MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

OCTOBER 19-20, 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 October 19-20, 2022. The meeting took place remotely via Zoom, teleconference, and live webcast.

WEDNESDAY: OCTOBER 19, 2022

WELCOME AND INTRODUCTIONS

Call to Order/Roll Call

Dr. Grace Lee (ACIP Chair) called to order and presided over the October 19-20, 2022 Advisory Committee on Immunization Practices (ACIP) meeting. Dr. Lee conducted a roll call, which established that a quorum was present. A list of Members, *Ex Officios*, and Liaison Representatives is included in the appendixes at the end of this summary document. No conflicts of interest (COIs) were identified.

Announcements

Dr. Melinda Wharton (ACIP Executive Secretary, CDC) noted that copies of the slides for the meeting were available on the ACIP website and were made available through a ShareLink™ file for ACIP Voting, *Ex Officio*, and Liaison Members. The ACIP is, at its heart, a public body. Engagement with the public and transparency in all of its processes are vital to the committee's work. She indicated that there would be 2 oral public comment sessions during this meeting. The first was scheduled for 3:30 PM Eastern Time (ET) on October 19, 2022 and the second was scheduled for 1:00 PM Eastern on October 20, 2022. To create a fair and more efficient process, individuals interested in making an oral comment were asked to submit a request online in advance of the meeting. Priority is given to these advance requests. If more people make requests than can be accommodated, a blind lottery is conducted to determine who the speakers will be. Speakers selected in the lottery for this meeting were notified in advance of the meeting. Members of the public also may submit written comments via https://www.regulations.gov using Docket Number ID CDC-2022-0111. Information on the written public comment process, including information on how to make a comment, can be found on the ACIP website.

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

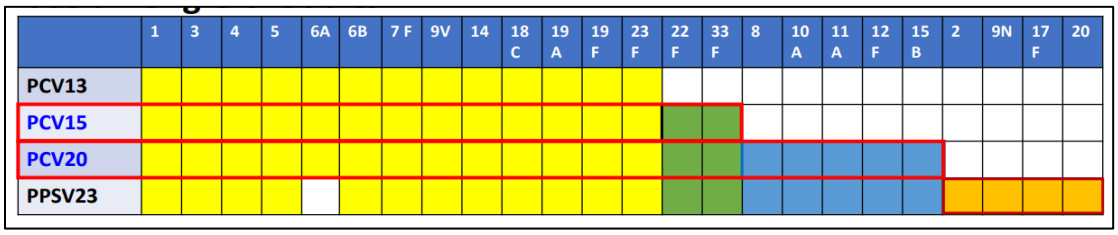
Dr. Wharton said she was very pleased to introduce a new member of ACIP, Dr. Nirav Shah, who is Director of the State of Maine Center for Disease Control and Prevention. He serves as the State Health Official for the State of Maine. He is the Recent Past President of the Association of State and Territorial Health Officials (ASTHO). When not working, Dr. Shah enjoys exploring Maine's beautiful outdoors with his dog, Quincy.

Dr. Lee (ACIP Chair) took a few moments to share gratitude for Dr. Kevin Ault, who has regularly attended ACIP meetings since 2004. He became a member of ACIP in 2018. He served on ACIP until the last meeting in September 2022 and there was not an opportunity to recognize him for the work that he has done for the committee and for his exemplary service, particularly during the COVID pandemic. During his tenure on ACIP, Dr. Ault was Chair of the ACIP Hepatitis Vaccine Work Group (WG), Chair of the Combined Immunization Schedules WG, and a member of the Influenza WG, the HPV WG, and the COVID-19 VaST Pregnancy Group. All of that has been incredibly impactful in terms of ACIP's deliberations. Dr. Ault's expertise is in the delivery of care to pregnant women, especially regarding vaccine use during pregnancy, which has been tremendous. Dr. Lee emphasized that she has personally learned a lot from Dr. Ault and that his very presence had been impactful in terms of making sure that ACIP is inclusive of pregnancy women in its deliberations and always attentive to evaluating the impact of vaccines and vaccine recommendations in this population. On behalf of ACIP, Dr. Lee expressed gratitude for Dr. Ault's service to this committee and wished him the best in his new role as Chair of the Department of Obstetrics and Gynecology (OB/GYN) at Western Michigan University, Homer Stryker School of Medicine.

