27, the interchangeability study, and Protocol 29, the pivotal study. Pentacel™ was used at study sites located in the US and Puerto Rico, and Pentavac™ was used at study sites located in Turkey and Thailand. Each of these vaccines is manufactured and marketed by Sanofi Pasteur and contains diphtheria, tetanus, acellular pertussis, inactivated polio, and polysaccharide conjugate antigen. Pentavac™ contains 2 components of pertussis antigen and Pentacel™ contains 5 components. In each study, approximately 70% of participants in each vaccination group received Pentacel™.

In March 2022, the FDA requested additional analyses for Protocol 29 and Protocol 27 based on a subgroup of study participants who received Pentacel™ concomitantly with PCV, excluding those who received Pentavac™. The conclusions of the subgroup evaluation limited to Pentacel™ recipients were largely unchanged from the original analysis despite the reduced sample size by approximately 30% in both groups in both studies. The ad hoc subgroup analyses are descriptive in nature and no formal statistical testing was performed, given that the studies were not powered for success with a smaller sample size. Nonetheless, all of the original criteria were met except for mumps. The 30% reduction in sample size led to a decrease in power for the MMR non-inferiority evaluation in the Pentacel™ subgroup. However, response rates to mumps were high in the V114 group and comparable to PCV13. To summarize, the immunogenicity and safety of V114 relative to PCV13 and the ad hoc subgroup analysis limited to participants who received Pentacel™ as a concomitant vaccine were consistent with the primary analysis in the overall population.

In terms of key conclusions of the V114 pediatric clinical program, in children with an unmet medical need for pneumococcal disease prevention, V114 is well-tolerated, with a safety profile that is consistent with licensed PCVs. V114 induces robust immune responses to the 13 shared serotypes with PCV13. V114 is superior to PCV13 for the shared serotype 3 and the unique serotypes 22F and 33L, which are of high public health importance. V114 can be administered concomitantly with routine childhood vaccines. Therefore, V114 has the potential to significantly address the burden of remaining pneumococcal disease due to vaccine types and leading non-vaccine types in children.

Discussion Summary

Dr. Kimberlin (AAP Redbook) asked when PCV15 was approved by the FDA for use in children.

Dr. Fink (FDA) indicated that FDA approved the efficacy supplement for use of PCV15 in children 6 months through 17 years of age on Friday, June 17, 2022.

Ms. Bahta asked whether influenza was confirmed for any of the 15 of the 19 children who had high fevers during that influenza season and/or whether other infections were confirmed.

Dr. Banniettis indicated that no cases of influenza were confirmed in any of those cases, but other infections were. These included RSV and other respiratory viruses and gastrointestinal viruses.

Referring to Slide 5, Dr. Daley noted that there were 2 listed SAEs in the PCV15 group for which he requested additional information.
Dr. Banniettis indicated that both were SAEs of pyrexia, one of which occurred on the same day as Dose 1. The maximum body temperature was 100.4°F. This participant was located in the US. The concomitant vaccines were received included RotaTeq™, Pentaxim®, and Hiberix™. The reasons for the admission for this particular child was due to significantly elevated hyperbilirubinemia in the context of a fever of 100.4°F. There was a concern for gram-negative sepsis, which was ruled out. The second case occurred on the same day as Dose 3. The maximum body temperature in that participant was 102.9°F. This participant was located in Thailand. Concomitant vaccines included DTaP, *Hib*, Hep B, and oral polio vaccine (OPV). This particular participant was admitted specifically because there was impressive tachycardia and suspicion of bacterial sepsis, which was ruled out.

Economic Analysis and Public Health Impact of PCV15 Use in Children

Dr. Andrew J. Leidner (CDC/NCIRD) presented the results of the economic analysis and public health impact of PCV15 use among children in the US. The contents of this presentation were developed by 2 different modeling teams, the CDC model team and the Merck model team. This presentation summarized the key findings from these 2 models. Previous studies have found that pneumococcal vaccination averts thousands of deaths and saves millions of dollars in direct medical costs.[3] In particular, previous studies found PCV13 was cost saving when compared to PCV7.[4] This presentation focused on 2 newer models that examined the cost and benefits of including PCV15 as an option in the childhood immunization schedule, the CDC and Merck models. Both models completed the CDC economic review following the procedures in the ACIP Guidance for Health Economic Studies.[5]

[3] Zhou et al. 2014
[4] Messonnier et al. 2009; Rubin et al. 2010
[5] Leidner et al. 2019

The broad research question motivating the CDC and Merck model studies was, “What is the cost-effectiveness and public health impact of including PCV15 as an option in the immunization schedule for children?” This broader question can be broken down into 2 sub-questions about cost-effectiveness and the prevented disease burden of using PCV15 as compared to PCV13. Notably, both models directly compared the use of PCV15 to the use of PCV13. In a direct comparison like these models have done, a practical implication is that the vaccinated individuals in a particular strategy in the model all will receive one type of vaccine. That is, all children in a PCV13 strategy received PVC-13 and all children in a PCV15 strategy received PCV15. Then the cost and benefits from these 2 strategies were compared directly. This issue will come up again later in terms of some of the limitations of the prevented disease burden results.

Starting with the first research question about the cost-effectiveness of PCV15, there were 2 key assumptions that went into both models. The first key assumption was VE. Both models assumed that PCV15 and PCV13 have the same VE for PCV13-type disease. They also both assumed that PCV15 offered additional disease protection for the 2 serotypes that included in PCV15 but not included in PCV13. These 2 assumptions taken together mean that in both models, the use of PCV15 prevents more episodes of pneumococcal disease than the use of PCV13. The second key assumption for the cost-effectiveness analysis was the cost of a dose of vaccine. In their base case, both models assumed that the average cost of PCV15 was less than the average cost of PCV13. There was a slight difference in these cost inputs across the 2 models. The CDC model base case assumed 1 dose of PCV15 was about $3 less than 1 dose of PCV13 on average. The Merck model base case assumed on average that 1 dose of PCV15 was about $1 less than a dose of PCV13.

Keeping in mind the 2 key assumptions, it should be no surprise that the base case results of both models were that PCV15 use was found to be cost-saving when compared to PCV13 use. This result was consistent across a number of sensitivity analyses and scenarios in which the cost of a dose of PCV15 was increased. To be clear, the term “cost-saving” in economic analyses like these means that the total costs are reduced and that the health outcomes are improved when the use of PCV15 was compared to the use of PCV13. Again, a cost-saving result was not surprising given that it was assumed PCV15 prevents more disease while costing about the same as PCV13. Another way to state that health outcomes are improved is to say that disease burden is prevented.

Focusing on approximately how much additional disease burden might be prevented by the use of PCV 15, Dr. Leidner addressed the question of preventive disease burden by first discussing a few more assumptions in the 2 models. A few key model characteristics include model type, model duration in years, and incidence rates. The CDC model followed a single cohort who were 0 years old (newborns) at the start of the model and followed them for 17 years. In contrast, the Merck model used a multi-cohort approach, meaning that at the start of the model, there was not a single cohort of newborns. Instead, there were 100 cohorts—1 cohort for each year of ages 0 to 100 years. The 100 Merck model cohorts were followed for 100 years, with a new cohort being born and added to the population at each year in the model. Considering these differences, the overall population size of the Merck model was considerably larger than the population represented in the CDC model. This model characteristic will go a long way toward explaining the differences between the base case results of the 2 models. While the Merck model had a much larger population in the base case, the Merck model also ran several scenarios using a single cohort very similar to the CDC model base case. These single cohort scenarios were the main results used in the discussion on preventive disease burden. While the

Merck model single cohort results and the CDC base case results were fairly comparable, they were not identical. Some of the remaining differences in the 2 models' estimates of preventive disease burden can be attributable to differences in incidence rate assumptions which for the CDC model included higher incidence rates for inpatient non-bactearemic pneumonia (NBP) and for the Merck model included higher incidence rates for invasive pneumococcal disease (IPD), outpatient NBP, and acute otitis media (AOM).

Now looking at the main results from the 2 models' estimates of preventive disease burden using PCV15 as compared to PCV13. The Merck base case represented a substantially larger population over much longer model duration, so those estimates are larger than the results in that used single cohorts. Much of the differences in IPD, NBP, AOM, and deaths can be explained by differences in inputs of incidence. The differences in quality-adjusted life year (QALYs) gained are due to both incidence inputs and health utility inputs. The estimates from the single cohort scenarios were used to construct the range for each of the prevented disease outcomes. If one cohort of infants received PCV15 instead of PCV13, the range of disease burden prevented might be expected to look like the values in this table:

Prevented outcomes	Range
IPD	220 to 490
NBP	3,900 to 10,100
AOM	80,600 to 108,000
Deaths	22 to 42

There are a few considerations to keep in mind. This table is for 1 cohort that receives PCV15 instead of PCV13. If multiple cohorts were given PCV15 instead of PCV13, the prevented disease burden would be greater. If adoption of PCV15 is lower, meaning that there is a mixture of use between PCV15 and PCV13, the prevented disease burden would be smaller. This point was alluded to early in the presentation when these models were described as using 1 vaccine or another for a given strategy in their direct comparisons. Finally, if indirect effects to older adults were included in these static cohort scenarios, the prevented disease burden would be greater. A caveat to that would be that if vaccination coverage rates among US adults for PCV15 and PCV20 were high, then any indirect effects from childhood use of PCV15 could be modest.

The first major conclusion from the 2 models was that PCV15 use appears to be cost-saving when compared to PCV13. PCV vaccines going back to PCV7 have been found generally to reduce direct medical costs and improve health outcomes. Two models in previous research have shown that PCV13 use was cost-saving when compared to PCV7. The 2 models presented during this session concluded that PCV15 use is cost-saving when compared to PCV13. In these 2 models and the key assumptions that led to this result were VE and vaccine cost. For VE, the WG discussed the uncertainty of the VE assumptions in light of these assumptions being based upon immunogenicity data. The other assumption was vaccine cost. Another interesting point about vaccine cost in these assessments is that PCV15 was less expensive or approximately the same as PCV13. In the older studies that compared PCV13 to PCV7, PCV13 was actually more expensive than PCV7 and was still found to be cost-saving when compared to the less expensive alternative. The second major conclusion was that pneumococcal vaccination of children has historically had a notable health impact. That also may be true for the use of PCV15 since both models estimated that overall health is improved

when PCV15 is used as compared to PCV13. This finding is certainly conditional on the assumption in both models that VE for PCV15 was equal to PCV13 for PCV13-type disease and was assumed to provide additional protection for the 2 additional serotypes. Differences in the estimated prevented disease burden appear to be due to differences in model structure and input values. With all these differences in consideration, the CDC model could be considered more conservative than the Merck model.

Discussion Summary

Dr. Loehr asked whether in the Merck 100-year cohort study consideration was given to the possibility that PCV15 would last beyond childhood to provide additional benefit to adults because there would be less disease in the environment.

Dr. Leidner acknowledged that this could be possible. Both models assumed that direct protection from the vaccine would wane to 0 after approximately 15 years. Both models also assumed that there is an amount of indirect protection or indirect effects, but it is quite complicated. In the Merck base case, indirect effects were allowed to protect individuals in Year 1 of the model who were ≥65 years of age. Indirect effects also were allowed to provide protection to the younger cohorts for whom direct protection had waned to 0 after the 15-year period. That said, the Merck model only assumed that indirect effects would occur with respect to IPD and not NBP or otitis media. To summarize the CDC model assumptions, in their single cohort base case, indirect effects did occur and did provide benefit to individuals who were non-vaccinated in that cohort and for individuals whose direct protection had waned to 0 over the 17-year duration of the model. What the CDC model did not include was protection from vaccinating newborns that would then immediately transfer to persons ≥65 years of age in Year 1 of the model. The caveat to assuming indirect effects would apply in Year 1 to persons ≥65 years of age is that those individuals are already recommended to receive PCV15 and PCV20. If they are getting direct protection from the vaccines that they are recommended to receive, the indirect effects may be more modest.

Dr. Sanchez asked whether the assumption that the average cost for PCV15 is less than that of PCV13 was a known fact. He was surprised that any new vaccine would be cheaper than an older one.

Dr. Kobayashi said that PCV15 is already licensed for use in adults. There is a private market price available on the CDC website for PCV15. When compared to the price of PCV13, PCV15 is actually priced lower. CDC also communicated with Merck about what the appropriate estimate for the vaccine cost would be. Sensitivity analyses were performed for both models, which provided some range to the estimated cost.

Updates to the EtR: Use of 15-valent Pneumococcal Conjugate Vaccine in Children

Miwako Kobayashi, MD, MPH (CDC/NCIRD) presented the summary of the Pneumococcal WG's interpretation of the EtR Framework for use of 15-valent pneumococcal conjugate vaccination in children. During the February 2022 ACIP meeting, the WG presented its interpretation of the EtR Framework domains of the public health problem, benefits and harms, values, and equity. After review of additional data and discussion following the February 2022 ACIP meeting, the WG updated the interpretation on EtR domains for benefits and harms and equity. During this session, Dr. Kobayashi provided a summary of the WG's interpretation of each EtR domain including the domains of acceptability, feasibility, and resource use that were

not presented previously, as well as the rationale for the WG's updated interpretation for the domains of benefits and harms and equity. As a reminder, the 2 PICO questions are:

- ❑ Should PCV15 be recommended as an option for pneumococcal conjugate vaccination according to currently recommended dosing and schedules for US children <2 years of age?

- ❑ Should PCV15 be recommended as an option for pneumococcal conjugate vaccination according to currently recommended dosing and schedules for US children 2–18 years of age with underlying medical conditions?

Both policy questions compare PCV15 to PCV13 use. The outcomes considered to be critical include vaccine type-IPD (VT-IPD), VT-pneumococcal pneumonia (VT-pneumonia), VT-AOM, VT-pneumococcal deaths, and SAEs following immunization.

The first domain is public health problems. In this presentation, IPD refers to an illness with pneumococcal detection in a normally sterile site such as blood or in cerebrospinal fluid (CSF). Examples include pneumococcal meningitis, bacteremia, or bacteremic pneumonia. Examples of non-invasive disease include NBP or AOM, which has higher disease burden. In children, AOM is one of the most common reasons for outpatient care and antibiotic prescribing.[6] In 2018, the incidence of AOM due to any cause in children <2 years of age was approximately 75,000/100,000 person years.[7] Pneumococcus is estimated to account for 24% of clinically diagnosed AOM in children.[8] In 2014, the estimated incidence of all caused pneumonia in children was approximately 1,300 to 4,000/100,000 person years in children ≤17 years of age.[9] Studies using administrative data have shown decline in incidence of AOM and hospitalization due to all-cause and pneumococcal pneumonia in children post-PCV introduction.[10]

Looking at the incidence rates of IPD among children <5 years of age during 2007-2019 in CDC's Active Bacterial Core Surveillance (ABCs) data, rates of PCV13-type IPD declined sharply after introduction of PCV13 for children in 2010. After 2013, declines in PCV13-type IPD rates plateaued at less than 2 cases/100,000. This trend continued through 2019. Rates of non-PCV13 serotypes remained relatively stable over this time period. In terms of IPD incidence by age in 2019[11] show that in children, pneumococcal disease burden decreases with increasing age. In children 5-17 years of age, around 25% of the cases had a medical condition that is an indication for PCV13.

In terms of children aged 6-36 months living in Rochester, New York,[12] children who developed AOM had nasopharyngeal (NP) swabs or middle ear fluid (MEF) collected. Among children with AOM with pneumococcal detection, the 2 additional serotypes included in PCV15 but not in PCV13 were identified in 6% to 8% of children. The proportion of IPD caused by the serotypes included in PCV13 was 21% to 34%. The proportion due to the 2 additional serotypes included in PCV15 but not in PCV13 was 16% to 17%.

The WG determined that pneumococcal disease is of public health importance in children. This interpretation is unchanged from February 2022.

[6] Tong BMC Health Services Research 2018; Lewnard CID 2021; Hersh et al. Pediatric 2011,
[7] Hu et al. BMCID
[8] Kaur et al. EJCMID 2022
[9] Tong BMC Health Services Research 2018
[10] Hu et al. BMCID; Simmonsent, Lancet Resp Med 2014
[11] Active Bacterial Core Surveillance (ABCs) Report Emerging Infections Program Network Streptococcus pneumoniae, 2019. Available: SPN_Surveillance_Report_2019.pdf (cdc.gov)
[12] Adapted from Kaur et al. EJCMID 202

Regarding the domain of benefits and harms, the WG determined that the desirable anticipated effects from PCV15 use were moderate for both PICO questions. This was unchanged from the February 2022 ACIP meeting. Dr. Kobayashi summarized the evidence that the WG reviewed during the February meeting. For evidence on routine PCV15 use in children <2 years of age, the WG identified 5 RCTs. All 5 studies were compared to those who received PCV13. The first 4 studies highlighted in the following table provided data on both immunogenicity and safety. This include V114-027, which evaluated the product interchangeability with PCV13 and PCV15 and V114-024, which evaluated catch-up schedules at different ages using PCV15:

Routine PCV15 Use for Children Aged <2 years

Author, year	Study design	Intervention	Country	Age	Total population	N Intervention	N comparison
Platt, 2020 (V114-008)	Phase 2 RCT (proof of concept); healthy children	PCV15 3+1 (2,4, 6, 12-15m)	Canada, Denmark, Finland, Israel, Spain, US	6-12 weeks at enrollment	1044	350 (Lot 1) 347 (Lot 2)	347
V114-029 Merck, unpublished	Phase 3 RCT (pivotal study); healthy children	PCV15 3+1 (2,4, 6, 12-15m); co-administration pentacel, recombivax, rotateq	Puerto Rico, Thailand, Turkey, US	42-90 days at enrollment	1714	858	856
V114-027 Merck, unpublished	Phase 3 RCT (product interchangeability); healthy children	Group 1: PCV13 @ 2,4,6, 12-15m Group 2: PCV13 + PCV13+ PCV13 + PCV15 (booster) Group 3: PCV13 + PCV13+ PCV15 + PCV15 (booster) Group 4: PCV13 + PCV15+ PCV15 + PCV15 (booster) Group 5: PCV15 @ 2,4,6, 12-15m	Puerto Rico, Thailand, Turkey, US	42-90 days at enrollment	896	Group 2 (n=181) Group 3 (n=178) Group 4 (n=179) Group 5 (n=179)	Group 1 (n=179)
V114-024 Merck, unpublished	Phase 3 RCT (catch up); healthy children	7-11m: 3 doses (dose 1 @ 0w, dose 2 @ 4-8w PD1, dose 3 @ 8-12w PD2 AND >12m 12-23m: 2 doses (dose 1 @ 0w, dose 2 @ 4-8w PD1) 2-17y: 1 dose (>8w after previous PCV)	Finland, Malaysia, Poland, Russia, Thailand	7 months – 17 years	606	2-11m (n=64) 12-23m (n=62) 2-17y (n=177)	2-11m (n=64) 12-23m (n=64) 2-17y (n=175)
V114-031 Merck, unpublished	Phase 3 RCT, full-term v. pre-term infants	PCV15 3+1 (2,4, 6, 12-15m)	Australia, Canada, Finland, Germany, Israel, Malaysia, Peru, Taiwan, Thailand, US	Full-term (>37 wks) and pre-term infants (<37 wks); 42-90 days at enrollment	2398	1965	433

Immunogenicity and Safety

All studies funded by Merck; comparator is PCV13 for all studies

The fifth study, V114-031, was an RCT focusing on safety and tolerability in healthy infants stratified between full term and preterm infants. Infants were given either PCV15 or PCV13 using the 3+1 schedule, which is the PCV schedule currently used in the US. This study was added to the 4 studies above for the assessment of evidence on safety.

To summarize the evidence for the studies considered for the benefits of routine PCV15 use in children <2 years of age, immunogenicity from PCV15 use was non-inferior to PCV13 for all 13 serotypes post-Dose 4. Post-Dose 3, immunogenicity from PCV15 was non-inferior to PCV13 for 12 of 13 shared serotypes, with serotype 6A missing the non-inferiority criteria. PCV15 had statistically significantly higher immunogenicity for serotype 3 and for the 2 serotypes unique to PCV15, which are 22F and 33F. The certainty assessment for indirectness was downgraded to serious since the 4 studies were all immunogenicity studies and correlates of protection have not been established for some of the critical outcomes considered. The overall certainty of evidence was 2 (moderate).

For evidence on PCV15 use in children with underlying medical conditions, the WG identified 2 RCTs by Merck. The first study, V114-023, evaluated 1 dose of PCV15 in children with sickle cell disease. The second, V114-030, evaluated PCV15 in series with PPSV-23 in children living with HIV. Both compared PCV15 use with PCV13 use. To summarize the evidence from these 2 studies, non-inferiority assessments were not performed in these studies, so the findings were descriptive. Post-PCV dose, PCV15 had higher immunogenicity compared with PCV13 for 6 to 7 of 13 serotypes and the 2 unique serotypes, 22F and 33F. In one study that assessed PCV15 or PCV15 use followed by PPSV-23, the immunogenicity after PPSV-23 in the group that received PCV15 was numerically higher compared with those who received PCV13 for 3 of 13 serotypes but not for unique serotypes 22F and 33F. For the assessment of certainty of

evidence, indirectness was downgraded to serious since the studies were immunogenicity studies and correlates of protection have not been established for some critical outcomes. Imprecision was downgraded due to small sample size. Therefore, the overall certainty of evidence was 3 (low).

For the second question regarding how substantial the undesirable anticipated effects are, the WG interpretation for the undesirable anticipated effects from routine PCV15 use in children aged <2 years of age was changed from minimal to small after further WG discussions. Upon closer review of safety data, some WG members were concerned about the potential for higher reactogenicity in children who received PCV15 compared with children who received PCV13. The safety data were based on descriptive analysis, and the WG believes that uncertainties remain. Infrequency of rare AEs, such as serious vaccine-related AEs or fever of ≥104.0°F post-Dose 4, certainty was reflected in the updated GRADE table for assessment on safety of routine PCV15 use compared with PCV13 use in children <2 years of age.

To summarize the findings from 5 RCTs, 5 vaccine-related SAEs were reported in children who received PCV15 across 5 studies. The WG downgraded the certainty assessment for imprecision twice, first due to the small number of events of the outcome in both arms and second due to a wide 95% confidence interval of the relative risk of events that could not exclude the potential for increased harm or benefit. As a result, the overall certainty of evidence on safety was changed from 2 (moderate) to 3 (low). The undesirable anticipated effects of using PCV15 in children with underlying medical conditions was determined to be minimal, which remained unchanged. In the 2 studies that assessed PCV15 use among children with underlying medical conditions, no vaccine-related SAEs were reported. The certainty assessment of imprecision was downgraded twice to very serious, once due to no report of the outcome of interest and again for very small sample sizes. Therefore, the overall certainty of evidence is 3 (low). The WG interpretation on the balance between desirable effects relative to the undesirable effects were changed from favors the intervention to favors both for both PICO questions. The changes were made after it was clarified that the comparison that is made is to PCV13 use in children, not the balance between undesirable and desirable effects of PCV15 use. While PCV15 is expected to prevent more disease against 2 additional serotypes compared with PCV13, the WG believes that there is uncertainty of the added impact of PCV15 use compared with PCV13 use given that there are currently no clinical efficacy data. Additionally, there are some uncertainties about the potentially higher reactogenicity from PCV15 use compared with children who received PCV13.

The next domain is values and preferences. Studies on values and preferences of PCV15 use in children were not identified. However, vaccination coverage for 3 or more doses of PCV13 by 24 months of age has been high, demonstrating that the target population probably feels that the desirable effects of PCV vaccination outweigh the undesirable effects. For the first question regarding whether the target population feels that the desirable effects from vaccination are large relative to undesirable effects, the WG interpretation was split between “probably yes” and “yes” mainly due to the uncertainties about the magnitude of added benefit of PCV15 use compared with PCV13 use. For the second question regarding whether there is important uncertainty about or variability in how much people value the main outcomes, the WG determined that there is probably non-important uncertainty or variability.

The next domain is acceptability. For this domain, the WG reviewed Merck's provider preferences survey related to multivalent pneumococcal conjugate vaccines that was administered in November 2021. Responders included a sample of 600 healthcare providers (HCPs) who prescribe or administer 10 or more pneumococcal vaccines per month. The HPCs consisted of 530 physicians and 70 physician assistants (PAs) or nurse practitioners (NPs). The key findings from the survey were that about 40% of HCP believe that the risk of developing pneumococcal disease is higher than the risk of developing other vaccine-preventable diseases such as measles, mumps, rubella, rotavirus, chickenpox, diphtheria, tetanus, or pertussis in children aged under 24 months of age. HCPs believe that pneumococcal vaccines are highly important for children under 24 months of age. HCP stated that the following clinical features were important in pneumococcal vaccine choice in children under 24 months of age: IPD indication (63%), safety and side effects (47%), greater immune response to certain disease-causing serotypes (46%), and overall immune response across vaccine serotypes (45%). Therefore, the workgroup believes that recommending PCV15 as an option for pneumococcal conjugate vaccination according to currently recommended dosing and schedules for children is "probably acceptable" to key stakeholders.

Next is resource use. As Dr. Leidner presented, assuming that PCV15 has similar effectiveness as PCV13 against PCV13-type disease, PCV15 protects against 2 additional serotypes in assuming that PCV15 is less expensive than PCV13. Both the CDC and Merck models show that use of PCV15 in the childhood immunization schedule reduces direct medical cost and improves health compared with using PCV13. Regardless, the WG interpretation on routine PCV15 use in children aged under 2 years of was split between "probably yes" and "yes." This was due to uncertainties about the clinical efficacy of PCV15, as well as the actual vaccine price. Some WG members considered the possibility of low but increased healthcare utilization in the PCV15 recipients due to increased reactogenicity. For similar reasons, the WG interpretation on resource use was "probably yes" for PCV15 use in children 2–18 years of age with underlying medical conditions.

The WG's interpretation for the equity domain was updated. Certain groups have lower pneumococcal conjugate vaccine coverage than others. According to the 2020 National Immunization Survey (NIS) data, PCV coverage of 4 or more doses by 24 months of age was lower among children who are uninsured, Black, non-Hispanic, living in a non-metropolitan statistical (MSA) area, or living in the lowest federal poverty level. There are certain populations who have higher pneumococcal disease burden than others. For example, IPD rates among Native American children <5 years of age remained approximately 4-fold higher than in children of all races in 2018.[13] Alaskan Native infants had a 1.6-fold higher rate of AOM-associated outpatient visits compared to all infants in the US.[14] Native American and Alaskan Natives experience cyclical outbreaks due to serotype 12F, which is not included in PCV13 or PCV15.[15] Black children continue to have higher IPD rates compared to white children. The remaining disparity is mainly due to IPD caused by serotypes that are not included in PCV13. Unpublished data from CDC's ABCs data show that the difference in IPD incidence due to the 2 additional serotypes included in PCV15 but not in PCV13 has been small between Black and White.

[13] Littlepage et al, 9th International Meeting on Indigenous Child Health, 2021
[14] Singleton et al. PIDJ 2018
[15] Zulz et al. JCM 2012

During the February 2022 ACIP meeting, the WG's interpretation for this domain was presented as "probably increased equity. After further discussion, the WG's interpretation was changed to "probably no impact." While disparities in pneumococcal disease burden exist, the proportion due to the 2 additional serotypes due to PCV15 was considered to be small. Some WG members noted that a differential PCV15 and PCV15 update may potentially lead to differences in the burden of pneumococcal disease caused by the 2 additional serotypes.

The last domain is feasibility. The current private section PCV15 price for adults is $216.086 and the PCV13 price for children is $226.43. PCV15 private sector price for adults is currently lower compared to that of PCV13 in children. However, the actual PCV15 price that will be used for children is currently unknown. Considering that PCV15 is likely to be priced similar to PCV13 and since PCV13 has achieved high coverage, the WG determined that recommending PCV15 as an option for pneumococcal conjugate vaccination according to currently the recommended dosing and schedule for children is probably feasible to implement.

To summarize the WG's updated interpretation of the EtR domains for the 2 PICO questions, for benefits and harms the WG believes that there are small undesirable effects from PCV15 compared with PCV13 use, and the overall certainty of evidence on safety is low due to imprecision. Balancing the desirable and undesirable effects from PCV15 use compared with PCV13 use, the WG believes that both PCV15 and PCV13 use in children is favorable. The WG's interpretation on equity was changed to "probably no impact" given that existing disparities in pneumococcal disease burden caused by the 2 additional serotypes is probably small. For the new domains presented during this session, the WG believed that PCV15 use is probably an acceptable, reasonable, or efficient allocation of resources and is feasible compared with PCV13 use. In summary, the WG believes that the balance between desirable and undesirable consequences is closely balanced for both policy questions. The WG's proposed policy statement for PCV15 use in children is:

> "PCV15 may be used as an option to PCV13 for children aged <19 years according to currently recommended PCV13 dosing and schedules."

Discussion Summary

Dr. Loehr pointed out that his experience with these recommendations was that there is often a delay in when the recommendations are actually practically usable in a private practice. Though specifically when there is something like the hepatitis B recommendations given to all adults, it would need to be published in the *Morbidity and Mortality Weekly Report* (*MMWR*). He then finds that it takes 6 months or so before insurance companies will actually start covering them. This has nothing to do with pneumococcal per se, but was just a general comment that ACIP recommendations sometimes take months before they actually can be implemented in private offices.

Dr. Lee noted that the wording on the ACIP policy statement was somewhat more permissive and there were many pieces of the presentation. She was swayed by the economic analysis that might suggest that perhaps a preference was discussed. She requested a reminder of the WG's discussion of the pros and cons.

Dr. Kobayashi indicated that the WG did not consider a preferential recommendation because of the uncertainties that exist. That is primarily reflected in the assessment of benefits and harms. The current assumption used in the economic analysis is that PCV15 may be priced lower, but again that is an assumption, and the actual vaccine price is not known. Additionally, in terms of the incremental benefit, the assumptions were based on available immunogenicity studies. There currently are no clinical efficacy data and there are uncertainties about the potential incremental benefits. Dr. Banniettis presented additional safety data, which was very helpful. However, there were still some concerns about uncertainties around some rare AEs. All of those issues considered, the WG believes that rather than a preferential recommendation, recommending PCV15 as an option might be more appropriate in this situation.

Dr. Lee asked Dr. Leidner to comment on whether there was a probabilistic sensitivity analysis performed or what types of sensitivity analyses were performed. In thinking about the economic analyses and the cost-saving quadrant, that is really helpful, but it depends on the cost of the vaccine. If it does not come out as planned, this will be a different conversation. If it is the same as the model price, the question would regard how stable that estimate is and what proportion of the analyses resulted in that cost-saving quadrant.

Dr. Leidner indicated that both models did perform probabilistic sensitivity analyses. If all of the simulation in the Merck model were in the cost-saving quadrant. For the CDC model, he recalled a confidence interval measure in which the 2.5% simulation was inside the cost-saving quadrant. That was the most expensive simulation for which they saw a result.

Proposed Recommendations for PCV15 Use in Children

Miwako Kobayashi, MD, MPH (CDC/NCIRD) reviewed the clinical considerations for use of PCV15 in children, including the proposed guidance for children who have not received either PCV13 or PCV15, children previously vaccinated with PCV13 or PCV15, PPSV-23 use for children aged 2–18 years who are at increased risk of pneumococcal disease, and recipients of hematopoietic stem cell transplant (HSCT). The proposed guidance will be based on the existing recommendations for PCV13 use.[16]

First is the proposed clinical guidance for children who have not received PCV13 or PCV15. Either PCV13 or PCV 15 is recommended as a 4-dose series at ages 2, 4, 6, and 12–15 months. PCV13 and PCV15 can be used interchangeably. Otherwise, the recommended number of PCV doses and intervals will remain the same. For children aged 2–6 months, either PCV13 or PCV15 can be administered using the current PCV doses and intervals. Everything else remains the same. The same changes will be made for infants aged 7–11 months, 12–23 months, ≥24 months, and children 6–18 years with an immunocompromising condition.

For children previously vaccinated with PCV13 or PCV15, children with complete PCV vaccination may receive PCV13 or PCV15 to complete the recommended vaccination series. The same changes will be made for children aged ≥24 months. For children aged 24–71 months with underlying medical conditions, changes are proposed to the current language to clarify confusion among providers on what an incomplete schedule of PCV doses means. For any incomplete schedule of fewer than 3 doses, a footnote will be included to provide more explanation of what that means. The footnote states, “Refer to Table 3 for the recommended number of PCV doses and schedule before age 24 months. If a child received 2 doses of PCV between age 12–23 months, the child has received a complete PCV schedule and does not

[16] *MMWR* 2010. 59(RR11); 1–18; *MMWR* 2013. 62(25); 521–524

require additional PCV doses, even though the total number of PCV doses given is 2." A supplemental dose of PCV15 is not indicated for children who have received 4 doses of PCV13 or another age-appropriate complete PCV13 schedule.

While no changes are being made to the recommended PPSV23 indications or schedule, PCV15 is being added as an option to PCV13 for the clinical guidance. The recommendations for PPSV23 revaccination for children with immunocompromising conditions will remain the same. No changes are being made to the PPSV23 indications for children who have underlying medical conditions. However, children with sickle cell disease or asplenia will be added under children with immunocompromising conditions because children with these conditions are all recommended to receive PPSV23 revaccination. The current pneumococcal vaccine recommendations do not specifically mention recommendations for children who are HSCT recipients. However, the *Best Practices Guidance of the Advisory Committee on Immunization Practices*[17] currently states that, "Recipients of hematopoietic stem cell transplants (HSCT) are recommended to receive 3 sequential doses of PCV followed by a dose of PPSV23 beginning 3–6 months after the transplant."

Discussion Summary

Dr. Sanchez observed that this is very comprehensive and important as clinicians deal with this vaccine on a regular basis. It will be interesting moving forward to see the uptake of PCV15, particularly since hospitals and healthcare organizations already have PCV13 available. The added benefits and potential lower cost than PCV13 would make him more included to use PCV15. Intuitively, protection for more serotypes is something everyone wants. PCV20 will be coming up in the second quarter of 2023, which will be another issue.

Dr. Kotton asked whether there would be further specifications about which vaccine would be recommended after HSCT, or if it will just state PCV.

Dr. Kobayashi said that to be consistent with the rest of the recommendations and the current proposal is not to make a preferential recommendation, the plan is to keep it as PCV and then include either PCV13 or PCV15.
Dr. Kotton expressed her hope that CDC would be able to answer at some point in the near future, at least for adults, because this community is left without guidance in the era of PCV20. Not to confuse adults with children, but so it would be good to provide clarity at least for the children.

Dr. Long emphasized that some things remain unknown. They can say that a certain percentage of disease can be reduced with PCV13, PCV15, and PCV15. They do not have the same degree of knowledge about the clinical efficacy of how good these vaccines be for these serotypes. It is known that the antibody response to serotype 3 is higher with this vaccine than with 13, but based on discussions with pneumococcal experts, serotype 3 in models may require even more antibody than the antibody response that PCV15 can provide. They can only deal with the information that they are given. With the information they have they just would say there is some oddness about the numbers of temperatures ≥104°F following PCV15 compared with PCV13. There is not an ability to ask any questions that could be statistically answered because of the small number of people and events in the studies, not to mention the heterogeneity of the nation and other issues. Why would there be more fever in the second week? This is assumed to be related to MMR vaccine, but why would there be more MMR

[17] https://www.cdc.gove/vaccines/hcp/acip-recs/general-recs/immunocompetence.html

vaccine high fever in PCV15 versus PCV13 recipients? This raises the possibility that maybe recipients do not respond as well to MMR as rapidly and there is more fever from MMR. The WG considered what the public would think of trading a very small incremental benefit for high fever, febrile seizures, and potentially more fever from MMR vaccine. This is without any clinical efficacy. Although ACIP certainly will approve vaccines without clinical efficacy from a bridge, the pneumococcal bridge is very shaky to begin with. For this vaccine, the WG did not think a preferential recommendation should be made when there is no clinical efficacy.

Dr. Lee acknowledged that this WG has a set of complicated decisions ahead. She requested confirmation about whether she understood correctly that a child had not received vaccine by 6 years of age, they would receive only PPSV-23 and not any conjugate vaccine.

Dr. Kobayashi clarified that the way the current recommendation is written is that a child with immunocompromising conditions, CSF, or a cochlear implant who has never received a pneumococcal conjugate vaccine is recommended to receive a dose of a pneumococcal conjugate vaccine followed by PPSV23. Immunocompetent children with chronic heart disease, lung disease, or diabetes have missed the opportunity to get a pneumococcal conjugate vaccine before 6 years of age are not recommended to receive a conjugate vaccine.

Dr. Lee recognized that this group of children is probably small given that vaccination rates are generally pretty high, but these recommendations were made a long while back. For simplicity, she asked whether the WG ever discussed whether to offer the ability to receive PCV followed by PPSV23 for anyone with high-risk conditions, such as those with chronic lung disease, chronic heart disease, et cetera and if there was evidence to suggest that this should not be done or if it might be considered in the future. Given that pneumococcal recommendations are probably the most complex, aside from COVID-19 right now, with the youngest children to implement, she was just trying to think of ways to make it easier and also hold to the principles of what they are trying to achieve.

Dr. Poehling responded that this raised a very important point since it would be recommended once someone is 19 years of age. The WG was working very fast to review data, so they did not spend as much time on these questions. However, the point is well-taken. To her knowledge, there is no data to say this should not be done and it would be more feasible to include that.

Dr. Kobayashi added that there also is the anticipation of another conjugate vaccine in the near future, so the hope was to try to minimize the confusion as much as possible by not making a lot of changes to the recommendations. Therefore, the focus was to follow the current recommendations on pneumococcal conjugate vaccine use and add PCV15 as an option.

Dr. Daley indicated that he was in favor of the approach recommended by the WG and that this felt like a time to make an incremental change and given the uncertainty that Dr. Long highlighted in terms of some of the important considerations.

Vote: PCV15 Vaccine Use in Children

Miwako Kobayashi, MD, MPH (CDC/NCIRD) presented the proposed recommendation for PCV15 use in children as follows:

> "PCV15 may be used as an option to PCV13 for children aged <19 years according to currently recommended PCV13 dosing and schedules."

Motion/Vote: PCV15 Vaccine in Children

Dr. Ault made a motion for ACIP to adopt the recommendation stating that, "PCV15 may be used as an option to PCV13 for children aged <19 years according to currently recommended PCV13 dosing and schedules." Dr. Brooks seconded the motion. No COIs were declared. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

VFC Vote: PCV15 Vaccines in Children

Jeanne Santoli, MD, MPH (CDC/NCIRD) the purpose of this resolution was to update the recommendations regarding the use of pneumococcal conjugate vaccines (PCV) to include PCV15 as an option. The resolution has 2 components, the PCV component and the PPV23 component. Both of them have been updated to reflect the inclusion of PCV15. The eligible groups for the PCV component of the resolution are unchanged. The table is slightly different in that 2 of the categories that were previously in a separate category called "Functional and Anatomic Asplenia" were now included under the "Immunocompromised Persons" category. Otherwise, the table is the same. PCV13 has been replaced with PCV in order to reference PCV13 or PCV15. Clarification was added to be clearer about what constitutes an incomplete schedule so that the wording is aligned with the ACIP recommendations. The first footnote now indicates that PCV13 or PCV15 may be used. A fourth footnote has been added to clarify what is meant by the text in the table. Recommended Dosages and Contraindications and Precautions were not changed, although the PCV 15 package insert will be added prior to posting this resolution. For the PPSV 23 component, the only change in the eligible groups is in Table 1, which asl is referred to in this component of the resolution. Again, reference to PCV has been updated to be inclusive of PCV15. Recommended Dosages and Contraindications and Precautions were not changed. The standard statement is made about published recommendations that are incorporated into the resolution by reference if they are published within the next 12 months.

VFC Resolution Motion/Vote: PCV Vaccines in Children

Ms. Bahta made a motion for ACIP to adopt the updates to the VFC Resolution recommendations regarding the use of pneumococcal conjugate vaccines (PCV) for children to include 15-valent PCV (PCV15) as an option. Dr. Brooks seconded the motion. No COIs were declared. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Discussion Summary

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

No additional comments were offered.

MEASLES, MUMPS, AND RUBELLA (MMR) VACCINE

Session Introduction

Lynn Bahta RN, MPH (ACIP WG Chair) provided and introduction to the MMR session, reporting that the FDA approved the GlaxoSmithKline (GSK) MMR vaccine, Priorix, on June 3, 2022. Until this month, there has been only one licensed MMR vaccine product in the US, M-M-R®II, manufactured by Merck. MMR vaccine is currently recommended for administration at ≥12 months of age for the prevention of measles, mumps, and rubella and for post-exposure measled prophylaxis. Additionally, MMR is recommended for off-label use in 2 situations. The first situation is for infants 6 through 12 months of age planning to travel or live abroad or during outbreaks.[18] The second situation is for a third dose in previously vaccinated persons with 2 doses who are identified as being at increased risk because of a mumps outbreak.[19] Since January 2022, the MMR Vaccine WG has been meeting to evaluate the safety and immunogenicity of Priorix as compared to M-M-R®II. The WG has been led by Dr. Elizabeth Krow-Lucal who has championed efficiency to bring them to this day for a proposed recommendation and vote.

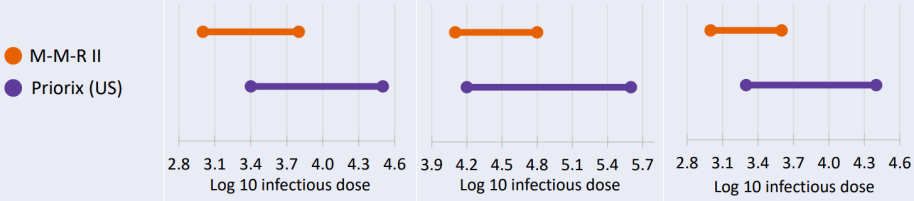
Priorix for Prevention of Measles, Mumps, and Rubella

Elisabeth Krow-Lucal, PhD, MPH (CDC/NCIRD) presented the EtR Framework and literature review on Priorix for the prevention of measles, mumps, and rubella on behalf of the MMR Vaccines WG workgroup. The policy question for this review was, “Should MMR vaccine, Priorix manufactured by GSK, be recommended as an option according to currently recommended schedules and off-label uses to prevent measles, mumps, and rubella?” The population is

[18] https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6204a1.htm
[19] https://www.cdc.gov/mmwr/volumes/67/wr/mm6701a7.htm

persons ≥6 months of age. The intervention is GSK's Priorix. The comparator is the existing MMR vaccine licensed in the US, M-M-R®II, manufactured by Merck. The outcomes of interest are prevention of measles, mumps, and rubella; short-term humoral immunity; persistence of the humoral immune response; reactogenicity Grade ≥3; and SAEs of interest identified by ACIP and the WG (e.g., febrile seizures, aseptic meningitis, and immune thrombocytopenic purpura).

As previously presented to ACIP, Priorix was first licensed in Germany in 1997. It has been approved in over 100 countries outside of the US and over 400 million doses have been distributed worldwide. Countries where Priorix has been approved include all European countries, all European Union countries, Canada, Australia, and many others worldwide. It also has been prequalified by WHO. Priorix is currently registered in 97 countries. Priorix is considered fully interchangeable with M-M-R®II or M-M-RVaxPro in a number of countries. Both vaccines contain live-attenuated measles, mumps, and rubella viruses. M-M-R®II and Priorix contain the same strains for mumps and rubella and a similar lineage of measles. Both of the measles and rubella strains found in M-M-R®II and Priorix are 100% identical on a nucleotide level. The Jeryl Lynn™ strain used in the mumps component of M-M-R®II is a mixture of 2 viral lineages, JL1 and JL2. RIT4385, the mumps component from GSK, is a pure clone of JL1 and is 100% identical on a protein level to Merck's JL1 component. For differences in inactive ingredients, M-M-R®II contains porcine gelatin and Priorix does not. This table shows the minimum and maximum potencies for M-M-R®II and Priorix in the US:

	Measles	Mumps	Rubella
M-M-R II	≥ $10^{3.0}$ – $10^{3.8}$ $TCID_{50}$	≥ $10^{4.1}$ – $10^{4.8}$ $TCID_{50}$	≥ $10^{3.0}$ – $10^{3.6}$ $TCID_{50}$
			
Priorix (US)	≥ $10^{3.4}$ – $10^{4.5}$ $CCID_{50}$	≥ $10^{4.2}$ – $10^{5.6}$ $CCID_{50}$	≥ $10^{3.3}$ – $10^{4.4}$ $CCID_{50}$
Priorix (Other)	≥ $10^{3.0}$	≥ $10^{3.7}$	≥ $10^{3.0}$

According to FDA's requirements for live viral vaccines, minimum and maximum viral potency titers for Priorix were defined during clinical development to ensure efficacy at minimum potency and an acceptable safety profile at maximum potency. The lines show the range from minimum to maximum potencies for M-M-R®II in orange and Priorix as licensed in the US in purple. GSK will be changing the dosage for all countries to align with the US dosage.

No turning to the EtR Framework beginning with the public health problem, attaining and maintaining high, 2-dose MMR coverage has led to measles and rubella elimination in the US and low levels of mumps. Despite high 2-dose vaccine coverage, measles and mumps continue to cause locally acquired and importation-related cases and outbreaks. Given this, the WG is of the opinion that the prevention of these diseases is a problem of public health importance.

In terms of the domain of benefits and harms and how substantial the desirable and undesirable anticipated effects are of Priorix compared with currently used M-M-R®II, the WG conducted a literature review to assess the safety and immunogenicity of Priorix. Studies in any language were identified from PubMed, Embase, CINAHL, Cochrane, Scopus, and clinicaltrials.gov databases using the following search string:

- "Measles-Mumps-Rubella Vaccine"
- And ("Priorix" or "MMR vaccine" or ("GlaxoSmithKline*" or "GSK") and "MMR*") or "GSK-MMR" or "MMR-RIT" or "SB-MMR")
- And "Safe*" or "effective*" or "efficacy" or "immun*" or "interchangeab*" or "inter-changeab*" or "adverse" or "M-M-R II" or "Merck" or "evidence*" or ("review" or "meta*")

Results were limited to RCTs or systematic reviews and meta-analyses. Of the 918 studies identified, 18 were relevant to the PICO question. Of those, 16 were RCTs that compared Priorix and M-M-R®II head-to-head, and 2 were systematic reviews that included Priorix-specific information. An additional 5 studies with a different study design or comparator vaccine also were reviewed for safety data on the conditions of interest identified by the WG and ACIP. For safety data, the WG focused on the 4 RCTs using a licensed US dose and 2 reviews and 5 studies with different designs or dosages to assess specific safety conditions indicated in February by ACIP. In terms of the characteristics of the 4 RCTs using the licensed US dose, the majority (90%) were conducted in the US. Approximately 68% received Priorix and 32% received a first dose of MMR. There was no significant difference in race and ethnicity between the Priorix and M-M-R®II groups. None of the studies examined prevention of disease directly. All 4 reported SAEs and reactogenicity of Grade 3 or higher. All studies used a comparator vaccine, as it would be unethical to compare against placebo alone in this situation.
From these studies and studies previously presented to ACIP, Priorix shows a similar safety profile to M-M-R®II. Follow-up time in these studies was from 40 days to 6 months post-MMR vaccination. The frequency of vaccine-related SAEs was low, ranging from 0% to 0.2% for the Priorix group and 0% to 0.03% in the M-M-R®II group. Vaccine-related SAEs identified in clinical trials were immune thrombocytopenic purpura in 1 participant each in the M-M-R®II and Priorix groups, inguinal adenitis in 1 Priorix participant, and 1 complex febrile seizure in an M-M-R®II participant. Additional safety information was collected from the literature based on questions from ACIP and WG members on conditions of interest indicated in February by ACIP including febrile seizures, aseptic meningitis, and immune thrombocytopenic purpura (ITP) compared to the current M-M-R®II vaccine. Because these events are very rare, it is difficult to identify this risk in the RCTs. For that reason, the WG looked more broadly in the literature.

The rate of febrile seizures is highest in the 6 to 11 days following vaccination for all MMR vaccines. The rate of febrile seizures in this period is estimated to be 3.3 to 8.7 per 10,000 doses based on 2 studies conducted in the UK that which included both Priorix and M-M-R®II.[20] From the clinical trials data provided by GSK and presented to ACIP in February, at the target minimum and maximum potencies, the rate of febrile seizures in the Priorix group was 9.5 per 10,000 doses in approximately 8,300 children studied and 14.8 per 10,000 doses in approximately 3,500 children studied. All studies included age-appropriate vaccine co-administration and all studies found the differences in rates of febrile seizures to be non-significant between the 2 vaccines. Similarly, the time-course of fever was comparable for both vaccines across all studies, with the majority of instances observed 5 to 12 days post-vaccination.

[20] Miller, E. et al. Risks of Convulsion and Aseptic Meningitis following Measles-Mumps-Rubella Vaccination in the United Kingdom. Am J Epidemiol 165, 704–709 (2007); and Farrington, P. et al. A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines. Lancet 345, 567–569 (1995)

The second issue raised was aseptic meningitis. While this has not been studied in an RCT, a paper from 2007 in the UK used active surveillance to identify aseptic meningitis and mumps meningitis in the 15 to 35 days post-vaccination from 1998 to 2004.[21] This was a comparison to the rate of the previously licensed vaccine in the UK, which contained the Urabe Am 9 strain of mumps, which is known to be associated with aseptic meningitis. There 2 case definitions used for aseptic meningitis, ICD-9 and 10 codes and chart review for aseptic meningitis and laboratory-confirmed mumps meningitis cases. In this time period, 0 cases of aseptic meningitis were identified from ICD-9 and 10 code and chart review out of 99,177 doses of Priorix given, and 0 cases of laboratory-confirmed mumps meningitis were identified out of approximately 1.6 million doses of Priorix given. Based on the number of doses and cases observed in the timeframe, risks as rare as 1 in 437,000 doses could be excluded for Priorix. Additional doses would need to be observed to rule out rarer risks. In addition, the WHO Global Advisory Committee on Vaccine Safety (GACVS) did not find any cases of virologically proven aseptic meningitis following Jeryl Lynn vaccination.[22] The most recent Cochrane Review from 2021[23] states that there is no evidence of association between aseptic meningitis and vaccines prepared with the Jeryl-Lynn strains, which includes RIT 4385, the mumps component found in Priorix.

The third condition of interest was ITP, which is associated with the receipt of live-attenuated measles vaccines. There is very limited brand-specific data available on ITP. From the 4 RCTs at the US dosage of Priorix, there was 1 case each in the Priorix and M-M-R®II groups. By comparison, for M-M-R®II a VSD study reported a rate of 2.5 cases per 100,000 doses.[24] In the literature, data is available from three studies and a Cochrane Review. All show an association with ITP. However, the case definitions varied across papers. ITP is a very rare event and when examining vaccine-specific events, the denominator is small. This leads to large confidence intervals and uncertainty around the point estimates of rate ratios. Based on the limited estimates available, the best interpretation is that the rates and rate ratios for M-M-R®II versus Priorix are not different from each other.

In summary of the conditions of interest, there was a similar rate and severity of febrile seizures after vaccination with Priorix or M-M-R®II. There is no evidence of association of aseptic meningitis with vaccines prepared Jeryl-Lynn strains and risks as rare as 1 in 437,000 doses can be excluded. Based on limited data available, there were similar rates of ITP after vaccination with Priorix or M-M-R®II.

To review the available information on immunogenicity of Priorix compared to M-M-R®II, of the 16 RCTs, 13 had immunogenicity data. Of these, 4 were of the licensed US dose and 9 were at a lower Priorix dose. All were reviewed for measles, mumps, and rubella seroconversion after first or second dose, as well as GMC after the first or second dose. All studies showed a GMC well above the estimated correlate of protection. Of the 13 RCTs reviewed, 12 showed no difference in anti-measles GMC. Unlike measles, mumps does not have a known correlate of protection. Seropositivity is defined as ≥10 EU/mL. All studies demonstrated that both vaccines exceeded the minimum threshold, and 10 of 13 studies showed no statistically significant

[21] Miller, E. et al. Risks of Convulsion and Aseptic Meningitis following Measles-Mumps-Rubella Vaccination in the United Kingdom. Am J Epidemiol 165, 704–709 (2007)
[22] World Health Organization Global Advisory Committee on Vaccine Safety. WER 32, 282–283 (2003)
[23] DiPetrantonj C, et al. Vaccines for measles, mumps, rubella, and varicella in children. Cochrane Database of Systematic Reviews 2021
[24] France, E. K. et al. Risk of Immune Thrombocytopenic Purpura After Measles-Mumps-Rubella Immunization in Children. Pediatrics 121, e687–e692 (2008).

difference between anti-mumps GMC levels. The rubella correlate of protection is estimated to be 10 IU/mL. All studies demonstrated that both vaccines exceeded this threshold, and 12 out of 13 studies showed no statistically significant difference between Priorix and M-M-R®II.

In summary of immunogenicity, of the studies conducted with the US dosage, there was no significant difference between Priorix and M-M-R®II GMC for measles, mumps, or rubella. Of the studies conducted at a lower dosage than the US, all studies show GMC higher than the correlate of protection for both measles and rubella and the seroresponse threshold for mumps. Of 13 studies, 10 showed no statistically significant difference between anti-mumps GMC levels. There was no significant difference for second dose between Priorix and M-M-R®II for measles, mumps, or rubella GMC levels at any potency.

To summarize the benefits and harms domain, the WG considered that the difference in both the desirable anticipated effects and the undesirable anticipated effects of Priorix compared with M-M-R®II were minimal and the balance between the vaccines favored both.

Regarding the feasibility domain and whether Priorix as an option for MMR vaccination is feasible to implement and the acceptability domain in terms of whether Priorix acceptable to key stakeholders, between 2000 and mid-2003,[25] the US experienced occasional shortages of a number of routinely recommended vaccines, including MMR. These shortages were due to 2 voluntary interruptions to manufacturing operations by Merck,[26] both of which took longer to resolve than anticipated and that were significant enough that the ACIP recommendations had to be temporarily modified, including suspension of the second dose of MMR in cases of insufficient vaccine quantities. Redundancy in supply is a critical component of sustainable public health.[27] An important point to note here is that MMRV, MMR, and varicella combination vaccine account for roughly 13% (5% to 24%) of first doses and roughly 80% (52% to 98%) of second doses in this childhood vaccine series.[28] Given this, the WG considered that an additional MMR vaccine (Priorix) that is safe and not inferior to the existing MMR vaccine (M-M-R®II) could be beneficial in maintaining measles and rubella elimination and mitigating mumps outbreaks in the US, as well as assuring supplier diversity.

To assess feasibility and acceptability, the WG conducted a focus group with state health department Immunization Managers to identify potential barriers to Priorix. Participants noted that the majority of VFC and vaccine programs order based on providers' demand and that this is the main factor driving new vaccine adoption. Adding Priorix into the routine immunization system, vaccine access, distribution, storage and handling, and implementation of communication and education strategies were not considered barriers. Participants welcomed the idea of having another brand available in case of outbreaks or manufacturing interruptions. In addition, 1 participant noted the benefit of having a gelatin-free vaccine (Priorix) for religious populations with objections to gelatin. A survey also was conducted of 400 pediatricians and 400 family medicine practitioners. Participants were asked a number of questions, including about their current MMR vaccination practices and barriers to having a second MMR product. The key findings from the survey as related to feasibility were concerns about the possibility of not being able to mix and match doses. A quarter of participants reported having

[25] Santibanez TA, et al. Differential Effects of the DTaP and MMR Vaccine Shortages on Timeliness of Childhood Vaccination Coverage. American Journal of Public Health. 2006
[26] Shortage of varicella and measles, mumps and rubella vaccines and interim recommendations from the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2002
[27] Shortage of varicella and measles, mumps and rubella vaccines and interim recommendations from the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2002
[28] Executive Order 14001 "On a Sustainable Public Health Supply Chain" https://www.phe.gov/Preparedness/legal/Documents/National-Strategy-for-Resilient-Public-Health-Supply-Chain.pdf

patients who did not receive an MMR vaccine due to allergy to a vaccine component. Of those, 30% to 40% reported that the allergy was to gelatin, and the majority of pediatricians had used the MMR vaccine for patients under the age of 1 year.

The major categories identified were concerns that the vaccines were not fully interchangeable, including off-label usage and a potential benefit for a gelatin-free vaccine to serve potentially allergic patients. Given the concerns identified around interchangeability in the survey, the WG looked at the available evidence for interchangeability. Previously presented studies showed non-inferior responses and similar safety profiles for individuals receiving a first dose with M-M-R®II, or ProQuad® (MMRV) and a second dose of Priorix. A number of countries (e.g., Australia, Canada, Denmark, France, New Zealand, the UK, Ireland, and others) consider Priorix and M-M-R®II or M-M-RVaxPro to be fully interchangeable. In addition, both the FDA and the European Medicines Agency (EMA)[29] allow for vaccination with Priorix in individuals who have previously been vaccinated with a different MMR vaccine. However, there are limited data on the interchangeability for those who receive Priorix as a first dose, followed by M-M-R®II or ProQuad®. There were no safety or immunogenicity differences identified in the available data as expected, given the vaccine component similarity.[30]

In summary, the WG considered that Priorix is acceptable to key stakeholders and feasible to implement. However, the WG is of the opinion that differences in off-label uses and interchangeability recommendations could negatively affect the acceptability and feasibility. M-M-R®II and Priorix will have the same VFC price. Given this and the similarities in formulation and storage, the WG considered that there would probably be no impact on health equity for Priorix as compared to M-M-R®II. Finally, the WG considered that the values and resource use based on similarities of schedule, anticipated harms and benefits, and VFC costs.

The 2 vaccines are comparable, with values and resource use similar to that of M-M-R®II. Based on EtR considerations, Priorix and M-M-R®II vaccines are closely balanced. Therefore, the WG judgment on adding Priorix as an option for MMR vaccination is as follows. The desirable consequences clearly outweigh the undesirable consequences in most settings. Given the similarities in dosage, vaccine components, evidence from the clinical trials, and literature review, the WG considers that Priorix and M-M-R®II should be considered fully interchangeable, including all off-label uses and may be administered in any situation in which a measles-, mumps-, and rubella-containing vaccine is indicated.

Discussion Summary

Dr. Long asked in the 400 million doses and 100 countries, how many other countries give varicella vaccine concurrently with the first dose of Priorix and if there are any data on that. She also inquired about AEs with the concurrent boatload of vaccines given to children at the time they are given their first MMR and whether there are any data on PCV, DTaP, and *Hib* in the beginning of the second year of life.

Dr. Krow-Lucal responded that all of GSK's clinical trials used the routinely given vaccinations in those age groups, including varicella, hepatitis A, and PCV13 in the US studies.

[29] https://www.ema.europa.eu/en/documents/referral/priorix-article-30-referral-annex-iii_en.pdf
[30] Abu-Elyazeed, R. et al. Immunogenicity and safety of a second dose of a measles-mumps-rubella vaccine administered to healthy participants 7 years of age or older: A phase III, randomized study. 2018. and personal communication 2022

Dr. Friedland, Medical Affairs Team at GSK Vaccines, thanked the CDC, the ACIP, and the members of the ACIP MMR WG for their evidence-based review of GSK's US-licensed MMR vaccine, Priorix. Before the CDC implemented a measles vaccination program in 1963, an estimated 3 to 4 million people got measles each year in the US. Since then, CDC's highly successful public health program resulting in widespread use of measles virus-containing vaccine has led to a greater than 99% reduction in measles cases compared with the pre-vaccine era. Recent US measles outbreaks and mumps cases highlight the importance of maintaining high vaccination rates to ensure control of the diseases. The availability of a second MMR vaccine in the US could help mitigate some of this public health risk. This past April, a CDC report noted 400,000 fewer children entered kindergarten in the 2020-2021 school year than expected nationally, meaning those children may not be up-to-date on childhood immunizations. The availability of a second MMR vaccine in the US will ensure health care professionals have more than one MMR option as they work to catch their patients up on recommended vaccinations. Data across 5 Phase 3 clinical trials and rolling over 16,000 children and adults demonstrate that Priorix is immunologically non-inferior to M-M-R®II and has a comparable safety profile. The FDA licensed Priorix on June 3, 2022. Based on FDA's review of the clinical trial results and use outside the US, there are no post-marketing commitments or requirements. The ACIP's recommendations and clinical guidance are crucial for providing clarity for providers on the appropriate use of the vaccine. Given the immunological and safety profile of Priorix, the committee's and center's clinical expertise and knowledge of MMR disease and immunization, GSK asks the ACIP to support the use of Priorix in the same routine catch-up and special situations for MMR disease prevention and control as with M-M-R®II. On behalf of all of his GSK colleagues, they are proud to bring an additional MMR vaccine option for providers and patients in the US.

Dr. Long asked whether there is a combined prior varicella vaccine that would be acceptable to children 4 to 6 years of age, referring to the comment that this vaccine could be substituted when MM and R are required. She recalled that ACIP's previous recommendation was a preference for MMRV as the second dose to reduce numbers of injections. If MMRV is preferred over MMR plus V at 4 to 6 years of age, this vaccine would not be preferred for the second dose. She wondered whether ACIP would need to say something about MMR plus V and if this vaccine for the second dose, whether it would require 2 injections.

Dr. Krow-Lucal indicated that there is an MMRV vaccine, Priorix-Tetra, that is licensed outside of the US. She did not have any information on whether GSK will bring that to the US. In terms of the question on the recommendation for MMRV as compared to MMR, as noted from the information they were able to get from their immunization colleagues, a majority of second doses in the US are given as MMRV.

Dr. Mona Marin added that MMRV is preferred for the second dose because it is part of the preference given to combination vaccines. It is not based on any immunogenicity of safety data. For the first dose, the recommendation is that providers can give either MMR and varicella or MMRV, but they should discuss the option with the parents. If the parents prefer MMRV, they would give MMRV. Otherwise, the CDC recommendation is to go with separate vaccination because of the increased risk for febrile seizures after MMRV for the first dose for young children. In this situation, it would be used the same as M-M-R®II. If a provider is going to give M-M-R®II as a second dose, this would be an option. If they are giving M-M-R®II alone, then they would have to do the same for the non-combination vaccine, which is not preferred.

Dr. Sanchez said he did not think that the AAP Red Book actually says anything about a preference for an MRV at 4 to 6 years of age. Regardless, this needs to be explained to parents. It certainly is great to have another vaccine available. He asked whether the storage requirement is the same as M-M-R®II to prevent activation; whether any of the studies looked at allergic reactions, which was brought up by the survey in terms of the urticaria and so-called allergic reactions to MMR that have been possibly attributed to gelatin; and whether the new vaccine is egg-based.

Dr. Krow-Lucal indicated that the difference is that Priorix should be stored refrigerated, not frozen, but that is similar to other routinely given vaccinations. To caveat the survey results in terms of allergic reactions, the WG asked only if a vaccination had been declined because of an allergy. They did not ask if it was a clinically-verified allergy. Of those in the survey, the WG does not have a good understanding of how many would be true allergies to be concerned about. In terms of the differences in potential allergic reactions, limited data are available and were not looked at in the clinical trials. There is literature primarily from Japan looking at the removal of gelatin from all vaccines that could be of interest, but it was not specifically looked at in these trials. The new vaccine, Priorix, is egg-based.

Dr. Kimberlin, AAP Red Book Editor, indicated that the Red Book on MMRV versus MMR plus varicella vaccine reads as follows, “Either MMRV or separate MMR and varicella vaccines are acceptable options for Dose 1 at 12 through 15 months of age. Pediatricians should discuss risks and benefits of the vaccine choices with the parents or caregivers. For the first dose of measles, mumps, rubella, and varicella vaccine at ages 48 months and older and for Dose 2 at any age 15 months through 12 years, use of MMRV vaccine generally is preferred over separate injections in MMR and varicella vaccines to minimize the number of injections.”

Referring to Slide 17, Dr. Brooks asked whether aseptic meningitis was found in Priorix-vaccinated individuals only, or if it also was found in M-M-R®II. Referring to Slide 23, he noticed that there were confidence intervals for the 4 US studies, but not the others above that.

Dr. Krow-Lucal indicated that the study to which Dr. Brooks referred was conducted in the UK. Prior to this, the vaccine that was licensed in the UK contained the Urabe Am 9 strain of mumps, which has been associated with aseptic meningitis. When that was replaced with Priorix, there was an interest in making sure that Priorix specifically was not associated with aseptic meningitis. This study was Priorix-specific and the paper was comparing to the previous Urabe Am 9 strain. The studies do have confidence intervals, but given the scale and the range of the differences, they were obscured.

In terms of the proposed recommendation language and based on what Dr. Kimberlin read, Dr. Long asked whether ACIP needed to state someplace that there currently is no combination MMRV vaccine. It seemed to her that families would need to be informed that they would have to get the V in another injection. Doctors may have one or the other vaccine in their offices. If a combination vaccine is preferred for the second dose, the doctor would have to tell the family that their child would need 2 injections at 4 to 6 years instead of 1 versus saying they got a better deal on the GSK vaccine, for example.

Dr. Krow-Lucal said this is something that could be included in the Clinical Considerations. This is not being recommended as a replacement for MMRV, merely as an additional option. Having that language available that MMRV is preferred will still be in place.

Ms. Bahta thought they should go back to the focus of the language that this is a vaccine that can be used interchangeably with M-M-R®II and that all of the rules and the recommendations would apply. That would include a provider using a combination vaccine. They already have to have that conversation if they are using separate or combined. Therefore, she thought they should stay relevant to the proposed language.

Dr. Poehling agreed and highlighted that large health systems do receive better deals if they use predominantly one or another product by a manufacturer. She emphasized the importance of giving providers the freedom to use products from different manufacturers.

Vote: MMR Vaccine

Elisabeth Krow-Lucal, PhD, MPH (CDC/NCIRD) presented the following proposed recommendation for influenza vaccine:

> "The MMR vaccine, Priorix, is recommended according to currently recommended schedules and off-label uses as an option to prevent measles, mumps, and rubella."

Motion/Vote: MMR Vaccine

Dr. Poehling made a motion for ACIP to adopt the recommendation stating that, "The MMR vaccine, Priorix, is recommended according to currently recommended schedules and off-label uses as an option to prevent measles, mumps, and rubella." Dr. Talbot seconded the motion. No COIs were declared. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Discussion Summary

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

Patsy Stinchfield (NAPNAP) first noted that she serves on the Influenza, MMR, and RSV WGs and wanted to publicly thank the CDC staff and point out that the work behind the scenes is phenomenal. The amount of rigor in the EtR Framework and the respect, thoroughness, and inclusiveness of those who are not part of the CDC are really commendable. She just wanted everyone in the vaccine arena of CDC to know how much they are valued. Second, she stressed that having an additional MMR option is very good. However, they must put these vaccines to use. MMR vaccine coverage rates in the US already were low before the pandemic and have been decreasing for a number of reasons, misinformation being one of them. She is very concerned about our next outbreak being measles. They have seen 2 cases in Minnesota, including a hospitalized child after international travel. She encouraged everyone to ensure that they are conducting remind/recall to get children vaccinated.

HUMAN PAPILLOMAVIRUS (HPV) VACCINE

Session Introduction

Lauri E. Markowitz, MD (CDC/NCIRD) gave a brief introduction to the human papillomavirus (HPV) vaccine session, explaining that the purpose of this session was to provide an overview of evidence on 1-dose HPV vaccination; summarize updated recommendations of the World Health Organization's (WHO's) Strategic Advisory Group of Experts on Immunization (SAGE) that were made in April 2022; and provide a brief update on HPV vaccination coverage and impact of the US HPV vaccination program. Given that the last presentation to ACIP on HPV vaccine was in 2009, Dr. Markowitz began with a short background overview.

All currently available HPV vaccines are virus-like particle (VLP) vaccines. These VLPs self-assemble spontaneously from 72 pentamers of the L1 major capsid protein expressed using recombinant technology. Because they are produced from a single virion protein, they are non-infectious and non-oncogenic. These VLPs are morphologically similar to authentic virus and induce high levels of neutralizing antibodies. There are 3 vaccines licensed in the US show in this table:

Vaccine and brand name	Quadrivalent (4vHPV) Gardasil	Bivalent (2vHPV) Cervarix	9-valent (9vHPV) Gardasil 9
Types	16, 18, 6, 11	16, 18	16, 18, 6, 11 31, 33, 45, 52, 58
Adjuvant	225 µg AAHS (amorphous aluminium hydroxyphosphate sulfate)	ASO4 (500 µg aluminium hydroxide, 50 µg 3-O-deacylated 4'-monophosphoryl lipid A)	500 µg AAHS (amorphous aluminium hydroxyphosphate sulfate)
Year licensed	2006	2009	2014
Manufacturer	Merck & Co.	GlaxoSmithKline	Merck & Co.

All 3 vaccines target 16/18 HPV types that cause most HPV-attributable cancers. The quadrivalent and 9vHPV vaccines also target 6/11 types that cause most genital warts. The 9vHPV vaccine targets 5 additional cancer-causing types. All of these vaccines have been found to have very high efficacy against vaccine targeted types. The quadrivalent vaccine was the first license in the US in 2006, followed by bivalent in 2009, and 9vHPV in 2014. Before 2015, almost all vaccine use in the US was the quadrivalent vaccine. Since the end of 2016, only the 9vHPV vaccine has been available in the US. All of these vaccines are available in other countries.

In the US, HPV vaccination was recommended in 2006 for females. At that time, HPV vaccine was only licensed in females and routine vaccination was recommended for persons 11-12 years of age. The series can be started at 9 years of age and catch-up was recommended through 26 years of age. In 2011, routine vaccination of males 11-12 years of age was recommended, with catch-up through 21 years of age. Vaccination was first recommended as a 3-dose schedule. In 2016, a 2-dose schedule was recommended for those starting vaccination before 15 years of age. In 2019, catch-up vaccination was harmonized through 26 years of age for everyone. Also in 2019, a recommendation was made for shared clinical decision-making for persons 27 through 45 years of age. The current recommendations for HPV vaccination include

routine, catch-up and shared clinical decision-making. The number of doses depends upon the age the series is initiated, with 2 doses recommended for those starting the series before 15 years of age.[31]

National and State-Level HPV Vaccination Coverage

Shannon Stokley, DrPH (CDC/NCIRD) discussed adolescent vaccination coverage levels, the impacts of the COVID-19 pandemic on routine vaccination, and efforts to increase routine vaccination. CDC monitors adolescent vaccination coverage through the National Immunization Survey-Teen (NIS-Teen). This is a cellphone-based survey of parents of adolescents 13 through 17 years of age. With consent from parents, the vaccination histories of adolescents are obtained from the medical provider and there are estimates based on medical records and not parental recall. Looking at trends in vaccination coverage from 2006-2020,[32] the most recent year of data available, nationally vaccination coverage for Tdap or Meningococcal vaccination was high at about 90%. This is much higher than coverage for the first dose of HPV vaccine of 75% and coverage for the HPV series of 59%. Although coverage for HPV is lower than other routinely recommended vaccines, it did continue to increase each year—even in 2020.

In terms of estimated vaccination coverage with at least 1 HPV vaccine, there is wide variation in coverage across the country that ranges from 55% in Mississippi to 93% in Rhode Island. Coverage is typically lower in the Southeast. Coverage for the HPV series ranges from 32% in Mississippi to 83% in Rhode Island and a similar pattern emerges with lower coverage in the Southeast. Since the HPV vaccine has been licensed and introduced, an interesting pattern has been observed in vaccination coverage by race/ethnicity. Consistently over time, vaccination coverage has been higher for Hispanic and non-Hispanic Black adolescents compared to non-Hispanic White adolescents. It is not clear what may be driving these differences, but the pattern holds whether evaluating initiation of a series or series completion. Differences are also seen in vaccination coverage by urbanicity, with vaccination coverage consistently being lower for adolescents living in rural areas by about 12 percentage points. This difference appears to be narrowing in the most recent years of data, but vaccination coverage for adolescents living in rural areas increases at the same rate as those living in urban areas. It is just much lower than in the urban population.[33]

In summary, high vaccination coverage for Tdap and meningococcal vaccines continue to be seen. While HPV vaccination is lower, it continues to increase. Differences in coverage continue to be seen by race/ethnicity and by metropolitan statistical area (MSA) or urbanicity.

In terms of the impact of the COVID-19 pandemic on adolescent vaccination, the past 2.5 years have been difficult on many and routine vaccination is no different. There were disruptions in health care services in 2020, some of which may continue. The results of the NIS-Teen for 2020 were somewhat surprising in that a drop in coverage was not seen. However, the 2020 survey was not able to assess the impact of the pandemic because most of the teens included in the survey had started the vaccination series prior to the pandemic. While the survey includes teens 13 through 17 years of age, it measures vaccination received at any point in their lives. Therefore, most of these teams started the HPV series before 2020. Additional years of data are needed to truly assess the impact of a pandemic. CDC is just now receiving the data from 2021 survey, which should be available later this year.

31 Recommendations of the Centers for Disease Control and Prevention and the Advisory Committee on Immunization Practices https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html
32 https://www.cdc.gov/mmwr/volumes/70/wr/mm7035a1.htm
33 https://www.cdc.gov/vaccines/imz-managers/coverage/teenvaxview/index.html

Absent survey data, another way the impact of the pandemic on routine vaccination can be assessed is by monitoring vaccine orders for the Vaccines For Children (VFC) Program. The VFC program provides vaccines at no cost for children who otherwise would not be able to afford vaccinations. In the US, about 50% of children receive their vaccines through the VFC program. Vaccine orders are monitored by fiscal year (FY), which aligns with the school year running from October 1 through September 30. In terms of VFC provider orders for HPV vaccine for FY 2019 through 2022. Using FY 2019 as the baseline, total orders decreased about 24%. In FY 2020 and FY 2021, there was improvement in total orders, but they were still about 9% lower than 2019. In terms of year-to-date orders for 2022, orders are about 10% lower than the same time period in 2019.

Another way the impact of a pandemic can be evaluated is by looking at data from Immunization Information Systems (IIS). CDC receives IIS data from 13 jurisdictions. HPV vaccination coverage was evaluated by age for 2018 through 2021. Coverage for 1 or more HPV vaccines, coverage increased slightly in 2020 and 2021 for adolescents 13 years of age and older. Where the impact is seen is with persons 11-12 years of age, which compared to 2019 coverage decreased 3 percentage points in 2020. Coverage continued to decrease in 2021. There were slight increases each year for the older adolescent age groups, with a slight decline for persons 11-12 years of age.

In summary, vaccine orders and vaccine administration have decreased since the start of the pandemic, leaving some children unprotected from vaccine-preventable diseases. Based on surveys CDC has conducted, parental concerns about potential exposure to COVID-19 may be contributing to declines for making well-child visits when vaccines are usually administered. Concerted efforts are needed to help children get caught up on vaccines that they may have missed during the pandemic. In the coming months, a multifaceted approach will be needed from all stakeholders to ensure that children get back on track with routine vaccination. CDC has launched the “Let’s Play Catch-Up On Routine Vaccines” campaign[34] to help with this effort. Materials available to help promote routine vaccination include a toolkit for providers, social media messages, and other materials to help promote vaccination. There are some activities in which healthcare systems and healthcare providers can engage now, including encouraging members to identify and follow-up with families whose children have missed doses to schedule appointments; implement clinician prompts to remind clinicians to review patients’ vaccination status during an office visit so they can offer vaccines that are due or overdue; communicate directly to families about the importance of well-child visits and routine vaccinations; and let families know about precautions that are in place for safe delivery of in-person services.

Discussion Summary

Dr. Goldman (ACP) said he wanted to impress upon the internal medicine community to talk about catch-up vaccines. He gives all adult vaccines in his office and routinely asks his patients who are 18-19 years of age whether they have received a Gardasil® vaccine. Outreach through the internal medicine community offers another opportunity to catch-up those who have not been vaccinated for whatever reason in the pediatric setting. He emphasized the important of engaging all stakeholders.

[34] https://www.cdc.gov/vaccines/partners/childhood/stayingontrack.html

Dr. Daley found the ordering data to be sobering. This means that millions of individuals in this age group are unprotected. He asked whether this scope matches with IIS data in terms of the number of people who are estimated to have missed their opportunity for HPV vaccination.

Dr. Stokely indicated that CDC is looking more closely at the data received from the 13 IIS jurisdictions. There is not always a one-to-one correlation between coverage and ordering data. While some jurisdictions had lower orders, their coverage did not show as large a decrease as some other jurisdictions where the ordering impact was not as large. Further analyses will be needed to better understand the relationship between orders and coverage in terms. For instance, the amount of stock providers had on hand at the beginning of the pandemic may have impacted the amount they needed to order based on fewer children presenting to their office.

Dr. Poehling highlighted that 2 doses work great for those who are immunocompetent who begin at 15 years of age. However, those who are immunocompromised always need 3 doses of vaccine. In addition, there is a major advantage in starting at a younger age.

Impact of the US HPV Vaccination Program on HPV-Associated Outcomes

Julia Gargano, PhD (CDC/NCIRD) presented an update on the impact of the US HPV vaccination program on HPV-associated outcomes. Monitoring the impact of the HPV vaccination program in the US has been done using a variety of early, intermediate, and late outcomes. HPV prevalence has been monitored in several populations using data from the National Health and Nutrition Examination Survey (NHANES), women undergoing cervical cancer screening, and men who have sex with men (MSM). Anogenital warts have been monitored through claims data. Juvenile onset recurrent respiratory papillomatosis (JORRP) has been monitored through a network of pediatric otolaryngologists. Cervical precancers have been monitored through population-based surveillance and administrative data and state-based data. HPV-associated cancers have been monitored through state-based cancer registries.

CDC has collected genital specimens using population-based surveys through the NHANES since 2003 for females and since 2013 for males. HPV typing results are linked to demographic data, limited behavioral data, and self- or parent-reported HPV vaccination history. In the first 4 years after the vaccination program began, quadrivalent vaccine-type HPV prevalence was 56% lower in females 14 through 19 years of age than in the pre-vaccine era.[35] By 2015-2018, quadrivalent vaccine-type prevalence was 88% lower than the pre-vaccine era among females 14 through 19 years of age and 81% lower among females 20 through 24 years of age. No significant decrease was seen in the older age groups and non-vaccine-type prevalence did not change significantly. This suggests that the declines in vaccine-type prevalence were not due to lower HPV exposure.[36]

Vaccine impact also was estimated among vaccinated and unvaccinated sexually experienced females. In females 14 through 19 years of age, quadrivalent vaccine-type prevalence was 97% lower among vaccinated females in 2015-2018 compared to the pre-vaccine era and 87% lower among unvaccinated females. In persons 20 through 24 years of age, prevalence was 86% lower in the vaccinated group and 65% lower in the unvaccinated group. These data show strong direct impact of vaccination, as well as robust evidence of herd protection.[37] NHANES data also were used to evaluate vaccine impact by race and ethnicity, comparing quadrivalent

[35] Markowitz et al. J Infect Dis 2013
[36] Markowitz et al. J Infect Dis 2013; Oliver et al. J Infect Dis 2017; Rosenblum et al. MMWR 2021
[37] Rosenblum et al. *MMWR* 2022

vaccine-type prevalence in 2013-2016 to the pre-vaccine era. Among females 14 through 19 years of age, declines in vaccine-type prevalence were significant for non-Hispanic White, non-Hispanic Black and Mexican American female.[38]

The JORRP outcome is caused almost entirely by HPV type 6 and 11 and mainly from vertical transmission at the time of delivery. In 2008-2009, declines in US JORRP incidence had begun to occur. Those declines continued in every subsequent set of years. The data suggests that the number of children with JORRP has declined significantly in the years following HPV vaccine introduction for adolescents and young women in the US, and that these declines are most likely due to HPV vaccination.[39]

Data from population-based surveillance, administrative claims, and cancer registries have been used to evaluate vaccine impact on incidence of cervical pre-cancers in the US. Monitoring impact on pre-cancers is challenging due to changes in cervical cancer screening recommendations during this time period, including a major change in 2012. Cervical pre-cancers are only detected by screening, so it is preferable to use the number of screened women as the denominator in incidence calculations. All approaches have shown decreases in cervical pre-cancers in young women consistent with vaccine impact.

The HPV-IMPACT project is a 5-site population-based monitoring project that is collecting data on pre-cancers and screening. Rates of pre-cancers (CIN2+) among screened women decreased between 2008-2015 among persons 18 through 20 years of age and 21 through 24 years of age. Rates increased in screening among women in older age groups. Similar increases in this in this age group have been found in other studies and are thought to be attributable to longer screening intervals and/or increased sensitivity of new screening tests.[40]

In HPV-IMPACT, typing is performed on tissues from pre-cancerous lesions. In one analysis, typing data were used to estimate the number of CIN2+ cases caused by HPV 16 and 18, the high-risk types targeted by the quadrivalent vaccine. The estimated numbers of vaccine-type CIN2+ declined significantly, whereas the estimated number of CIN2+ not caused by HPV 16 and 18 remained approximately constant, showing that the vaccination program is the most likely cause of the observed declines in CIN2+ incidence. Finally, trends in invasive cervical cancer have been evaluated using data from US Cancer Statistics, which is a database of cancer registry data that covers 97.8% of the US population. An analysis by Mix et al, among persons 21 through 24 years of age, incidence of invasive squamous cell carcinoma (SCC) of the cervix has been in decline for many years due to the cervical cancer screening program. This analysis showed that starting in 2012, the slope of the trend became more pronounced. These data do not account for changes in cervical cancer screening that started in 2012, so it is difficult to know how much HPV vaccination contributed to this trend. Of note, there also was an inflection point in persons 15 through 20 years of age in 2011-2012, which is less likely to have been influenced by screening.[41]

In summary, data from impact monitoring projects has shown that prevalence of the quadrivalent HPV vaccine types has declined markedly among vaccinated and unvaccinated young females in the US. The declines in high-risk HPV types 16 and 18 have translated into declines in cervical pre-cancer incidence in young women. The declines in HPV type 6 and 11 have resulted in a reduced incidence of JORP. Early impact on invasive cancer in young women

[38] McClung et al. *J Adolesc Health* 2019
[39] Meites et al, Clin Infect Dis 2021
[40] Gargano et al. Clin Infect Dis 2019; https://www.cdc.gov/ncird/surveillance/hpvimpact/index.html
[41] Mix et al, Cancer Epidemiol Biomarks Prev 2020

might be occurring. Monitoring will continue to assess the impact of vaccination in females and males, and the impact of 9vHPV vaccine.

1-Dose HPV Vaccination: Overview of Current Evidence

Lauri E. Markowitz, MD (CDC/NCIRD) presented an update on data regarding 1-dose HPV vaccination and a review of the recently revised HPV vaccination recommendations of WHO's SAGE, noting that this was not meant to be a comprehensive review or an assessment of the data. Instead, it was meant to be an information only update. Currently, there is no active ACIP HPV Vaccines WG. This presentation included background information on data that were required for initial licensure of HPV vaccines in 2006 and the change to a 2-dose schedule in 2016; a summary of the 1-dose vaccination evidence; and a summary of the SAGE HPV vaccination recommendations from the April 2022 meeting.

Efficacy and immunogenicity data that were submitted to FDA for initial licensure of HPV vaccines were from trials conducted with a 3-dose schedule, with the second and third doses administered 1-2 and 6 months after the first dose. These data were from randomized control efficacy trials in women 15 through 26 years of age, The trial endpoints were cervical pre-cancer lesions.[42] Efficacy against vaccine-type endpoints was over 96% in per protocol analyses, which included women who were naive to the vaccine types. Seroconversion 1 month after the last dose was close to 100%. There also were immunobridging trials in persons 9 through 15 years of age as it was not feasible to conduct efficacy studies in this age group and licensure in individuals 9 through 15 years of age was based on non-inferior antibody response compared to women in the age group of the efficacy trials.

Interest in a 2-dose schedule was stimulated by a post-hoc analysis of a 3-dose RCT in which not all individuals completed the schedule. In these analyses, efficacy is against HPV16/18 infection that was similar after 3, 2, and 1 doses. Following publication of these data, immunobridging trials were conducted to evaluate 2 doses given an interval of 6 or 12 months in persons 9 through 14 years of age compared with 3 doses in women 15 through 23 years of age from the efficacy trials. Seroconversion and GMTs were non-inferior in the 2-dose groups compared with those in the 3-dose group.[43]

Looking at some of the results from a 9vHPV 2-dose immunobridging trial, GMTs were non-inferior at 1-month post-last dose in girls 9 through 14 years of age who received 2 at 0-6 months compared with young women 16 through 26 years of age who received 3-doses.[44] In terms of the immunobridging data from a 4vHPV 2- versus 3-dose immunobridging trial, there were 3 groups: 2 doses (0,6 months) in 9–13-year-olds; 3 doses (0,2,6 months) in 9–13-year-olds; and 3 doses (0,2,6 months) in 16–26-year-olds. These data demonstrate titers through 36 months in which there is non-inferiority of the antibody titers in the 2-dose compared to the 3-dose group, similar antibody kinetics in all 3 groups, a decline 1 month after the last dose, a plateau, and stable antibodies regardless of the number of doses.[45]

The 9vHPV manufacturer submitted a supplemental Biologics License Application (sBLA) for a 2-dose series for individuals 9 through 14 years of age in 2016. FDA approved this application in October 2016. ACIP recommended a 2-dose series for persons starting vaccination at 9

[42] Future II Study Group, NEJM 2007; Garland S, et al. NEJM 2007; Paavonen J, et al. Lancet 2007
[43] Kreimer AR, Rodriguez AC, Hildesheim A, et al. Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine. *J Natl Cancer Inst*. 2011;103(19):1444-1451. doi:10.1093/jnci/djr319
[44] Iversen O-E, et al. JAMA 2016 and https://www.fda.gov/media/90064/download
[45] Adapted from: Dobson SR, et al. JAMA 2013

through 14 years of age, while 3 doses are still recommended for persons with immunocompromising conditions and for persons starting the series at older ages.