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. As a reminder, 2 new pneumococcal conjugate vaccines were licensed for use among US adults in 2021. As depicted in this table the new 15-valent pneumococcal conjugate vaccine (PCV15) includes PCV13 serotypes + 22F and 33F and the new PCV20 includes PCV13 serotypes + 22F, 33F, 8, 10A, 11A, 12F, and 15B:



In addition, 23-valent pneumococcal polysaccharide vaccine (PPSV23), Pneumovax23® by Merck continues to be available.

The WG has been working on the current pneumococcal vaccine recommendations for adults. The current adult pneumococcal vaccine recommendations are as follows:

- Adults ≥65 years and 19–64 years with chronic medical conditions (CMC), immunocompromising conditions (IC), cerebrospinal fluid (CSF) leak, and cochlear implant are currently recommended to receive PCV20 or PCV15 followed by PPSV23 if they have not previously received a pneumococcal vaccine.

- For those who have received PPSV23 only, any adult with these indications who received PPSV23 more than 1 year earlier may receive PCV15 or PCV20.

Adults who previously received PCV13 (with or without PPSV23) are currently recommended to "complete the previously recommended PPSV23 series." The recommendations for these individuals are as follows:

- Adults 19–64 years of age with a CSF leak or cochlear implant who previously received PCV13 only should receive PPSV23 at least 8 weeks following PCV13 and then a final dose of PPSV23 at ≥65 years at least 5 years after receipt of PPSV23.

- Adults 9–64 years of age with IC who previously received PCV13 only should receive PPSV23 at least 8 weeks following PCV13, PPSV23 at least 5 years after that, and then a final dose of PPSV23 at ≥65 years of age at least 5 years after receipt of the previous dose of PPSV23.

- ≥65 years of age who received PCV13 only should receive PPSV23 ≥8 weeks if they have an underlying condition (IC, CSF leak, cochlear implant) or ≥1 year if they have none of these conditions. In either case, they should receive one final dose of PPSV23 at ≥65 years of age.

- Adults ≥65 years of age who receive PCV13+PPSV23 after age 65 years do not need an additional vaccine dose.

This has been the topic of conversation during many ACIP meetings, with many comments received from the WG and the public. The WG is tackling these issues. Adults 19–64 years of age with a cochlear implant, CSF, or immunocompromising conditions were previously recommended to receive PCV13 and PPSV23 with repeat doses of PPSV23 after 5 years if immunocompromised. Adults ≥65 years of age with none of these conditions or with CMCs were recommended to receive both PPSV23 and PCV13 based on shared clinical decision-making. Adults ≥65 years of age of age with a cochlear implant, CSF, or immunocompromising conditions were previously recommended to receive both PCV13 and PPSV23. The policy questions the WG is tackling include the following:

1. Should US adults aged ≥19 years who previously received PCV13 only be recommended to receive a dose of PCV20 to complete their pneumococcal vaccine series?

2. Should US adults aged 19–64 years with an immunocompromising condition, CSF, or cochlear implant who previously received both PCV13 and PPSV23 be recommended to receive a dose of PCV20 to complete their pneumococcal vaccine series?

3. Should US adults aged ≥65 years who previously received both PCV13 and PPSV23 be recommended to receive a dose of PCV20?

The guiding principles the WG has used throughout are that: 1) decisions on policy options should be supported by the best-available evidence; 2) simplifying existing pneumococcal vaccine recommendations could help improve vaccine coverage among adults; 3) disparities in pneumococcal disease burden and vaccine coverage should be reduced; and 4) timely recommendations for each new vaccine should be made after Food and Drug Administration (FDA) licensure.