Moving to the evidence for 1-dose vaccination, the same studies that stimulated interest in 2-dose schedules led to interest in 1-dose vaccination. However, immunobridging studies were not possible because 1 dose results in lower antibody titers than 2 or 3 doses. The basis of protection after vaccination is thought to be neutralizing antibody. However, there is no minimum antibody threshold for protection. Very low levels of antibody are thought to be protective against HPV. Levels lower than those detectable by available assays and efficacy trials were felt to be needed to evaluate 1-dose vaccination. There is an efficacy trial being conducted by the US National Cancer Institute (NCI). The objectives of this large randomized double-blind trial are to: 1) evaluate the non-inferiority of 1 dose compared with 2 doses of bivalent and 9-valent vaccines for prevention of 16/18 infections; and 2) evaluate 1 dose compared to unvaccinated. Bivalent and 9-valent vaccines are being evaluated separately among girls 12 through 16 years of age in Costa Rica who are being followed for up to 5 years. The study also includes surveys of unvaccinated women to allow estimates of vaccine efficacy by comparing persistent infection in these women with the vaccinated trial participants. No interim analysis is planned in this ongoing trial and results should be available in 2024.[46]

Meanwhile, interest in 1 dose vaccination has increased for several reasons. A global HPV vaccine supply and demand imbalance was recognized,[47] and this limited HPV vaccine introductions in some countries. While more countries have introduced vaccines, global vaccination coverage continues to be low.[48] In 2020, it was estimated that only 13% of girls worldwide were fully vaccinated by age 15. There continued to be challenges implementing HPV vaccination programs. Additional studies were initiated to evaluate 1-dose vaccination and studies provided the initial data on 1 dose had further follow-up data shown in this table:

Trial/country	Evidence	Vaccine	Age (yrs) at vaccination	Description
CVT Costa Rica	Efficacy/ Immunogenicity	2vHPV	18–25	Post-hoc analyses: participants randomized to 3 doses or control, but analyzed as 1-, 2-, 3-dose groups
India IARC India	Efficacy/ Immunogenicity	4vHPV	10–18	Post-hoc analyses: participants randomized to 2 or 3 doses but analyzed as 1-, 2-, 3-dose groups
KEN SHE Kenya	Efficacy	2vHPV 9vHPV	15–20	Randomized trial: 1 dose of 2vHPV, 9vHPV, meningococcal vaccine
DoRIS Tanzania	Immunogenicity	2vHPV 9vHPV	9–14	Randomized trial: 1-, 2-, 3-dose groups
Thailand Impact Thailand	Impact/ effectiveness	2vHPV	grade 8	Students in one province received 1 dose; in another 2 doses

In the first 2 trials, Costa Rica and India, participants were not randomized to a 1-dose group but there was 1-dose data from post-hoc analyses. The Costa Rica Vaccine Trial (CVT) was the trial that originally raised interest in 2 and 1 dose schedules. This study now has data through 11 years after vaccination from a post-hoc analysis of a RCT. A control group of unvaccinated women was recruited after the blinded phase to allow for continued efficacy determination. Prevention of prevalent HPV 16/18 infection was similar in all dose groups. Antibody also was measured through 11 years of follow-up in this study. While the antibody titers were lower in the

[46] Porras, et al. Vaccine 2022
[47] WHO. Global Market Study, HPV. who-hpv-vaccine-global-market-study-april-2022.pdf
[48] Bruni L, et al. Preventive Medicine 2019

1-dose group than the 2 or 3 dose groups, titers were relatively stable in all dose groups to 11 years after vaccination and at least 10-fold higher than in the unvaccinated group.[49]

The India IARC trial was designed as a cluster randomized trial to compare 2 versus 3 doses of 4vHPV vaccine and was initiated in 2009. Less than a year after vaccination, HPV vaccinations were stopped by the Indian government due to issues unrelated to this trial. However, much of the enrollment randomization and initial vaccination had occurred. Although not all participants could complete the schedule to which they were randomized, the study has been analyzed as an observational cohort with 4r different vaccination schedules, including a 1-dose group.[50] Participants were followed yearly, and data are now available through 10 years after vaccination. Cervical specimens were collected 18 months after marriage or 6 months after first childbirth to assess HPV infection. Unvaccinated women were age-matched to the married vaccinated participants and recruited as controls. VE against persistent 16/18 infections was analyzed adjusting for the imbalance and distribution of potential confounders, and efficacy against persistent 16/18 infection was similar in all dose groups.[51]

Now moving to the more recently conducted trials in which participants were randomized to a 1-dose group, the KENya Single-dose HPV-vaccine Efficacy (KEN SHE) Study is a randomized, Double-blind controlled trial conducted in Kenya published last year. Young women aged 15 through 20 years of age were randomized to 1 dose of 9vHPV, 1 dose of 2vHPV, or 1 dose of meningococcal vaccine (MCV). A total of 1458 women were evaluated for efficacy at month 18 in the modified intent-to-treat cohort who comprise participants who tested HPV antibody-negative at enrollment and DNA-negative at enrollment in month 3. There were 38 incident persistent infections detected, one each among participants in the 2vHPV and 9vHPV groups and 36 in the MVC. VE was 97.5% for both HPV vaccines. In the efficacy data against all 7 oncogenic types targeted by the 9vHPV vaccine, there were 29 infections in the control group and 4 in the 9vHPV group for efficacy of 88.9%.[52]

The Dose Reduction Immunobridging & Safety Study (DoRIS) in Tanzania is a randomized trial of 1, 2, and 3 dose of 2vHPV or 9vHPV vaccine. The study included 930 Tanzanian girls aged 9 through 14 years. The objectives were to demonstrate non-inferiority of HPV 16/18 antibody after 1 dose compared with 2 or 3 doses of the same vaccine at Month 24 and to demonstrate non-inferiority of HPV 16/18 GMCs comparing 1 dose in this study with 1 dose in studies that evaluated efficacy. For HPV-16, non-inferiority criteria were met for 1 dose compared to 2 or 3 doses for both vaccines. For HPV-18 seropositivity was greater than 97.8% in all dose groups, but non-inferiority criteria were not met for 1 compared with 2 or 3 doses. GMCs declined for 1 and 2 doses after a peak of 1 month. The levels plateaued and were similar at all time points. The GMCs for 1 dose were lower than for 2 or 3 doses; however, there was a stable plateau as has been seen in other HPV vaccine studies. This study also conducted a variety of other evaluations. One analysis looked at avidity, which is a measure of the strength of binding of antibody to antigen. This was similar regardless of number of doses received or the vaccine. Immunobridging analyses showed that seropositivity and GMCs were non-inferior in the 1-dose groups in this study compared with those in the 1 dose groups in the trials where efficacy was observed.[53]

[49] Kreimer AR, et al. J Natl Cancer Inst 2020
[50] Sankaranarayanan R, et al. Lancet Oncol 2016
[51] Basu P, et al. Lancet Oncology 2021, with updated data
[52] Barnabas R, et al. DOI 10.21203/rs.3.rs-1090565/v1; NEJM Evidence 2022
[53] Watson-Jones D, et al. http://dx.doi.org/10.2139/ssrn.4055429

The Thailand impact study is an observational study of 1 dose and 2 doses of 2vHPV vaccine given to Grade 8 girls <15 years of age in 2 similar provinces in Thailand. The primary objectives are to demonstrate HPV VE of 1 dose and 2 doses at Years 2 and 4 post-vaccination. Effectiveness was measured by comparing vaccine-type prevalence in Years 2 and 4 versus unvaccinated same grade girls in a baseline survey. There also will be an evaluation to determine if the HPV VE of 1 dose is non-inferior to 2 doses, which will be done at Year 4. The results for Year two are available and found that crude VE against HPV 16/18 was 83.3% in the 1 dose province and 93.6% in the 2-dose province. Of note, there were some differences between the provinces, with more girls in the 1-dose province being sexually active at baseline. In both provinces, there were differences in risk behavior in the Year 2 survey compared with the baseline survey. There were several methods used to adjust for exposure risks, none of which these resulted in important changes in the effectiveness estimates.

Extensive modeling has been conducted to evaluate the potential impact of 1 dose vaccination under assumptions that efficacy and duration are less than for 2 doses, although most of the clinical studies have not shown this. Dr. Markowitz shared some of the modeling findings. Compared to no vaccination, 1-dose vaccination yields substantial health benefits and is a good value for the money even if the efficacy is lower (80%-85% vs 100%) and duration of protection is shorter (10-20 years vs lifelong) than with 2 doses. The impact and cost-effectiveness of adding a second dose is driven by duration of protection and possibly the ability to achieve higher coverage or expand catch-up with 1 dose versus 2 or 3 doses. The projected impact and cost-effectiveness of 1 versus 2 doses using a comparative modeling approach has been conducted by 3 modeling groups with extensive experience with HPV vaccine modeling.[54]

WHO's SAGE reviewed these and other data in April 2022 and made revised recommendations, which were published on June 17, 2022.[55] This report states that:

> "On the basis of recent data on efficacy and effectiveness, SAGE endorsed the optimization of the HPV vaccine schedules. For 9-14-year-olds, national immunization programmes can use either a single-dose or a 2-dose vaccination schedule with an interval between doses at least 6 months."
>
> "This off-label option for routine and multi-age cohort (MAC) catch-up vaccination is recommended from a public health perspective, on the basis of providing comparable levels of individual protection while being more cost-effective and efficient (fewer doses per cancer case prevented), providing more programme flexibility, and enabling the expansion of the MACs targeted."

[54] Jit M, et al. Fewer than three doses of HPV vaccine. Lancet Oncol 2015; Burger E, et al. Health and economic benefits of single-dose HPV vaccination in a GAVI-eligible country. Vaccine 2018; Prem K, et al. Global impact and cost-effectiveness of one-dose versus two-dose human papillomavirus vaccination schedules: a comparative modelling analysis. medRxiv. 2021:2021.02.08.21251186. https://terrance.who.int/mediacentre/data/sage/SAGE_Slidedeck_Apr2022.pdf

[55] Meeting of the Strategic Advisory Group of Experts on Immunization, April 2022: conclusions and recommendations https://apps.who.int/iris/bitstream/handle/10665/356579/WER9724-eng-fre.pdf

This table shows 2017 WHO recommendations, which are still considered the current recommendations until publication of the revised position statement and the 2022 Sage recommendations:

2017 WHO recommendations (current)[1]			2022 SAGE recommendations[2]
Primary age group		Girls aged 9-14 years	Girls aged 9-14 years
Vaccination Schedule	**9-14 years**	2-dose schedule	Either a 1-dose* or a 2-dose schedule can be used
	15-20 years	3-dose schedule	Either a 1-dose* or a 2-dose schedule can be used
	≧21 years	3-dose schedule	2-dose schedule can be used
	Immuno-compromised	3-dose schedule	at least 2 doses but ideally 3 doses, if programmatically feasible

The primary group recommended for that vaccination programs is unchanged (e.g., girls aged 9-14 years). Either a 1-dose or 2-dose schedule can be used for individuals 9-14 or 15-20 years of age. SAGE recommended that a 2-dose schedule can be used for persons ≥21 years of age. At least 2 doses, but ideally 3 doses if feasible, are recommended for persons who are immunocompromised. The recommendations for the number of doses for boys and men remained the same.

There are at least 3 additional studies shown in the table below that are anticipated to provide additional data on 1-dose HPV vaccination:

Trial/country	Evidence	Vaccine	Age (yrs) at vaccination	Description
HOPE South Africa	Impact/ Effectiveness	2vHPV	15–16	Students in one district received 1 dose as catch-up in grade 10. Baseline and post-vaccination cross sectional prevalence surveys; includes WLWH
HANDS The Gambia	Immunogenicity	9vHPV	4–8, 9–14 15–26	Randomized to 1 or 2 doses 3 doses in 15–26-year-olds
ESCUDDO Costa Rica	Efficacy/ Immunogenicity	2vHPV 9vHPV	12–16	Randomized trial: 1 or 2 doses of 2vHPV or 9vHPV

In summary, HPV vaccines were first studied and licensed in a 3-dose schedule in persons aged 9 through 26 years and later in a 2-dose schedule in persons aged 9 through 14 years. There are now data on 1-dose vaccination, including efficacy data from an RCT with 18-month follow-up. Long-term follows from other studies suggest good duration of protection with 1 dose. SAGE recommends 1 or 2 doses in the primary target age groups. WHO will consider and revise recommendations later this year. There is no regulatory approval for 1-dose vaccination in any age group or for 2-dose vaccination in any age group older than 14 years of age. The HPV team in the Division of Viral Diseases of NCIRD will continue to provide updates on these data and will discuss them with ACIP as requested and will collaborate with and provide assistance to international partners.

Discussion Summary

Referring to Slide 15, Dr. Daley said his crude understanding of antibody titers was that they typically would decline over time at some rate. In the context of all the other vaccine work that the ACIP does, including COVID-19 vaccination, he asked whether something is different about the HPV vaccine being VLPs or if there was something else that explained why there is not a declining antibody titer over time.

Dr. Markowitz indicated that there has been a lot of discussion about this. She summarized some data from a talk that Professor Stanley from Cambridge recently gave. The feeling right now is that it is that the VLP size and geometry make this highly efficacious and immunogenic. The size is optimal for entry into the lymphatics and transport to the B-cell follicles. This particle size is readily taken up by dendritic cells. There has been a lot of focus on the VLP because it is a multivalent protein antigen with 360 copies of the L1 proteins that are assembled in a very dense, repetitive array, which is felt to be very important for the immunogenicity of this vaccine. It is fascinating and if ACIP is interested, a session could be arranged for discussion about the current thinking regarding why this vaccine is so highly immunogenic and effective.

Dr. Daley asked whether the size of the VLPs is related to the size of the virus in terms of the outer membrane of an HPV virus, or if it is independent of that and is just a really efficient way to present antigen to the immune system that does not relate to the size of the virus it is trying to mimic.

Dr. Markowitz said she thinks it is related to that because the VLP is like an authentic virus and looks like the HPV virus.

Miss Bahta recalled the presentations in 2006 and beyond and thinking long-term outcomes were so far away, yet they are now hearing about long-term outcomes that are incredibly encouraging. However, many adolescents are still missing the opportunity for protection. Related to Dr. Gargano's presentation, on Slide 8 there was a 74% lower prevalence in non-Hispanic Black compared to 86% in non-Hispanic White females 14–19 years of age from 2013–2016 compared to the pre-vaccine era. She wondered why that not lower if the vaccination rates were higher, and whether perhaps there are some HPV types that are not being covered by the vaccine.

Dr. Gargano said she did not think it was related to the types, because the McClung study was looking at the vaccine targeted types and the prevalence of those types. While she did not have the data to give a definitive answer on why the percent decrease was somewhat lower in that particular group, it may have to do with a discrepancy in the age of vaccination and age at onset of sexual activity. Those are not captured in the data.

Dr. Sanchez stressed how remarkably effective this vaccine has been, particularly in terms of the decreases in cases of JORRP. He was somewhat hesitant in terms of recommending a 1-dose schedule given the progress that has been made and even though many people are still unvaccinated. He would want more long-term follow-up information before making a recommendation about giving 1 or 2 doses. In addition, he thought they should be firmer about recommending 1 dose or 2 doses. He did not like saying either one could be done.

Dr. Poehling emphasized how wonderful it was to see the impact that the HPV vaccine has had throughout the world. She asked whether any manufacturers would be submitting a 1-dose request to the FDA.

Dr. Kimberlin (AAP Redbook) asked whether there are any other vaccine-preventable diseases for which VLP vaccines are in development.

Dr. Fink (FDA) emphasized that the FDA is not allowed to disclose non-public information about vaccine developers who may have products under development or under the Investigational New Drug (IND) program. However, there are examples of VLP platform vaccines that have been in the public domain, including a COVID-19 vaccine manufactured by Medicago, a Canadian manufacturer that uses a VLP platform.

Dr. Long observed that pharmaceuticals have focused on immediate antibody responses at 1 or 2 months and want to present that, and that has been thought of as the "Holy Grail." In fact, that is probably not even close. It is a cellular response and is about how the first exposure alters the immune response and makes memory cells that result in continuous stimulation of antibody responses. In this case, it looked as if the second and the third dose achieved spurious levels that did not really matter. The graph showing what happened after 1 dose that did not decrease as abruptly and suggested that overstimulating when it is not needed can get an antibody response for a short period of time and could be good for the short-run, but says nothing about the long-run. The short-term responses for the Coronavirus vaccines seems to be spurious in that they are very high, but they go away very fast. Here, 2 and 2 doses are spurious because they are very high, but they do not mean anything. She wished they could get to more sophisticated requirements for antibody tests further down the line, not just the one after the last dose of vaccine, in order to have more sophisticated ways to look at immunization responses that are not dependent on just antibodies. She asked whether the FDA could say whether they were thinking about any new paradigms of how to assess vaccine responses, and what the optimal way would be to determine an adequate versus an inadequate response.

Doran Fink (FDA) responded that clearly, at least with certain vaccines, antibodies are not the whole story. To explain the mechanism of protection, antibodies historically have been the component of the immune response that is most amenable to evaluation including for bridging analyses that require the use of validated assays and high throughput assays to assess large numbers of samples. Clearly, there is interest in exploring how other components of the immune response, such as cell-mediated immunity (CMI), can be leveraged to inform regulatory decisions and understanding of VE. At this point, they are not able to use CMI response assays in the same way that they have come to rely on antibody-based assays. To the extent that the field can move forward and develop the assays and the science, FDA is happy to be involved in the discussion.

PUBLIC COMMENTS JUNE 22, 2022

Overview

The floor was opened for public comment on June 22, 2022 at 3:00 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 No. CDC-2022-0062. Visit http://www.regulations.gov for access to the docket or to submit comments or read background documents and comments received.

Public Comments

Karyne Jones
President and Chief Executive Officer
National Caucus and Center on Black Aging

My name is Karyne Jones. I am the President and Chief Executive Officer (CEO) of the National Caucus and Center on Black Aging (NCBA). We appreciate this committee's ongoing commitment to ensuring access to a wide variety of vaccines, especially in the wake of the ongoing COVID-19 pandemic. However, I must use my time today to express my disappointment that this committee chose once again not to include clarification of the needed use of new adult vaccines for pneumonia. While these vaccines were approved last June by the FDA, the guidelines which were released by the CDC in January of this year did not provide clear guidance on whether older adults who had already received the pneumonia vaccine were eligible for the new and improved vaccines. This leaves two-thirds of Americans over the age of 65 uncertain of whether they too can have access to these new protections. As we continue to face respiratory threats with COVID-19 and the upcoming flu and pneumonia season this fall, why wouldn't we also take up the important step to ensure such a vulnerable population has access to the best protections available? While we certainly support the focus on ensuring that the newest vaccines are available for children, we can't help but wonder why this can't be done at the same time as offering clarification for older adults as well. I have also previously shared comments with this committee on the importance of lowering the age-based recommendation for adult vaccines to those aged 50 and over. In ACIP's 2021 meeting, data was presented showing that this change would increase vaccinations among those living with risk of serious illness and therefore would likely to help address disparities and the uptake in these vaccines among minority populations, as well as provide cost-savings for the system. This was incredibly encouraging and yet, we've not heard any further discussion on this proposal. Given that black and brown communities often experience the onset of chronic illnesses earlier than 65 due to environmental factors beyond their control and the effect of lifetime of inequitable care, providing protection for these individuals earlier in life will not only offer earlier intervention for those at risk, but provide critical protections before immune system efficacy wanes as part of normal aging. We strongly encourage this committee to review any remaining data needed and provide clear guidance on the use of the pneumonia vaccines to ensure they are available to a full population of vulnerable Americans before the upcoming flu and pneumonia season. We also welcome the opportunity to continue discussions around the benefits of lowering the age-based recommendations to help close the disparity gaps and reduce the number of preventable deaths in this country. Thank you very much.

Kevin Tuttle
Public Relations Director
Schara Family

Hi. I'm Kevin Tuttle, the Public Relations Director for the Schara Family. I'll get to their story in a moment. No matter what I say to the ACIP board today, they'll ignore it like they've ignored grieving parents over vaccine injury for decades. We know this board has no conscience, but I'm not trying to reach them. I'm trying to reach those of you who know that something is up but can't figure it out. It's called genocide. Why have myocarditis, blood clots, Bell's palsy, infertility, and Gavin Newsom's favorite, GBS, skyrocketed since jabs got into arms warp speed? What about death? All-cause mortality was not higher in 2020 than 2019. Isn't that odd for such a deadly pandemic? But it's certainly higher since the COVID jabs came out. Must be those darn

anti-vaxxers. Why are the jabbed keeling over? Medical professionals are baffled, but they created a term, Sudden Adult Death Syndrome (SADS). This is history repeating itself. The '86 National Childhood Vaccine Injury Act (NCVIA) created a system that denies the link between vaccines and harm. When vaccines and doses increased after that act, babies started dying and they called it sudden infant death syndrome (SIDS). See how that works? "Died suddenly" is all the rage these days amongst the jabbed, followed closely by "half my face doesn't work." This criminal board won't address it and put an end to these toxic jabs because that would mean they're culpable for the deaths occurring. The AAP just announced updated infant sleep recommendations right after the jab was approved. Is that odd to anyone? This means they will blame parents for their child's death rather than look at the jab having caused the death. SIDS is about to explode, and this board needs to be held accountable. This is genocide led by medical institutions and government. They did the same thing in Nazi Germany. Doctors worked for the regime. They would order dangerous medicines be given to the disabled, the useless feeders, and nurses would administer the deadly drugs. It was a government-planned, government-supported mass extermination of people. They could not have done it then without the support of diabolical physicians, scientists, nurses and media just like now. That's why they tried to silence non-conformists like Drs. Nicola, Corrie, Paul, Thomas—something Josef Goebbels would have done in 1939. What was good for the state was more important than what was good for the individual, just like now. Nothing has changed despite the Nuremberg Code. Take Grace Schara for example. Within a 29-minute window, she was given Precedex, Lorazepam, and morphine without reason. She was 19, but Grace had Down's Syndrome, which was apparently enough for St. Elizabeth's Ascension Hospital in Appleton, Wisconsin to designate her a useless feeder and kill her off through health care. Did Dr. Gavin Shokar know a max dose of Precedex could take Grace out? Is that why he submitted a DNR order on her without family consent eight minutes after the sedative was given? This is the type of care one should now expect in hospitals. Avoid them at all costs. Let history be your guide. "I was just doing my job," didn't fly in the Nuremberg trial. It won't fly for this board or those injecting people with the death shot at the next trial. Stop the genocide. Say "no" to all jabs, people. Thank you.

Milena Berhane, MPH
Health Policy Associated
National Consumers League

Thank you, Dr. Lee. My name is Milena Berhane and today I'm representing the National Consumers League (NCL). Since NCL's founding in 1899 by social reformer Florence Kelley, we have advocated for the critical role that immunizations play in the preservation and improvement of public health. We extend our gratitude to this committee for the opportunity to present public comments. According to the National Foundation for Infectious Diseases, pneumococcal disease is a leading cause of serious illness throughout the world. In the US, nearly 50,000 people die each year from pneumonia, and the death rate is even higher in those ages 65 years of age and older. Vaccination is a critical public health measure for preventing disease, hospitalizations, and deaths, so it is critical that access to the pneumococcal vaccine is expanded. We are concerned about the lack of clarity surrounding the current ACIP recommendations regarding the pneumococcal vaccine for adults ages 65 years of age and older. It is critical that the recommendations for this age group is clear so that patients and providers are better able to understand who should receive which vaccine and when. The pneumococcal vaccine will continue to be a safe and effective measure in protecting Americans from disease, and it is imperative that older adults are able to receive them. Having clear recommendations for adults 65 years of age and older is also critical in addressing health equity issues, especially among older Black and Latinx populations that already face issues and lack access to health care. Pneumococcal vaccine uptake needs to increase in these populations, so

that the currently existing health disparities are not further exacerbated. Therefore, in order to promote health equity among all older adults and increase vaccination rates, it is critical that clear recommendations are provided for this age group. The National Consumers League recognizes the extreme importance of immunizations in protecting the health and safety of all Americans, and we'll continue with efforts to increase vaccine confidence and uptake across lifespan. We look forward to the upcoming recommendations by this committee regarding the pneumococcal vaccine for older adults. Thank you.

Vangelis Russos
Individual

There is no long-term safety data for COVID-19 vaccinations in young children, so vaccinating them is an experiment, and this experiment is not looking good. We already know that COVID-vaccinated children 12 to 17 years old have a 5-fold increase in myocarditis. Those are not my words. Those are the words of Dr. Peter Marks from the FDA. Currently, about 1.3 million injuries have been reported to VAERS for all age groups. This includes anaphylactic shock, allergic reactions, blood clotting and other bleeding disorders, myocarditis, pericarditis, stroke, heart attacks, tinnitus, death, and more. Some children will die, and others will be permanently injured from these shots. Why should children be forced to take this risk when they have a 99.995% recovery rate, which means that almost zero kids have died from COVID-19? In February 2022, the CDC said over 75% of children already have partial or full immunity to COVID. COVID vaccines do not stop transmission or infection. There is no statistically valid evidence that they prevent severe disease or death in children. The current COVID vaccines were formulated based on the original Wuhan strain, and were not tested for benefit against current variants in clinical trials. These vaccines are not science-based medicine. They are neither safe or effective. In fact, Pfizer's clinical trials for 2- to 4-year-olds failed to meet FDA requirements to show 50% efficacy. The vaccine failed the FDA's established criteria in its clinical trials. This is clearly not about science and facts, so what is it about? If we don't stick to the facts in science, this will lead the public into thinking something more nefarious is going on. Is it? COVID is not a public health threat. You know what the real health threat is? People in the position to protect the public that do not, so I want to ask if any of you have the courage to be real scientists. You actually have a chance to be true heroes. The facts clearly show that this vaccine will do more damage than it will prevent, so why are you doing it? So, you actually have a chance to be true heroes. So, now is the time to be remembered in history as a hero, or you could be remembered as a coward. The choice is yours. Thank you.

Itzia Irineo
Individual

Hi. Good afternoon. Thank you. My comment is going to be very quick. Why are we giving this injection to especially kids that are 5 years and under, when clearly their immune system and brains isn't fully developed? That's my question. And number two is most vaccines takes up to 10 years to get approved by the FDA. And why are we giving this injection still when it's under EUA? And that's all.

Robert Blancato
Executive Director
National Association of Nutrition and Aging Services Program

Members of the committee, my name is Bob Blancato. I'm Executive Director of the National Association of Nutrition and Aging Services Program (NANASP). NANASP has appreciated the opportunity to submit an oral comment. As I have done in my prior testimony, I start by commending ACIP for your hard and dedicated work throughout this pandemic. I join my colleague Karyne Jones and offer my comment to specifically register our deep disappointment in the failure of this committee to include any discussion or action on clarifying current CDC guidance on older adults having access to new and improved pneumococcal vaccines on the agenda, including all those over 50. NANASP was joined by several other national aging patients and healthcare organizations in petitioning ACIP to include this discussion on the June agenda. In fact, we also specifically wrote to four ACIP members, all of whom expressed some sympathy with our request. At the heart of the matter is that under the current guidance, only those older adults who have never received a pneumococcal vaccine are eligible to receive a new vaccine. The rationale as provided in an email from Melissa Wharton was that, "The greatest benefit from the new pneumococcal vaccines now will be in adults who have not yet received pneumococcal vaccines." Overlooked by this rationale is the 67% of older adults who have already received a pneumococcal vaccine who have no access to the new vaccine. Also overlooked is how long it may have been since some of these older adults received their first vaccine. And given that we know the strength of the immune system wanes as individuals age, ensuring access to improved versions of the vaccine which protect against more strains of disease is a critical and greater level of protection that we should not be denying older Americans. We should never forget that older adults had a disproportionately higher death rate from pneumococcal pneumonia than other groups. Their vulnerability is genuine. Our main point is that CDC should consider the benefit that access to these new vaccines for all older adults would have. Our nation's health care system can "walk and chew gum at the same time." It is possible to both vaccinate older adults who have already received vaccines and those who have not. Older adults who were previously vaccinated should not be penalized for having done the right thing already. We implore members of ACIP to clarify this guidance by recommending these new and improved pneumococcal vaccines be made available to all older adults previously vaccinated or not. That is the most equitable approach. We thank the committee for considering our comments.

THURSDAY: JUNE 23, 2022

WELCOME & INTRODUCTIONS

Call to Order/Roll Call

Dr. Grace Lee (ACIP Chair) called to order and presided over the second day of the June 22-23, 2022 ACIP meeting. She conducted a roll call, which established that a quorum was present. A list of Members, *Ex Officios*, and Liaison Representatives is included in the appendixes at the end of this summary document. The following COIs were declared:

- ❑ Dr. Chen indicated that his employing institution, the University of Maryland, received a grant from Emergent BioSolutions that supported work he conducted to develop a shigella vaccine. This relationship with Emergent BioSolutions ended about 6 months ago in December 2021. Given that vaccines in development by Emergent BioSolutions may be discussed during the day, although there would not be any related votes and it did not seem to be an actual COI, he mentioned it as a potential perceived conflict.

AGENCY UPDATES

Centers for Disease Control and Prevention

Dr. Romero began by saying how honored he was to be back with ACIP as the new Director of the CDC's National Center for Immunizations and Respiratory Diseases (NCIRD). He reported that in early May, Dr. Georgina Peacock accepted the permanent position as Director of the NCIRD Immunization Services Division (ISD). Dr. Peacock joined the team almost 10 months ago serving as the Acting ISD Director. She brought valuable and relevant experience, most recently from her leadership roles in the COVID-19 Response Vaccine Task Force, the Georgia Department of Public Health (DPH), and the CDC's Division of Human Development and Disability (DHDD) within the National Center for Birth Defects and Developmental Disorders (NCBDDD). NCIRD is thrilled to have Dr. Peacock as part of its leadership team. She will apply her wide-ranging expertise and experience in implementing population health programs to face challenges and reimagining the pillars of preventive healthcare and pandemic response, the domestic immunization portfolio, and emergency capability.

Dr. Romero thanked everyone who worked on the important issues and votes the previous day. Regularly scheduled ACIP meetings are essential to the work CDC must do to revitalize and prioritize routine immunization for all ages. Despite signs that the pandemic has clearly disrupted childhood immunizations, routine vaccine coverage remains high, and the agency looks forward to working with the broader public health community to recover ground that was lost during the pandemic. This work includes gearing up for the upcoming influenza season. The US is well-positioned with vaccines that can protect people from influenza's most serious consequences. The preferential recommendation vote will continue to help make certain that older adults receive the influenza vaccines that best protect them. It also may assist in efforts to address health disparities by making these vaccines more available to racial and ethnic minority groups. CDC looks forward to working with all of its partners on the implementation challenges and considerations in removing these disparities as quickly as possible.

In terms of outbreaks, meningococcal disease is a major issue in Florida at this time. There is an ongoing deadly meningococcal disease outbreak in Florida spreading primarily among gay and bisexual men. It is one of the worst outbreaks of meningococcal disease among gay and bisexual people in the history of the US. At least 24 cases and 6 deaths have been reported among gay and bisexual men. CDC currently is recommending that gay, bisexual, and other men who have sex with men (MSM) get a MenACWY vaccine if they live in Florida or talk with their healthcare provider about getting vaccinated if they are traveling to Florida. CDC also is emphasizing the importance of routine MenACWY vaccination for individuals with Human Immunodeficiency Virus (HIV). With regard to monkeypox, the CDC continues to track multiple cases of monkeypox that have been reported in several countries that do not normally report monkeypox—including the US. The agency also is closely watching the World Health Organization (WHO) International Health Regulation (IHR) Emergency Committee meeting through the day to determine whether the multi-country monkeypox outbreak constitutes a public health emergency of international concern (PHEIC). The CDC will provide frequent updates as more is learned.

Centers for Medicare and Medicaid

Ms. Hance reported that during the February ACIP meeting, she mentioned that the Center for Medicare and Medicaid Services (CMS) has established a policy of covering stand-alone vaccine counseling. Guidance was issued on that on May 12, 2022 and CMS announced the new stand-alone vaccine counseling program on June 8, 2022. CMS continues to provide updated information around COVID-19 vaccines after decisions are made by the FDA and CDC. They issued a listserv announcement on June 22, 2022 regarding a decision over the weekend to expand the vaccines to the youngest children. They will continue to update toolkits, websites, and all other materials that CMS releases whenever those decisions are made to keep them current.

Food and Drug Administration

Dr. Fink presented the Food and Drug Administration (FDA) update, reporting that on Tuesday, June 28, 2022, the FDA will convene its Vaccines and Related Biological Products Advisory Committee (VRBPAC) to discuss potential updates to the strain composition of COVID-19 vaccines for use in the US. Available data continue to support that current vaccines, which are based on the ancestral Wuhan strain of SARS-CoV-2, continue to offer protection against more severe COVID-19, especially when booster doses are administered as part of the vaccination regimen. However, circulating variants of SARS-CoV-2 are becoming increasingly antigenically distinct from the vaccine. There is an opportunity ahead of the fall and winter months when there is expected to be the potential for additional surges and the potential for other emerging variants, to improve the protection afforded by vaccines by bringing their antigenic components more in line with the variants that are circulating and may emerge in the future.

In terms of the 2 ACIP votes the previous day on the recently approved Priorix™ MMR vaccine and VAXNEUVANCE™ 15-valent pneumococcal vaccine was approved for use in pediatric populations, these approvals were the result of a tremendous amount of work by the FDA review staff—especially considering the complexity of the applications that both included multiple studies involving many thousands of study participants and the level of review resources that the FDA currently has at its disposal given other competing priorities. The fact that the FDA was able to get these approvals completed within the statutory timelines speaks to the tremendous dedication and sacrifice that FDA’s review staff continue to make during these times.

Health Resources and Services Administration

Dr. Rubin presented the update for the Health Resources and Services Administration (HRSA) Division of Injury Compensation Program (DICP). The National Vaccine Injury Compensation Program (VICP) continues to process an increased number of claims. In fiscal year 2022, as of June 1, 2022, petitioners filed 601 claims with the VICP. Nearly $120 million was awarded to petitioners, including their attorneys' fees and costs. As of June 6, 2022, the VICP had a backlog of 1,439 claims alleging vaccine injury awaiting review. As of June 1, 2022, the Countermeasures Injury Compensation Program (CICP) had received 8,439 claims alleging injuries or deaths from COVID-19 countermeasures. This included 5,449 claims alleging injuries from COVID-19 vaccines. Of these, 31 claims have been denied compensation and 1 claim has been determined medically eligible for compensation. However, compensation has not been awarded yet and is pending a review of eligible expenses. More information can be found on the VICP and the CICP websites.

Indian Health Service

Dr. Clark presented an update on behalf of the Indian Health Service (IHS), reporting that IHS continues to confront the SARS-CoV-2 pandemic and its impact on population health and routine immunization efforts. Since September 2020, the IHS COVID Vaccine Task Force has coordinated the distribution and administration of COVID-19 vaccines agency-wide, including at federal direct care facilities, tribal health programs, and urban Indian organizations that receive vaccines through the IHS jurisdiction. Collaborating with its federal, tribal, and urban Indian organization partners, the IHS has prioritized equitable access to COVID-19 vaccines through Indian country. To date, participating federal, tribal, and urban facilities within the IHS jurisdiction have administered over 2.2 million COVID-19 vaccines. According to current CDC tracker data, among the estimated 2.1 million people served at IHS facilities, including American Indian and Alaska Native (AI/AN) individuals, healthcare workers, and community members, approximately 42% are fully vaccinated and 32% of those who are fully vaccinated have received a booster dose as IHS continues to mitigate the impact of serious COVID-19 illness in Indian Country. Following recent regulatory actions by the FDA and CDC earlier in the week, the IHS rapidly communicated information regarding COVID-19 vaccines for children under 5 years of age. They anticipate that a majority of children in this age group will be vaccinated in their IHS medical homes. Federal, tribal, and urban facilities are now actively engaged in implementation. Across IHS's 3 surveillance systems, IHS COVID-19 vaccine safety monitoring has demonstrated a reassuring safety profile to date that is consistent with other national vaccine safety surveillance systems. Meanwhile, the IHS routinely collaborates with the CDC and engages with tribal leaders to support vaccine confidence among the AI/AN service population. Lastly, the IHS immunization program has leveraged COVID-19 vaccination strategies to efficiently implement new and expanded ACIP eligibility recommendations within its service population for adult pneumococcal, zoster, and hepatitis B vaccines. The immunization program developed a resource and clinical guidance document and conducted training to support implementing pneumococcal and zoster recommendations in the field. The IHS looks forward to continued collaboration with its tribal, urban, and federal partners to ensure access to safe and effective vaccines across the age spectrum for AI/AN populations served by the IHS.

National Institutes of Health

Dr. Beigel presented the National Institutes of Health (NIH) update, reporting that the NIH continues to invest in multiple COVID-19 vaccine efforts. In March 2022, the National Institute of Allergy and Infectious Diseases (NIAID) began a study using both prototype and variant vaccines to try to inform how best to cover the COVID-19 antigenic landscape in terms of known variants and variants that may emerge in the ensuing months. The study examined 5 to 6 strategies for 3 vaccine manufacturers (e.g., Moderna, Pfizer, Sanofi) using the covariant vaccines. The goal is to understand the immediate need and how to modify the immune response in the future. This study should contribute a lot of interesting data. The NIH continues to evaluate work on allergic reactions to COVID-19 vaccines. A new study was recently started at the NIH Clinical Center in Bethesda to evaluate people who have had allergic reactions from COVID-19 mRNA vaccines. This very detailed analysis will try to understand the etiology of some of these reactions. The NIH has published an interesting article looking at maternal vaccinations that details immunology regarding transplacental antibodies and antibodies in the newborn in terms of the kinetics.

In terms of non-COVID-19 work, the NIH launched a clinical trial with 3 mRNA HIV vaccines which like the mRNA platform that has been incredibly valuable for COVID-19, have resulted in robust immune responses in HIV. The hope is that this will enable diseases such as HIV to be treated with vaccines. The NIH is very excited about this vaccine that is being studied through the HIV Vaccine Trials Network (HVTN). There is a new vaccine for the Eastern Equine, Western Equine, and Venezuelan encephalitis viruses. This is a trivalent virus-like particle (VLP) vaccine that has been developed at the NIH Vaccine Research Center (VRC) that has been shown to be safe and has generated robust immune responses. Given that these viruses cause diseases with often fatal encephalitis, having an effective vaccine is critical. Lastly, the NIH launched a new clinical trial for Epstein-Barr vaccine. Epstein-Barr causes infectious mononucleosis and also is associated with certain cancers and autoimmune diseases. This vaccine uses novel ferritin nanoparticles for vaccine development. There has been limited work on Epstein-Barr vaccines in over a decade. The details for all this work will be provided in summaries to the ACIP.

Office of Infectious Disease and HIV/AIDS Policy

Dr. Kim presented the Office of Infectious Disease and HIV/AIDS Policy (OIDP) update on behalf of the National Vaccine Program Office (NVPO), OIDP, and the Office of the Assistant Secretary for Health (OASH). Earlier in the month, the Associate Secretary of Health (ASH) named B. Kaye Hayes, MPA, as the Deputy Assistant Secretary for Infectious Disease and Director of the OIDP. Ms. Hayes has been the Acting Director of OIDP for the last 2 years. She comes to the position with over 25 years of experience in in the Office of the ASH (OASH). The first in-person meeting of the National Vaccine Advisory Committee (NVAC) since the pandemic started was convened on June 15-16, 2022 in Washington, DC. The ASH, Admiral Rachel Levine highlighted 2 issues of concern, immunization equity and health worker burnout and identified 2 new charges for NVAC. The first focuses on innovation. By September 2023, the NVAC is charged to develop recommendations to start innovations in vaccine development and related technologies. The second focuses on vaccine safety. By June 2023, the NVAC is charged to review vaccine safety systems and vaccine safety strategies to determine what should be maintained and what new strategies are indicated. The next NVAC meeting will be on September 22-23, 2022.

The Vaccines Federal Implementation Plan is currently under development and is nearing the finish line. The implementation plan is a complementary document to the National Vaccine Strategic Plan and the target audience is the federal agency. OIDP has incorporated public comments received from the *Federal Register* into the draft implementation plan and it will be reviewed by the Interagency Vaccine Group (IAVG) for their review before going through interdepartmental and HHS clearance. The Implementation Plan is expected to be released by late summer. The National Vaccine Program Office (NVPO) is collaborating with the CDC and the OASH Office of Disease Prevention and Health Promotion (ODPHP) on converting developmental immunization objectives to core measures in Healthy People 2030. The Healthy People 2030 sets data-driven national objectives to improve health and well-being over the next decade. The immunization objectives are aimed to improve adult immunization across the lifespan and increase the number of pregnant women who receive the Tdap vaccine during pregnancy.

ACIP Chair

Dr. Lee took a moment to thank all of ACIP's colleagues from the federal agencies for their service, dedication, and continued focus on improving the health of the nation's populations. She highlighted to the public that these people working in US federal agencies have been working around the clock to protect the public, and it seems like there is no end to the series of crises that are coming their way. It is important to be mindful of burnout in the public health sector just as much as there is concern about burnout amongst healthcare providers and staff. While they continue to thank people, it is simply not enough. She expressed her hope that these systems will continue to be supported to ensure that the workforce is able to function. Based on her perspective, continuing at this pace is unsustainable.

CORONAVIRUS DISEASE 2019 (COVID-19) VACCINES

Session Introduction

Dr. Matthew F. Daley (ACIP WG Chair) introduced this session on behalf of the COVID-19 Vaccines WG. He indicated that there have been more than 85 million reported cases of COVID-19 in the US since the start of the pandemic.[56] Currently, the 7-day average is more than 100,000 cases per day. There have been over 1 million deaths from COVID-19 since the beginning of the pandemic. The 7-day average is currently 266 deaths per day.[57] Based on data for the 12 months from April 2021 to April 2022, the rate of COVID-19 deaths by vaccination status in people ≥5 years of age show that unvaccinated persons had a 10 times greater risk of dying from COVID-19 compared to people vaccinated with at least the primary series. This is one of the stronger pieces of evidence to emphasize the fact that COVID-19 vaccination is effective at preventing death from COVID-19.[58] Between December 14, 2020 – June 16, 2022, the percentage of children and adolescents who have received at least 1 dose of COVID-19 vaccine was 69.7% of persons 12 through 17 years of age and 36.2% of children 5 through 11 years of age who had received 1 dose. This translates to 7.5 million people 12 through 17 years of age and 18 million children 5 through 11 years of age who have yet to receive any COVID-19 vaccination.[59] This is a stark reminder of all of the work that needs to continue to increase vaccination coverage.

[56] Source: COVID Data Tracker, https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases Accessed 6/21/2022
[57] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#trends_dailydeaths Accessed June 21, 2022
[58] https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status Accessed June 12, 2022
[59] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends Accessed June 20, 2022

In terms of recommendations for COVID-19 vaccines, only the Pfizer BioNTech vaccine is currently authorized by FDA and recommended by CDC for use in children 5 through 17 years of age. With that in mind, the focus of this session was an update on the FDA-authorized Moderna COVID-19 vaccine for children 6 through 17 years of age under Emergency Use Authorization (EUA) on June 16, 2022. This is a 2-dose Moderna COVID-19 vaccine primary series for administration in individuals 6 through 17 years of age. Also authorized was the third primary series dose among individuals ages 6 through 17 years of age with certain kinds of immunocompromise.[60]

Recommendations following the emergency ACIP meeting on June 17-18, 2022 were as follows:

- ❑ A two-dose Moderna COVID-19 vaccine series (25µg) is recommended for children ages 6 months through 5 years, under the EUA issued by the FDA.

  (Two doses of 25µg Moderna COVID-19 vaccine: ≥4 weeks between Doses 1 and 2)

- ❑ A three-dose last Pfizer BioNTech COVID-19 vaccine series (3µg each) is recommended for children ages 6 months – 4 years, under the EUA issued by FDA.

  (Three doses of 3µg Pfizer-BioNTech COVID-19 vaccine: 3-8 weeks between Doses 1 and 2; ≥8 weeks between Doses 2 and 3)

The agenda for this session included presentations on the burden, prevalence, and trends of long-term sequelae of SARS-CoV2; updates on safety of COVID-19 vaccines in children and adolescents; a VaST assessment; safety and immunogenicity of Moderna 2-dose primary series in children ages 6–17 years; the EtR Framework for Moderna COVID-19 vaccine in children and adolescents ages 6–17 year; public comments; and a vote on Moderna COVID-19 vaccine in children and adolescents ages 6–17 years.

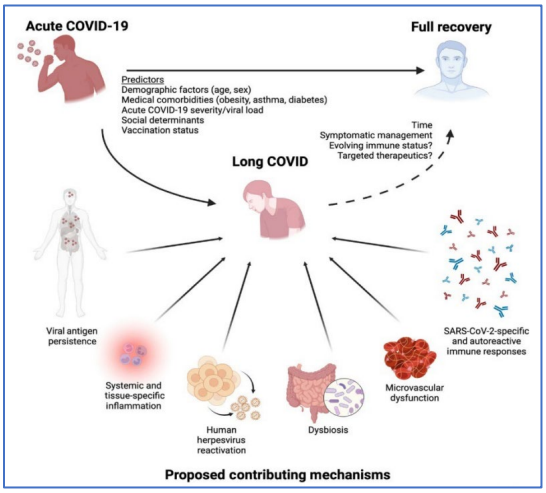
Burden, Prevalence, and Trends of Long-Term Sequelae of SARS-CoV-2

Sharon Saydah, PhD (CDC/NCIRD) presented on the burden, prevalence, and trends of the long-term sequelae of SARS-CoV-2. There are many terms used to refer to these conditions. The term “long COVID” is commonly used by patients who experience these problems. Similar terms include “long-hauler” or “long-haul COVID.” CDC and WHO use “post-COVID conditions.” NIH uses the term “post-acute sequelae of SARS-CoV-2 (PASC). The variety of terms reflects that there is still a lot to learn about the longer-term consequences of SARS-CoV-2 infection. While there might be minor differences in what is meant by each of these terms, they are often used interchangeably.

The post-COVID conditions refers to a wide range of physical and mental health consequences present 4 or more weeks after SARS-CoV-2 infection. These conditions can occur in patients with severe disease and also in patients who had mild or asymptomatic acute infection. It is important to remember that these groups are not mutually exclusive. A general framework for post-COVID conditions includes a definition that describes the variety of these conditions that can occur as a result of any severe illness, hospitalization, or treatment, such as post-intensive care syndrome. “Post-COVID conditions is an umbrella term for the wide range of physical and

[60] https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-moderna-and-pfizer-biontech-covid-19-vaccines-children

mental health consequences, present for 4 weeks and beyond after SARS-CoV-2 infection, including for patients who had initial mild or asymptomatic acute infection. There are general consequences of illness and hospitalization, such as post-intensive care unit (ICU) syndrome and/or other complications of treatment or illness. Then there are processes that are likely more specific to SARS-CoV-2 infection that include system-specific effects such as newly diagnosed or identified neurological conditions, kidney damage or failure, diabetes, cardiovascular damage, or skin conditions. There also are symptoms that may have an unclear pathology and can involve a range of problems that can last for months after the acute infection or can even appear weeks or months after the acute phase has resolved. This unexplained group has features that are similar to other post-infectious syndromes. Included in this group are also ongoing symptoms following multisystem inflammatory syndrome in children (MIS-C). There are multiple mechanisms proposed for post-COVID conditions as depicted in this graphic:[61]



Many people who experience acute COVID go on to make a full recovery. Others may experience long COVID. Some of the risk factors seem to include those that predispose people to more severe COVID, such as increased age, underlying medical conditions, and vaccination status. Post-COVID conditions may be explained by viral antigen persistence, systematic and tissue-specific inflammation, auto-immunity, microvascular dysfunction, or SARS-CoV-2 specific immune response. It is unknown whether these mechanisms differ among children. This is a list the commonly reported symptoms for post-COVID conditions. The ones noted in bold blue are symptoms that are more commonly reported by children:[62]

- **Dyspnea or increased respiratory effort**
- **Fatigue**
- **Anosmia or dysgeusia**
- **Chest pain**
- **Headache**
- **Lightheadedness**
- Palpitations and/or tachycardia
- Arthralgia
- Myalgia
- Paresthesia
- Cough
- Abdominal pain
- Diarrhea
- Insomnia and other sleep difficulties
- Fever
- Impaired daily function and mobility
- Pain
- Rash (e.g., urticaria)
- Mood changes
- Menstrual cycle irregularities
- Post-exertional malaise and/or poor endurance
- "Brain fog," cognitive impairment

[61] Peluso and Deeks. Early clues regarding the pathogenesis of long-COVID: Trends in Immunology (cell.com) 2022
[62] https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html; Borch L et al. Long COVID symptoms and duration children. European Journal Pediatrics 2022

There has been a wide range of reported problems of post-COVID conditions among adults. Based on self-report data using a mobile app, 13% of individuals with incident COVID-19 followed up prospectively reported symptoms ongoing at 1 month and 2.5% reported ongoing symptoms at 3 months.[63] When electronic health data were used among adults who were not hospitalized for COVID-19, 7.7% had 1 or more of the 10 common post-COVID conditions 1 to 4 months post-infection.[64] The severity of acute COVID-19 illness also is associated with the occurrence of at least 1 symptom at 6 months.[65] Among patients from the VA, non-hospitalized patients (44.5/1,000 patients) had a lower frequency of post-COVID conditions compared to those who were hospitalized (217.1/1,000 patients) and patients who were in the ICU with COVID had the highest occurrence (360.5/1,000 patients).

Most patients recover from the acute illness within 4 weeks and the proportion reporting on-going symptoms decreases 4-12 weeks. This is part of the reason why CDC considers illness persisting beyond 4 weeks as warranting that initial clinical evaluation and supportive care. The proportion who report ongoing symptoms continues to decrease from 4 to 12 weeks, with improvement slowing around 12 weeks. When stratified by sex, the pattern is the same although a higher proportion of women report symptoms compared to men.[66]

Children present a unique challenge in assessing post-COVID conditions. Younger children particularly may have difficulty verbalizing symptoms, and they have a developmentally different understand of time. This makes it difficult to tease apart frequency, chronicity, and other details of their symptoms. Symptoms also may present in different ways with different children. There is not one specific symptom or even a cluster that is exclusive to long-COVID. An assessment of these conditions also may be dependent on what is expected at different developmental milestones. For example, sleep cycle changes might be perceived as developmentally accepted officially among very young children. Picky eating could be due to a loss of taste or smell or it could be because children are often picky eaters. There also are numerous limitations in the current research for post-COVID conditions among children, including varying time points from infection to the assessment, lack of control groups, and a small sample size for many reports. Similar to adults, prevalence of post-COVID conditions can vary depending upon the setting and methods used. Symptoms lasting for 4 weeks or longer from infection are common among children and adolescents. The most common symptoms include headache or respiratory symptoms (~7%), sleep disorders (~8%), fatigue (~9%), and mood disorders (~16%).[67]

In terms of results of non-hospitalized children who had mild or acute infections from a survey of children in the United Kingdom (UK), the percent reporting positive SARS-CoV-2 tests ranged from 20% in children 5–11 years of age to 30% in those 11–16 years of age. Among those who had a positive test, 7% had ongoing symptoms at 12 weeks and approximately 4% in the oldest age group had symptoms that impacted their activities of daily living for 12 weeks or longer.[68] A prospective cohort study by Osmanov et al highlights the risk factors and symptoms experienced by children who are hospitalized with COVID-19.[69] Compared to the youngest children, those ages 6 to 11 years and those 12 to 18 years had the highest risk for post-COVID

[63] Sudre CH et al Nature Medicine 27, 626-631 (2021) https://www.nature.com/articles/s41591-021-01292-y
[64] Chevinsky JR et al. Clinical Infectious Diseases 73 (S1) 2021 https://academic.oup.com/cid/article/73/Supplement_1/S5/6257082?login=true
[65] https://www.nature.com/articles/s41467-021-26513-3
[66] https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/articles/technicalarticleupdatedestimatesoftheprevalenceofpostacutesymptomsamongpeoplewithcoronaviruscovid19intheuk/26april2020to1august2021
[67] https://journals.lww.com/pidj/Fulltext/2022/05000/The_Challenge_of_Studying_Long_COVID__An_Updated.16.aspx; https://www.medrxiv.org/content/10.1101/2022.03.10.22272237v2
[68] https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/covid19schoolsinfectionsurveyengland/mentalhealthandlongcovidnovembertodecember2021
[69] https://erj.ersjournals.com/content/early/2021/06/10/13993003.01341-2021

conditions. Children with a history of allergic diseases also were more likely to report post-COVID conditions compared to those without the history of allergies. Many of the common symptoms experienced by adults also are experienced by children, with fatigue being the most common followed by sleep problems. Similar to adults, the duration of symptoms decreases over time.

A recently published study[70] from the Distributed Research Network (DRN), with 42 participating healthcare systems and 2 health plans, compared patients who had a COVID-19 test between March and December 2020 and then received medical care for any reason in the 31 to 150 days after they were tested. Children with a positive SARS-CoV-2 test were more likely to receive the diagnosis for a new condition or symptom in the 5 months after their acute infection compared to those who received a negative test. Comparing prevalence ratios for children who tested positive compared to those who tested negative broken down by severity of illness, fatigue and shortness of breath were more common among children testing positive, particularly those who were hospitalized. The study also looked at several conditions that were more likely to be newly diagnosed in children testing positive compared to those testing negative. Type 2 diabetes was more common among children hospitalized with COVID-19.

Children and adolescents with COVID-19 appeared to be at a higher risk for newly diagnosed diabetes. This was investigated further using electronic health data sources to examine newly diagnosed diabetes in children and adolescents.[71] Retrospective cohorts were constructed using IQVIA healthcare claims data from March 1, 2020 through February 26, 2021. Children and adolescents with COVID-19 were compared to those without COVID-19 during the same time period, as well as to a group with acute respiratory illness (ARI) in the pre-pandemic period. Children and adolescents with COVID-19 were 2.7 times more likely to be newly diagnosed with any type of diabetes in the months following infection compared to those without COVID-19 or those diagnosed with other respiratory infections prior to the pandemic. Similar results have been observed in the adult population.

An unpublished analysis looking at the incidence of 12 conditions and 8 symptoms in close to 2 million children with and without COVID-19 in a closed medical claims dataset found 9 post-COVID conditions and 4 post-COVID symptoms, most of which were rare or uncommon, that were more likely to occur among children with COVID-19 compared to those without COVID-19.[72] Children with MIS-C also appear to have a higher risk of ongoing symptoms following MIS-C. Continued difficulties are reported by 35% of the children and 21% of the children's parents at 6 months. The number of systems affected at baseline is greater than those at 6 weeks and 6 months, though a number of children and adolescents still have impact at 6 months.[73] Most studies that have looked at post-COVID conditions occurring after vaccine breakthrough have focused on adults, though 2 published were identified that included adolescents.[74] These studies found that post-COVID conditions and symptoms were less likely to occur in 12 to 20 weeks after infection among those previously vaccinated compared to the unvaccinated. While the exact mechanism through which vaccines may prevent long-COVID symptoms are unknown, vaccines can prevent post-COVID conditions by preventing infections.

[70] Hernandez-Romieu AC et al. JAMA Netw Open. 2022
[71] https://www.cdc.gov/mmwr/volumes/71/wr/mm7102e2.htm?s_cid=mm7102e2_w
[72] US Commercial Medical Claims Data, March 1, 2019–September, 2021. Unpublished CDC data.
[73] Penner J. et al. 6 month follow-up MIS-C. Lancet Pediatric 2021
[74] Simon et al. Reduced Incidence of Long-COVID Symptoms | medRxiv 2022; Tarquet et al. Six-month sequelae of post-vaccination SARS-CoV-2 infection| medRxiv 2022

In summary, post-COVID conditions occur among children and adolescents with COVID-19 regardless of acute illness severity and appear to occur at higher frequency among those who are hospitalized and adolescents. Remaining areas of uncertainty include the frequency, severity, and duration of post-COVID conditions; understanding of the groups who might be disproportionately impacted by post-COVID conditions; whether the associations with different SARS-CoV-2 variants changes; and how post-COVID conditions may impact the daily activities and participation in school among children and adolescents.

Discussion Summary

Referring to Slide 6, Dr. Loehr observed that there was a large number of people who had symptoms after being hospitalized and in the ICU and asked whether there is a comparison group to know how many people in the ICU who did not have COVID-19 might have these symptoms.

Dr. Saydah said that while she would have to look at the specific study to get the exact estimate, the analysis included adults. This analysis compared those who were mechanically ventilated with these conditions and symptoms and identified an increase among the mechanically ventilated for many of these conditions among adults compared to those who did not test positive for SARS-CoV-2.

Dr. Brooks found the odds ratio of 2.66 for new diagnosis of diabetes to be fascinating and concerning. While the summary indicated that there is not information on groups disproportionately affected, he assumed that there are race and ethnicity data on a lot of the patients in the studies presented. He asked if there is information on race and ethnicity in terms of the effects of long COVID in those populations.

Dr. Saydah indicated that CDC is planning to publish more detailed results focused specifically on race and ethnicity. Many of the data sources they have published on so far are missing some of the components for race and ethnicity, which is one reason they have not published that yet. However, they are actively working on that.

Dr. Daley asked what is known about vaccination among those who already have been infected with respect to the trajectory of post-COVID conditions, which he raised because there will certainly be a number of children ≥5 and 5–17 years of age who were infected prior to vaccination who may or may not have symptoms of post-COVID conditions at the time of vaccination.

Dr. Saydah responded that there has not been as much published looking among people who have been infected and report symptoms who were then vaccinated. There is one study based on a survey in which individuals reported that their symptoms improved after vaccination. There is a recently published article from the UK from their Coronavirus Community Survey that looked at this. As she recalled, they did not find a strong association of reduction in post-COVID conditions among those who are vaccinated after infection compared to those who remained unvaccinated.

Dr. Sanchez said his understanding on variants was that there have been recent reports showing that post-COVID symptomatology has been less with the new variants. He asked whether any assessments had been done on the timeline of when post-COVID symptomatology was reported with more recent changes in the new variants. He also noted that there have been reports of post-COVID symptomology after vaccination.

Dr. Saydah indicated that there has not yet been an opportunity to assess this, but do recognized that this is important. There are number of factors related to that as well. Moving out of this pandemic, individuals are more likely to report reinfections. How that might impact post-COVID conditions still needs to be assessed along with the effects of vaccinations. While CDC has received reports of post-COVID symptomology after vaccination, they have not seen anything specific based only on vaccination without any evidence of infection.

Dr. Shimabukuro added that think with respect to reports of the conditions described, CDC is aware of reports of people experiencing debilitating and long-lasting health problems after COVID-19 vaccination. In some cases, the clinical presentation of people suffering these health problems is variable and no specific medical causes for the symptoms have been found. Illness is always disruptive and stressful, especially under these circumstances. CDC acknowledges that these health problems have substantially impacted the quality of life for some people and also have affected those around them and wishes for improvement in recovery. CDC will continue to monitor the safety of these vaccines and will work with partners to try to better understand these types of AEs and the impact of disease in the development of these AEs.

Dr. Poehling found it very convincing that COVID-19 in children is not a benign illness and that many children are suffering long consequences. Like Dr. Brooks, she impressed with the test-positive, test-negative studies showing in the subsequent 5 months that there is an increased risk of a new diagnosis of diabetes mellitus among those that have been hospitalized and that this also was found in the claims data. In terms of the medical claims data presented showing symptoms and conditions, myocarditis and pulmonary embolism were 2 that struck her. Also what struck her was in regard to MIS-C in that 35% of children reported having symptoms 6 months later.

Dr. Lee expressed appreciation for the work that CDC is beginning in order to understand what may be a huge public health burden due to PASC or due to long-term complications of the COVID-19 infection. She stressed that while there has been a heavy focus on the acute period, there is a lot more to learn about the chronic burden of this condition. She acknowledges that NIH has initiated the Recover NIH Initiative that is following cohorts over time in an effort to understand the national history of long-haul COVID. Looking at real-world data for an EHR cohort to try to understand and better characterize what PASC can help to improve the detection of PASC, understand the risk factors, and think about treatment and prevention in children better characterize and understand what needs to be done to address this emerging public health burden.

Updates on Safety of COVID-19 Vaccines in Children and Adolescents

Tom Shimabukuro, MD, MPH, MBA (CDC/NCEZID) provided updates on the safety of COVID-19 vaccines in children and adolescents, including background on classic myocarditis and myocarditis associated with mRNA COVID-19 vaccination; an update on myocarditis following mRNA COVID-19 vaccination with a focus on children ages 5–17 years, which included findings from the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD); and data on comparative risk for myocarditis between the 2 mRNA COVID-19 vaccines, Moderna and Pfizer-BioNTech.

With respect to classic myocarditis in children, there is usually an infectious cause that is typically viral or presumed to be viral, although infection with a pathogen is frequently not identified.[75] It can be due to direct microbial infection of myocardial cells and/or ongoing inflammatory response with or without clearance of the pathogen.[76] Rare causes include autoimmune, hypersensitivity, and giant cell myocarditis. Incidence in males is greater than females starting after age 5 years.[77] Previously, unrecognized myocarditis was identified as a cause of death in 8% of cases of sudden unexplained death in 1–17-year-olds[78] and 9% of sudden death in athletes.[79] It is common not identify a pathogen or possible infectious etiology for myocarditis. In some case series, less than half of the time a specific infectious cause was identified.

In children, with the exception of very early in life when there may be genetic or other medical conditions playing a role, incidence is fairly low in early childhood and then begins to increase when children enter adolescence.[80] Incidence peaks in adolescence and then gradually decreases with age. Most cases are male, but that male-to-female predominance tends to even out in about middle age.[81] This table shows the characteristics of myocarditis associated with mRNA COVID-19 vaccination versus viral myocarditis:

Characteristic	Myocarditis associated with mRNA COVID-19 vaccination*,†	Viral myocarditis‡
Inciting exposure	mRNA COVID-19 vaccination • Dose 2 > Dose 1	Viral illness • 30–60% with asymptomatic viral course
Demographics	Most cases in adolescents and young adults, males > females	Males > females, male incidence peaks in adolescence and gradually declines
Symptom onset	A few days after vaccination, most within a week	1–4 weeks after viral illness
Fulminant course	Rare¶	23%
ICU level support	~2%	~50%
Mortality/transplant	Rare¶	11–22%
Cardiac dysfunction	12%	60%
Recovery of cardiac function	Nearly all	~75%
Time to recovery of cardiac function (ejection fraction on cardiac echo), if initially poor	Hours to days	Days to weeks to months

* https://www.cdc.gov/vaccines/acip/meetings/index.html, https://www.cdc.gov/vaccinesafety/research/publications/index.html
† Oster et al. JAMA. 2022;327:331-340.
‡ Law et al. Circulation. 2021;144:e123-e135. Ghelani et al. Circ Cardiovasc Qual Outcomes. 2012;5:622-7. Kim et al. Korean Circ J. 2020;50:1013-1022. Messroghli et al. Am Heart J. 2017;187:133- 144. Patel et al. J Am Heart Assoc. 2022;11:e024393.
¶ There are rare reports in the literature, especially from other countries, but it is unclear to what extent such cases were investigated

Moving now to data from VAERS, which is the national spontaneous or passive surveillance system that is co-managed by CDC and FDA. VAERS accepts reports from everyone (healthcare professionals, patients, parents, caregivers, manufacturers, et cetera) regardless of the plausibility of the vaccine causing the event or the clinical seriousness of the event. The key limitation of VAERS is that as a passive surveillance system, it is generally not possible to determine cause and effect from VAERS data alone. In terms of reports to VAERS of

[75] Bowles et al. J Am Coll Cardiol. 2003;42:466-72; Simpson et al. J Am Coll Cardiol. 2013;61:(10_Supplement) E1264; and Park et al. J Korean Med Sci. 2021;36:e232.
[76] Caforio et al. Eur Heart J. 2013;34:2636-48, 2648a-2648d; Feldman et al. N Engl J Med. 2000;343:1388-98; and Guarner et al. Hum Pathol. 2007;38:1412-9
[77] Arola et al. J Am Heart Assoc. 2017;6:e005306.
[78] Burns et al. J Pediatr X. 2020;2:100023.
[79] Maron et al. Circulation. 2009;119:1085-92.
[80] Vasudeva et al. *American J Cardiology*. 2021.
[81] Kyto et al. Heart. 2013.

myocarditis after Pfizer-BioNTech vaccination among children ages 5–17 years, there were 972 preliminary reports of myocarditis to VAERS as of May 26, 2022. Of these, 214 remain under review, 123 did not meet the CDC case definition, and 635 reports were verified to meet the CDC case definition. To put that number into context, there have been 54.8 million total Pfizer doses administered to children ages 5–17 years in the US during that surveillance period. Of the 635 verified reports, 630 (99%) had a known time to symptom onset from vaccination, demonstrating a clustering of symptom onset within several days of vaccination. The overwhelming majority of these case reports in VAERS have onset within a week of vaccination.

Looking at VAERS reporting rates of myocarditis per 1 million doses administered after mRNA COVID-19 vaccination for Days 0–7 and 8–21 post-vaccination, observed reporting rates to VAERS exceeded the expected background incidence, with the risk appearing to be concentrated in the first week after vaccination in both males and females. Reporting rates were substantially higher in males compared to females and were higher for Dose 2 compared to Dose 1 for both sexes. In the age group 5–11 years, there was an elevated observed to expected ratio in the male Dose 2 0–7 day age-sex-dose strata. Otherwise, the reporting rates in that age group were within background incidence.

CDC enhanced surveillance for myocarditis outcomes following mRNA COVID-19 vaccination in VAERS case reports includes 2 projects with 2 separate cohorts, children ages 5–11 years and people ages 12–29 years. Data were used from both cohorts to combine them into a 5–17 years of age group.[82] The purpose of this project was to assess functional status and clinical outcomes among individuals reported to have development of myocarditis after mRNA vaccination. This is a 2-component survey conducted at least 90 days after the onset of myocarditis symptoms that includes a patient or parent survey and a healthcare provider (HCP) survey. During the surveillance periods, (through November 2021 for 12–17 years and April 2022 for 5–11 years), VAERS received 430 reports of myocarditis or myopericarditis after vaccination in this age group that met CDC case definition and were at least 90 days post-myocarditis diagnosis. For the patient or parent survey, 190 surveys were completed, 128 were unreachable on multiple attempts, 98 had no telephone contact information in the report, and 7 declined to participate. Among the cardiologists or other HCP surveys, 226 completed a survey, 120 were unreachable on multiple attempts, and 65 had no telephone contact information in the report. The main finding based on cardiologist or HCP assessment was that most patients appear to have fully or probably fully recovered from their myocarditis. Of the total patients, 226 received a follow-up assessment by a cardiologist or other HCP regarding their myocarditis recovery. Among these patients, 80.1% were judged by their provider to be fully or probably fully recovered.

In terms of the key findings from the CDC enhanced surveillance for myocarditis outcomes following mRNA COVID-19 vaccination in VAERS case reports among children ages 5–17 years of age, most patients who were reached with a patient survey reported no impact on their quality of life and most did not report missing work or school at least 90 days after myocarditis diagnosis. Most HCP (80.1%) who completed surveys indicated that the patient was fully recovered or probably fully recovered. Of note, there was substantial heterogeneity in initial and follow-up treatment and testing, and there did not appear to be a single test that was indicative of recovery. The next step, which was occurring right now, is additional follow up with patients who were not yet fully recovered at the 90+ day survey and also with their HCP to further assess their recovery status at 12+ months.

[82] https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myo-outcomes.html

Moving on to findings from the VSD, which is CDC's EHR-based system that is used for surveillance and research, the VSD conducts Rapid Cycle Analysis (RCA), which is weekly sequential monitoring. The aims of the RCA are to monitor the safety of COVID-19 vaccines using prespecified outcomes of interest and to describe uptake of COVID-19 vaccines over time among eligible VSD members. The VSD COVID-19 vaccine RCA pre-specified surveillance outcomes and the settings in which they are being monitored are shown on the following table:

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

Though the primary analysis in the VSD RCA is the vaccinated concurrent comparator analysis, it is looking at vaccinated patients only and cases in a risk interval compared to cases in a comparison interval adjusted and matched by certain characteristics. For the pre-specified outcome myocarditis/pericarditis, which is a combined outcome, the cases were verified using the CDC case definitions. Over 2 million total Pfizer primary series doses have been administered to children ages 5–11 years during the surveillance period. There have been no statistical signals to date for myocarditis and pericarditis in the analysis in children ages 5–11 years. At this time, there are primary series vaccination only as there were not sufficient booster doses to do the analysis.

For people ≥12 years of age, including adults, statistical signals were detected for myocarditis and pericarditis for Pfizer-BioNTech and for both mRNA COVID-19 vaccines combined for primary series vaccination. Statistical signals were detected for myocarditis/pericarditis for both mRNA COVID-19 vaccines combined for the first booster dose. Based on data through May 28, 2022 of cases with symptom onset of verified myocarditis/ pericarditis cases among children 5–17 years of after either primary series dose of mRNA COVID-19 vaccines, there is a clear clustering of cases with symptom onset within Days 0–3 and Day 0–4 in the VSD data for the primary series.

Verified myocarditis and pericarditis in the 0–7-day risk interval among male children ages 5–17 years by age group and dose were split into 2 separate analyses, 5–11 years and 12–17 years of age, with some subgroup analyses for the 12–17-year-old age group. The adjusted rate ratio is the statistic and there were no statistically significant elevated rate ratios in the age group 5–11 years for myocarditis or pericarditis. However, the case counts are very small. For age group 12–17 years, there were elevated rate ratios following Dose 1, Dose 2, and the booster dose. The rate ratio was most elevated after Dose 2 at 160.52 (30.19 – 3343.73), which was highly statistically significant. Looking at the subgroups within that age group and the age group 16–17 years. There was an elevated rate ratio for subgroup within the age group 12–17 years of 18.15 (1.62 – 558.73), which was statistically significant. For the age group 16–17 years, it was not possible to estimate rate ratio because there were no events in the comparison window. However, it was possible to estimate a lower bound of the 95% confidence interval, so after Dose 2 and after a booster dose were statistically significantly elevated. The case counts, events, risk interval, and comparison interval were substantially lower for females than for males as might be expected. The adjusted rate ratios tended to be lower, and there were less significant adjusted rate ratios. There was a statistically significant elevated rate ratio in females in the 12–17-year-old age group for Dose 2 and in the 12–15-year subgroup for Dose 2. Looking at straight VSD incidence rates of verified myocarditis and pericarditis in the 0–7 days following vaccination, there is a general trend that the incidence rate is higher in males compared to females and tends to be highest in Dose 2. While in some age and sex strata the incidence rates are higher for booster doses, there are relatively small case counts and very wide confidence intervals overlapping with the confidence intervals of the Dose 2 estimates. The level of care and status for the cases after the primary series and booster dose were quite similar, with most of these patients being admitted to the hospital. Most of them had relatively short lengths of stay of 1 or 2 days and 100% were discharged home.

Looking now at some findings on comparative risk of myocarditis between the 2 available vaccines, Moderna and Pfizer, Dr. Shimabukuro reviewed some data that were presented previously to ACIP in October 2021 from VAERS.[83] Reporting rates per million doses administered among males tended to be higher for Moderna compared to Pfizer. Reporting rates were substantially lower for females, but there was a similar trend in which the reporting rates for Dose 1 or Dose 2 tended to be slightly higher for Moderna compared to Pfizer. Notably, those VAERS reporting rates are not a direct comparison. This was a side-by-side comparison looking at the data individually by individual product.

A direct comparison was done using the VSD, the results of which were presented to ACIP during the February 4, 2021 ACIP meeting.[84] Looking at case counts, onset, and incidence of myocarditis cases following Pfizer and Moderna vaccine, the same clustering was observed in which the cases tended to cluster within several days after vaccination. There was a higher rate for Moderna compared to Pfizer in the Day 0–7 risk period. When a formal statistical comparison was done for Moderna versus Pfizer, the statistic was a rate ratio. In all of these analyses regardless of dose and with both sexes combined, consistently elevated rate ratios are observed, although some of the confidence intervals on these point estimates were quite wide. There was a statistically significantly elevated rate ratio when looking at either dose and for both sexes combined of 1.61 (1.02 – 2.54) that was statistically significant. This translates into 8 excess cases in the risk period per million doses for Modern compared to Pfizer. Looking at

[83] Presented during the October 21, 2021 ACIP meeting: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/07-COVID-Su-508.pdf

[84] Presented at the February 4, 2021, ACIP meeting: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-02-04/10-COVID-Klein-508.pdf

straight incidence rates of verified myocarditis and pericarditis in Days 0–7 following vaccination with Pfizer or Moderna, the general trend was that there were higher post-vaccination incidence rates per million doses administered for Moderna compared to Pfizer.

To summarize, the current evidence supports a causal association between mRNA COVID-19 vaccines and myocarditis and pericarditis cases clustering within the first week of vaccination. Myocarditis is a rare event following vaccination. CDC has verified 635 myocarditis case reports in children ages 5–17 years after 54.8 million Pfizer doses administered in this age group in the US. The risk appears greatest in adolescence in the age groups 16–17 and 12–15 years and is generally higher after Dose 2 compared to Dose 1 of the primary series and in males compared to females. In the VSD analysis, in the minority of age and sex strata, incidence is highest following a booster dose. The reporting rate in VAERS of myocarditis following Pfizer in male children ages 5–11 years after Dose 2 of the primary series is slightly elevated when compared to background rates. Otherwise, reporting rates are within background incidence. To date, myocarditis/pericarditis has not statistically signaled in VSD RCA surveillance in children ages 5–11 years. The available information suggests that most persons with myocarditis after mRNA COVID-19 vaccination recover from their myocarditis by 90+ days after diagnosis. In age groups where product comparisons can be made, some evidence suggests that myocarditis and pericarditis risk may be higher after Moderna than after Pfizer. However, the findings are not consistent in all US monitoring systems.

As a reminder, CDC needs the help of state and local public health partners, partners in the healthcare community, and parents and caregivers who are enrolling children in v-safe[SM] in promoting v-safe[SM] in practice. HCP can provide the v-safe[SM] information and can direct patients to the v-safe[SM] website.[85] Ideally, this should occur before vaccination. Parents need to enroll themselves before they can enroll children, but are strongly encouraged to enroll children into v-safe[SM]. CDC appreciates any assistance HCP can give in making sure that parents can caregivers are aware of the v-safe[SM] program. CDC's Clinical Immunization Safety Assessment (CISA) project is also available to US HCP who wish consultation on complex AEs following immunization.[86]

Vaccine Safety Technical Work Group (VaST) Assessment

H. Keipp Talbot, MD MPH (VaST Chair) Dr. Talbot presented the Vaccine Safety Technical WG (VaST) assessment of the data that just been presented, as well as some other data VaST was able to review. As a reminder, VaST's objectives are to: 1) review, evaluate, and interpret post-authorization/approval COVID-19 vaccination safety 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. Since December 21, 2020, VaST has met 59 times to review the vaccine safety data.

VaST reviewed data about the Pfizer-BioNTech vaccine in children 5–17 years of age and compared data on safety monitoring from Moderna and Pfizer-BioNTech in the older age groups. To put that into context, VaST reviewed US safety monitoring systems for Pfizer-BioNTech in children 5–17 years of age and comparative data on safety monitoring for Moderna and Pfizer-BioNTech vaccines in older age groups where comparisons were possible. From the

[85] https://vsafe.cdc.gov/en/; https://www.cdc.gov/coronavirus/2019ncov/vaccines/safety/vsafe/printresources.html
[86] http://www.cdc.gov/vaccinesafety/Activities/CISA.html

v-safe[SM] system, VaST was able to obtain injection site and systemic reactions data. Among 49,392 v-safe[SM] participants ages 5–11 years who received Pfizer-BioNTech COVID-19 vaccination reported to v-safe[SM], the reactions are generally mild to moderate and most were reported the day after vaccination. Reactions were more frequently reported after Dose 2 than Dose 1. Patterns in these children are generally similar to those observed in older age groups. In age groups ≥18 years of age where comparison between the mRNA vaccines was possible, injection site and systemic reactions are reported more frequently after Moderna than Pfizer-BioNTech COVID-19 vaccination.[87]

In terms of VAERS and the enhanced follow-up data, myocarditis following Pfizer-BioNTech vaccination, 54.8 million Pfizer BioNTech doses have been administered to children ages 5–17 years. Of these doses, 27.7 million were Dose 1, 23.3 million were Dose 2; and 3.8 million were first booster doses in children 12–17 years of age. VAERS has received 635 myocarditis case reports that met the CDC case definition. Symptom onset clusters within several days of vaccination, mostly within the first 0–7 days. Reporting rates are generally higher for males than females, especially for age groups 16–17 and 12–15 years. Differences by sex in children ages 5–11 are much less pronounced. The reporting rate of myocarditis in male children ages 5–11 years after Dose 2 of the primary series is slightly elevated when compared to background incidence. Otherwise, reporting rates for both sexes is similar to background incidence. Regarding enhanced follow-up of myocarditis cases,[88] most patients reached for follow-up reported no impact on quality of life or missing school or work. Most HCP indicated that the patient fully recovered or probably fully recovered.

With regard to information on Pfizer-BioNTech vaccination in children 5–11 years of age in the VSD, among approximately 878,000 children ages 5–11 years of age VSD, 41% had completed the Pfizer BioNTech vaccine primary series and no statistical signals were identified in the 21-day risk interval for any outcomes identified.[89] Where data for both vaccines, Moderna and Pfizer-BioNTech vaccines were compared for the outcome of myocarditis/pericarditis in Days 0–7 post-vaccination among persons 18–39 years of age. Both vaccines are associated with increased risk of myocarditis/pericarditis in the 0–7 days post-vaccination, particularly after Dose 2. No noticeable differences have been observed in the level of care and clinical status between the cases following Moderna or Pfizer vaccination. Most cases were hospitalized and had stays of 1 day or less. Direct head-to-head comparison in ages where possible provides evidence that the risk of myocarditis and pericarditis may be higher after Moderna than after Pfizer vaccination.[90]

The FDA shared data from its Biologics Effectiveness and Safety System (BEST) system on Pfizer-BioNTech vaccination in children 5–17 years of age showing that among 5.4 million Pfizer-BioNTech doses in this age group, there were no statistical signals among children ages 5–11 years. However, there were statistical signals for myocarditis/pericarditis among children 12–15 and 16–17 years of age.[91] Still using the BEST system, myocarditis/pericarditis in Days 1–7 post-vaccination among persons 18–25 years of age were compared between Moderna and Pfizer vaccination. A large study in several US administrative health plan claims databases of people aged 18–64 years of age[92] found that the occurrence of myocarditis/pericarditis after

[87] Rosenblum et al. Lancet ID 2022. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8901181/
[88] Shimabukuro, ACIP presentation, June 23, 2022
[89] Through April 2022; Shimabukuro, ACIP presentation, May 19, 2022
[90] Klein, ACIP presentation Feb 4, 2022 https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-02-04/10-COVID-Klein-508.pdf
[91] Wong, FDA's VRBPAC presentation, June 14, 2022. https://www.fda.gov/media/159224/download
[92] Wong et al, Lancet 2022

COVID-19 mRNA vaccination was rare. There were 411 events per 16.9 million doses of Pfizer-BioNTech and 10.6 million doses of Moderna. The 95% confidence intervals for the incidence rate ratio comparing the brands ranged from 0.80 to 1.94. The risk was highest in men aged 18–24 years of age 1–7 days after Dose 2. Among men 18–25 years of age, there was an elevated rate ratio for Moderna compared to Pfizer-BioNTech vaccination, but this was not found to be statistically significant like in other systems.[93]

To summarize the VaST assessment of the data from v-safe[SM], VAERS, VSD, and BEST, there is a risk of myocarditis/pericarditis after both mRNA COVID-19 vaccines. Most cases had prompt improvement in symptoms. Follow-up surveys suggest most fully recovered that most people fully recover from myocarditis. Risk has been observed in adolescents and adults. Potential risk is under assessment in children <12 years of age and this age group will continue to be monitored. Continued monitoring and natural history studies are needed for myocarditis/pericarditis following mRNA COVID-19 vaccinations in order to better understand rates, outcomes, risk factors, and mechanisms. Monitoring data for Moderna vaccine are available for persons ≥18 years of age who received a 100 ug dose. Currently, the EUA is for a 100 ug dose for those 12–17 years of age and a 50 ug dose for those 6–11 years of age. It is unknown whether the lower dose of 50 ug will pose a lower risk.

VaST will continue to review safety data for multiple US safety systems, in specific age groups, and after primary series and booster doses. In addition, VaST will continue to collaborate with global vaccine safety colleagues on key issues and will continue to provide updates to the ACIP COVID-19 Vaccines WG and ACIP during future meetings.

Discussion Summary (Shimabukuro & Talbot)

Dr. Poehling observed that data from Canada showed that persons who received the primary series doses ≥8 weeks apart had less evidence of myocarditis. She wondered whether there were any plans to evaluate this through the US surveillance systems.

Dr. Shimabukuro responded that information from the VSD shows that adherence to the schedule in the US is quite high. Most persons get their second dose of the primary series on or about 21 days after the first dose as per the recommendations. Canada has a somewhat different situation because there are actually alternate recommendations on dosing for the booster. Canada had more data to make that assessment. In the US, there are limited data to make that assessment, given that adherence to the recommended schedule is quite high. As data continue to be collected, it may be possible to get more information on some of these alternate intervals between the first and second doses. However, there is currently not sufficient information to assess that.

Dr. Long noted that the only surprise to her was the occurrence of myocarditis/pericarditis following a booster, which she anticipated would be lower. She wondered if perhaps it is becoming more common following a booster dose and with the prevalence of Omicron.

Dr. Shimabukuro indicated that the in general, the data are showing that the reporting rates and the risk in terms of the rate ratios are lower after a booster dose compared to Dose 2. This is less clear in terms of incidence rates. The general trend is for lower risk after the first booster dose compared to Dose 2. There may be multiple reasons for that, one of which may be the interval. In some cases, there is a lower dose for the booster dose. There might be some

[93] Wong, FDA's VRBPAC presentation, June 14, 2022. https://www.fda.gov/media/159224/download

selection out of people who got myocarditis after Dose 2 who do not receive a booster dose. CDC will continue to monitor safety of additional booster doses and because myocarditis/pericarditis has signaled and a causal relationship has been established, that will be a focus of the ongoing surveillance. Based on the current data, there does not appear to be greater for the booster dose after Dose 2. If anything, the general trend seems to be a lower risk after at least the first booster compared to Dose 2.

Dr. Klein pointed out that in addition to the rate ratios appearing to be numerically lower after the booster dose in the VSD analyses, it has been after the second dose. All of the analyses are tightly adjusted for calendar time. Issues such as Omicron are taken into account when the booster dose analyses are done.

Dr. Sanchez emphasized that there seemed to be 2 issues, interval and dosing, which may be important in the case of children 5–11 years of age in terms of the perceived fewer cases in Pfizer versus Moderna recipients. Moving forward, it will be important to assess how this risk can be further minimized in the age group that is at highest risk. As he recalled, not vaccinating those with a prior myocarditis/pericarditis report is stated as a precaution not a contraindication and he wondered if CDC is keeping track of that as well to determine how many people have been vaccinated post-myocarditis/pericarditis.

Dr. Shimabukuro indicated that CDC is aware of some case reports of persons with myocarditis being vaccinated. While he was not aware of any recurrence of myocarditis in a vaccinated patient with prior myocarditis, he would say it is probably a fairly rare occurrence. He did not think there was sufficient data to assess risk right now for essentially what would be a "re-challenge." Regarding the younger age groups, he referred to Slide 4 in his presentation. With respect to children 5–11 years of age, vaccine-associated myocarditis tends to follow the same general trend as classic myocarditis. Children 5–11 years of age tend to be a low-risk group for myocarditis in general.

Ms. Bahta that with regard to the earlier discussion about long-haul COVID-19, there has been a cluster in her area of Minnesota of people who are developing chronic symptoms after vaccination. Perhaps long-haul COVID is not rising to the level of creating a signal, but it certainly seems to be a distressing pattern for the people experiencing these chronic long-term symptoms after they have been vaccinated. She asked whether more could be said about this.