To put the policy questions into context, pediatric PCV15 use was approved in June 2022. Approval of PCV20 use among children is anticipated in the second quarter of 2023, which will be the focus of the Pneumococcal Vaccines WG after this meeting. New adult pneumococcal vaccines in advanced stages of development include the following:

- A 24-valent pneumococcal vaccine (AFX3772, GSK) has completed a Phase 1/2 study for adults[1]

- A 21-valent pneumococcal conjugate vaccine (V116, Merck) has completed Phase 1/2 study for adults[2] and Phase 3 immunobridging studies in adults are currently ongoing

Presentations during this session included a cost-effectiveness analysis of PCV20 use among adults who previously received PCV13, a summary of the WG's interpretation of the Evidence to Recommendation (EtR) Framework, and proposed recommendations, and proposed updates to clinical guidance on pneumococcal vaccine use among adults.

Cost-Effectiveness Analysis of PCV20 Use among Adults Who Previously Received PCV13

Charles Stoecker, PhD, MA (Tulane University) shared the findings of the cost-effectiveness analysis of PCV20 use among adults who previously received PCV13. The study question was to evaluate the cost-effectiveness of using PCV20 after PCV13 in adults. The methods included assessment of program costs and medical savings and tracking changes in disease, medical costs, and non-medical costs. A societal perspective was utilized, meaning that all relevant medical costs were incorporated. The population included cohorts of 42+, 65+, or 75+ year olds who have had PCV13 and model reports were separated for the immunocompromised (HIV, cancer, organ transplants, dialysis) or the healthy bundled together with those with CMCs (diabetes, heart disease, lung disease, liver disease, alcoholism).

For Question 1 regarding the use of PCV20 in adults who previously received PCV13 only, the model looked at several types of people:

Comparator	Adding
PCV13 at Age 65 (Healthy/CMC)	PCV20 at Age 66
PCV13 at Age 75 (Healthy/CMC)	PCV20 at Age 76
PCV13 at Age 65 (IC)	PCV20 at Age 66
PCV13 at Age 75 (IC)	PCV20 at Age 76
PCV13 at Age 42 (IC)	PCV20 at Age 43

[1] Chichili et al. Vaccine 2022
[2] Platt et al. Lancet ID 2022

For Question 2 regarding the use of PCV20 in adults with IC aged 19-64 years who previously received PCV13 and PPSV23, the model looked at the following:

Comparator	Adding
PCV13+PPSV23 at Age 42	PCV20 at Age 47
PCV13+PPSV23 at Age 42	PCV20 at Age 43

For Question 3 Use of PCV20 in adults aged 65+ without IC (healthy/CMC) who previously received PCV13+PPSV23, the model looked at the following:

Comparator	Adding
PCV13+PPSV23 at Age 65/66	PCV20 at Age 71
PCV13+PPSV23 at Age 65/66	PCV20 at Age 67
PCV13+PPSV23 at Age 65/66	PCV20 at Age 76
PCV13+PPSV23 at Age 75/76	PCV20 at Age 77
PCV13+PPSV23 at Age 75/76	PCV20 at Age 81

For Question 3 Use of PCV20 in adults aged 65+ with IC who previously received PCV13+PPSV23, the model looked at the following:

Comparator	Adding
PCV13+PPSV23 at Age 65	PCV20 at Age 66
PCV13+PPSV23 at Age 65	PCV20 at Age 70
PCV13+PPSV23 at Age 65	PCV20 at Age 75
PCV13+PPSV23 at Age 75	PCV20 at Age 76
PCV13+PPSV23 at Age 75	PCV20 at Age 80