Building on what he said earlier, Dr. Shimabukuro indicated that CDC is aware of reports of people experiencing debilitating and long-lasting health problems, acknowledges that this can be disruptive, stressful, and can substantially impact the patient and those around them, and wishes for improvement and recovery. With respect to CDC's systems and monitoring, most AEs reported after COVID-19 vaccines are mild and transient events in general such as injection site and systemic reactions. CDC's safety and monitoring systems are robust and have identified rare, serious events and unanticipated conditions like thrombosis with thrombocytopenia (TTS) and myocarditis. But these systems are dependent on identifying patterns and specific diagnoses or patterns and symptoms following vaccination. That is how TTS and myocarditis were identified. Some patients who become ill experience a wide range of symptoms that can make diagnosis and treatment for their condition challenging, and this understandably can be frustrating for patients, families, and their doctors. It also makes it difficult to identify whether these illnesses are linked to vaccination. Both CDC and FDA use methods that can identify unexpected patterns or diagnoses or symptoms, but it still requires a detectable pattern. Without a specific diagnosis, which is what they are dealing with in many cases, it is much less that these specific patterns will be found in the surveillance systems.

COVID-19 vaccine safety monitoring will continue. CDC will continue to work with partners (e.g., within the federal government, HCP, and provider organizations to better understand these types of AEs.

Dr. Daley asked what the long-term plans are to study the biology or the pathophysiology of pf myocarditis to be better able to reduce it in the future. Related to that, he asked whether Dr. Beigel or others could help him understand the exact dose difference between the Moderna and Pfizer vaccine platforms. They were hearing 25, 50, or 100 micrograms for Moderna or 3, 10 or 30 micrograms for Pfizer, but it was not clear whether that was an apples-to-apples measurement or it includes other things that come along with the mRNA so that it is not an exact comparison of dose amount.

Dr. Beigel indicated that he was not aware of any studies specifically evaluating the pathophysiology, but said he would delve into that and would you a written response to make sure he does a comprehensive review of all the possible paths for that.

Dr. Oliver added that fundamentally in terms of a Pfizer vaccine at 30 µg compared to a Moderna vaccine at 100 µg, there are different components such as the spike protein and lipid nanoparticles. They are not a one-to-one comparison in that the Moderna vaccine at 100 µg in not expected to be 3 times as high as Pfizer at 30 µg. They both have been shown to elicit similar levels of antibodies and efficacy.

In terms of the availability of a consultation, Dr. Poehling asked whether CISA's work could help to understand what is occurring with long-COVID.

Dr. Shimabukuro clarified that the CISA clinical consult service is available to consult with US HCP who request a consultation on a specific patient, largely in terms of how to manage the patient moving forward and issues about additional vaccination. The broader issue of analyzing this condition is that it is difficult to hone in on a certain pattern in the absence of diagnoses and it makes monitoring quite difficult. He emphasized that CDC recognizes and acknowledges that there are reports of people experiencing these conditions. The presentation can be quite heterogenous and variable, which makes it difficult to assess whether what role, if any, vaccination may have played. CDC is certainly exploring ways to further assess these conditions and work with partners, particularly healthcare partners, to better understand these kinds of AEs.

Ms. McNally asked Dr. Shimabukuro to remind ACIP of the impact of other countries' safety monitoring systems in the VaST review and in the ISO's work to monitor safety, especially as it relates to myocarditis and pericarditis.

Dr. Shimabukuro indicated that CDC has regular contact with international partners. In particular, they have spoken with their colleagues in Canada and have been briefed by colleagues in Israel on VaST calls. Data from multiple sources outside of the US are certainly taken into consideration. With respect to myocarditis, the data have been remarkably consistent across systems and across other public health and regulatory agencies that are looking into this condition. International partners, regulatory and public health agencies, and academic institutions are regularly invited to brief the WG in order to gain perspective on what is occurring in states and outside of US safety monitoring systems.

Dr. Duchin (NACCHO) observed that about half of the reports of myocarditis have been followed up with the parent and/or the HCP. He wondered what the implications were of following up only half of the cohort in terms of potential limitations on the interpretation of the cohort that has been followed up.

Dr. Shimabukuro said he did not have the information available right then on how the individuals or HCP who could not be reached for follow-up or who declined to participate may compare to the individuals in the cohort who decided to participate in the survey. While he did not believe that there were any substantial differences, he indicated that he would check on that and report back. With respect to the project to follow-up on the long-term outcomes in these case reports, CDC made every effort to try to reach out to individuals and HCP providers in advance to try to maximize the response rate. In addition, they are engaging in longer-term follow-up at 12+ months and are reaching out to patients they were not able to contact during the first iteration of interviews during which they spoke with providers but did not get a chance to contact the actual patient or the parent.

Safety & Immunogenicity of Moderna 2-Dose Primary Series in Children Ages 6-17 Years

Rituparna Das, MD, PhD reminded everyone that in January 2020, Moderna's 100 µg 2-dose primary series was approved in the US for adults ≥18 years of age after being authorized for emergency use since December of 2020. mRNA-1273 is authorized or approved in 86 countries for a primary series worldwide and in 48 countries for boosters. This vaccine is now authorized for children and adolescents 6–17 years of age outside of the US. For adolescents, 100 µg 2-dose primary series is available in 42 countries. Approval has been received for the 50 µg 2-dose primary series in children 6–11 years of age in 40 countries. More than 6.4 million adolescents and 300,000 children have been fully vaccinated with a primary series of mRNA-1273 outside of the US.

The purpose of this presentation was to discuss the use of mRNA-1273 as a 2-dose primary series for the prevention of COVID-19 caused by SARS-CoV-2 in adolescents 12–17 years of age and children 6–11 years of age. The proposed 2-dose primary series of the 100 µg for adolescents and 50 µg for children 6–11 years of age are to be administered 1 month apart. The pediatric development program has 2 clinical studies. Study 203 in adolescents 12–17 years of age enrolled more than 3,700 participants, nearly 2500 of whom received mRNA-1273. Study 204 enrolled children 6–11 years of age among whom more than 3,300 children received mRNA-1273 at the 50 µg dose. There are 5,800 children total in the whole age group, which established a substantial pre-licensure safety database. In terms of the median safety follow-up times for the studies, Study 203 was blinded and placebo controlled. This trial had about 11.1 months of follow-up at the time of the data cut. Study 204 that investigated the lower doses started as an open-label dose escalation design. The second part of the study was the placebo-controlled trial. There are 8 months of follow-up from the open-label portion and 5.6 months of follow-up for the larger study cohort.

In both studies, you know, safety was a primary objective. Specific safety endpoints included local and systemic adverse reactions that were collected for 7 days post-vaccination. All unsolicited events were captured for 28 days. Serious, medically attended, and AESIs were followed throughout the whole study. Myocarditis emerged as a post-authorization safety signal. This occurred when both studies already were ongoing. Moderna updated its Fact Sheets, Investigative Brochures, and Informed Consent Forms to increase awareness among investigators, study participants, and parents. These conditions also were specified as AESI to

ensure that they would be reported rapidly. To further increase the sensitivity of detection, a script was added to ask about the CDC symptoms of myocarditis and pericarditis during safety follow-up calls on Day 8 and Day 36 post-vaccination. The clinical database also was actively reviewed for any symptoms that could have reflected myocarditis. All potential events were submitted to an independent Cardiac Event Adjudication Committee (CEAC) that was composed of expert cardiologists. There were 2 overlapping approaches to evaluate all unsolicited AEs for any potential cases for myocarditis or pericarditis. Standard MedDRA queries were applied first and a specific algorithm was generated using the MedDRA terms included in the CDC case definitions. Ongoing post-authorization safety studies continue to capture myocarditis and pericarditis as AESIs.

VE was the primary objective in both of these studies. It was successfully inferred by meeting the pre-defined immunogenicity criteria that were agreed upon beforehand with the FDA. In each age group, immune responses were compared to the subset of adults 18–25 years of age from Study 301 that demonstrated efficacy against SARS-CoV-2. The younger adult subset was chosen to ensure sufficiently high immunogenicity from the inference of VE, given that immune responses in younger adults have been observed to be higher than those in older adults. There were 2 non-inferiority criteria. The lower bound of the GMT ratio had to be ≥0.67 and the point estimate had to be ≥0.8. FDA requested a point estimate of ≥1.0 if doses <100 µg were selected. Second, the lower bound of the difference in the seroresponse rate, which is a 4-fold rise baseline, had to be > -10%. An efficacy evaluation was a pre-specified secondary objective in the trial.

As in the 301 study, 2 case definitions were applied 1) the CDC case definition, which requires 1 systemic or respiratory symptom; and 2) the Study 301 case definition, which requires 2 systemic symptoms or 1 respiratory symptom. Both case definitions required an RT-PCR that is positive for SARS-CoV-2. The CDC case definition was considered primary since children tended to have less severe symptoms of COVID-19 than adults. Given that the studies were conducted during different periods of the COVID-19 pandemic, an efficacy follow-up was performed. During Study 301, the original strain was almost exclusively circulating. The efficacy follow-up for adolescents was conducted when the original strain and Alpha variant were circulating. The cohort of children 6–11 years of age were followed when the Delta variant was dominant.[94]

Now to review the safety, immunogenicity, and efficacy data from the Study 203 in adolescents 12-17 years of age. Aa total of 3,732 adolescent participants were randomly assigned 2:1 to receive either 100 µg of mRNA-1273 or placebo. The dose level and schedule were identical to the adults in Study 301. The interval between doses was 1 month apart, with which study participants were extremely compliant. Participants received a booster dose subsequently and are being followed for an additional 12 months. Overall, the 2 groups were well-balanced demographically.[95]

In terms of solicited local AEs within 7 days after Doses 1 and 2, injection site pain was the most commonly reported solicited local AE after either injection. The majority of the reported events were Grade 1 or 2 in severity and lasted for a median of three days. The reactions were reported approximately at the same frequency after Doses 1 and 2 and were reported more frequently in the mRNA-1273 group than in the placebo group. The reactions also were reported more frequently in adolescents than in young adults. The majority of the systemic reactions also

[94] https://covid.cdc.gov/covid-data-tracker/#trends_dailycases
[95] Ali et al., NEJM 2021

were Grade 1 or 2 in severity, with a median duration of 2 days. Consistent with the established profile of mRNA-1273, systemic reactions were reported more frequently post-Dose 2 than post-Dose 1. The reactions tended to be reported as a similar to lower rate in adolescents than in young adults, which suggests that the reactogenicity profiles at the 100 µg dose in adolescents is acceptable and generally comparable to young adults.

In terms of unsolicited AEs recorded up to 28 days after vaccination, 21% of participants in the mRNA-1273 group and 16% of the placebo group reported unsolicited AE, and 13% and 6%, respectively were considered by the investigators to be potentially vaccine related. This was primarily driven by reports of lymphadenopathy and injection site reaction. The percentage of medically attended adverse events (MAAEs) was similar between the 2 groups, and there were very few SAEs, severe AEs, or AEs leading to discontinuation. No vaccine-related SAEs or deaths were reported.

Long-term safety data are now available for a median follow-up of 11.1 months after Dose 2 for the original vaccine recipients. The safety profiles were typical for this age group and no new safety concerns were identified. The most commonly reported MAAE was COVID-19, although importantly, there were no SAEs of COVID-19. The increased rates of COVID-19 likely reflect the Omicron surge and the fact that these participants were nearly a year out after vaccination when a number of these events were reported. There were no confirmed cases of myocarditis or pericarditis in the long-term follow-up assessments.

Given the importance of these events, Dr. Das also discussed Moderna's post-authorization surveillance since mRNA-1273 is authorized for adolescents in 42 countries worldwide. These data come from the Moderna Global Safety Database and are analyzed by each cohort's dose number and gender. Consistent with other reports in the published literature and what was discussed throughout regarding the higher reporting rate for myocarditis after Dose 2 in males, the highest rates were in males 18–24 years of age after Dose 2 with approximately 43 cases per million doses. The rate for the adolescents was 13.3 cases per million doses. For comparison, Block, et al[96] recently reported the incidence of myocarditis after SARS-CoV-2 infection. The incidence of myocarditis in adolescent and young adult males diagnosed with SARS-CoV-2 is over 500 cases per million, suggesting that the rate is substantially higher than after Dose 2 of mRNA-1273.

For the primary effectiveness objective, the primary hypothesis was to demonstrate that immune responses in adolescents were non-inferior to the young adult cohort in Study 301 study where efficacy of the vaccine against COVID-19 was demonstrated. The first criterion was a GMT ratio in the adolescent group over the young adult group. The observed GMT ratio was 1.1 with a lower limit of 0.9. The second criterion was the group difference in seroresponse rate. The rate was 98.8% in the adolescent group and 98.6% in the adult group, with a difference of 0.2 percentage points and a lower limit of -1.8. Therefore, the primary effectiveness hypotheses were met. VE was evaluated as a secondary objective. In terms of the case definition used by the CDC, there were 7 cases reported in the placebo group and 1 reported in the mRNA-1273 group, for VE of 93.3%. When the more stringent case definition from Study 301 was used, there were 4 cases reported in the placebo group and 0 cases in the mRNA group, with an observed VE of 100%.[97]

[96] Block, J. P. et al. Cardiac Complications After SARS-CoV-2 Infection and mRNA COVID-19 Vaccination — PCORnet, United States, January 2021–January 2022. *MMWR Morbidity Mortal Wkly Rep* 71, (2022).
[97] Ali et al, NEJM, 2021

Study 204[98] regarding the safety, immunogenicity, and efficacy of mRNA-1273 in children 6–11 years of age was conducted in 2 parts. The first part was to identify the correct dose of mRNA-1273 in children 6–11 years of age and the second part was to evaluate that dose in a randomized placebo-control study. In part one, 2 doses of mRNA 1273 were evaluated in an open-label design. The lower 50 µg dose was selected as it showed an acceptable tolerability profile and demonstrated a high likelihood of meeting the pre-specified immunogenicity success criteria. After the first part was completed, a DSMB meeting occurred to ensure the committee's concurrence with the selected dose. The second part of the study was designed to randomize the children in a 3:1 ratio to receive either mRNA-1273 or a saline placebo. The data presented during this session focused on the randomized phase of Study 204, which evaluated the 2-dose 50 µg primary series in children 6–11 years of age. All study participants will be followed for 12 months after their last dose of vaccine. The demographics for the children ages 6–11 years were well matched among vaccine and placebo recipients. The mean age in both age groups was 8.5 years, with a good balance of males and females.

In terms of solicited local reactions in children 6–11 years of age, pain was the most common event with similar rates and severity following Dose 1 and Dose 2. Most local AEs, including pain, were Grade 1 or 2 and there were few Grade 3 reactions. The median duration of local adverse reactions in this age group was 2 to 3 days. Fatigue and headache were the most commonly reported systemic adverse reactions. Reporting rates for fatigue and headache were similar to those seen in adolescents and young adults. The rest of the systemic adverse reactions were reported at a lower rate in the older children compared to the young adults. The rates of systemic adverse reactions post-Dose 1 were similar to placebo. Among vaccine recipients, systemic adverse reactions were more frequently reported post-Dose 2 than post-Dose one. Events were mostly Grade 1 or 1 in severity, with a median duration of 2 to 3 days.

Regarding unsolicited AEs reported up to 28 days after any injection in children 6–11 years of age, 30% of participants in the vaccine group compared to 25% in the placebo group reported any unsolicited adverse reactions. The imbalance in AEs was primarily driven by local AEs in axillary swelling or tenderness, similar to what was seen in adolescents. MAAEs were similar among the 2 groups at 13% and 14%, and there were no SAEs considered related to vaccinations by the investigators. There were no fatal AEs, events of MIS-C, or myocarditis/pericarditis.

Long-term safety data are now available for a median duration of 5.6 months among the original vaccine recipients. Looking at cumulative incidence of unsolicited AEs through this time, no new safety signals were observed and there were no deaths, related SAEs, or AEs of MIS-C or myocarditis in this original vaccine group. Safety data also were collected on the original placebo recipients who got vaccine in the crossover. There was 1 related SAE after vaccination. This was a case of ileus reported in a participant with a complex gastrointestinal (GI) medical history from the placebo crossover group.

Immunogenicity was a primary objective of the study. After the 2-dose 50 µg primary series in children 6–11 years of age, the GMT was 1,610 in the older children compared to 1,300 in the young adults. This resulted in a GMT ratio of 1.2, which met the prespecified non-inferiority criteria. The seroresponse rate was 99.1%, which also met the non-inferiority seroresponse criteria. The efficacy assessment was a secondary objective. Assessment of placebo-controlled VE in children 6-11 years of age group was limited due to the authorization of another COVID-19 vaccine. Per the study protocol, participants were unblinded then to offer them access to

[98] Creech et al., NEJM, 2022

mRNA-1273. The number of COVID-19 cases in the per protocol population post-Dose 2 with a 1.8 median follow-up time was small and did not allow for meaningful assessment. Dr. Das presented the assessment that was conducted in the mITT population, which was based on a higher number of cases because the mITT population allowed counting of cases 14 days after post-Dose 1. The mITT calculation is typically a more conservative calculation because it does not require a follow-up time after the whole vaccine dosing and it allowed an additional month for case accrual. The overwhelming majority of study participants in the mITT cohort received their second dose of vaccine. Efficacy was high at 88% using the broad CDC definition and was 92% using the more stringent Study 301 definition. Given that this trial was conducted during the Delta period, this represents direct efficacy against the Delta variant. The immune response of mRNA-1273 has been remarkably consistent across each cohort despite administering lower doses to children. Across the pediatric age group, the ratio of immune responses compared to young adults 18–25 years of age ranged from 1.01 to 1.28, successfully meeting all of the immunogenicity hypotheses.

To summarize, the totality of data from the pediatric development program in these age groups from 8,000 children, 5,800 of whom received vaccine and had a median duration of follow-up of over 5.6 months, supported the benefits of mRNA-1273 in school-aged children and adolescents and that these benefits outweigh the known and potential risks. mRNA-1273 was generally well-tolerated, with a safety profile consistent with that observed in young adults. No new safety concerns have been identified. Moderna's pediatric studies were designed to meet the FDA criteria for inference of VE compared to young adults as the VE in a population of adults already has been demonstrated. In both age groups, the co-primary immunogenicity hypotheses were met. In addition, there was evidence of efficacy against COVID-19 conferred by mRNA-1273 ranging from 88% to 100% during original, Alpha, and Delta variant circulation. Moderna has established a robust plan to continue to evaluate safety and effectiveness in its clinical trials and in post-authorization studies.

Discussion Summary

Dr. Poehling requested additional information about any Grade 4 AEs that were detected in either cohort.

Dr. Das indicated that there were no Grade 4 events for either local or solicited systemic AEs. In the adolescent group, there were no Grade 4 local solicited AEs. There were 4 Grade 4 systemic AEs. Of those, 3 occurred in vaccine recipients and 1 was in a placebo recipient. The vaccine recipient had events of fever, headache, nausea, and vomiting.

Referring to Slide 18, Dr. Daley requested additional information about the data source in terms of strengths and limitations.

Dr. Das indicated that these data were from Moderna's Global Safety Database. All global reports for myocarditis are contained in this database. The denominator is the estimated per million doses administered by the different age groups. The limitations are that it is passive reporting from patients' parents and providers. Moderna attempts to get as much information on the cases as possible, but are probably not as good as the CDC assessment are at times in terms of being able to get all of the detailed follow-up, which is a challenge for everyone.

Referring to Slide 32, Dr. Daley asked what was being measured when in the 100 µg in terms of whether that was just mRNA or mRNA plus other elements and how does that translates into how a 50 µg dose compares to a 100 µg dose and whether post-vaccination myocarditis has any sort of dose response.

Dr. Das explained that the mRNA contents ratios are exactly as would be expected for the mRNA contents. What is being measured is only the mRNA. In terms of whether post-vaccination myocarditis has any sort of dose response, it would be very hard to opine on that based on the dataset.

Dr. Sanchez emphasized that it is critical to know what exactly is being measured and to understand more about the pathogenesis in order to try to prevent it. He asked if there is a standard measurement of mRNA content or if each company or each laboratory measures mRNA differently. It is not clear if/how Moderna's 50 µg and 100 µg can be correlated to Pfizer's 30 µg.

Dr. Das indicated that Moderna has a validated method for mRNA measurement, which is how they are reporting their doses. She was not aware of other vaccine manufacturer's measurement methodology. Perhaps it would be better for FDA to comment on this.

Dr. Sanchez recognized that it has been stated that mRNA disappears quickly, but he inquired as to how long spike proteins have been detected in patient's serum or tissues following mRNA vaccination and what the molecular weight is of the spike protein that human bodies produce—with respect to transplacental transfer as well.

Dr. Das indicated that the detectability of spike protein and mRNA have been assessed. The mRNA degrades quite quickly, and spike protein availability is on the order of days, but less than a week. She will confirm this with their toxicology folks as well. The molecular weight is what would be expected for the full spike.

Dr. Daley asked Dr. Das to comment on the thoughts about interval with respect to myocarditis and future plans Moderna has with respect to studying that.

Dr. Das indicated that they looked again at all of their studies and the interval is very tight. The checked whether it would be possible to tease out a 6-week interval, but the numbers are very small. They are using an 8-week interval in their infant study so it will better coincide with childhood immunizations. They have heard the feedback about studying at least the immunogenicity at the longer intervals and will take this back to find out what could be done from a clinical study immunogenicity standpoint in terms of the interval. Certainly, their animal studies show that the longer intervals are good for immunogenicity.

EtR Framework: Moderna COVID-19 Vaccine in Children & Adolescents Ages 6-17 Years

Sara Oliver, MD, MPH (CDC/NCIRD) presented the EtR framework for the Moderna COVID-19 vaccine in children and children 6–11 years of age and adolescents 12–17 years of age. The policy questions for this EtR Framework analysis were as follows:

- ❑ Should vaccination with Moderna COVID-19 vaccine (2-doses, 50 mcg, IM) be recommended for children ages 6–11 years, under an Emergency Use Authorization?

- ❑ Should vaccination with Moderna COVID-19 vaccine (2-doses, 100 mcg, IM) be recommended for adolescents ages 12–17 years, under an Emergency Use Authorization?

In terms of the PICO question, the population is people ages 6–17 years of age with the comparison group of no vaccine. The outcomes of interest include symptomatic laboratory confirmed COVID-19, hospitalization due to COVID-19, MIS-C, SARS-CoV-2 seroconversion to a non-spike protein, asymptomatic SARS-CoV-2 infection, SAEs, reactogenicity Grade ≥3. While the analysis addressed individuals 6–17 years of age overall, the differences were highlighted in instances where there were data for children 6–11 years of age and adolescents 12–17 years of age.

Regarding the public health problem domain, there have been more than 85 million total reported cases of COVID-19 in the US as of mid-June 2020. Since April, there has been an increasing number of cases. This has been leveling out since late May, with a current 7-day average of around 100,000 cases.[99] In total during the pandemic, over 5.1 million cases have occurred among children ages 5–11 and more than 5.6 million cases have occurred among adolescents ages 12–17 years.[100] In April, unvaccinated individuals ages 5–17 years overall had a 2 times greater risk of testing positive for COVID-19 compared to children and adolescents vaccinated with at least a primary series.[101] There has been an increase in hospitalizations among children and adolescents during the peak of the Omicron surge, leading to the highest hospitalization rates for these age groups to date during the pandemic.[102] It is known that vaccination prevents hospitalization. Although children ages 5–11 years had lower hospitalization rates overall than adolescents, the same pattern can be seen after they became eligible for vaccination in late 2021. It also is important to note that the benefits of vaccination are always more pronounced when the disease burden is high. It can be predicted that with future COVID-19 surges, the unvaccinated will continue to bear the burden of disease.[103]

To put the burden of COVID-19 illness in context, data from COVID-NET and FluSurv-NET, which conducts surveillance for influenza-associated hospitalizations from October 1st through April 30th of each year—the typical US influenza season. Among children ages 5–11 years, COVID-19 hospitalization rates from October 2020 through September 2021 were lower than influenza hospitalization rates during the 2017-2018 or 2019-2020 influenza seasons. However, the preliminary hospitalization rates during the 2021 through April 2022 influenza season, which included the Omicron surge, were as high or higher than the influenza hospitalization rates for the prior included influenza seasons in this age group. However, the cumulative rates of COVID-19 hospitalizations for both years are considerably higher than influenza hospitalization rates during all the prior influenza seasons among adolescents 12–17 years of age.[104]

[99] Source: COVID Data Tracker, https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases Accessed 6/21/2022
[100] Source: COVID Data Tracker, https://covid.cdc.gov/covid-data-tracker/#demographicsovertime Accessed 6/16/2022
[101] CDC COVID Data Tracker, https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status Accessed May 20, 2022
[102] Source: COVID-NET, https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html Accessed 6/20/22
[103] Source: CDC COVID Data Tracker: COVID-NET Hospitalizations by Vaccination Status. Accessed June 20, 2022
[104] Delahoy MJ, Ujamaa D, Taylor CA, et al. Comparison of influenza and COVID-19-associated hospitalizations among children < 18 years old in the United States-FluSurv-NET (October-April 2017-2021) and COVID-NET (October 2020-September 2021). Clin Infect Dis. 2022 May 20:ciac388. doi: 10.1093/cid/ciac388

Moving to mortality associated with COVID-19 from January 2020 through May 2022, data from the National Center for Health Statistics (NCHS) showed that there were 189 COVID-19-related deaths among children 5–11 years of age. This represents 2.5% of all deaths in this age group. There were 443 COVID-19 deaths among adolescents 12–17 years of age, which represents 2.4% of all deaths in this age group.[105] Approximately 36% of children ages 5–11 years of age and nearly 70% of adolescents have received at least 1 dose of COVID-19 vaccine through mid-June. Overall, 18 million children ages 5–11 years and 7.5 million children ages 12–17 years remain unvaccinated.[106]

In summary of the available data for the public health problem domain, children and adolescents ages 5–17 years are at risk of severe illness from COVID. There have been over 10.3 million cases reported in this age group and to date, sadly, over 600 deaths. Children and adolescents who have received COVID-19 vaccines have better outcomes than children who are unvaccinated, particularly against severe illness. Approximately 65% of children 5–11 years of age and about 30% of adolescents have not yet received a COVID-19 vaccine. The WG determined that COVID-19 among children and adolescents is of public health importance.

Moving to benefits and harms domain, it is known that the timeframe during which studies were conducted is critically important in the interpretation of efficacy results. The RCT, Study 203 for adolescents 12–17 years of age, was conducted during the original or ancestral strain and into the Alpha variant. The RCT, Study 204 for children 6–11 years of age, was conducted during Delta.[107] Neither of these studies was conducted during the Omicron surge, which is different than the VE results heard during the past weekend where the trials were conducted during Omicron.

First, to review the data for children 6–11 years of age. Overall, there are data from 1 study from the Moderna Phase 2/3 RCT. Participants were randomized 3:1 vaccine to saline placebo. Data included all eligible randomized participants who received vaccination through the data cutoff of November 10, 2021. The available body of evidence is primarily from the Delta variant. The VE estimates do not represent the most recent epidemiology. Per protocol, there were 2 co-primary endpoints for efficacy based on immunobridging, GMRs and seroresponse. Data on symptomatic COVID-19 using various definitions also were supplied. The 2-dose VE estimate was 75.8%. When those with prior infection are included, the CDC definition, VE is 80.6%. Based on 8 total cases, each of these 2-dose estimates has a wide confidence interval. The immune response to vaccine was evaluated using the GMR of children to young adults. The non-inferiority criteria are met when the lower bound of the 95% confidence interval for the ratio comparing the geometric mean neutralizing antibody titers for the 2 groups is not less than a pre-specified value, which for this study was set at 0.67. The immune response to the vaccine in children 6–11 years of age was noninferior to that observed in those 18–25 years of age, with a ratio of 1.2 (1.1, 1.4). Therefore, the non-inferiority objective was met.

The GRADE assessment for symptomatic laboratory-confirmed COVID-19 using the direct efficacy had serious concerns of imprecision due to the small number of events, with a final evidence type of Type 2 (moderate certainty). The GRADE evidence assessment for the outcome of symptomatic laboratory-confirmed COVID-19 using immunobridging had serious concerns of indirectness, but immunogenicity is an indirect measure of efficacy. The final evidence type was Type 2 (moderate certainty). Next is the GRADE evidence for the outcome of

[105] https://data.cdc.gov/NCHS/Provisional-COVID-19-Deaths-Counts-by-Age-in-Years/3apk-4u4f/data Accessed 5/14/22
[106] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends Accessed June 20, 2022
[107] Source: COVID Data Tracker, https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases Accessed 6/16/2022

asymptomatic SARS-CoV-2 infection. During the Phase 2/3 trials, participants were evaluated for asymptomatic infection using a nasopharyngeal (NP) swab for reverse transcriptase polymerase chain reaction (RT-PCR) testing on Day 57 or when unscheduled illness visits were triggered by a SARS-CoV-2 exposure. Participant with documented COVID-19 symptoms were excluded. There were 9 asymptomatic RT-PCR positives among over 2,600 vaccine recipients and 10 asymptomatic RT-PCR positive among 853 placebo recipients for an efficacy estimate of 71% (28.8%, 88.1%). There was serious concern of indirectness because the full cohort was only PCR tested on Day 57 and serology was not done for all participants. Therefore, the results do not represent full serologic testing. There also were serious concerns of imprecision due to the small number of events, so the final evidence type was Type 3 (low certainty).

Next is the outcome of SAEs. In the Phase 3 trial, 6 of approximately 3,000 participants in the vaccine group and participants out of almost 1,000 participants in the placebo group experienced SAEs for a comparison of 0.20%. No SAEs were deemed related to the vaccine. All participants who received at least 1 dose were included through the data cutoff of November 10, 2021. For the GRADE assessment, there were serious concerns of indirectness due to the short duration of follow-up. There also were serious concerns of imprecision due to the width of the confidence interval, which included estimates for which other policy options might be considered. The final evidence type was Type 4 (very low certainty).

For the outcome of reactogenicity, reactions were solicited through electronic diaries for 7 days after each dose. The criteria for meeting Grade 3 or higher include local reactions of pain at injection site, redness, swelling, axillary swelling; and systemic events of fever, nausea/ vomiting, headache, fatigue, chills, new or worsened muscle pain, and/or new or worsened joint pain. Grade 3 local or systemic events were reported in 17% of persons in the vaccine arm and 3% of those in the placebo arm. No Grade 4 events were observed in vaccine recipients. The GRADE assessment for this outcome with a relative risk of 5.2 (3.6, 7.3), there were no serious concerns in the certainty evidence estimate, so the final evidence type was Type 1 (high certainty).

To summarize the GRADE assessment for the Moderna vaccine in children 6–11 years of age in terms of benefits, the available data indicate that the vaccine was effective at preventing symptomatic COVID-19 with direct efficacy and indirect immunobridging, both with an evidence of Type 2. Data also estimated the prevention of asymptomatic infection with less certainty and evidence of Type 3. In terms of harms, SAE reporting was comparable. Given that there was concern for indirectness and imprecision, the evidence was Type 4. SAEs were judged to be related to the vaccine. Reactogenicity was more common in vaccinated persons, so the evidence was Type 1.

Moving to adolescents ages 12–17 years, participants were randomized 2:1 vaccination to saline placebo. Data included all eligible randomized participants who received vaccine through the data cutoff of May 31, 2021. The available body of evidence was predominantly from a time period when either the original ancestral strain or the Alpha variant was the dominating circulating variant. Therefore, these VE estimates do not represent the most recent epidemiology. The data on symptomatic COVID-19 also was supplied using various definitions. Per protocol, there were 2 co-primary endpoints for efficacy based on immunobridging, the GMR, and seroconversion. Using the CDC definition, the VE estimate was approximately 89% based on 11 total cases. For the immunobridging assessment, the immune response to vaccine in those 12–17 years of age was non-inferior to that observed in those 18–25 years of age, with a GMR of 1.1 (0.9, 1.2). Therefore, the non-inferiority objective was met.

For the GRADE assessment of symptomatic laboratory-confirmed COVID-19 using the direct efficacy, there was serious concerns of imprecision due to the small number of events and the final evidence type was Type 2 (moderate certainty). For the GRADE assessment of aymptomatic laboratory-confirmed COVID-19 using immunobridging, there was serious concern for indirectness because immunogenicity is an indirect measure of efficacy. The final evidence type was Type 2 (moderate certainty). For asymptomatic SARS-CoV-2 infection, asymptomatic infection was measured in 2 ways with seroconversion from blood drawn on Day 57 and by NP swab for PCR at Day 57 if an unscheduled visit was triggered by SARS-CoV-2 exposure. There were 21 asymptomatic cases among around 2,000 vaccinated persons and 16 asymptomatic cases among just over 1,000 placebo recipients for an efficacy estimate of 36.1% (-22.0%, 66.5%), but the confidence interval was wide and included zero. For the GRADE assessment of asymptomatic SARS-CoV-2 infections, there were serious concerns of imprecision due to wide confidence intervals and study size. The final evidence type was Type 3 (low certainty).

For the outcome of SAEs, 6 out of approximately 2,400 participants experienced an SAE in the vaccine group and 2 participants out of approximately 1,200 experienced an SAE in the placebo group for a comparison of 0.16%. In terms of the GRADE assessment for this outcome, there were serious concerns for indirectness due to short duration of follow-up and very serious concerns for imprecision due to the wide confidence interval and study size. The final evidence type was Type 4 (very low certainty). For the outcome of reactogenicity in the Phase 3 study, local or systemic reactions were reported in about 25% of persons in the vaccine arm and about 4.8% of persons in the placebo arm. The majority of these events were Grade 3. There were 3 Grade 4 events in vaccine recipients, including 1 fever ≥40° C, 1 headache, and 1 nausea and vomiting. The GRADE assessment for reactogenicity had a relative risk of 5.2 (4.1, 6.8). There were no serious concerns in the certainty assessment, so the final evidence type was Type 1 (high certainty).

To summarizes the GRADE assessment for Moderna COVID-19 vaccine in adolescents, as seen for children 6–11 years of age, the efficacy estimates for direct efficacy and immunobridging were Type 2. SAE reporting was comparable, but there were concerns for indirectness and serious concerns for imprecision, so the evidence type was Type 4. The evidence type for reactogenicity was Type 1. In conclusion, the efficacy seen after 2 doses of the Moderna COVID-19 vaccine in children 6–17 years of age is consistent with the real-world VE seen with SARS-CoV-2 variants at that time, which were Alpha or Delta depending on the age. Antibody levels after 2 doses in children and adolescents 6–17 years of age produced similar antibody levels after 2 doses in individuals aged 18–25 years. Reactogenicity after the vaccine is consistent with what has been seen in the Moderna vaccine in other age groups.

For the outcome of myocarditis considerations, from the safety presentation earlier from Dr. Shimabukuro showing the rates of myocarditis after mRNA vaccine, the rates were highest in males 12–29 years of age and after the second dose. Note that for those <18 years of age, the results were for only the Pfizer vaccine. Based on data presented to the ACIP in February 2022,[108] some but not all observational analyses of post-marketing data suggest that there may be an increased risk of myocarditis and pericarditis in males 18–39 years of age following the second dose of a Moderna vaccine relative to Pfizer vaccine. In summary of the findings from the data presented in February, the risk of myocarditis may be higher for Moderna than Pfizer, but there were important limitations to note, including that the data were observational, the rates were not readily comparable to differences in case definition and risk interval length,

[108] Presented to ACIP Feb 4, 2022: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-02-04/11-COVID-Moulia-508.pdf

subpopulations, case ascertainment, calendar time, and implementation factors. In addition, a limited number of geographic locations were administering both mRNA vaccines and had data available on myocarditis. The ACIP also has heard data regarding the impact of extended intervals between Dose 1 and Dose 2 from Canadian colleagues showing that for both vaccine products, the overall myocarditis rates were higher when the interval between the doses was shorter, and myocarditis rates were lower with an extended interval between the two doses.[109]

To generally summarize myocarditis risk, the risk of myocarditis after the Modern vaccine is unknown in children and adolescents ages 6–11 and 12–17 years of age. Some observational data in adults suggest a possible increased risk after the Moderna vaccine compared to Pfizer. However, there is information on risk mitigation measure for myocarditis. Extending the interval between Dose 1 and Dose 2 of these mRNA COVID-19 vaccines to 8 weeks may further lower the myocarditis risk.

To summarize the known and potential benefits, the clinical trials provide data for protection against symptomatic infection. The clinical trials were not powered to detect efficacy against severe disease, but similar patterns are expected to what those seen with mRNA COVID-19 vaccines overall with higher protection against severe disease. As ACIP heard earlier in the day, emerging data in adults suggest that post-COVID-19 conditions may be less likely to occur in vaccinated individuals. In summary of the known and potential harms, there are post-authoritarian safety data showing that after almost 600 million doses of COVID vaccines given in the US, the risk of adverse cardiac outcomes were 1.8–5.6 times higher after SARS-CoV-2 infection than after mRNA COVID-19 vaccination among adolescent males 12–17 years of age. Importantly, there is a mitigation measure in that extending the interval between Dose 1 and Dose 2 of the mRNA vaccines to 8 weeks may further lower the myocarditis risk.

In summary of benefits and harms overall, the clinical trials were conducted prior to Omicron predominance. Post-authoritarian VE studies particularly against infection have shown lower VE against Omicron compared to previous variants. However, the Moderna COVID-19 vaccine for older children and adolescents met the non-inferiority criteria for neutralizing antibody levels. Receipt of a primary COVID-19 vaccine series can provide protection against both COVID-19 disease and severe outcomes. Overall, the benefits of the Moderna vaccine in both children and adolescents ages 6–17 years of age outweighs the risks and extending the interval between Dose 1 and Dose 2 to 8t weeks may further optimize that benefit-risk balance by lowering the myocarditis risk as well. The WG felt that the desirable anticipated effects are large, the undesirable effects are small, and the desirable effects outweigh the undesirable effects in favor of the intervention.

Moving on to the values domain, adolescents 13–18 years and parents of adolescents 13–18 years of age were surveyed using national research panels on 3 occasions or waves.[110] Wave 1 was before the COVID vaccine was available, Wave 2 was after vaccine was available for adults, and Wave 3 was after vaccine was available for persons ≥12 years of age. In terms of parent survey responses regarding the importance of both routine vaccines and COVID-19 vaccines, COVID-19 vaccines and influenza vaccines were rated similarly by parents. Overall, parents reported relatively high importance of getting the COVID-19 vaccines, although at times this was slightly less important than what was reported for other routinely recommended

[109] Presented to ACIP Feb 4, 2022: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-02-04/09-COVID-Tunis-508.pdf

[110] Middleman, A. B., et al. (2022). "Vaccine Hesitancy in the Time of COVID-19: Attitudes and Intentions of Teens and Parents Regarding the COVID-19 Vaccine." Vaccines 10(1):4. https://doi.org/10.3390/vaccines10010004

vaccines. Regarding parents' willingness to have their teen get the COVID-19 vaccine and other routine vaccines together, the CDC and AAP support giving other recommended childhood and adolescent immunizations at the same time as COVID-19 vaccinations, particularly for children and teens who are behind on their routinely scheduled immunizations. When parents were asked for the willingness to have their teen get a COVID-19 vaccine and routine vaccine they may need at the same time, 70% were supportive. For those who selected "no" or "not sure," further information was collected. The most common reason for not wanting this was that the teen was already up-to-date on recommended vaccines. However, some parents expressed concern regarding safety with concomitant administration.

Looking over time at parents' willingness, 56% of parents said that their teen 12–17 years of age had been vaccinated, which has been fairly steady since January. About 3 in 10 parents said they would definitely not get their teen vaccinated. Over time, the "wait and see" population has declined. The results were similar parents of children 5–11 years of age who have been eligible for vaccinations since early November. About 4 in 10 of these parents said that their child has been vaccinated, 12% said that they will only get their child vaccinated if they are required to do so, and 32% said they definitely would not get their child vaccinated. While the "wait and see" population has declined in this age group over time as well, 10% to 13% of parents are still taking a "wait and see" approach.[111] From the same survey that was conducted but this time in February, parents of adolescents expressed the most confidence in the safety of the vaccines for their children. Over half of parents of adolescents said that they were confident in the safety of vaccine, many of whom already had been vaccinated. Slightly fewer parents were confident in the safety of vaccine for children 5–11 years of age. Adolescents themselves were surveyed to gain a better perspective of potential factors that would increase their intent. Potential factors among adolescents were more information on safety and efficacy, preventing the spread of COVID-19 to family and friends, and resumption of or increases in social activities or traveling.[112]

In summary of the values domain, over half of parents of adolescents 12–17 years of age and nearly 40% of children 5–11 years of age report that their child is already vaccinated or around 30% of parents of both age groups report that their child definitely will not get vaccinated. Parents of adolescents expressed the most confidence in safety whereas fewer parents of children 5–11 years of age are confident. Further information on the vaccine and resumption of social activities are important to adolescents. The WG felt that how the target population feels about the balance of desirable and undesirable effects varies. Not surprisingly, there was important uncertainty or variability in how much people value the main outcomes.

Regarding the domain of acceptability, pediatricians and HCP are the top trusted source for information about the COVID-19 vaccines for children among parents across community types. While majorities or urban and suburban parents also trust their local health department or the CDC, rural parents are somewhat less trusting of these sources. Around half of parents across community types say their child's school has provided them with information on how to get a COVID-19 vaccine for their child. However, smaller shares of rural parents say that their child's school has encouraged them to get vaccinated compared to parents in urban areas. This difference may play an important role in vaccine uptake for children across communities. As previously reported, parents whose children's schools encourage vaccination are more likely

[111] KFF COVID-19 Vaccine Monitor: February 2022. https://www.kff.org/coronavirus-covid-19/dashboard/kff-covid-19-vaccine-monitor-dashboard/#parents Accessed May 4, 2022

[112] Scherer AM, Gedlinske AM, Parker AM, et al. Acceptability of Adolescent COVID-19 Vaccination Among Adolescents and Parents of Adolescents — United States, April 15–23, 2021. MMWR Morb Mortal Wkly Rep 2021;70:997–1003. DOI: http://dx.doi.org/10.15585/mmwr.mm7028e1

than those whose school do not encourage vaccination to say their child had received a vaccine. Around half of all parents across community types say their child's school provided them with information around the COVID-19 vaccine. However, it is known that this varies by location.[113]

Jurisdictions have taken a broad approach to provide COVID-19 vaccines to children. Based on survey data among children and adolescents who received their COVID-19 vaccines,[114] most received their vaccine at either their medical home or pharmacy. This was even more important among children 5–11 years of age. Schools and other mass vaccination sites were used less frequently, especially for children 5–11 years of age.

To summarize acceptability, most jurisdictions were utilizing a variety of implementation strategies to vaccinate children and adolescents. However, it is known that most children in this age group are receiving their vaccine at either their medical home or a local pharmacy. Pediatricians or other HCP are the top source for information about COVID-19 vaccines for children among parents across community types. The WG felt that the Modern vaccine is acceptable to key stakeholders.

For the domain of feasibility,[115] the 50 mcg product for children 6–11 ships at -20°C. The product that will be used has the same cap color as the product for young children, but with a different border color. It has a different concentration than the adult primary series, although it has the same concentration as the product for young children. However, the vial authorized for this age group will be labeled as "Booster dose 18 years and over" authorized for use and it does not require diluent. The product for adolescents 12–17 years of age at 100 mcg has a red cap with a light blue border and is the same products and vial as used for adults. It is given at the 0.5 mL volume for primary series in individuals ≥12 years of age. Currently, the 0.25 mL volume is also being given for booster doses for those ≥18 years of age. There will not be a new national drug code (NDC) code for this as it is the same product for the primary series in those ≥18 years of age that already is available. This product also does not require diluent. As additional vaccines and vaccines products continue to be rolled out, vaccines.gov is a way that parents and their children can find a COVID-19 vaccine.

To summarize the feasibility domain, the Moderna products for children and adolescents ages 6–17 years of age may be less familiar to pediatric healthcare providers. However, they can be stored at a traditional freezer temperature and do not require diluent. The product for children 6–11 years of age will be labeled as a "booster dose for those 18 years and older," which will require considerable education. The adolescent product is the same as the adult formulation and will be more familiar to providers. The WG felt that the vaccine is feasible to implement, although challenges were noted with labels and the vials.

[113] KFF COVID-19 Vaccine Monitor: Winter Update on Parents' Views (November 8-23, 2021). https://www.kff.org/coronavirus-covid-19/poll-finding/kff-covid-19-vaccinemonitor-vaccine-attitudes-rural-suburban-urban/ Accessed March 7, 2022

[114] National Immunization Survey Child COVID-19 Module (NIS-CCM) is an on-going random-digit-dialed telephone survey that began in July 2021 to collect COVID-19 vaccination status and intent for children from adult respondents knowledgeable about the child's vaccination status. All estimates are weighted to represent the non-institutionalized U.S. population of children and mitigate possible bias that can result from an incomplete sample frame or non-response. Survey weights were calibrated to vaccine administration data reported to CDC. For more information about the survey, see https://www.cdc.gov/vaccines/imz-managers/nis/about.html#nis-ccm and https://www.cdc.gov/vaccines/imz-managers/coverage/covidvaxview/index.html

[115] CDC. Updated Pediatric COVID-19 Vaccination Operational Planning Guide – Information for the COVID-19 Vaccine for Children 6 Months through 4 Years Old and/or COVID-19 Vaccine for Children 6 Months through 5 Years Old. https://www.cdc.gov/vaccines/covid-19/down

For the domain of resource use, vaccines are currently available at no cost to recipients and that protection against severe disease is likely to result in a considerable reduction of healthcare cost. Cost-effectiveness is not the primary driver for decision-making during a pandemic, but will continue to be assessed. The WG felt that vaccines are a reasonable and efficient allocation of resources.

For the equity domain, vaccination coverage and parental intent suggest that for children 5–17 years of age, older children are more likely to be vaccinated than younger children and multi-racial and Hispanic children are more likely to be vaccinated than Black or White children.[116] Coverage among children 5–11 years of age varies by race and ethnicity, with nearly 72% of Black children 5–through 11 years of age remaining unvaccinated as of late April. Looking at coverage among adolescents 12–17 years of age with at least 1 COVID-19 vaccine dose by race and ethnicity shows that the unvaccinated population varies by race and ethnicity, with just over 40% of both Black and White adolescents who are unvaccinated. In terms of the percent of children and adolescents 5–17 years of age by Metropolitan Statistical Area (MSA), coverage is considerably lower among rural children.[117] The potential drivers of this disparity are that rural parents reported less intent to vaccinate their children, there is lower vaccine safety confidence, and more than half of rural parents stated that getting their children vaccinated against COVID-19 would be a bigger risk for their children than the COVID-19 infection itself. [118]

CDC has numerous communication resource materials available for vaccine providers and for partners, including vaccine pages focused on vaccinating children with disabilities, an updated quick conversation guide for talking with families, a Medscape commentary on routine pediatric and COVID-19 vaccination, customizable materials that align with key messages, and updated information for schools to include content for childcare partners.[119] Culturally and linguistically appropriate materials including printable fact sheets are available in a variety of languages (Amharic, Arabic, Chinese, English, French, Korean, Portuguese, Spanish, Vietnamese).[120] There also are focused resources to promote COVID-19 vaccine for children and teens with diverse images.[121]

In summary of the available evidence for the equity domain, there are noted disparities in vaccination coverage and parental intent for children by age, race and ethnicity, and MSA. Communication materials that are culturally appropriate and diverse, including materials for children with special healthcare needs, are important. Overall, the WG felt that there potentially would be no impact for equity with the additional Moderna products. However, it is known that equity requires more of a call to action than a singular question.

[116] CDC COVID Data Tracker. Trends in COVID-19 Vaccine Confidence in the US. https://covid.cdc.gov/covid-data-tracker/#vaccine-confidence Accessed May 20, 2022
[117] Source: Estimates produced by NORC at the University of Chicago using CDC's National Immunization Survey-Adult COVID-19 Module (NIS-ACM). COVID-19 Vaccination Coverage and Vaccine Confidence Among Children | CDC. Accessed May 25, 2022.
[118] Source: Estimates produced by NORC at the University of Chicago using CDC's National Immunization Survey-Adult COVID-19 Module (NIS-ACM). COVID-19 Vaccination Coverage and Vaccine Confidence Among Children | CDC. Accessed June 2, 2022.
[119] CDC. Vaccinating Children with Disabilities Against Disabilities. https://www.cdc.gov/vaccines/covid-19/planning/children/disabilities.html Accessed June 21, 2022; CDC. Quick Conversation Guide on Pediatric COVID-19 Vaccination. https://www.cdc.gov/vaccines/covid-19/downloads/talking-to-parents.pdf Accessed June 21, 2022
[120] and additional resources: www.cdc.gov/vaccines/covid-19/planning/children/resources-promote.html
[121] CDC. Vaccines and Immunizations. https://www.cdc.gov/vaccines/covid-9/planning/children/resources-promote.html Accessed June 21, 2022

To summarize the WG's interpretations for the EtR Framework domains, the WG discussed each age group for the Moderna COVID-19 vaccine primary series compared to no vaccine. As discussed during the ACIP meeting the previous week, 2 vaccine options may allow parents and providers a choice. The Moderna COVID-19 primary series in older children and adolescents met the non-inferiority endpoints, providing protection against symptomatic COVID-19 disease and are expected to provide higher protection against severe disease. The WG felt strongly that an interval of 6 weeks between Dose 1 and Dose 2 likely would improve safety and effectiveness of the Moderna vaccine in older children and adolescents.

For the Moderna vaccine in children 6–11 years of age and adolescents 12–17 years of age, the WG found that the desirable consequences clearly outweighed the undesirable consequences in most settings. With this in mind, the WG proposed the following recommendations for separate ACIP votes:

- ❑ Moderna COVID-19 vaccine (2-doses, 50 µg, IM) is recommended for children ages 6–11 years, under an Emergency Use Authorization.

- ❑ Moderna COVID-19 vaccine (2-doses, 100 µg, IM) is recommended for adolescents ages 12–17 years, under an Emergency Use Authorization.

The WG discussed that an 8-week interval would increase the benefits and decrease the harms, improving the balance of consequences for the 100 µg of Moderna in adolescents.

Clinical Considerations Update

Elisha Hall, PhD (CDC/NCIRD) presented updates to the Clinical Considerations. Beginning with a summary of the pediatric schedule for Moderna COVID-19 vaccine for ages 6–17 years, people who are not moderately or severely immunocompromised should receive 2 primary doses separated by 4 to 8 weeks. People who are moderately or severely immunocompromised should receive 3 primary doses each separated by 4 weeks. Like when other COVID-19 vaccines were first authorized for a specific age group, only primary doses are authorized at this time for people ages 6–17 years who receive the Moderna primary series. In terms of all of the recommendations for those who are not immunocompromised, depending on the age and product, people 6 months–17 years of age should receive either 2 or 3 doses. People who are moderately or severely immunocompromised, and depending on age and product, should receive between 3 and 5 total doses.

During the last ACIP meeting, there was discussion about considerations for an extended 8-week interval between Dose 1 and Dose 2. Dr. Hall emphasized that the extended 8-week interval was particularly relevant to this meeting's discussion in terms of the adolescent group. It may be more appropriate than the 4-week authorized interval in situations when the priority is to reduce myocarditis risk. Some studies in adolescents and adults have shown that the small risk of myocarditis associated with mRNA COVID-19 vaccines might be reduced with this longer interval. Use of this interval is especially important for adolescent and young adult males where higher risk has been observed, including among males 12–17 years of age.

Transitioning to the Moderna product for children and adolescents 6–17 years of age, the product authorized for children 6 months–5 years of age has a dark blue cap and magenta border label. A dose is 25 micrograms or 0.25 mL. The product authorized that will be available for primary series doses for children 6–11 years of age also has a dark blue cap, but the label border is purple. This product also is authorized for booster doses for adults ≥18 years of age. The label for this product reads "booster doses only" in all caps, but it is authorized for primary doses in children 6–11 years of age. For both children 6–11 years of age and adults ≥18 years of age, the dose is 50 micrograms or 0.5 mL. Like all Moderna COVID-19 vaccine products, it should not be diluted and there are 5 doses per vial. Another product is authorized for children 6–11 years of age with a dark blue cap and teal border label. Given that it is not available, Dr. Hall did not into detail on that product and discussed only the product with the dark blue cap, purple border label for ages 6–11 years, and "booster doses only" in all caps.

The Moderna product with the dark blue cap, purple border label for ages 6–11 years, and "booster doses only" in all caps is authorized for primary doses in children 6–11 years of age and booster doses in adults ages 18 years of and older. It also states on the label "2.5 mL Multi-Dose Vial Booster Dose 0.5 mL." However, 0.5 mL is the correct dose volume for both the booster dose and primary doses for children 6–11 years of age. The currently available product for ages 18 years and older has been amended to include ages 12 years and older. It has a red cap and a light blue label. A primary series dose will continue to be 100 mcg or 0.5 mL for adolescents 12–17 years of age. The booster dose is authorized only for persons for 18 years of age and older. Adolescents 12–17 years of age can receive only the primary series dose at this time.

CDC recognizes that that label for children 6–11 years of age stating "booster doses" in all caps is very confusing. There will be multiple education and communication materials and efforts to communicate the authorized use of this vial for ages 6–11 years. A wall chart is available from the FDA with color photographs of the Moderna COVID-19 vaccine presentations.[122] Additionally, the EUA for ages 6–11 includes the picture of the booster-only vial of both the label and the vial to show what providers would actually see in their stock.[123] CDC also will have multiple products and communication efforts to communicate the use of the vial. The Clinical Considerations[124] will be updated and will have information on the different products. CDC has a multiple product-specific job aids, including an at-a-glance job aid and prep and administration summary.[125] Additionally, CDC will be educating through webinars, calls, and partners to help providers with this confusing label situation.

As discussed during the last ACIP meeting, children should receive the age-appropriate vaccine product and follow the schedule based on their age on the day of vaccination regardless of their size or weight. If a person moves from a younger to an older age group during the primary series or between the primary series and receipt of a booster dose, they should receive the vaccine doses for the older age group for all subsequent doses. The booster does not apply to this particular product and age group combination. Even though CDC recommends using the product based on age on the day of vaccination, there are some different FDA allowances for aging up. Children who age from 5 to 6 years between any does in the primary series may

[122] Wall chart: https://www.fda.gov/media/159306/download
[123] Fact Sheet for Healthcare Providers: 6 Through 11 Years: https://www.fda.gov/media/159308/download; and 12 Years and Older: https://www.fda.gov/media/157233/download
[124] Clinical considerations: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html
[125] Job aids: https://www.cdc.gov/vaccines/covid-19/info-by-product/moderna/index.html

receive either the Moderna product authorized for children 6 months–5 years of age (dark blue cap, magenta label border) and the Modern product authorized for children 6–11 years of age (dark blue cap, the purple border) for Dose 1 and at 4 to 8 weeks later, the product with magenta or purple border can be used. Children who turn from age 11 to 12 years between any dose in the primary series may receive either the Moderna product authorized for children ages 6–11 years of age or the Moderna product authorized for children ages 12–17 years of age. For Dose 1, this would be the dark blue cap with the purple border or the red cap with the light blue border. For Dose 2 at 4 to 8 weeks later, either vial is acceptable.

In terms of administration, the existing guidance applies to children and adolescents 6–17 years of age. COVID-19 vaccines may be administered without regard to timing of other vaccines. COVID-19 vaccines are not interchangeable. The same products should be used for all doses of the primary series. With all of these new products and products not labeled for the indicated age group, there may be more opportunities for vaccine administration errors. Additionally, new pediatric providers may be unfamiliar with COVID-19 vaccines. There are some stark differences between routine vaccines. Some of the most likely errors to look out for within this context would be incorrect product and/or dose volume, resulting in a higher than authorized dose; incorrect product and/or dose volume resulting in a lower than authorized dose; a correct dose from an incorrect product; and/or vaccine administered beyond use date. There are a number of resources available for preventing administration efforts.[126]

Discussion Summary (Oliver & Hall)

Dr. Lee said that as someone who cares about implementation, she wanted to ask their manufacturer colleagues to make it easier for providers to do the right thing. She was looking at teal, magenta, maroon, orange, red, lots of blue, and sometimes with the same color cap and sometimes with a different color caps. Now there are labels that differ from how the products are actually supposed to be used. She expressed appreciation to the CDC for putting together the types of training and support that will be needed to implement this product. She also recognized that this will impact acceptability from a provider standpoint because there is a lot of complexity to incorporate into the busy practice. She asked Pfizer and Moderna whether they have any plans to improve the design and labeling of these vials, because this is quite overwhelming her even though she feels like she knows COVID-19 pretty well.

Dr. Das said that Moderna definitely hears the feedback, which has arisen at the speed with which these have come forward. They are actively working on how to simplify this.

Dr. Poehling emphasized concern about the confusion on the labels for both doses and highlighted that there are people who are color blind, which she worries will contribute to errors. She pointed out that the vast majority of vaccines for children 5–11 and 12–17 years of age will be given in the medical home. She requested additional information about persons who do and do not have immunocompromising conditions in terms of the booster dose recommendation, though it was not part of the upcoming vote.

[126] Web-on-demand “mini” webinar: https://www2.cdc.gov/vaccines/ed/covid19/videos/va/va.asp; Vaccine Administration: Preventing Vaccine Administration Errors https://www.cdc.gov/vaccines/hcp/admin/downloads/vaccine-administration-preventing-errors.pdf; and Vaccine storage, handling, preparation, and administration materials: https://www.cdc.gov/vaccines/covid-19/info-by-product/moderna/index.html

Dr. Hall indicated that this is another difficult communication point. For Moderna, there is no current booster recommendation for persons 6 months–17 years of age because the FDA has authorized only the primary doses at this time and has not yet authorized a booster dose. It is assumed that by the time this age group who receive Moderna would be eligible for a booster, there probably would be a booster dose authorized because there would be more data at that point. For the Pfizer product, 1 or 2 booster doses are authorized for children and adolescents 5–17 years of age depending on the exact age and immune compromise. The at-a-glance schedule should be more helpful as well.

Dr. Fink indicated that FDA would expect to be addressing this gap in booster dose recommendations over the Summer and into early Fall.

Ms. Bahta requested clarification from Dr. Hall about children needing a dose based on the age of the day they were vaccinated, given that she went on to explain that there are exceptions related to the Moderna vaccine for children in the transition age being able to get either dose. This seems complicated and confusing.

Dr. Hall used the example of aging from 5 to 6 years. The CDC recommendation would be to use the product based on the age the day of vaccination. A child 5 years of age in the provider's office would be vaccinated with the product for children 6 months–5 years of age. Within the 4 to 8 weeks before the second dose, they age up to 6 years and present to the provider's office for the second dose. On that day, they can be vaccinated with the product authorized for children 6–11 years of age. However, the FDA authoritarian allows for either of those products to be administered for either the first or the second dose. This allows for more flexibility. CDC is working on a visual for this because this is a very confusing concept.

Dr. Sanchez agreed that this is extremely confusing, and consistency is needed. He joined in urging the manufacturers to work on this to minimize any errors and to improve safety. In addition to color, there should be information about micrograms.

Dr. Fryhofer (AMA) said that speaking as a practicing physician, she echoed some of the concerns about the colorful caps and labels being complex and confusing. She was shocked that the concentration was not listed on the label. The concentration should be on the bottles as a final check before these doses are administered.

Dr. Rita Das indicated that the concentration is the only thing that is different. The product is the same.

Dr. Hogue (APhA) pointed out that pharmacists are very focused on ACIP recommendations and CDC's Clinical Guidelines for the use of vaccines. It has not been unusual in the past to have had vaccine products that contain an FDA label that is for a different age range than CDC recommends. The APhA has been strong about promoting to pharmacists that they always should follow CDC's Clinical Guidelines. He thought that was true for his colleagues in nursing as well. He also inquired as to when the teal-colored label for the Moderna product that is not yet available and would be at the appropriate dosage for children 6-11 years of age is likely to be available in the US so that providers do not have to deal with these extraordinary mislabeled products.

Dr. Das indicated that Moderna is actively assessing this, but does not have a definitive timeline at this point.

Dr. Lee pointed out that this is a slightly unique situation with EUAs in terms of provider agreements and in which there are CDC recommendations, but the FDA has written allowances. She emphasized that the CDC recommendation is to the appropriate dose for the age on the day of presentation for the vaccine. It seems purposeful to have included the allowances so that people can have the assurance that that is not considered an error and that there is some flexibility.

Dr. Daley extended gratitude to Dr. Fink and his team for his leadership and for their reviews, emphasizing that it was not an overstatement to say that they were asked to do a year's worth of work in several weeks and they had done so without skipping any steps. It also was not an overstatement to say that Dr. Oliver and her team was asked to complete a year's worth of work in several weeks without skipping steps and in bringing all of these data to ACIP. It struck him that simplification was going to require collaboration between manufacturers, the FDA, and the CDC to avoid vaccine administration errors. For other vaccines, there is the concept about minimum and recommended intervals and accelerated schedules. If more data become available about the benefits of 8 weeks between a first and second dose of an mRNA vaccine, it was his understanding that some regulatory steps would need to be taken. He requested additional information about this.

Dr. Oliver emphasized that the votes during this session would be for the authorized schedule in terms of doses and intervals. This is a unique situation in terms of EUAs, legal ramifications, and everything that is tied to that. However, the 8-week interval is included in the Interim Clinical Considerations. This will continue to be stressed in terms of education and the schedule. The hope is that over time, there will be a less constrained environment.

Dr. Fink agreed that it has been challenging to navigate the various legal considerations around EUAs and provider agreements in terms of trying to address various clinical scenarios. Considering whether and how to update FDA labeling to include a different interval is tied together with an EUA having to be reflected in the approved labeling. The situation is somewhat paradoxical in that the level of evidence that typically would be required to support a revision to labeling of a BLA product is higher than what might be necessary to support a change to an EUA. Ultimately, FDA would have to work with the manufacturers to consider available data and whether those data would meet FDA's evidentiary standard for a labeling change. He thought they could do this at the BLA stage, but then there is the paradox at the BLA stage when there is probably more flexibility in what ACIP is able to do with regard to off-label recommendations.

Dr. O'Leary (AAP) said that speaking as a colorblind person himself, the colors are a nightmare. It would simplify the lives of those stocking vaccines to simply have 1 product rather than having to stock 2 different products for the 2 different age groups. The doses essentially would be the same for children 6–11 years of age. This potentially could decrease administration errors and simplify stocking from the standpoint of general pediatricians, family doctors, pharmacists, et cetera.

Dr. Sanchez emphasized that dosing needs to be clarified with respect to Moderna dosing and immunocompromised individuals. He remains concerned that there may be a switch over to Pfizer to provide further doses. Timely guidance is needed on further dosing of the Moderna vaccine in immunocompromised children.

Dr. Oliver clarified that for the Moderna product for persons 6 months–17 years of age, there will be a third dose in the primary series as a part of the CDC recommendations. Boosters are not yet approved by FDA, but that may change over time. It is a 3-dose primary series for children who are immunocompromised. If the vote results in a CDC recommendation, the extra dose of Moderna for immunocompromised children will be take care of.

Votes: Moderna COVID-19 Vaccine in Children & Adolescents Ages 6-17 Years

Sara Oliver, MD, MPH (CDC/NCIRD) reminded everyone that since the beginning of the COVID-19 pandemic, there have been over 10 million COVID-19 cases, over 45,000 hospitalizations, and tragically over 600 deaths among children ages 5 through 17 years of age. COVID-19 can cause severe disease and death among children and adolescents, including those without underlying medical conditions. Future surges will continue to impact children, with unvaccinated children remaining at higher risk of these severe outcomes. As with all other age groups, the priority is vaccination of unvaccinated individuals. Currently, there are 25 million unvaccinated children and adolescents. The benefits are known to outweigh the risks for mRNA COVID-19 vaccine in all ages. Receipt of this primary series continues to be the safest way to prevent serious COVID-19. She then presented the following proposed recommendations, each of which was to be voted on separately:

> **Vote #1**
> "A two-dose Moderna COVID-19 vaccine series (50 µg) is recommended for children ages 6–11 years, under the EUA issued by FDA."
>
> **Vote #2**
> "A two-dose Moderna COVID-19 vaccine series (100 µg) is recommended for adolescents ages 12–17 years, under an EUA issued by FDA."

Discussion Summary

Dr. Long acknowledged that Moderna vaccine compared with Pfizer was not studied head-to-head to be able to say the intervention favors both and she understood why. However, the fact is that the Pfizer vaccine is currently recommendation in these age groups. There have been many presentations and she thought the world would expect ACIP to weigh in on whether the possible increase in myocarditis dissuades them from considering these vaccines differently. She thought they needed to state somewhere that this offers the option and there is not a preference. It is an unusual situation to have had a research vaccine approved during the research for this vaccine, so there is a standard. They would not let anybody use a placebo any longer.

Dr. Lee said that while she understood the recognition that there is no preference and she also thought it should go into a statement, it would be her preference not to get into a pattern of incorporating that into every single vote with multiple vaccine products.

Dr. Wharton added that there were several votes the previous day in which the committee recommended products as acceptable alternatives to already recommended products. This discussion seemed analogous to what the committee did the previous day.

Dr. Sanchez asked whether anything needed to be said in the vote language about the 3-dose series for children who are immunocompromised or if it would just appear in the Clinical Considerations.

Dr. Oliver clarified that the 3-dose series for children who are immunocompromised would not be included in the vote language, but will be taken care of within the official CDC recommendation. ACIP voted previously and broadly for the additional dose in immunocompromised children, which would stand as ACIP's endorsement.

Motion/Vote #1: Moderna COVID-19 Vaccine in Children & Adolescents Ages 6-11 Years

Dr. Poehling made a motion for ACIP to adopt the recommendation stating that, "A two-dose Moderna COVID-19 vaccine series (50 µg) is recommended for children ages 6–11 years, under the EUA issued by FDA." Ms. Bahta seconded the motion. No COIs were declared. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Motion/Vote #2: Moderna COVID-19 Vaccine in Children & Adolescents Ages 12-17 Years

Dr. Kottong made a motion for ACIP to adopt the recommendation stating that, "A two-dose Moderna COVID-19 vaccine series (100 µg) is recommended for adolescents ages 12–17 years, under an EUA issued by FDA." Dr. Sanchez seconded the motion. No COIs were declared. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

RESPIRATORY SYNCYTIAL VIRUS (RSV) VACCINES

Session Introduction

Camille Kotton, MD (Chair, Adult RSV WG) introduced ACIP's Adult Respiratory Syncytial Virus (RSV) WG. This WG will complement the one chaired by Dr. Sarah Long that focuses on RSV disease in infants and children. During this session, these 2 WGs jointly presented information on the epidemiology of RSV across the lifespan. Dr. Kotton shared the current membership roster and noted that the Adult RSV WG may still welcome liaisons from additional professional organizations, such as the Infectious Disease Society of America (IDSA), the National Foundation for Infectious Disease (NFID), et cetera. She highlighted that one of the

WG's consultants, Marie Griffin (Vanderbilt University Medical Center), recently had a nice editorial published in the in the *New England Journal of Medicine* (*NEJM*) about RSV vaccines.

In terms of the purpose of the Adult RSV WG, RSV is a major cause of lower respiratory illness, particularly among infants and children and among older adults and adults with chronic medical conditions. RSV vaccine and immune-prophylaxis development has progressed in the past decade, with over 40 candidate vaccines and monoclonal antibodies currently in development. Target populations for whom these products are intended include infants and young children, pregnant women, and older adults. This WG will consider policy questions related to adult vaccination.

The WG activities include considering recommendations for use of RSV vaccines in adults by: 1) reviewing the epidemiology and burden of RSV disease in older adults; 2) reviewing the efficacy, immunogenicity safety, and cost-effectiveness of these vaccine in older adults; 3) providing evidence-based recommendations regarding routine use of RSV vaccines in older adults; and 4) identifying areas in need of further research for informing potential future vaccine recommendations, including risk-based indications for adults with underlying medical conditions younger than the age for routine immunization recommendation.

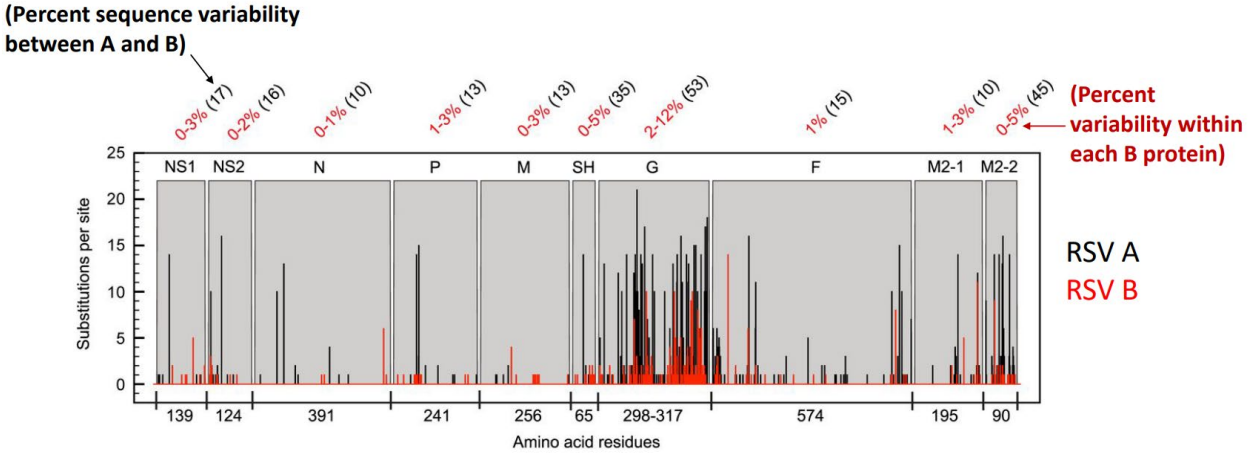
There are 5 adult RSV vaccine products expected to be reviewed by the WG in the near future. GSK started its pivotal Phase 3 trial in May 2021. They have developed a protein-based vaccine adjuvanted with their proprietary compound, which also is used in Shingrix and other GSK vaccines. Pfizer started a Phase 3 trial in September 2021. They have a protein-based vaccine with no adjuvant. Janssen also started its pivotal Phase 3 trial in September 2021. They have an adenovirus vector, the same as used in the COVID-19 vaccine made by them, combined with a soluble protein. Moderna started its Phase 3 trial in February 2022. They have an mRNA vaccine. Bavarian Nordic started their Phase 3 trial in April 2022. They have a vaccinia vector, including multiple RSV vaccine antigens.

In terms of the tentative timeline, this ACIP session focused on the epidemiology and burden of RSV disease. During the October 2022 ACIP meeting, the WG will have 1 to 2 manufacturer presentations and GRADE reviews for 1 to 2 vaccine products. During the February and June 2023 ACIP meetings, there will be more manufacturer presentations, GRADE reviews, cost-effectiveness reviews, EtR Framework presentations for 1 to 2 vaccine products, and presentation of policy options over time as there may be an effective vaccine on the market for the season in later 2023.

RSV Virion and Vaccine Products

Natalie J. Thornburg, PhD (CDC/NCIRD) provided background about the virus and the vaccines that currently are in pre-clinical and clinical trials. RSV is a filamentous virus that is part of the orthopneumovirus family. It has a 15.2-kilobase (kbp) pair genome. It has a single-stranded negative sense RNA genome that encodes 11 proteins. It can be broadly divided into two subgroups or serotypes, A viruses and B viruses. RSV A viruses and B viruses are known to co-circulate within communities at the same time. The RSV virion has an envelope and 2 major proteins, Attachment (G) or glycoprotein and Fusion (F) protein. Both of these proteins can be targets for neutralizing antibodies. There are products in pre-clinical and clinical trials that target F alone, some that contain both F and G, and some that contain other antigens as well.

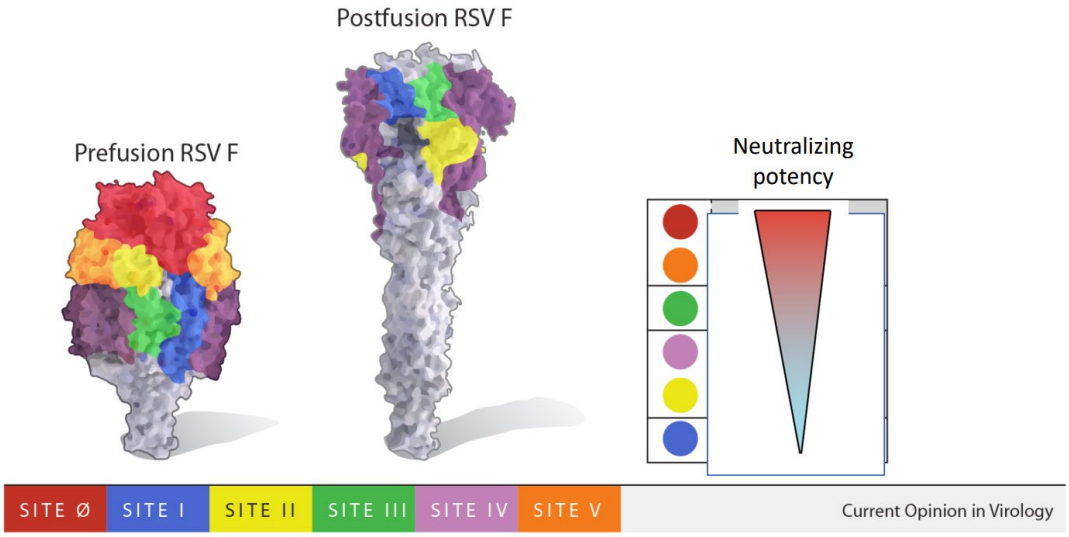
F and G are both targets of neutralizing antibodies. It is known through absorption assays that most of the neutralizing activity is directed against the F protein, but not all. The G protein is what defines RSV A versus RSV B. It is used because it has a heterogeneous sequence. It has 2 large mucin-like domains, which provide antigen masking. RSV G establishes the A and B viruses because it is the most variable in the genome, while F is more conserved. This figure[127] from a paper in the *Journal of Virology* of a map of the variability in the first half of the genome. This map lacks the second half of the genome, which encodes just 1 protein, the L polymerase, which is fairly conserved and not a target for neutralizing antibodies. Across the top of this map, gene products are listed, with the percent variability within an entire gene between A and B viruses shown in parenthesis. The percent variability across the entire gene within B viruses is listed in the top in red. The substitution per site of each amino acid is shown in the graph, with RSV A viruses being in black and RSV B viruses being in red:



Specifically paying attention to the G gene and the F gene, or G protein and F proteins, because those are the targets of neutralizing antibodies, the number of substitutions per site of RSV A is higher and RSV B, in red, is higher in each residue. Across the whole gene in G, there is about 53% difference between A and B viruses in gene and across F there is only a 15% difference between A and B viruses in F. For context, like in H1 versus H3, hemagglutinin is about 60% divergent. An Omicron spike versus an ancestral spike has about 3% amino acid changes. Not as much divergence is being seen in RSV viruses between A and B, but it is somewhat more in Omicron versus ancestral strain. Though the Omicron mutations were more concentrated in the receptor-binding domain, which may have contributed to partial escape.

F may not have much sequence diversity, but it has a lot of structural diversity and it exists in at least 2 or more structural forms that present very differently to the immune system. This figure[128] is 2 crystal structures of the same protein with the same sequence. The left is a semi-stable prefusion form of the RSV F protein and the right is a more stable postfusion RSV F protein:

[127] Lydia Tan et al. J. Virol. 2013;87:8213-8226
[128] Graham B. Current Opinion in Virology. 23: 107-112. 2017



Different anagenic regions or epitopes are colored on the surface. Some sites are present in the prefusion stable site that are not accessible in the postfusion site. Antibodies that bind these antigenic regions can have different potencies. It is known that antibodies against Site 0 (red) and Site 5 (orange) are more potent. Site 1 (blue) tends to be less potent. As noted earlier, the most potently neutralizing antibodies are directed against F. In these same studies, pre-absorption of sera with prefusion F removes almost all neutralizing activity, consistent with the idea that Site 0 and Site 5 have the most potently neutralizing antibodies directed against them.

There are at least 5 general categories of RSV preventatives in clinical trials. There are 4 vaccine products: 1) live attenuated and chimeric vaccines, which would contain many antigens; 2) protein-based, which can be subdivided into at least 3 different kinds of protein-based vaccines (e.g., inactivated, whole virus particle-based vaccines, or subunit traditional protein vaccines); 3) nucleic acid vaccine products; and 4) recombinant vectors such as the Bavarian Nordic product. The fifth category in clinical trials are immunoprophylaxis products. There is one already being used for pediatric cases, Synagis® or palivizumab, and there are multiple new monoclonal antibody immunoprophylaxis products in pre-clinical and clinical trials. PATH maintains an RSV vaccine and monoclonal antibody snapshot that tracks the various products that are in preclinical and clinical trials and is updated this frequently.[129] And you can see on the bottom left when this was most recently updated.

The variability in G and across F is somewhat more complicated in F. While there is not a lot of variability in F, there is structural variability. Some sequence variability is observed in RSV F. All products target F or contain F. F sequence variability in circulating viruses will affect different types of products' difference. A manuscript published by Piedra and Hause from Baylor[130] looked at amino acid variability for more than 1,000 sequences from RSV A and RSV B viruses collected between 1961 and 2014. This was mapped on top of the anagenic regions and they found that there was more variation in RSV B viruses in the fusion protein. There are regions where there is quite a lot of variation and regions where there is not so much variation. The RSV A regions that encode Site 0 are generally fairly conserved, but there is some mutation in RSV B viruses in Site 0.

[129] https://path.org/resources/rsv-vaccine-and-mab-snapshot/
[130] Hause et al. Plos One. 0175792. 2017

In summary of the virus and vaccine products, F and G are on the surface of the virus and are targets for neutralizing antibodies, with the most potent antibodies directed against the F protein. Some RSV trial vaccine products have just the F protein or a combination of F and other RSV antigens. Immunoprophylactics are directed against the F protein. There is some heterogeneity in the RSV F protein, which could affect monoclonal antibody prophylaxis or potentially vaccines.

Discussion Summary

Dr. Poehling asked whether the outcomes have been synchronized across these studies as was done with COVID-19 vaccines.

Dr. McMorrow confirmed that the majority of the trials look at medically attended lower respiratory tract infection (LRTI) as a primary outcome and RSV-associated hospitalizations as a secondary outcome.

Dr. Long asked whether Dr. Thornburg could speculate on the fact there are multiple RSV infections, even in the same season, so that it is not predominantly related to mutation and escape but rather some variances of the mucosal immune response that is very short-lived.

Dr. Thornburg agreed with that hypothesis. Within a season, there does not tend to be a lot of virus drift. RSV is well known not to establish good immunological memory, RSV infections, and particularly not good mucosal immunological memory.

Based on the data shown, Dr. Lee asked whether Dr. Thornburg would hypothesize that nirsevimab would potentially be more protective in a way than palivizumab has been.

Dr. Thornburg said she thought that the IC50 value of nirsevimab is that is known to be higher than palivizumab. Whether having more potent neutralizing activity means that it is more effective will be for the trials to determine.

Dr. Lee asked when infection becomes established in an individual who might have received monoclonal antibody whether more of a prefusion or postfusion state is anticipated, with the assumption that the prefusion state would be ideal.

Dr. Thornburg indicated that the prefusion state is most likely what it looks like on a viral particle when someone is infected. It is hypothesized that it is triggered to the postfusion state after it enters a cell. The hypothesis is that the immune system is seeing the fusion protein in a state that looks more like prefusion than postfusion.

RSV Seasonality in the US and the Burden of RSV in Children

Meredith McMorrow, MD, MPH, FAAP (CDC/NCIRD) provided a brief introduction to RSV seasonality in the US and the burden of RSV in children. The CDC's National Respiratory and Enteric Virus Surveillance System (NREVSS) is its primary source for monitoring RSV seasonality in the US. The NREVSS is a passive, laboratory-based surveillance system that includes commercial, hospital, and state and local public health laboratories. Approximately 300 laboratories routinely report RSV results. They provide weekly reporting of the total tests performed for RSV and RSV-positive tests to monitor real-time virus circulation. All test types

are reported. In recent years, the majority of tests are PCR assays. Testing is primarily clinician-directed and includes persons of all ages.

Looking at normalized RSV detections by epidemiologic week from NREVSS during 2011–2020, RSV circulation was highly seasonal in the US, with predictable peak activity during December to February annually. Using NREVSS data (excluding Alaska, Florida, and Hawaii) CDC assessed geographic differences in RSV seasonality in the US in the 3 seasons preceding the COVID-19 pandemic. A threshold of a 10-fold increase over baseline was applied to calculate median seasonal onset, peak, and end weeks over 3 seasons from July 2017 through June 2020. Using this method, the onset of the RSV season in the US overall and in the Northeast and Midwest Census regions was in late October. Typical onset was approximately 1 week earlier in the South region and approximately 2 weeks later in the West region. Seasonal peaks and offsets also were earlier in the South and later in the West. RSV seasonality also was compared from NREVSS to pediatric hospitalizations in children <2 years of age from 7 pediatric medical centers across the US that from the New Vaccine Surveillance Network (NSVN). The onset of RSV-associated hospitalizations in NVSN was 1 week after the US onset peaked in mid-December and ended 2 to 3 weeks earlier than the US average.

The seasonality of RSV may be different in Florida, Hawaii, and Alaska where seasons may start earlier, later, or maybe longer than the US average. Although there are slight differences in onset, peak, and offset across US Census regions, peak RSV transmission in the US and all regions occurs on average during December to February. More than 90% of RSV detections reported in NREVSS occurred during the 4 pre-pandemic seasons occurred between November 1st and March 31st. 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 that peaked in early August 2021. That peak continued through the Fall into late December. Although nationally RSV circulation has remained near the inter-seasonal baseline, increased RSV circulation is currently being seen in HHS regions 4 and 6. These increases may be limited or may herald another atypical RSV season. However, it is anticipated that RSV circulation eventually will return to typical winter seasonality.

In terms of burden in children, RSV infection is the leading cause of hospitalization in US infants. Most infants are infected in the first year of life and nearly all by 2 years of age.[131] Approximately 40% of infected infants will develop a LRTI called bronchiolitis, among whom 3% to 5% will require hospitalization. Premature infants born at less than 30 weeks gestation have hospitalization rates 3 times higher than term infants.[132] Preterm infants also have higher rates of intensive care unit (ICU) admission and mechanical ventilation than term infants. The average cost of hospitalization in infants less than 29 weeks gestation is about 4 times higher than for a term infant.[133] Although prematurity is an important risk factor for hospitalization, RSV also is the leading cause of hospitalization in healthy term infants. An estimated 79% of children hospitalized with RSV age less than 2 years had no underlying medical conditions.[134] In short, all young infants are at risk of severe RSV and 2% to 3% of all infants will be hospitalized for RSV in the first year of life.[135]

[131] Glezen et al, Arch Dis Child, 1986
[132] Hall et al, Pediatrics, 2013
[133] McLaurin et al, J Perinatol, 2016
[134] Hall et al, Pediatrics, 2013
[135] Hall et al, Pediatrics, 2013 and Langley & Anderson, PIDJ, 2011

It is estimated that each year in the US among children less than 5 years of age, RSV is associated with 100 to 300 deaths;[136] 58,000 to 80,000 hospitalizations;[137] 520,000 ED visits;[138] and approximately 1.5 million outpatient visits.[139] Estimates of RSV-associated hospitalization rates vary by year, study design, and assumptions. An industry-sponsored systematic review published earlier this year estimated a median annual rate of 25.6 per 1000 infants age 0–5 months across 25 studies.[140] This rate included 4 cities with a single year of hospital data and 5 studies with 2 years of data. Rates were imputed, not directly reported, from all but 9 studies. Median estimates varied considerably based upon methods, with the lowest estimates (15.8) derived from active surveillance and the highest (31.2) from modeling studies. Clear outliers were not excluded from calculations. For cost-effectiveness analyses, CDC will use estimates from active surveillance in primary analyses and other estimates will inform sensitivity analyses.

CDC generates RSV-associated disease burden estimates from the NVSN. NVSN conducted year-around acute respiratory illness surveillance at 3 sites during 2000-2009 and expanded to 7 sites during 2016-2021. These same 7 sites have continued prospective surveillance in inpatient, ED, and outpatient clinics. Following enrollment, respiratory samples are collected and undergo PCR testing for multiple respiratory viruses, including RSV. Population denominators and market share are used to estimate disease burden, including hospitalization rates per 100,000 population. NVSN data have consistently demonstrated in 2 4-year surveillance periods that RSV-associated hospitalization rates are highest in children aged 0–5 months of age and decrease with increasing age. Published NVSN hospitalization rates from 2000-2004 and recent unpublished NVSN estimates from 2016–2020 demonstrate consistency in estimates from the 2 time periods. Rates in infants 0–5 months of age are slightly higher in the initial surveillance period. Rates in infants ages 6–11 months, young children ages 12–23 months, and children age 24–59 months are slightly higher in the more recent surveillance period. The overall rate in children ages 0–59 months and those under 5 years of age is consistent across the 2 surveillance periods, with overlapping confidence limits.[141]

NVSN data have also been used to develop estimates of ED and outpatient clinic visits. As with hospitalization rates, the highest ED rates have typically been seen in the youngest infants. In one surveillance period, rates were nearly equal among infants ages 0–5 months and those ages 6–11 months. In the second study period, 2004-2009, the highest rates of ED visits were in infants ages 0–5 months. Outpatient clinic rates were highest in slightly older infants ages 6–11 months in both surveillance periods.[142] A closer look at RSV-associated hospitalization rates in children ages 0–11 months demonstrates that the highest incidence of RSV-associated hospitalization occurs in infants ages 1 and 2 months and then decreases with increasing age.[143]

[136] Thompson et al, JAMA, 2003
[137] Hansen et al, JAMA Network Open, 2022; and McLaughlin et al, J Infect Dis, 2022
[138] Hall et al, NEJM, 2009
[139] Hall et al, NEJM, 2009
[140] McLaughlin et al, J Infect Dis, 2022
[141] 2000-2004: Adapted from Hall et al, NEJM 2009; 2016-2020: CDC unpublished data
[142] Hall et al, NEJM, 2009; and Lively et al, J Ped Infect Dis Soc, 2019
[143] 2000-2005: Adapted from Hall et al, Pediatrics 2013; 2016-2020: CDC unpublished data

Because of the high incidence of severe disease in the first months of life, RSV prevention products have focused on maternal immunization and immunoprophylaxis with monoclonal antibodies. Palivizumab (Synagis®) is the only RSV prevention product currently licensed in the US. It is a humanized monoclonal IgG antibody directed against F glycoprotein. It requires monthly administration due it to its short half-life of 28 days. Initial clinical trials demonstrated 55% efficacy against RSV-associated hospitalization in preterm infants and infants with chronic lung disease (CLD)[144] and 45% efficacy against RSV-associated hospitalization in infants with congenital heart disease (CHD).[145] Currently, the AAP recommends its use in infants less than 29 weeks gestation during the first year of life, pre-term infants with CLD, infants with hemodynamically significant CHD, and infants with profound immune compromise.[146] This recommendation means that approximately 5% of US infants are eligible for immunoprophylaxis with Synagis®. However, data suggests that only about 2% receive 1 or more doses.[147] There currently is no ACIP recommendation on the use of palivizumab.