In terms of the model, a cohort model was utilized that tracked cost per quality adjusted life (QALY) year gained and cost per life year gained. The cohort sizes that were run through the model depended upon the age and the percent vaccinated with PCV13 or PCV13+PPSV23 (e.g., Model size = cohort 75-IC-year-olds * % IC vaccinated with PCV13+PPSV23). All outcomes (case counts, deaths, QALYs, LYs, etc.) and costs were discounted by 3%. All costs were adjusted to 2021 dollars using the Consumer Price Index (CPI). The time horizon was 15 years. Each recommendation was compared to the status quo and the incremental cost effectiveness ratio was calculated by dividing the change in costs by the change in QALYs. A probabilistic sensitivity was performed in which the model was run 50,000 times. The cumulative distribution function (CDF) of dollars per QALY was assessed. The 5^{th} and 95^{th} percentiles of all outputs were assessed and a “tornado” was created of all of the influential inputs. The health outcomes assessed included:

- ❑ Cases of Invasive Pneumococcal Disease (IPD)
- ❑ Cases of hospitalized Nonbacteremic Pneumonia (NBP)
- ❑ Cases of outpatient NBP
- ❑ Deaths due to IPD
- ❑ Deaths due to hospitalized NBP
- ❑ QALYs
- ❑ Life Years

The disease inputs in the model included community-acquired pneumonia (CAP) per 100,000 population from 2013-2015[3], IPD rates per 100,000 population from 2017-2018[4], and case fatality rates (CFRs) for IPD and pneumonia[5]. In terms of serotype distributions in the healthy population, these people have already been protected with PCV13. The additional protection each age group (65-74, 75-84, 85+) would receive from PCV20 were broken down by the serotypes covered by PCV13 (+6C-3-19F). Serotype 3 was tracked separately because it is thought that vaccines may work differently against that particular serotype. Serotype 19F also was tracked separately for indirect reasons. The model also tracked serotypes for PCV15 only (ST 22F, 33F), PCV20 only (ST 8, 10A, 11A, 12F, 15B), and PPSV23 only (ST 2, 9N, 17F, 20). This was done separately for IPD and hospitalized all-cause pneumonia. The same serotype tracking was done for CMC population age groups of 65-74, 75-84, and 85+ and the IC population age groups of 19-49, 50-64, 65-74, 75-84, and 85+.

Vaccine effectiveness (VE) was incorporated for healthy/CMC and IC populations.[6] The IC VEs were found to be about a third of the healthy/CMC VEs, except that slightly different numbers were assumed for the effectiveness of PCV vs VT (except ST3) NBP (Healthy) and PCV vs VT (except ST3) NBP (CMC). The numbers for PPSV were lower than for the conjugate vaccine for Healthy/CMC and IC.

The cohort size modifiers were based on PCV13 and PPSV23 coverage data.[7] For instance, a healthy cohort who previously received only PCV13 is going to represent about 13% of the 65+ cohorts. That is, the number of healthy adults 65+ was determined and that number was multiplied by 30%. That result was the starting cohort for any run that looked for adding PCV20 to a healthy population who previously received only PCV13. The same process was applied to the other cohorts as well. Some of these were quite small. For instance, the IC cohort who received only PCV13 was about 3.1%.

The in-model coverage rate was 100% for PCV13 because the model already was conditioned on the people who received PCV13. PPSV23 also was 100% in scenarios that considered PPSV23. There were no scenarios in which the coverage rate for PPSV23 was not either 0% or 100% because those were split out into separate model runs. For adding PCV20 in cohorts <75 years old, a coverage rate of 63.8% was assigned. For PCV20 in cohorts 75 years of age, a coverage rate of 72.7% was assigned. Those numbers were obtained by looking at the ratio of the PPSV23 coverage to PCV13 coverage in CMS data. The idea is that this is about the rate that people go on to get the second vaccine in a series, so these people already have received either 1 or 2 doses previously in a series.