In conclusion, 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 early childhood. Prematurity and other chronic diseases increase the risk of RSV-associated hospitalization, but most hospitalizations are in healthy term infants. The only currently licensed prevention product targets only 5% of US infants. There are new RSV prevention candidates targeting infants in late stages of development, including one product to be introduced by the manufacturer during this session.

Discussion Summary

Ms. Bahta asked whether there is any speculation about why higher rates were seen in the 2016-2020 seasons.

Dr. McMorrow indicated that for the rates overall in children under 5 years of age, there was no statistically significant difference. There was a slight increase in the 2016-2020 seasons, but those were before the pandemic in the older age groups, not in the youngest infants. Again, they were slight increases of about 10% that were not statistically significant but were not considerably different. During the 2021 atypical circulation, slightly higher rates of circulation were observed after more than a year without activity.

In terms of the 5% eligible and only 2% receiving immunoprophylaxis, Dr. Lee asked whether there is any information on whether there are disparities or equity issues in relation to access to therapies and if those data would be available from any of the data sources that CDC is aware of.

Dr. McMorrow said that most Medicaid-eligible children are provided immunoprophylaxis and that she suspects that the children who are not being targeted are on the edge of aging out of eligibility. Many of their ACIP colleagues are likely aware of barriers. Given the cost of this product, there are important barriers. There are centralized clinics to maximize the distribution and utility of the product that often limits its broader availability in the general pediatric office.

[144] IMpact-RSV Study group, Pediatrics, 1998
[145] Feltes et al, Pediatrics, 2003
[146] American Academy of Pediatrics, Red Book, 2021
[147] Ambrose et al, Human Vaccines Immuno, 2014

Epidemiology and Burden of Respiratory Syncytial Virus in Older Adults in the US

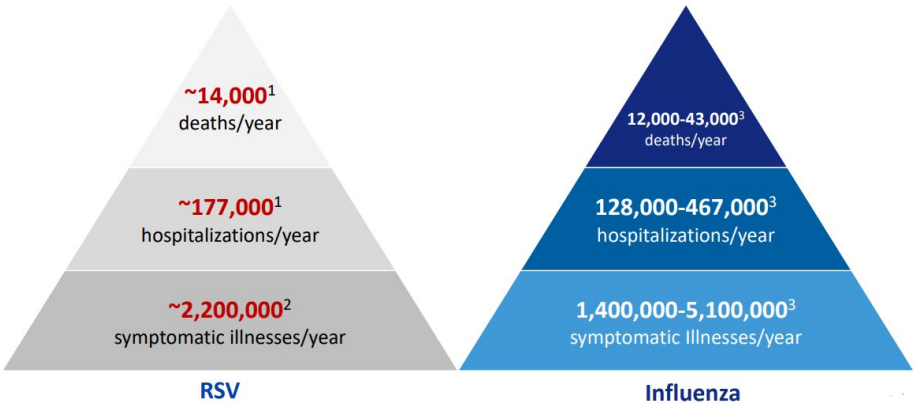
Fiona Havers, MD, MHS, FIDSA (CDC/NCIRD) presented an update on the epidemiology and burden of RSV in older adults in the US, RSV burden in comparison to influenza, and the impact of comorbidities on the risk of RSV and severe outcomes. RSV is a frequent cause of severe respiratory illness in older adults. While it is well-recognized by pediatricians, there is lower awareness of RSV in adults among HCP and the public. RSV is undetected as RSV testing is often not performed, even in hospitalized adults. This is understandable because there is currently no vaccine or recommended treatment in most RSV cases. Even though it is often not recognized as a cause of illness in adults and there are gaps in recent epidemiologic data for RSV, it is known that the burden of disease in older adults is substantial. There are an estimated 2.2 million symptomatic illnesses per year,[148] approximately 177,000 hospitalizations annually, and 14,000 deaths in adults ≥65 years of age.[149] Even though RSV is often thought of as more of a pediatric disease in terms of numbers of hospitalizations and deaths, the burden in older adults is very high.[150]

RSV is a frequent cause of pneumonia in hospitalized adults. This was shown in one large study, the Etiology of Pneumonia in the Community Study (EPIC),[151] which was a multi-center study of patients hospitalized with a community-acquired pneumonia. For patients who met study criteria, extensive testing for multiple pathogens was undertaken. The study found that RSV is a leading cause of community-acquired pneumonia. RSV was detected in 3% of adults hospitalized with pneumonia. Although it should be noted that in this study, 62% of patients had no pathogen detected. Other studies have shown the proportion of those with pneumonia who have RSV to be higher. Regardless, RSV was the fifth most commonly detected pathogen of all types in adults hospitalized with community-acquired pneumonia.

There are gaps in estimates of RSV disease burden in older adults and estimates vary by study design and can vary widely. There are estimates from studies looking at the incidence of RSV among hospitalized patients with annual estimates of hospitalizations per 100,000 population. There are 2 population-based studies with multi-season estimates from hospitalized patients who were tested for RSV.[152] A third study uses national syndromic and hospital data to estimate RSV incidence.[153] Despite differing methodologies, all of these studies demonstrate a high annual incidence of RSV hospitalization, particularly in patients ≥65 years of age. RSV also causes a substantial burden of outpatient disease in adults. Looking at data on rates of medically attended visits for RSV in adults ≥60 years of age over 10 seasons, investigators tested patients who presented to outpatient clinics with acute respiratory infections and found that among those, 11% had RSV. Among those with RSV, 19% had a serious outcome defined by the investigators as hospitalization, ED visit, or pneumonia. Rates were nearly 2 times higher among patients with chronic cardiopulmonary disease compared to those without underlying diseases.[154]

[148] Adapted from Falsey et al, NEJM (2005)
[149] Falsey et al, NEJM (2005)
[150] Thompson et al, JAMA, 2003; Hansen et al, JAMA Network Open, 2022; Hall et al, NEJM, 2009; and McLaughlin et al, J Infect Dis, 2022
[151] Jain S et al. N Engl J Med 2015;373:415-427
[152] 1 Branche AR, et al. Clin Infect Dis. 2021. doi: 10/1093/cid/ciab595. [Epub ahead of print]; Funding: Merck. Hospitalized adults ≥ 18 years old with ≥ 2 ARI symptoms or exacerbations of underlying cardiopulmonary disease in Rochester, NY and NYC; and Widmer, K. et al. JID 2012; 206:56-62. Funding: NIH/CDC.
[153] Matias, et al. BMC Public Health, 2017 Mar 21;17(1):271. Funding: GSK
[154] Belongia, et al. Open Forum Infect Dis, Volume 5, Issue 12, December 2018, ofy316, https://doi.org/10.1093/ofid/ofy316

Among adults ≥65 years of age in the US, RSV is associated with a somewhat similar burden of disease as influenza. To put RSV burden in context, these pyramids compare published estimates for influenza on the right in blue compared to RSV on the left in gray:[155]



For influenza, the data shows the range of point estimates for the 2015-2016 through the 2019-2020 seasons. The burden of disease varies annually for both RSV and influenza. While there are limited recent data on RSV burden, the burden of RSV in older adults for illnesses, hospitalizations, and deaths are in a similar range as those for influenza generally speaking based on these estimates. Notably, influenza has widely used vaccines without which the burden of influenza would be much higher.

Data from other studies have demonstrated similar RSV influenza hospitalization rates in older adults. Data from one of the studies looked over 3 seasons at hospitalized patients.[156] Among this population who was highly vaccinated with influenza vaccine who had acute respiratory illnesses who were tested for both pathogens, 6.1% had RSV and 6.5% had influenza. Of note, investigators found that hospitalized patients with RSV had clinical outcomes that were as or more severe than those who were hospitalized with influenza as measured by length of stay, ICU admission, mechanical ventilation, or death.

Data from the Respiratory Syncytial Virus Associated Hospitalization Surveillance Network (RSV-NET), a population-based surveillance network that covers 8.6% of the US population in 12 states,[157] provide information about clinical outcomes and co-morbid conditions. All cases included had a laboratory-confirmed, RSV-associated hospitalization based on clinician-driven testing. Based on RSV-NET data from 2014-2018,[158] 94% of adults hospitalized with RSV over these 3 seasons had an underlying condition and nearly half (48%) had ≥3 conditions. Cardiovascular disease, chronic lung disease, and diabetes were the 3 most frequent underlying medical conditions among approximately 5,000 patients. Again, these were among patients who had clinician-directed testing. While patients with underlying medical conditions may be more likely to be tested for RSV than those who do not have underlying conditions, the proportion of patients hospitalized for RSV who have co-morbid conditions is very high.

[155] 1) Falsey et al, NEJM (2005); 2) Adapted from Falsey et al, NEJM (2005); 3) Estimated Influenza Disease Burden 2015-2016 through 2019-2020, CDC (2022): https://www.cdc.gov/flu/about/burden/past-seasons.htm
[156] Widmer et al, JID (2012)
[157] Oregon, California, Utah, Colorado, New Mexico, Minnesota, Michigan, Tennessee, Georgia, New York, Connecticut, Maryland
[158] Source: CDC unpublished data.

Co-morbid conditions greatly increase the risk of hospitalization from RSV. One condition that clearly increases risk is congestive heart failure. Data from a published study with RSV-NET data from 2015-2017[159] looked at population-based rates of RSV-associated hospitalizations among patients with congestive heart failure. Overall, 28% of hospitalized RSV cases had congestive heart failure and hospitalization rates were 8 times higher in patients with congestive heart failure compared to those without. The difference between the groups was larger in those who were 50 to 64 years of age at 14 times higher rates in those with congestive heart failure compared to those without in that age range. This is compared to adults ≥65 years of age who had rates 3.5 times higher in those with congestive heart failure compared to those without.

Immunocompromised adults are also at increased risk of severe disease from RSV, including LRTIs, ICU admission, and death. The greatest risk is among lung transplants[160] and hemolytic cell transplant (HCT) patients,[161] as well as other immunocompromised populations such as those receiving chemotherapy for leukemia or lymphoma. Incidence of symptomatic illness is high in some of these groups. For example, in 2 prospective studies of lung transplant patients, the incidence of symptomatic RSV illness was 12% over a 2-year period and 16% over a single season.[162] Severe outcomes are frequently seen in immunocompromised patients with RSV infection. Progression to lower respiratory tract illness is very common and mortality can be very high. For example, a study of HCT patients showed that mortality was 26% in those with LRTI due to RSV.[163]

Long-term care facility (LTCF) residents are another population who are vulnerable to RSV infection, which is a frequent cause of respiratory illnesses in this population. It is well-documented as a cause of severe outbreaks in long-term care facilities.[164] For example, 1 study showed that 13.5% of all residents of a single facility had symptomatic PCR-confirmed illness in a single month during an outbreak.[165] RSV in LTCF also contributes substantial disease burden and cost to the healthcare system. In an industry-sponsored study using Medicare data to estimate RSV-attributable hospitalizations among long-term care facility residents, the authors estimated that these cost more than $50 million per year, with an average length of stay of 5.3 days per hospitalization and accumulative hospital stay days of more than 32,000 days per year.[166]

Among all adults hospitalized with RSV, a large proportion are severely ill as measured by the proportion admitted to the ICU and the proportion who died. In these RSV-NET data from over 3 seasons,[167] about 19% of hospitalized adults of all ages were admitted to the ICU and 4% died. The mortality was highest in those ≥65 years of age at 5%. However, the proportion admitted to the ICU was high, even in younger patients 18–49 years of age, likely reflecting that younger patients hospitalized with RSV are likely to have underlying conditions that make them more vulnerable to severe outcomes. In addition, RSV leads to exacerbations of underlying chronic disease and long-term sequelae, including contributing to acute myocardial infarctions, strokes,

[159] Kujawski SA, Whitaker M, Ritchey MD, Reingold AL, Chai SJ, et al. (2022) Rates of respiratory syncytial virus (RSV)-associated hospitalization among adults with congestive heart failure—United States, 2015–2017. PLOS ONE 17(3): e0264890. https://doi.org/10.1371/journal.pone.0264890 https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0264890
[160] Manuel O, et al. Clin Transplant 2019 Sep; 33(9):e13511
[161] Chemaly RF. CID 2014; 59 Suppl5; S344-51
[162] Weinberg A, et al. Transpl Infect Dis 2010 Aug 1; 12(3):330-5; and Milstone AP, Eur Respir J 2006; 28: 131-137
[163] Waghmare A., et. al. JI. 2017;216:1235–44
[164] Childs A., et al. BMC Geriatr. 2019 Aug 5; 19(1):210. Funding: Sanofi Pasteur. Caram LB, et al. J Am Geriatr Soc 2009; 57(3): 482-5.
[165] Bosco E, et al. JAMA Netw Open. 2021 Jun 1; 4(6): e2111806. Funding: Sanofi Pasteur
[166] Bosco E, et al. JAMA Netw Open. 2021 Jun 1; 4(6): e2111806. Funding: Sanofi Pasteur
[167] Source: CDC unpublished data

exacerbations of asthma and chronic obstructive pulmonary disease that can result in a long-term decline in respiratory function, and other long-term sequelae.

In terms of the impact of the COVID-19 pandemic on RSV in adults, looking at data from RSV-NET from 2014-2022, the COVID-19 pandemic affected RSV in the 2020-2021 and 2021-2022 seasons. There was highly abnormal circulation during the pandemic, with almost no RSV-associated hospitalizations in the first year and an atypical surge in Summer and Fall 2021. CDC continues to monitor whether there are long-term impacts on RSV circulation from the pandemic that will affect the burden of disease in adults.

To summarize, RSV is a major cause of severe illness in older adults. It is a frequent but often unrecognized cause of severe respiratory illnesses in this population. The burden of disease is comparable to that of influenza, with some variability across seasons. Adults with comorbidities, including immunocompromised adults and LTCF residents, are among those at risk for severe illness. A high proportion of those hospitalized with RSV have severe outcomes, including ICU admission and death. RSV illness can result in long-term health consequences.

Discussion Summary

Ms. McNally expressed interest in understanding household transmission rates from household contacts (brothers, sisters, parents) to grandparents. Her understanding is that children can have RSV more than once and the symptoms they experience the second or third time can be less severe. A runny nose in a 5-year-old could be very dangerous to an infant. Her understanding also is that it is important for parents to understand that management of infants who become sick is largely supportive care and there is not always treatment that will improve symptoms once they present to the hospital. From the consumer perspective, she is happy to see that there has been positive development toward an RSV vaccine.

Dr. Havers responded that there have been limited household transmission studies of RSV in children. The attack rate in household transmission studies varies and is likely about 20%, but varies by age. In younger children, the attack rate can be 45% to 50%. In older adults, it may be less. The assumption and understanding are correct that the second and third infections in later childhood tend to be considerably less severe and have a lower risk of LRTI and associated sequelae. It also is correct that there is no current therapy specific to RSV that is widely used and highly effective.

Nirsevimab For The Prevention of RSV Disease In All Infants

Dr. Christian Felter (Sanofi) presented on the nirsevimab program for the prevention of RSV disease in all infants. Nirsevimab is being brought forward through a collaboration between Sanofi and AstraZeneca. AstraZeneca is responsible for regulatory, clinical, manufacturing, and development activities. Sanofi is responsible for commercialization activities. As already stated, RSV is the leading cause of hospitalization in infants <1 year of age. This is true whether the child is born premature or term or if they are born in April or December. Despite this, the current approach to RSV prevention in infants is a risk-based one, which means that 98% of infants do not get prevention for RSV. There are many reasons for this, such as the feasibility of the implementation of a large-scale RSV prevention program. It is clear that what is being done currently does not address the needs of a majority of infants.

However, Sanofi and AstraZeneca are on the cusp of a new era where protection from RSV can be made available to all infants. To realize this vision, several conditions have to be met. The WHO has told them what some of these conditions are. First, a product needs to be indicated for the prevention of RSV disease in the first year of life to ensure that severe disease is examined. Second, the primary target population aims to protect most infants during their first RSV season. Third, a single dose must provide protection from birth. Fourth, safety must be akin to other vaccines that are given at birth. Fifth, efficacy must be at least 70% against severe disease and protection must be for at least 5 months.

In the US, more than half a million infants receive medical attention for an RSV LRTI each year.[168] Most of these cases are in infants who were healthy and born at term. In addition, RSV does not discriminate based on when an infant was born, it remains the leading cause of hospitalization regardless of when an infant is born.[169] Nirsevimab is a recombinant monoclonal antibody[170] that is targeted at the RSV F protein in its prefusion conformation. It has a modification that prolongs the half-life, making it possible to prevent RSV throughout the entirety of the RSV season with a single dose by tripling the half-life of the antibody.

The nirsevimab clinical development program consists of 3 pivotal studies that, when taken together, span the entirety of the infant population.[171] The most recent study is the MELODY study, which looked at the safety and efficacy of nirsevimab in late preterm and healthy term infants. The Phase 2b study examined the safety and efficacy of the product in the early preterm infants who are not currently eligible for palivizumab. The program completed its look at all infants with the MEDLEY study, which was the head-to-head safety and pharmacokinetic study in the Palivizumab-eligible population, which included children with chronic lung disease at prematurity or congenital heart disease. MEDLEY and the Phase 2b study that both looked at the efficacy of nirsevimab and had nearly identical study designs with the notable exception that the MELODY study extended its surveillance through the second RSV season. The primary endpoint of both of these studies was the relative reduction in the instance of medically attended LRTI caused by RT-PCR-confirmed RSV at 5 months. The secondary endpoints were the relative reduction in hospitalization, safety, pharmacokinetics, and anti-drug antibodies. Infants in the Phase 2b study received either nirsevimab 50 mg or placebo. The Phase 2b study results informed the dosing in the MELODY study, where infants under 5 kilograms received 50 mg and those above 5 kilograms received 100 mg. Because of the complementary populations and the matched study designs, the investigators plan to look at the pooled efficacy of these 2 studies to show the effect of nirsevimab in all infants not eligible for palivizumab.

Now turning to COVID-19. As discussed with so many things, COVID-19 had an immense, although indirect, impact on RSV circulation. The lockdowns and the use of non-pharmaceutical interventions for the prevention of COVID-19 reduced the circulation of RSV to near zero in early 2020. The MELODY study began in July 2019 and enrolled 1,027 subjects in the 2019 Northern Hemisphere RSV season. The study continued into the Southern Hemisphere, where 462 subjects were enrolled in South Africa. However, there were no cases in either area. Since it could not be predicted when RSV circulation would resume, the trial was paused and discussions with the FDA were undertaken. It was agreed that the 1,490 subjects enrolled before the pause would be evaluated as the primary efficacy cohort, later noted as Cohort 1.

[168] Rainisch G, et al. Vaccine. 2020;38(2):251-257 2. Zhu Q, et al. Sci Transl Med. 2017; 9(388)
[169] Rainisch G, et al. Vaccine. 2020;38(2):251-257; and Zhu Q, et al. Sci Transl Med. 2017; 9(388)
[170] Rainisch G, et al. Vaccine. 2020;38(2):251-257 2. Zhu Q, et al. Sci Transl Med. 2017; 9(388); and 9. Domachowske JB et al, Pediatr Infect Dis J. 2018;37(9):886-892
[171] 1) Hammitt LL,et al N Engl J Med. 2022 Mar 3;386(9):837-846; 2) Griffin MP, et al. N Engl J Med. 2020 Jul 30;383(5):415-425; and. 3) Domachowske Joseph et al. N Engl J Med 2022 Mar 386:9, 892-894

RSV circulation has since resumed as has the MELODY trial, which has now completed its enrollment of the second cohort to get to the originally planned 3,000 subjects. The evaluation of the safety and efficacy data is ongoing, with publication expected before the end of 2022.

In both the MELODY and the Phase 2b studies, the primary efficacy endpoint was the relative reduction in medically attended LRTI caused by RSV. In the MELODY study, the result was a 74.5% reduction. This is similar to what was seen in the Phase 2b study. It is important to note that in the Phase 2b studies, all subjects were given nirsevimab 50 mg regardless of their weight. When analyzing the pharmacokinetics along with the efficacy results, it was clear that those over 5 kilograms needed a higher dose. This was taken into the MELODY study, wherein those above 5 kilograms receive 100 mg. The secondary endpoint reported for both study was hospitalization due to RSV LRTI. There was a strong result in the Phase 2b study but a non-significant result in the MELODY study. It is important to note that this was due to underpowering because of the study interruption.

The full dataset will be forthcoming shortly. These studies were not planned to be taken in isolation. As mentioned previously, the Phase 2b and MELODY studies essentially were 2 halves of the same study, with one looking at pre-term infants and the other at term. The study designs were similar and equally important, nirsevimab was the protection itself rather than the stimulation of protection. It functions in the same manner, regardless of gestational age, by directly blocking the entry of RSV at the cellular level. For those reasons and because the product is designed to be used in all infants and not in a particular subpopulation, the studies were combined based on a pre-specified analysis plan.

As stated in the introduction, the WHO has said that efficacy against severe RSV disease must be examined and efficacy proven. Based on the results of the combined analysis when the efficacy of nirsevimab is examined in all cases of RSV LRTIs, as well as the subgroup of all LRTIs that resulted in hospitalization and those that were classified as very severe (meaning that the infant required supplemental oxygen or intravenous fluids), the efficacy is consistent regardless of the subpopulation being examined. This is in line with the mechanism of action of the product, which does not rely on the generation of an immune response but rather on the direct protection of the infant. The efficacy of nirsevimab against all medically attended RSV LRTI is 79.5%. Regardless of how the data are examined (e.g., age at randomization, geography, or gender), the answer is essentially the same. Another important factor when evaluating any potential protection from RSV is the durability of that protection. Protection from the nirsevimab is consistent across the 5 months of a normal RSV season. At 5 months, the curves continue to diverge. There are now additional data suggesting that protection lasts beyond 5 months.

While a great deal of focus is rightfully put on RSV hospitalization, it is important to look at the burden that RSV presents in the outpatient setting as well. Looking at the impact of nirsevimab on outpatient visits for all-cause medically attended LRTI in the infants from the MELODY study and the number of antibiotics prescribed over the season, children receiving nirsevimab had received less courses of antibiotics over the season regardless of indication. This is perhaps because nirsevimab prevents the bacterial infections that may be associated with RSV, or perhaps it is because these children seek medical attention less frequently and hence there is less over-prescribing. Overall, nirsevimab has a favorable safety profile and one that is comparable to placebo or palivizumab, depending on the study. None of the SAEs or deaths were considered by the investigators to be related to the product. With regard to hypersensitivity, there was 1 case of a cutaneous reaction to nirsevimab in the MELODY study.

In conclusion, RSV represents a significant yearly burden on the healthcare system in the US and is the leading cause of hospitalization in infants, regardless of the month of birth. Severe RSV disease is unpredictable, with most medically attended cases occurring in healthy infants born at term. This means that despite all infants being at risk of RSV disease, only 2% currently are being protected. All infants need direct protection from RSV regardless of their gestational age or when they were born. Nirsevimab is designed to be that protection for all infants. The 3 major clinical trials taken together demonstrate the efficacy of the product in preventing RSV in all infants, with more data that will complete the story in the near future. Nirsevimab also has been shown to have a favorable safety profile across all 3 studies and is designed to be easily implemented with a single injection, either at birth or alongside routine infant immunization.

Discussion Summary

Dr. Poehling requested additional information about how nirsevimab is administered, the route of administration, and the dose volume.

Dr. Villafana indicated that the 15 mg dose is half a mL and the 100 mg dose is 1 mL that will be in the form a prefilled syringe.

Dr. Sanchez emphasized the need for a product like this for prevention of severe RSV and medically attended RSV, so this is very exciting news. He requested a definition for “medically attended LRTI” and what definitions were used for the trial outcomes.

Referring to back-up Slide 20, Dr. Leach indicated that the case definition of medically attended RSV LRCI included all children presenting for medical care. They were RSV-confirmed by a central laboratory PCR assay and were ensured to have had lower respiratory tract involvement by chest examination, looking for a clinical sign. Each of these children also had at least 1 sign of clinical severity. These include raised respiratory rate, hypoxemia, acute hypoxia or ventilatory failure, new onset apnea, nose flaring, retractions, grunting, dehydration due to respiratory distress. “Very severe” included a subset of the children who were admitted to the hospital who either required oxygen during their hospital stay or required IV fluids.

Dr. Daley asked what the age distribution was among those who were vaccinated at birth or within the first 2 months of life. In addition, he asked what was known about vaccinating in the Spring for protection the following season (e.g., 8 months before the typical respiratory season), acknowledging that this was incredibly complicated due to the COVID-19 pandemic.

Dr. Leach indicated that in the primary analyses that have been reported to date, more than 500 neonates (less than 28 days of age) were enrolled who would have been randomized to either nirsevimab or to comparator. Going forward, additional data will be coming in to support this in the ongoing MELODY trial. In the 2 trials, MELODY and MEDLEY, infants enrolled in the preterm trial were less than 35 weeks gestational age and the late preterm and term were 35 weeks gestational age and above. There were definitely neonates in substantial numbers in both trials. All of the trials were designed to immunize prior to the RSV season. The data presented here were censored after 5 months when the primary endpoint was examined. Serendipitously in the COVID-19 epidemic, RSV disappeared. The investigators had immunized over 500 children in South Africa, who they were able to follow. No RSV season appeared during that time. When RSV reemerged after 5 months of follow-up, there was an indication of protection in those children. While it was not statistically significant, it was a very intriguing observation.

Dr. Felter indicated that these data are shown on back-up Slide 19. Back-up Slide 18 shows the demographic breakdown by gestational age group. To add to the question regarding the definition of medically attended, this could include medical attention sought in a doctor's office, ED, or hospital in this context.

Dr. Brooks asked for clarity regarding whether all children are being followed for up to a year or just out to the 5-month data cutoff. Like Dr. Daley, he wondered about the duration of protection.

Dr. Leach indicated that all children would have been or are in the process of being followed for a year. The primary efficacy endpoint reported was over the 5-month period, which is anticipated to be the duration of a typical season. All of the children in the clinical studies will be followed for a full year of protection. There will be more information on duration of protection beyond the 5-month period.

Dr. Sanchez noted that it is important to clarify that this is not a vaccine and that no children are being immunized. Thinking about the potential for FDA approval, he asked the age of the youngest babies who were medicated.

Dr. Felter confirmed that this is not a vaccine. It is passive immunization through a monoclonal antibody that it is meant to be given at birth or at the start of the RSV season for those who are born prior to the season.

Dr. Leach indicated that the study protocols allowed for the immunization to be given on the first day of life. Though there were not many, a number of children were dosed on the first day of life. A substantial number of children were immunized in the first week of life.

Dr. Loehr said that his sense was that Sanofi/AstraZeneca were advocating for all babies born in the hospital in September or October to receive nirsevimab in the hospital, maybe even throughout the winter. If they were born in January, they would get it because it is still RSV season. The goals would be for all outpatients to try to receive it the September/October time range.

Dr. Felter confirmed that babies born before the season would be getting nirsevimab as outpatients in doctors' clinics. For those born in season, as close to birth and ideally before discharge from the hospital would be the proposed implementation time to make sure that they got the maximum benefit from the prevention provided.

Dr. Kotton observed that it was interesting for the ACIP to be discussing use of a monoclonal antibody, which seemed somewhat different than what has been done in the past as far as she understood it. The ACIP has not addressed products such as Evusheld™, which is for prevention of COVID-19 and has been underutilized. People are confused in terms of the recommendations. It seems like a loss that the CDC and the ACIP have not taken that on, though now it was unclear why they were looking at a monoclonal antibody for RSV. She has been involved in the stewardship of palivizumab for years. It is phenomenally expensive, so she expressed her hope to see a good cost-benefit analysis with this new monoclonal antibody.

Dr. Poehling requested further information about the Grade 4 events and deaths that were reported.

Dr. Leach indicated that in total in all of the pivotal trials, there have been 14 fatalities. Of those, 10 occurred in nirsevimab recipients and 4 were in placebo recipients of placebo. As a reminder, randomization was 2:1 in all of the clinical trials. Essentially, the deaths were balanced by group. The investigators reported that none of the deaths were related to the product. The overall assessment was that the causes of death observed were in line with expected mortality rates of that population. She indicated that she was not immediately able to respond to the question about Grade 4 events without reviewing the data, though they always are concerned about safety. She agreed to follow-up via written response.

Dr. Sanchez wondered whether follow-up beyond a year might be needed. Thus far, the experience is anecdotal. Given the lack of RSV during the previous season in the second year of age, some of these children were being hospitalized with RSV infection and they were older. In terms of this anecdotal experience, it is important to know whether some of the very high-risk premature infants not only get through their first season, but also are not presenting with more severe RSV in their second season.

Dr. Villafana indicated that they followed all of the children through Day 361, but in the MELODY study, children are followed through a second RSV season. They will have information from that second season of follow-up to share with the ACIP in the future. Though not presented during this session, there are data showing that children mount an immune response to natural RSV infection when dosed with nirsevimab.

MONKEYPOX INFORMATIONAL SESSION

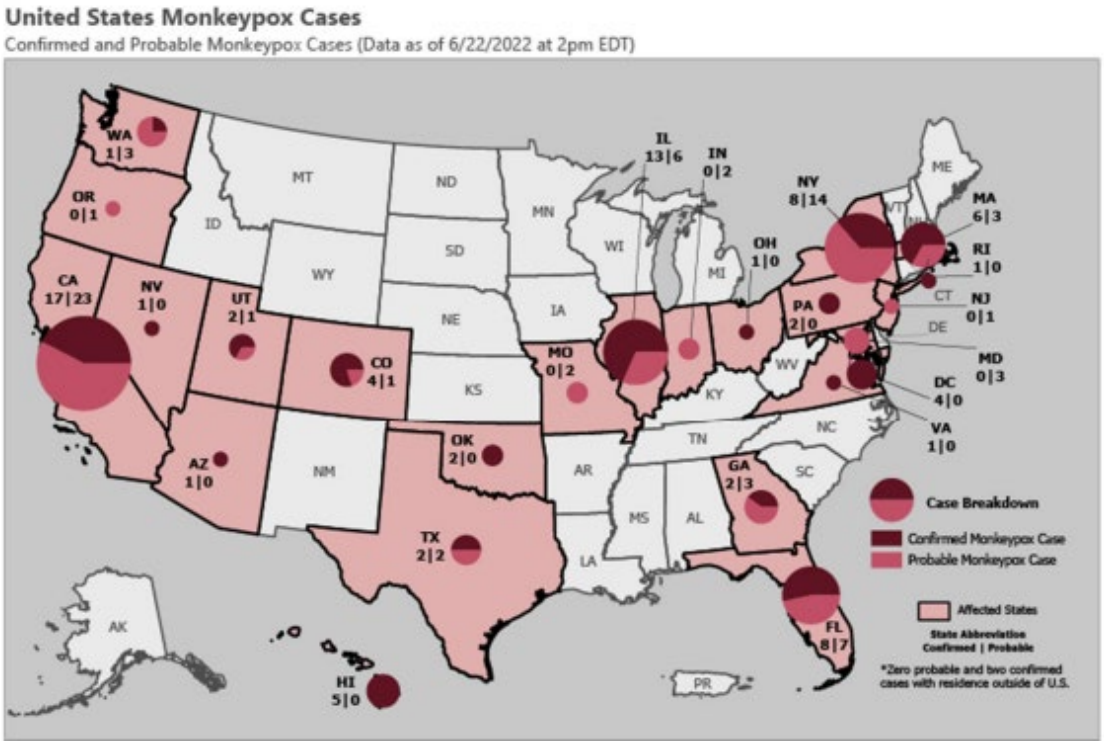
Situational Update

Agam Rao, MD, CAPT USPHS (CDC/NCEZD) introduced this session with some background information about monkeypox. Monkeypox is a rare, sometimes life-threatening zoonotic infection that is endemic in West and Central Africa. It is caused by monkeypox virus, which is an orthopoxvirus. The specific animal reservoir for monkeypox virus is unknown but is probably small mammals. It can spread from infected animals to humans and person-to-person through respiratory secretions, skin-to-skin contact with infected bodily fluids (e.g., fluid from vesicles and pustules), and fomites (e.g., shared towels and contaminated bedding). Before 2022, there were US cases. In 2003, there was an outbreak linked to small mammals imported from Ghana. There were 47 cases associated with that multi-state outbreak involving the upper Midwest US. The cause was traced to the spread of monkeypox virus from imported African rodents to pet prairie dogs and then to people who had contact with the pet prairie dogs. In 2021, there were 2 unrelated cases in travelers from Nigeria. The first was in July in Texas and the second was in November in a patient who resides in Maryland. These cases were similar to imported cases during 2018-2021 in 4 travelers returning from Nigeria to the UK (4), 1 traveler returning from Nigeria to Singapore, and 1 traveler returning from Nigeria to Israel. Nigeria experienced a large outbreak in 2017 that resulted in cases continuing to occur afterward. There were decades of no cases in Nigeria until the outbreak in 2017.

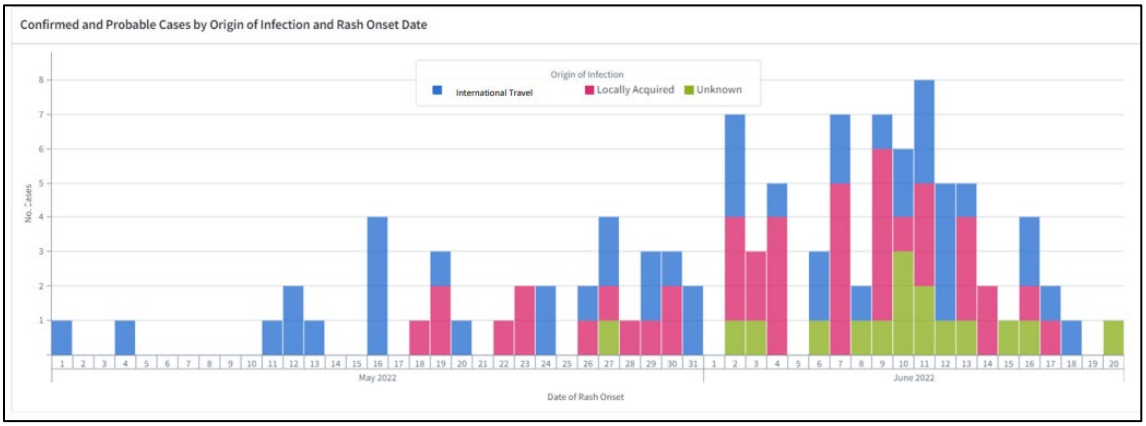
Cases among patients involved in the 2003 US monkeypox outbreak were due to bites and scratches for the most part. These individuals had firm, well-circumscribed, deep-seated, and painful lesions. Lesion in endemic countries were the same. Everything changed in May 2022. The UK had cases in 3 distinct clusters that they announced on May 7th, 14th, and 16th. The first was a travel-associated case from a traveler, so it sounded similar to some of the other cases seen outside of the African Continent since 2018. The next 3 were from a family cluster of

unknown etiology. Given that none of the individuals in the family had actually traveled outside of that area, the source remains unknown. On the 16th is when 4 cases were identified at sexual health clinics among gay, bisexual, or other men who have sex with men (MSM) and reported on. US public health authorities were first notified of a suspected case in Massachusetts on the 17th in a Massachusetts resident who had traveled to Canada, where CDC had heard that there also were cases occurring. The Massachusetts rash began as an anogenital rash with vesicles and pustules, which spread to the face in trunk. Testing was done at the Laboratory Response Network (LRN) laboratory in Massachusetts, which was positive for non-virial orthopoxvirus through the OPX generic positive test.

Since then, cases have steadily increased in the US. As of 2:00 PM ET on 22 June 2022, there were 155 cases diagnosed in the US among residents of 24 states and the District of Columbia (DC). Cases are updated every day at 2:00 PM ET, so Dr. Rao already knew that the case count was somewhat higher than the previous day. The data presented during this session focused on the 155 cases from the previous day. These states in which these cases were identified are depicted on the following map, with the highest number occurring in California, New York State, Illinois, Florida, and Colorado:



Case patients for whom CDC has information about the data of rash onset are depicted in this epidemiologic curve. Of note, the date of rash onset was selected because a lot of the case patients involved in this outbreak have not had the typical prodromal symptoms associated with Monkeypox or the typical symptoms have occurred, but have been very mild and not easily recognized:

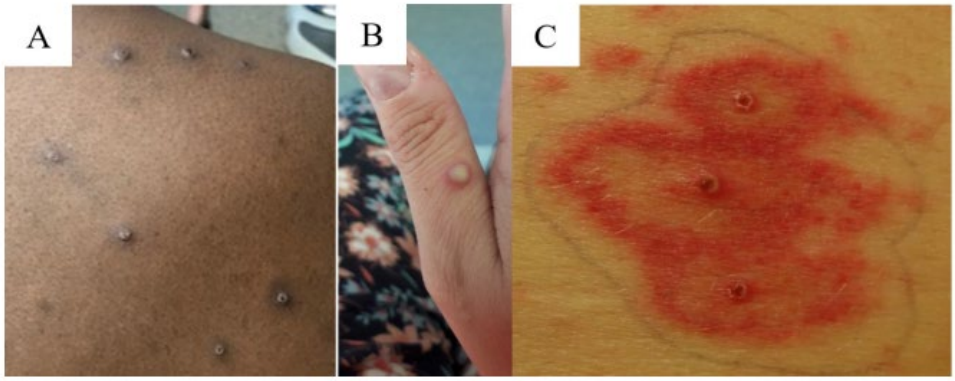


The earliest date of rash onset was at the beginning of May 2022. The initial cases identified in the US were in people who had traveled abroad who attended large gatherings internationally in Spain, France, and Germany. As time has gone on, there still have been reports of case patients who traveled abroad themselves. However, locally acquired infection is also now occurring through local transmission.

In terms of basic demographics among the 155 cases, the median age is 37 years (range 20–76 years). Most of the case patients are of male sex at birth among whom 56 are cisgender men, 82 are of unknown gender identity, and 1 refused to identify. CDC has information about male-to-male sexual contact (MMSC) for 120 out of 121 who have reported MMSC but does not have information from 29 individuals because that information has not been reported to CDC. There are 5 cases for female sex at birth, including transgender males and cisgender women. There have been no deaths, nor have any HCP acquired the infection due to providing care for a patient.

In terms of clinical presentation, every US patient has had a rash or enanthem. Only 1 patient had an enanthem at the time that illness was suspected, and that individual was a contact of someone else, which is why it was identified rapidly. The swab from those lesions inside the mouth tested positive, but everybody else has gone on to develop a rash on their body. Lesions in different phases of development have been seen side-by-side on the same body site, which historically has not been reported for monkeypox. The rash is either scattered or diffuse and is sometimes limited to 1 body site and mucosal area (e.g., anogenital region or lips/face), while at other times it is spread throughout the body. The presenting complaint for some patients has been anal rectal pain or tenesmus. Physical examination has yielded visible lesions and proctitis. No cases have been seen that have involved people who have not had visible lesions somewhere. Prodromal symptoms have been mild or not occurring. Fever and lymphadenopathy, which are commonly associated with monkeypox, are not necessarily occurring in all of the patients. Some co-infections with sexually transmitted infections (STIs) have been seen. A diagnosis of an STI like syphilis or herpes does not rule out monkeypox, which has been observed in some of the case patients.

Despite all of these features that are perhaps not considered typical of classic monkeypox, the lesions are still firm, deep-seated, well-circumscribed, and sometimes umbilicated. The lesions in the current outbreak are sometimes very small. In this photograph, Panels A and B are from individuals in the current outbreak and Panel C is from the 2003 US outbreak:



Photos A and B from NHS England High Consequence Infectious Diseases Network; photo C from Reed KD, Melski JW, Graham MB et al. The detection of monkeypox in humans in the Western Hemisphere. Page 346. Copyright © 2004. Massachusetts Medical Society. Reprinted with permission

While the lesions in the current outbreak are consistent with monkeypox, they seem to be much smaller and there are some atypical aspects to them. Papulovesicular and pustular lesions are being seen side-by-side. Additional images are available that include photographs of lesions in the anogenital region.[172, 173]

CDC guidance to clinicians is changing more information is learned. Guidance was conveyed in the previous week through the Health Alert Network (HAN) for clinicians to observe for classic monkeypox rash and to obtain swabs from that. In addition, clinicians should observe for rash that could be consistent with monkeypox in persons with epidemiologic risk factors, including contact with a person or people with a similar-appearing rash or who has been diagnosed with monkeypox; close or intimate in-person contact with people in a social network experiencing monkeypox activity (e.g., MSM who meet partners through an online website, digital app, social event); or a history of recent international travel to a country currently reporting cases. Clinicians were alerted to obtain swabs from those lesions, not to rule out co-infection with monkeypox when an STI is diagnosed, and to conduct a full body examination when lesions are not consistent with classic lesions. CDC has heard that even though not all of the lesions on an individual might be consistent with classic presentation, clinicians are finding firm, deep-seated, well-circumscribed, sometimes umbilicated lesions somewhere on the body.

Some of CDC's current priorities are to try to understand the clusters and cases occurring in various parts of the country, risk factors for acquiring infection, and outcomes. The CDC laboratory is sequencing genomes to try to understand how these might be related to previous genomes based on the sequencing that done in Nigeria as part of the work that CDC has done for years in Africa, the Democratic Republic of Congo (DRC), and Nigeria. The agency is launching retrospective and prospective serosurveys to try to understand whether cases were occurring before the cases were identified in the US and before the travel to Europe may have occurred. A natural history study is being developed to understand this better. Testing capacity is being expanded to commercial laboratories, and CDC is providing case-by-case consultations

[172] Ogoina D et al. Clinical course and outcome of human monkeypox in Nigeria. Clin Infect Dis. 2020; 71(8): 210-214
[173] Antinori A et al. Epidemiological, clinical, and virological characteristics of four cases of monkeypox support transmission through sexual contact, Italy, May 2022. Euro Surveill. 2022 June; 27 (22).

for treatment and post-exposure prophylaxis (PEP). These and other agency priorities/activities, interim information, and tolls for HCP and public health authorities can be found on the CDC website, which being updated regularly as new information is acquired.

Discussion Summary

Dr. Loehr asked Dr. Rao to further explain what was meant by “deep-seated,” which he was interpreting to meant that it goes down below the skin and is deeper.

Dr. Rao indicated that it is not superficial the way varicella-zoster looks. It is not something that can be unroofed with the fingertip, for example.

Dr. Bell requested additional information about the settings in which transmission is assumed to have occurred. She got the sense from the points made during the presentation that this is associated with large gatherings or certain specific settings.

Dr. Rao responded that CDC is looking into clusters across the country. It appears in the US to be similar to what international scientific communities have observed, that most of the cases are occurring in MSM among individuals who seem to have gotten the cases through secondary and tertiary spread from having sex with other men. There have been some women who appear to have gotten it through intimate contact with men. This continues to be evaluated. In terms of large gatherings, there were some large pride events internationally that occurred in the Canary Islands, Berlin, and some other places and there seem to be some clusters around that. Montreal has reported that a bathhouse is associated with many of their cases. Large events in the US are being investigated as well. CDC has heard about some private sex parties that have been associated with some cases. Worldwide, there have been cases among close contacts who perhaps shared bedding or towels. Transmission is not just among males and not just through close intimate contact.

To follow-up on Dr. Loehr’s comment about “deep seated,” Dr. Romero learned from historical reference that a “thumb sign” was used for smallpox. If the vesicles are particularly tough and a thumb can be run over the vesicle without it rupturing like it would with chickenpox, that is the deep-seated nature of the vesicle itself. Looking at the pictures Dr. Rao showed, it seemed that some of them would probably not pass the thumb sign.

Dr. Rao indicated that CDC has heard that none of the vesicles have been superficial like chickenpox. Or if they have been, there is possibly co-infection. It is known from CDC’s work in Africa that co-infection with varicella does occur with monkeypox.

Dr. Shaffner (NFID) said his historical reference was that smallpox lesions often were described as firm or rubbery. He asked whether there is any sense that there might be transmission before the rash is present.

Dr. Rao indicated that this is being assessed as part of the natural history study CDC is conducting but is not aware of asymptomatic transmission or transmission before someone develops symptoms from years of working on monkeypox at CDC.

Dr. Goldman (ACP) said was finding the website extremely helpful. He asked whether clinicians should contact CDC directly or the health department if they suspect one of their patients has monkeypox, and whether samples should be sent to a commercial laboratory.

Dr. Rao indicated that clinicians should contact their local health departments, which are coordinating the obtaining of specimens and sending them to the local LRN laboratory. That may change once testing is rolled out to other laboratories, such as commercial laboratories. This information will be updated on the website.

Medical Countermeasures

CAPT Brett W. Petersen, MD, MPH (CDC/NCEZID) provided an overview of the medical countermeasures for monkeypox, first pointing out that a number of medical countermeasures have been stockpiled for smallpox and can be used for other orthopoxviruses like monkeypox. There are 2 vaccines available, JYNNEOS and ACAM2000. Tecovirimat, a first-line agent; vaccinia immune globulin intravenous (VIGIV); and cidofovir are treatments that are available in the Strategic National Stockpile (SNS).

The first medical countermeasure is JYNNEOS,[174] which is a live vaccine produced from the strain Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN). This is an attenuated, non-replicating orthopoxvirus. It is also known as in IMVAMUNE, IMVANEX, or MVA. This vaccine was licensed by FDA in September 2019 for the prevention of smallpox and monkeypox disease in adults ≥18 years of age. CDC is developing an Expanded Access Investigational New Drug (IND) protocol to allow the use of JYNNEOS for monkeypox in pediatric populations. Currently, 1 pediatric patient has received JYNNEOS under a Single Patient IND protocol. The second countermeasure is ACAM2000,[175] which is a live vaccinia virus vaccine. This is a replicating virus. ACAM2000 was licensed by FDA in August 2007. It replaced the previously licensed vaccine Dryvax. ACAM2000 is specifically licensed for active immunization against smallpox disease for persons determined to be at high risk for smallpox infection. Consequently, CDC does hold an Emergency Access IND protocol to allow the use of ACAM2000 for Non-Variola Orthopoxvirus infection (e.g., monkeypox) during an outbreak.

There are significant differences between these 2 vaccines. The first and perhaps most important is the vaccine virus themselves, with ACAM2000 being a replicating vaccine and JYNNEOS being replication deficient. Consequently, ACAM2000 does produce a “take” or a vaccine site lesion at the site of inoculation and JYNNEOS does not. And as such, ACAM2000 does have a risk of inadvertent inoculation and autoinoculation from the infectious virus that is present in these vaccine site lesions. ACAM2000 also has a risk for SAEs due to uncontrolled replication, which is not expected to occur with JYNNEOS. With respect to cardiac AEs, ACAM2000 has myopericarditis reported at a rate of 5.7/1,000 primary vaccinees. Myopericarditis has not been reported in association with JYNNEOS vaccine. If there is any risk present, it is believed to be lower than that for ACAM2000. With respect to effectiveness, ACAM2000 was licensed by FDA based on comparisons of the immunologic response and “take” rates to Dryvax, the previously licensed vaccine. JYNNEOS similarly was assessed by comparing the immunologic response to ACAM2000 and also taking into account animal studies. For administration, ACAM2000 is given percutaneously by a multiple puncture technique in a single dose. JYNNEOS is given subcutaneously in 2 doses separated by 28 days.

[174] https://www.fda.gov/vaccines-blood-biologics/jynneos
[175] https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5708a6.htm; https://www.fda.gov/media/75792/download

With respect to vaccine supply, as of June 14, 2022, the SNS held more than 36,000 courses of the 2-dose regimen for JYNNEOS that are available for immediate release. To date, a little more than 4,000 courses have been requested and distributed to a total of 28 jurisdictions. There are an additional 150,000 courses available at the manufacturer that are expected to be delivered over the next few weeks. In addition, there are 500,000 courses available at the manufacturer awaiting release that are expected to be delivered this year. There has been an order for 250,000 additional courses to be manufactured from existing bulk vaccine, which also are expected to be delivered later this year. This comes from a total of 7.9 million courses of bulk drug that could be filled and finished upon request by the US Government (USG). For ACAM2000, there are currently more than 100 million doses in the SNS.[176]

In terms of recommendations for pre-exposure prophylaxis (PrEP), ACIP voted in November 2021 to recommend vaccination for select persons at risk for occupational exposure to orthopoxviruses. These recommendations were published in June 2022 in a Policy Note, which is currently available.[177] In those recommendations, people who are recommended to receive PrEP include the following:[178]

- ❑ Clinical laboratory personnel who perform testing to diagnose orthopoxviruses, including those who use PCR assays for diagnosis of orthopoxviruses, including monkeypox virus.
- ❑ Research laboratory workers who directly handle cultures or animals contaminated or infected with orthopoxviruses that infect humans, including monkeypox virus, replication-competent vaccinia virus, or recombinant vaccinia viruses derived from replication-competent Vaccinia virus strains.
- ❑ Certain healthcare and public health response team members designated by public health authorities to be vaccinated for preparedness purposes.

PrEP for healthcare workers is possible under shared clinical decision-making. At this time, most clinicians in the US and laboratorians not performing the orthopoxvirus generic test to diagnose orthopoxviruses are not advised to receive prthopoxvirus PrEP. Laboratorians should consult with laboratory biosafety officers and supervisors to identify risks and precautions, depending on the type of work that they are doing. Clinicians and laboratorians should use recommended infection control practices. ACIP contraindications for ACAM2000 and JYNNEOS for PrEP are outlined in the following table:

Contraindication	ACAM2000 Primary Vaccinees	ACAM2000 Revaccinees	ACAM2000 Household Contacts[1]	JYNNEOS
History or presence of atopic dermatitis	X	X	X	
Other active exfoliative skin conditions	X	X	X	
Conditions associated with immunosuppression	X	X	X	
Pregnancy	X	X	X	
Aged <1 year	X	X	X	
Breastfeeding	X	X		
Serious vaccine component allergy	X	X		X
Known underlying heart disease (e.g., coronary artery disease or cardiomyopathy)	X	X		
Three or more known major cardiac risk factors	X			

[176] https://aspr.hhs.gov/ASPRBlog/Pages/BlogDetailView.aspx?ItemID=432; https://www.bavarian-nordic.com/investor/news/news.aspx?news=6584
[177] https://www.cdc.gov/mmwr/volumes/71/wr/mm7122e1.htm
[178] https://www.cdc.gov/poxvirus/monkeypox/clinicians/smallpox-vaccine.html

In terms of CDC's response in the current outbreak, the agency is focusing on tried-and-true public health measures, including robust surveillance to identify cases and confirm through laboratory diagnosis, followed by containment through isolation of cases and contact tracing, and vaccination of close contacts with PEP based on a risk exposure assessment for which guidance is available on the CDC website.[179] This includes PEP being recommended for individuals with a high degree of exposure, those with an intermediate degree of exposure to be recommended PEP based on an individual basis to determine whether benefits of PEP outweigh the risks. It is important to note that brief interactions and those conducted using appropriate personal protective equipment (PPE) in accordance with Standard Precautions are not high risk and generally do not warrant PEP.

With respect to other vaccine strategy considerations, CDC is aware that there are jurisdictions with larger numbers of cases that are reporting high percentages of contacts that cannot be identified. Several are considering, planning, and even implementing expanded vaccination programs at this time. Many are following similar approaches to strategies being used in Montreal and the UK. However, there are currently limited supply of JYNNEOS. CDC, in planning for expanded vaccination in the US, is carefully considering how best to use these limited supplies. The agency has heard from some jurisdictions that there are concerns about potential serious AEs with the use of ACAM2000, especially considering that milder disease is commonly being reported in this outbreak. CDC is working with the ACIP and federal, state, local, and other community partners to move forward as quickly as possible to provide recommendations to expand vaccination. The EtR Framework is being used to structure these deliberations and guide the development of vaccine strategies.

In terms of treatment considerations for monkeypox, it is important to start with the statement that many individuals infected with monkeypox virus have a mild self-limiting disease course, even in the absence of specific therapy. The prognosis for monkeypox does depend on multiple factors, including previous vaccination status, initial health status, and concurrent illnesses or comorbidities. With that in mind, CDC has provided some treatment considerations for monkeypox and recommends considering treatment following consultation with CDC for the following:

- ❑ Persons with severe disease (e.g., hemorrhagic disease, confluent lesions, sepsis, encephalitis, or other conditions requiring hospitalization).
- ❑ Persons who may be at high risk for severe disease:
  - People with immunocompromising conditions (e.g., HIV/AIDS,
  - leukemia, lymphoma, generalized malignancy, etc.)
  - Pediatric populations, particularly patients younger than 8 years of age
  - Pregnant or breastfeeding women
  - People with a history or presence of atopic dermatitis and people with other active exfoliative skin conditions
  - People with one or more complication
- ❑ Persons with monkeypox virus aberrant infections that include its accidental implantation in eyes, mouth, or other anatomical areas where monkeypox virus infection might constitute a special hazard (e.g., the genitals or anus)

[179] https://www.cdc.gov/poxvirus/monkeypox/clinicians/monitoring.html#exposur

Tecovirimat[180] is an antiviral medication that is approved by the FDA for treatment of human smallpox in adults and pediatric patients weighing at least 3 kilograms. This is also known as TPOXX or ST-246. An oral capsule and IV formulations were approved by FDA in July 2018 and May 2022, respectively. Tecovirimat is indicated for the treatment of human smallpox only. CDC does hold an Emergency Access IND protocol to allow the use of Tecovirimat for non-virial orthopoxvirus infections, including monkeypox. Currently, Tecovirimat is available from the SNS as an oral capsule formulation or an intravenous vial. VIGIV[181] is licensed by the FDA for the treatment of complications due to vaccinia vaccination, including eczema vaccinatum, progressive vaccinia, severe generalized vaccinia, vaccinia infections in individuals who have skin conditions, and aberrant infections induced by vaccinia virus (except in cases of isolated keratitis). CDC similarly holds an Emergency Access IND protocol to allow the use of VIGIV for non-virial orthopoxvirus infections, including monkeypox. This product may be used in unique cases, severe cases, as adjunctive therapy, or otherwise. The SNS holds Cidofovir, also known as Vistide,[182] which is an antiviral medication that is approved be FDA for the treatment of cytomegalovirus (CMV) retinitis in patients with Acquired Immunodeficiency Syndrome (AIDS). CDC has an Emergency Access IND protocol to allow for use of this product for monkeypox.

CDC is available for consultations to assist with medical countermeasure utilization, including appropriate vaccine and antiviral use. Clinicians can work with their state or territorial health authorities to request vaccines, Tecovirimat, VIGIV, or Cidofovir. Health departments can reach out to CDC consultants through the CDC Emergency Operations Center (EOC).

Discussion Summary

Dr. Kotton inquired as to whether brincidofovir (BCV), a liquid preparation of cidofovir that is much better tolerated and is approved for smallpox, has been considered for use with monkeypox.

Dr. Petersen indicated that brincidofovir is a lapidated formulation of cidofovir that is licensed by FDA for treatment of smallpox. CDC is working with government agencies and the manufacturer of this product, which is not currently available in the SNS, to investigate ways to make it available if needed for monkeypox. In addition, CDC is working with regulatory authorities to make sure that the agency has a regulatory mechanism to use it, given that it is not licensed for monkeypox, such as the Expanded Access IND protocol.

Dr. Chen asked whether there are similar limits for the tecovirimat and the VIGIV products as there are for the vaccines. He also observed that the New York City Department of Health has been coordinating with the CDC and is trying to stage a vaccination clinic in Manhattan and asked whether there are similar movements by other health authorities in other regions that are also trying to access vaccines and/or therapeutics and if perhaps these need to be wider dissemination more rapidly regarding those types of activities.

Dr. Petersen indicated that the precise numbers of tecovirimat, VIGIV, and cidofovir stockpiles have not been released, but there is sufficient quantity. CDC does not expect any supply limitations in any of those medical countermeasures. He confirmed that CDC is coordinating with New York City and other jurisdictions that are working to expand their vaccination programs. Fortunately, they are working with the SNS, which is able to ship these medical countermeasures very rapidly. In general, it is possible to get these products where they need to

[180] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208627s000lbl.pdf
[181] https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/vaccinia-immune-globulin-intravenous-human
[182] https://www.accessdata.fda.gov/drugsatfda_docs/label/1999/020638s003lbl.pdf

go within 28 hours. However, there are some supply limitations with JYNNEOS that CDC is working to address to make sure that this medical countermeasure is being provided and used in an optimal and equitable fashion.

Dr. Sanchez asked how to access the vaccines and/or medications from a practical standpoint in terms of the chain of events and whether requests all go through local health departments who contact CDC.

Dr. Petersen replied that CDC is requesting that medical countermeasure requests come from health departments so that appropriate public health authorities are aware of what is happening and what is available in their jurisdictions. Clinicians on the ground, as with any suspect cases, are advised to go directly to their local and state public health authorities.

Dr. Maldonado (AAP) said it was her understanding that the WHO is considering designating this as a Public Health Emergency of International Concern (PHEIC), and she imagined that CDC was involved in those conversations as well. Given that they were approaching the end of this ACIP meeting and we may not receive updates in the near future, she asked whether there might be anything different about recommendations from CDC that this international designation might lead to. In addition, it seemed to her that this is not the traditional presentations for orthopoxvirus or monkeypox virus infections seen on the African subcontinent, particularly for children. She asked whether there have been cases reported in children that are the usual, typical manifestation or this atypical manifestation and whether there should be concerns about other precautions that would need to be taken for children regarding treatment or prophylactic interventions.

Dr. Petersen confirmed that the WHO convened a meeting earlier in the day. On their agenda was a discussion of whether to declare this current monkeypox outbreak a PHEIC. CDC was participating in that meeting, though he had not yet heard the readout from that meeting to know whether that would occur. Ultimately, that is a decision for the WHO Director General. If a PHEIC is declared and the US follows suit and declares a public health emergency as well, that could change some of the regulatory mechanisms in terms of these medical countermeasures, opening up the possibility that they may be used under an EUA or under Emergency Use Instructions (EUI).

Dr. Rao indicated that there have not been any cases in children in the US. Internationally, CDC has heard very little about cases in children. Cases that have occurred in Nigeria, in general, have been somewhat strange for other reasons. This particular clade of monkeypox has not resulted in more severe illness and has not spread person-to-person as much. Even before the 2022 cases were identified, the West Africa clade associated with Nigeria infections has been a somewhat unusual in that some deaths have been reported and there has been person-to-person spread, including in settings like prisons and among household members. An imported case resulted in secondary cases, including in one healthcare worker. It is difficult to know for sure why this is presenting unusually in terms of whether it is something related to what has been seen for the last few years in West Africa or if it is something different. CDC is trying to understand that. At this point, CDC is relying on what is known from the agency's work before 2022 in Africa. While the clinical presentation itself has been similar, the illness has sometimes been more severe in children.

Dr. Drees (SHEA) noted that the PPE recommended for care of suspected monkeypox cases includes gloves, eye protection, and a respirator. However, a healthcare provider may not realize that they should be worried about monkeypox until they are actually examining the patient and seeing typical lesions. They would not necessarily have a respirator, especially in outpatient locations. But she recalled from the presentation that this would not be considered an exposure in terms of the use of PEP. This seemed like a disconnect, so she wanted to confirm that this was correct. Thankfully, people in healthcare are still masking routinely, but she wondered about what advice CDC would give for healthcare workers who saw the patient initially without use of the full PPE in terms of self-monitoring.

Dr. Rao said that she and Dr. Petersen both were involved in developing the initial guidance. With the growth of this outbreak, there have been others from CDC's Division of Healthcare Quality, and Promotion (DHQP) and other groups taking the lead on that. In the interest of not misspeaking, they offered to check and get back to ACIP on that.

Dr. Petersen added that the risk exposure assessment is currently being revised and will provide specific recommendations for healthcare workers as well as community members at large. Some of that information will be revised in the near future.

Dr. Fryhofer (AMA) said she had read that brincidofovir has an improved safety profile over the cidofovir and requested additional information about that and also what side effects to expect with these antivirals.

Dr. Petersen indicated that cidofovir does carry a risk of renal toxicity and is administered intravenously in conjunction with cimetidine for renal protection. In contrast, brincidofovir is orally available and in clinical trials has not shown the same renal toxicity and has shown some potential for hepatoxicity as well as some GI side effects. But in general, the safety profile of brincidofovir does show less severe side effects compared to cidofovir. Tecovirimat has shown to be quite safe and well-tolerated without any specific safety concerns for SAEs.

Dr. Long noted that the epidemiology of the cases described gives a somewhat different image of potential spread to the population in general and through non-sexual contact. She asked if there is reason to believe that this virus is transmissible without very close personal contact, and what CDC's expectations are of cases outside of sexual transmission. Her concern is about the likelihood that the general US population might be susceptible and if they should be worried about usual casual contact with one another.

Dr. Rao indicated that the cases CDC is aware of have occurred through direct skin-to-skin contact, contact with fomites (towels, bedding), and close contact with a household member. Historically, the recommendations have been that monkeypox can be spread through direct contact as well as through close proximity because of secretions. Someone in close proximity for a prolonged period of time to somebody else could be exposed through secretions. There is no reason at this time to suspect spread in any other way. It is not even clear whether transmission is through seminal fluids or if is through the close contact that occurs when people have intimate contact. CDC is trying to understand this and is planning semen and other studies to understand this better. At this moment, all signs are that it has still not spread to a large number of people, and it is believed that a lot of the case patients have had a large number of contacts. CDC is trying to get to the bottom of exactly how many contacts and how many people it might have been spread to, but it appears to be a small number of exposed contacts who have gotten it and their contact has been pretty intimate. There is no reason at this time to

suspect that this is a risk to the wider population. The risk to the general public is believed to be very low at this time.

Ms. Howell (AIM) pointed out that the awardees in the 64 immunization programs have been rolling out COVID-19 vaccines, which has been taking a lot of their time. If a larger campaign may be needed in the future for JYNNEOS or other vaccination, planning assumptions or guidance would be appreciated as early as possible. A lot of the COVID-19 vaccine funding is very specific to COVID-19 vaccine and cannot be used for any rollout of a monkeypox vaccine initiative.

Dr. Fryhofer (AMA) noted that the CDC website states that monkeypox also can be spread through respiratory secretions during prolonged face-to-face contact for which she requested further explanation.

Dr. Rao reiterated that DHQP has taken this over because it is their area of expertise, but this is about close contact, such as being within 6 feet for a prolonged period of time and the opportunity to be exposed to someone's saliva or droplets from respiratory secretions. Someone kissing and saliva is what they are trying to get at with that.

Thinking about the fact that there have been no deaths among the 155 cases that have been identified, Dr. Sanchez asked how many have been treated to prevent progression or how many have been severe enough that they have required therapy either with this tecovirimat or cidofovir.

Dr. Rao indicated that the cases that have occurred in the US have been managed mostly through outpatient care. There have been some hospitalizations, but those have been due to things like pain control if there is proctitis.

Dr. Petersen shared some additional information on medical countermeasures that have been released for treatment. A total of 197 courses of oral tecovirimat have been distributed to a number of jurisdictions. At this point, a total of 18 patients in 8 jurisdictions have received oral tecovirimat. Similar to Dr. Rao's point, severe cases have not been observed. Some IV tecovirimat has been distributed, but no patients have yet received IV tecovirimat. CDC is working with its state partners who have received these medical countermeasures in order to monitor the outcomes of treatment and vaccine use to help inform the vaccine strategy and future clinical consultations.

PUBLIC COMMENTS JUNE 23, 2022

Overview

The floor was opened for public comment on June 23, 2022 at 2:09 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 No. CDC-2022-0062. Visit http://www.regulations.gov for access to the docket or to submit comments or read background documents and comments received.

Public Comment

Jonathan Couey, PhD
Gigaohm Biological

Thank you. My name is Jonathan Couey. I have no conflicts of interest. The ethical principle of informed consent has been effectively ignored for the duration of the pandemic. The FDA and the CDC long ago failed to meet their responsibility to ensure informed consent in those healthy adults who have been already transfected most egregiously in the health of college students and teens for whom there was never an emergency. The CDC and FDA failed again just days ago to provide the opportunity for informed consent, this time for parents and children under 5 who on recommending transfection as safe and effective, after nearly 2 years of calling transfection by a lipid nanoparticle an investigative vaccine, you have failed to provide informed consent by pushing a false equivalence between transfection and traditional live-attenuated and recombinant vaccines. You have failed to inform the public that transfection, the expression of a viral protein via injection of synthetic RNA is a highly variable and tissue-dependent process that we are unsure can provoke meaningful immune memory—the goal of any vaccination. You have failed to notify the public of the potential for autoimmunity while also failing to look for this known downside of this technique. The FDA has no data support recommending transfection for any healthy human in 2022. After more than 2 years, you have failed to inform the public that you know the studies upon which these recommendations are based are woefully underpowered. In place of informed consent, you have pushed the vague concepts of safe and effective until they were devoid of meaning. The studies used to specifically recommend transfection to the under 5 age group are statistical jokes without clinically meaningful endpoints. You know immunobridging to non-inferiority is useless. Do your job. Of course, the CDC, NIH, and NIAD also failed to inform the public that they knew late in 2019 that the virus had already several key molecular aspects that indicated both its origin and the many known countermeasures that would be expected to work. Instead, they said they knew nothing, they could see nothing unusual, and that our immune systems were equally vulnerable, and you ran with it. Data from your own presentations demonstrate the vast majority of kids have been infected, a primary counter indication for the administration of any vaccine before 2020. You are pushing products under the guise of a regulatory framework that we know by your actions is proforma only. You failed to inform the public that you know from studying influenza and other viruses that the developing immune system is an impossibly complicated process that involves imprinting mechanisms that cannot be reversed. The catalog of molecular immune memories that protects us for a lifetime is formed through the countless exposures of pathogen in our childhood, and you have failed to inform the public that you know that transfection to a 2020 viral code protein cannot be useful in augmenting this process. You know it will not meaningfully protect these children because there's a planet worth of data informing you of this. It's biology. Please gets some and then please do your job.

Dr. David Wisemen
Synechion

Thank you, Dr. Lee. CDC's website asserts the FDA has determined that COVID vaccines are safe and effective for everyone 6 months and older. It certainly has not. FDA's guidance describes the EUA standard as "may be effective lower than the conventional effectiveness standard." For EUA safety, FDA must determine that maybe benefits outweigh the risks. FDA has published its methodology in the journal *Vaccine* and the VRBPAC meetings for 5- to 11-year-olds. Why has this analysis been absent in recent VRBPAC deliberations? Well, according

to FDA's Dr. Fink, Pfizer efficacy estimates are preliminary, imprecise, and potentially unstable. If FDA does not know the vaccine's "maybe effectiveness," how can it calculate benefit over risk? The green light to vaccinate millions of children based on 3 Pfizer vaccines and [unclear] is stunningly absurd and impugns all related decisions about Moderna. These data also show negative VE for Pfizer in some scenarios, also shown in waning by CDC. Moderna provides no waning data, but surely must have it as they will be reportedly presenting booster data next week. In a paper by Dr. Walensky and colleagues, warnings of waning natural immunity present a risk to vulnerable populations apply equally to vaccination. Moderna's 2-dose data for 6 and above were pre-Omicron, a problem FDA invoked [unclear] EUA. Why not here? FDA's Dr. Fink tells us that immunobridging may not be scientifically established. Worst still, it targets Wuhan. Pfizer and Moderna [unclear] are unvalidated with data FDA states they have not verified. Claims of clinical relevance are ridiculed by CDC's analysis Friday of 2 Pfizer doses showing significant VE to toddlers with failed immunobridging, but the reverse to infants. VSD's myocarditis rates are 6 times higher in 5 to 11-year-olds [unclear]. Dr. Long appropriately notes that myocarditis booster rates match or exceed the primary series rates. A new disclosure reveals that CDC has not [unclear] conducted safety analysis, which we have provided to FDA and CDC several times. Confusing intervals, labels, and guidance will surely add to the 1,300+ children noted by CDC. VRBPAC's Dr. Pointer asked Pfizer which cells produce spike, how much they produce, and for how long. Pfizer dismissed this question as academic. It is certainly not. Understanding these basic questions is vital to understand safety. Moderna's answer to Dr. Sanchez's similar question today was that the spike persists for less than a week. The Stanford study [unclear] showed persistence of vaccine message and antigen for at least 60 days. Unless FDA, Moderna, CDC, and Pfizer can provide this information, parents have every reason to avoid injecting their children with these "may be effective" therapies. Thank you very much.

Mrs. Melissa Chios
AMHFC

Good afternoon. Melissa Chios here to speak on Moderna COVID-19 shots vote for kids aged 6 to 17 years. I'm hoping that prior to the vote, Dr. Sara Oliver, who is up next, can address the many dangerous datapoints emerging over which tenured medical professionals all over the world are sounding the alarm, some of whom are the most published in their field. Let me be clear. Children's death rate from COVID-19 is statistically zero with a survival rate of 99.98%. Dr. Eric Rubin, CDC advisory committee member, has acknowledged, and I quote, "We're never going to learn about how safe the vaccine is until we start getting it. That's the way it goes." If our children have a statistical risk of zero from dying from COVID, why on Earth are we to assume a risk with a vaccine for which we have no real risk profile? These trials will not be concluded until 2024, meaning our children are the experiments. During Tuesday's VRBPAC meeting, Dr. Ruth Link-Gelles from CDC admitted that the COVID-19 shot had negative efficacy. One of the already known and acknowledged CDC, I'm sorry, COVID-19 shot risks includes myocarditis. Even Dr. Tom Shimabukuro here has previously acknowledged that these shots caused myocarditis, citing his own slides, and those of John [unclear] and Nicola Klein. Why are so many healthy children and young adults developing myocarditis? Why are so many athletes dropping on the ball field? And why is this panel making recommendations in favor of [unclear]. You acknowledged it caused severe adverse reactions. Why is no one here discussing the serious issue of antibody-dependent enhancement, and prion disease, and cancer? Why are 236 records of the 270 pregnant women disappeared from the Pfizer trial, and why did 28 of those 34 women whose records remained lose their babies? At Rambam Hospital in Haifa, Israel, reports indicate 34% more spontaneous abortions and stillbirths occurred in vaccinated women compared to those unvaccinated. This presents a statistically significant increase in fetal demise. Why is this all being ignored? Various studies have now confirmed

menstrual dysregulation in women who've had the COVID-19 shot as well as heavy spike protein accumulation in the ovaries. Studies have also found that these shots affect male fertility. Among semen donors, studies show that those vaccinated for COVID-19 have been impaired semen concentration and reduced total motile counts. How can anyone ignore these signals of infertility, and how can you have another answer or a plan for those who plan to procreate in the future? How is it not gross negligence for this panel to continually ignore blatant cries of tens of thousands of researchers and doctors across the globe while these alarming signals remained unaddressed? Do not turn the other way and vote for another unproven shot while these alarming datapoints exist. Doctors, scientists, and parents are watching, and we deserve answers. I don't know how any of the panel can sleep at night knowing that there are so many dangerous signals that are being blatantly ignored, and it is unconscionable to continue to keep voting for additional vaccines. Has anyone looked at the VAERS reports? By the way, 85% of those VAERS reports are reported by healthcare professionals—not the general public.

Mrs. Barbara Loeppke
Loeppke Professional Services

Thank you. My name is Barbara Loeppke. I have no conflicts of interest. Regarding the presentation about the HPV vaccine yesterday, it is concerning that the word "estimated" was used over and over and over. Do we not have any real data? There was no mention about the adverse events that are experienced by some here—the infertility, the gastroparesis, and the other neurological problems. And frankly, I'm really appalled that no one in the committee even batted an eye about the studies use for yesterday's HPV presentation, that they were all conducted in third world communities. The reference to the India trials was stopped by their government and was quickly brushed over and not discussed. All there was just a general applause for the vaccine and what it's done, but no real data. On to the COVID vaccine. The use of the phrase, "putting the incidence in context" is definitely bypassing the "first do no harm" ethics which used to be part of medicine. Harm of children is now acceptable for the greater good. If we know that myocarditis can be caused by the vaccine, why is there only one entry that's been determined to be compensable by the countermeasures program? There's no help for the injured. Today, finally, Dr. Shimabukuro had admitted that there are many experiencing injuries. He has admitted that they don't know the mechanism or how to help them. Continuing to put these harmful vaccines onto the schedule when you know people are being injured—these injuries and the lives affected are on your hands. There's no other answer. With the official acknowledgement today, you can't say you don't know about them, but there have already been 2,176,799 reports filed in VAERS for the COVID vaccine. Last week, the committee said that putting the COVID vaccine on the schedule just means that parents who want the vaccine for their children can get it. However, we all know that if a vaccine is recommended for children by the CDC, it will be made mandatory for daycare and school. As several states only have a medical exemption, and doctors that give medical exemptions in those states are having those medical licenses attacked for doing so, there will be no choice allowed for many parents. The decision took away choice. Regarding the allowance of the use of the 10-dose vial for babies and toddlers, it is just a disaster waiting to happen. As quoted from a renowned statistician,"10-dose vials are terrible because administration errors go up and because it's impossible to guarantee consistency across doses." Different cap colors have not stopped errors. Currently, there are 21,012 dosage errors in VAERS. President Biden on June 10th stated that parents could make appointments for . . . time expired.

Thair Phillips
Seniors Speak Out

Thank you for having me. I'm Thair Phillips of Seniors Speak Out. I want to start by thanking this committee for your continued diligence toward ensuring vaccines are available for Americans throughout our lifespan. As many of us are parents, grandparents, aunts, and uncles, we were particularly grateful for the recent approval of the vaccines for the youngest children. As you know, older Americans can benefit greatly from vaccines as we are most likely to be managing chronic conditions and a weakening immune system. As we learned early on in the pandemic, COVID-19 posed a greater threat to older Americans than in any other age group. In fact, grim statistics recently released by the Associated Press showed that 3 out of 4 COVID deaths were older Americans, which further illustrated this very real threat. Despite entering into year 3 of this pandemic, our generation has not lost our resolve in fighting back against this violence and has embraced the vaccine more than any other age group, with 95% of Americans over 65 having received at least 1 dose. With that in mind, it is particularly important to those of us who serve older Americans to continue our work to keep their vaccination rates high and for COVID, added booster doses if necessary. Now that we as a country are able to vaccinate to prevent COVID from the very young to the very old, we should remain steadfast in our efforts to keep COVID boosters at the front of older Americans' minds. To that end, the work of ACIP will be critically important in the months to come so that groups like ours can help encourage our fellow Americans to remain up-to-date on boosters as well as being vaccinated for other respiratory illnesses like the flu and pneumonia. As you know, vaccination rates pre-pandemic were not ideal. The pandemic squashed those routine vaccination numbers even further. COVID vaccinations were somewhat of a bright spot, with older Americans lining up. Let's build on that. Let's continue to work together to benefit this important community and ensure that they are informed, and most importantly, protected against COVID-19 and other preventable diseases. Thank you.

Daniel Grenier
Citizen of the United States of America

The authorization of this experimental mRNA gene therapy will forever be a dark moment in human history where kids became sacrificial lambs for pharmaceutical profits. Don't take my word for it. Read the BioNTech SEC filing where it says "our revenue heavily depends on COVID-19 vaccine sales." The CDC frequently parrots "the benefits outweigh the risks." Is that so? The only benefit I can see is 50 billion in expected sales for Pfizer and Moderna in 2022, and the only risk I see are 1,291 side effects from Pfizer's documents that the company, in collusion with the FDA, attempted to hide from us for 75 years. These are the side effects that this advisory panel has placed babies as young as 6 months old at risk of. Since these shots do not prevent transmission, they are in fact useless and make the public more at risk of COVID. In the words of virologist Geert Vanden Bossche, scientifically, there is no rationale whatsoever to vaccinate children. There is no added value, only major concerns and major risk, and it is criminal. It is especially criminal since children have a 99.995% recovery rate and over 75% of American children have already built superior natural immunity. In short, this agency has faked an emergency for children to gain emergency use authorization to shield itself and the pharmaceutical companies from liability for serious and permanent injuries and death. The 1986 National Childhood Vaccine Injury Act has given rise to a criminal enterprise that allows pharmaceutical companies to kill and maim with their shots. It's especially disturbing that the United States of America is the only country in the world conducting this medical experiment on children under 5. Countries like Sweden and Finland, for instance, have banned the shot from Moderna for under 30 years of age and other younger populations, citing the risk of heart

inflammation that CDC itself recognizes. But even in the [unclear] it's explicitly stated in the 1.3 million adverse in the VAERS database including 48,500 in children as of May 20th this year. In summary, there is absolutely zero health benefits from these mRNA gene therapies. Preliminary data from these shots show that they cannot even meet a 6% efficacy to meet EUA approval. In short, I urge every parent to keeping the poisonous shots away from your children and do not sacrifice them to the altar of science where the S is a dollar sign. Thank you.

CLOSING REMARKS

Dr. Lee expressed gratitude for these timely updates and emphasized that based on the discussion, there is going to be a lot of interest in this particular topic going forward. As the meeting was coming to a close, she thanked everyone for all of their work over the past week. She said that she was feeling pretty exhausted and thought everyone else must be feeling the same way. ACIP had 4 days of meetings in the last 7 days, including a Saturday in a week that was inclusive of Father's Day and Juneteenth so that the committee could provide timely and transparent information to the public about vaccines and the decision-making process. She stressed that she and Dr. Wharton were extremely grateful for everyone's extra time and willingness to go above and beyond in their service to the public.

Dr. Wharton echoed Dr. Lee's appreciation to the committee, *ex officios*, liaisons, presenters, and members of the public who were listening in.

CERTIFICATION

Upon reviewing the foregoing version of the June 22-23, 2022 ACIP meeting minutes, Dr. Grace Lee, ACIP Chair, certified that to the best of her knowledge, they are accurate and complete. Her original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

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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
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
aIIV	Adjuvanted Influenza Vaccine
AE	Adverse Event
AESI	Adverse Event of Special Interest
AHIP	America's Health Insurance Plans
AI/AN	American Indian/Alaskan Native
AIDS	Acquired Immunodeficiency Syndrome
AIM	Association of Immunization Managers
AIRA	American Immunization Registry Association
AMA	American Medical Association
AOA	American Osteopathic Association
AOM	Acute Otitis Media
APhA	American Pharmacists Association
AR	Adverse Reaction
ARI	Acute Respiratory Illness
ASTHO	Association of State and Territorial Health Officers
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CHD	Congenital Heart Disease
CICP	Countermeasures Injury Compensation Program
CLD	Chronic Lung Disease
CMI	Cell-Mediated Immunity
CMS	Center for Medicare and Medicaid Services
CMV	Cytomegalovirus
COD	Cause of Death
COI	Conflict of Interest
CSF	Cerebrospinal Fluid
CSTE	Council of State and Territorial Epidemiologists
CVD	Cardiovascular Disease
CVT	Costa Rica Vaccine Trial
DC	District of Columbia
DFO	Designated Federal Official
DHDD	Division of Human Development and Disability
DICP	Division of Injury Compensation Program
DoD	Department of Defense
DoRIS	Dose Reduction Immunobridging & Safety Study
DRN	Distributed Research Network
DSMB	Data Safety Monitoring Board

DVA	Department of Veterans Affairs
ED	Emergency Department
EMA	European Medicines Agency
EMR	Electronic Medical Record
EPIC	Etiology of Pneumonia in the Community Study
ESRD	End-Stage Renal Disease
ET	Eastern Time
EtR	Evidence to Recommendation
EUA	Emergency Use Authorization
EUI	Emergency Use Instructions
eVRC	Electronic Vaccination Report Card
FDA	Food and Drug Administration
FRN	Federal Register Notice
FY	Fiscal Year
GBS	Guillain-Barré Syndrome
GI	Gastrointestinal
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
HCP	Healthcare Personnel / Providers
HCT	Hemolytic Cell Transplant
HSCT	Hematopoietic Stem Cell Transplant
HD-IV	High-Dose Influenza Vaccine
HHS	(Department of) Health and Human Services
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
HSCT	Hematopoietic Stem Cell Transplant
HVTN	HIV Vaccine Trials Network
HA	Hemagglutinin
IARC	International Agency for Research on Cancer
IAVG	Interagency Vaccine Group
ICU	Intensive Care Unit
IDSA	Infectious Disease Society of America
IHR	International Health Regulation Emergency Committee
IHS	Indian Health Service
IIS	Immunization Information System
ILI	Influenza-Like Illness
IND	Investigational New Drug
IPD	Invasive Pneumococcal Disease
ISD	Immunization Services Division
ISO	Immunization Safety Office
ISS	Integrated Safety Summary in Infants
ITP	Immune Thrombocytopenic Purpura
IV	Intravenous
J&J	Johnson & Johnson
kbp	Kilobase
KEN SHE	KENya Single-dose HPV-vaccine Efficacy Study
KFF	Kaiser Family Foundation

LRN	Laboratory Response Network
LTCF	Long-Term Care Facility
MAC	Multi-Age Cohort
MAAE	Medically Attended Adverse Event
MCV	Meningococcal Vaccine
MIS-C	Multisystem Inflammatory Syndrome in Children
MMR	Measles, Mumps, Rubella
MMSC	Male-to-Male Sexual Contact
MMWR	*Morbidity and Mortality Weekly Report*
MSA	Metropolitan Statistical Area
MSM	Men who have Sex with Men
MVA-BN	Modified Vaccinia Ankara-Bavarian Nordic
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization Canada
NAPNAP	National Association of Pediatric Nurse Practitioners
NBP	Non-Bactearemic Pneumonia
NCBDDD	National Center on Birth Defects and Developmental Disabilities
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHS	National Center of Health Statistics
NCIRD	National Center for Immunization and Respiratory Diseases
NEJM	*New England Journal of Medicine*
NFID	National Foundation for Infectious Diseases
NHSN	National Healthcare Safety Network
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIS-CCM	National Immunization Survey Child COVID-19 Module
NIS-Teen	National Immunization Survey-Teen
NMA	National Medical Association
NREVSS	National Respiratory and Enteric Virus Surveillance System
NP	Nasopharyngeal Swab
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
NVSN	New Vaccine Surveillance Network
OASH	Office of the Assistant Secretary for Health
ODPHP	Office of Disease Prevention and Health Promotion
OIDP	Office of Infectious Disease and HIV/AIDS Policy
OPV	Oral Polio Vaccine
PASC	Post-Acute Sequelae of SARS-CoV-2
PCP	Primary Care Provider/Practitioner
PCR	Polymerase Chain Reaction
PEP	Post-Exposure Prophylaxis
PHAC	Public Health Agency Canada
PHEIC	Public Health Emergency of International Concern
PICO	Population, Intervention, Comparison, Outcomes
PIDS	Pediatric Infectious Disease Society
PPE	Personal Protective Equipment
PrEP	Pre-Exposure Prophylaxis
QALY	Quality-Adjusted Life Year
RCA	Rapid Cycle Analysis

RCT	Randomized Controlled Trial
RIV	Recombinant Influenza Vaccine
RN	Registered Nurse
RNA	Ribonucleic Acid
RR	Relative Risk
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
RVE	Relative Vaccine Efficacy
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts on Immunization
SAHM	Society for Adolescent Health and Medicine
sBLA	Supplemental Biologics License Application
SD-IIV	Standard-Dose Unadjuvanted Influenza Vaccines
SHEA	Society for Healthcare Epidemiology of America
SME	Subject Matter Expert
SNS	Strategic National Stockpile
STI	Sexually Transmitted Infection
TTS	Thrombotic Thrombocytopenia Syndrome
UK	United Kingdom
US	United States
USG	United States Government
VA	(US Department of) Veteran's Affairs
VAERS	Vaccine Adverse Event Reporting System
VaST WG	Vaccine Safety Technical Work Group
VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VFA	Vaccines for Adults
VFC	Vaccines For Children
VICP	National Vaccine Injury Compensation Program
VIGIV	Vaccinia Immune Globulin Intravenous
VLP	Virus-Like Particle
VRBPAC	Vaccine and Related Blood Products Advisory Committee
VRC	Vaccine Research Center
VSD	Vaccine Safety Datalink
WG	Workgroup
WHO	World Health Organization