[3] Source: MarketScan & Optum databases (Pelton et al. CID 2019)
[4] Source: Active Bacterial Core Surveillance System (ABCs), 2017-2018
[5] IPD CFR from ABCs data. Pneumonia CFR from NIS 2018
[6] PCV vs VT (except ST3) IPD: Bonten NEJM 2015 (per protocol)
PCV vs ST3 IPD: Point estimate from Pilishvili et al. ISPPD2018 abstract, lower bound set to 0, upper bound from Lewis 2020 ISPPD poster
PCV vs VT (except 3) NBP: Suaya Vaccine 2018; 1477-1483.
PCV vs ST3 NBP: applied the ratio of IPD VE/Pneumonia VE for all PCV13 types to the point estimate for ST3 IPD VE.
PPSV vs VT IPD: CDC meta-analysis of 7 studies using indirect cohort methods 4/15/2021
PPSV vs VT NBP: Lawrence, 2020 (meta-analysis of 3 studies, Kim, Suzuki and Lawrence: 19.2% (0-39.1)
All IC estimates: Apply ratio of VE for IC in Djennad 2018 to estimates for Healthy/CMC
PCV15 & PCV20 VE: Hurley CID 2020; Stacy Human Vaccines & Immunotherapeutics 2019
[7] 42+ IC coverage from Deb et al. “Pneumococcal vaccination coverage among adults aged 19 to 64 years with immuno-compromising conditions, cerebrospinal fluid (CSF) leaks, or cochlear implants in the US”, Exp Rev Vac, 2021. All other coverage rates from CMS Claims 2020

For herd effects from PCV15 or PCV20, the serotype group-specific declines were applied that previously were observed in PCV13 types (+6C, -3) in adults after PCV13 introduction in children. In anticipation of a PCV15 recommendation beginning in 2023 and a PCV20 recommendation starting in 2024, a similar experience was applied for what was observed with PCV13 and the model also was run with and without the herd effects to assess the importance.

For utility decrements, a way was needed to add up all of the disparate end points (IPD, IPT NBP, and OPT NBP). For instance, a case of IPV would be tracked and counted as a QALY decrement of 0.0709 (0.0509, 0.0909). All of the cases of IVP prevented by adding PCV20 were added and then multiplying that by the QALY values of each outcome prevented. The result is the total QALY saved by adding PCV20.[8]

For waning for PCV13 and PCV20,[9] no decline was assumed in the first 5 years and then a linear decline over the next 10 years. PPSV23[10] will decline similarly over 15, but slightly more aggressively at the start. The assumption was that there would be a linear decline to 50% of initial over first 5 years, a linear decline to 30% of initial over next 5 years, and linear to 0% of initial over next 5 years. The vaccine prices[11] that were used were $257.99 for PCV13, $283.72 for PCV20, $133.47 for PPSV23, and $56.73 for Administration + Time cost.[12]

To highlight some of the results, in the run for PCV13 @65, PCV20 @66, in the base case, 97 cases of pneumococcal disease were prevented. Key from this run is the cost/QALY or the cost effectiveness ratio, which is a compilation of all of the costs (e.g., the amount spent on vaccines and the amount saved on medical costs divided by the QALYs). The QALYs are the index way of adding up in-patient and outpatient cases. For this run, the cost/QALY is $493,242. The 5th and 95th percentiles from the 50,000 runs of the model were $399,996 and $741,184, respectively.

The tornado diagram is one way to track the inputs to which the model is most sensitive. The size of the bars indicate how sensitive the model is to that particular input. The widest bar at the top of this tornado diagram is the VE of PCV versus PCV-type (except ST3) Pneumonia in the CMC population, which is a population who has very high disease rates. The diagram shows that the cost-effectiveness ratio for this group can range from $446,603.54 to $696,068.63. The way these 2 numbers are determined is to look at the cost-effectiveness ratio of the VE versus PCV-type pneumonia for the PCV13 @65, PCV20 @66 population is in the bottom 10% within the top 10% of distribution. This is the most influential parameter on the cost-effectiveness ratio, which are organized in decreasing order of influence:

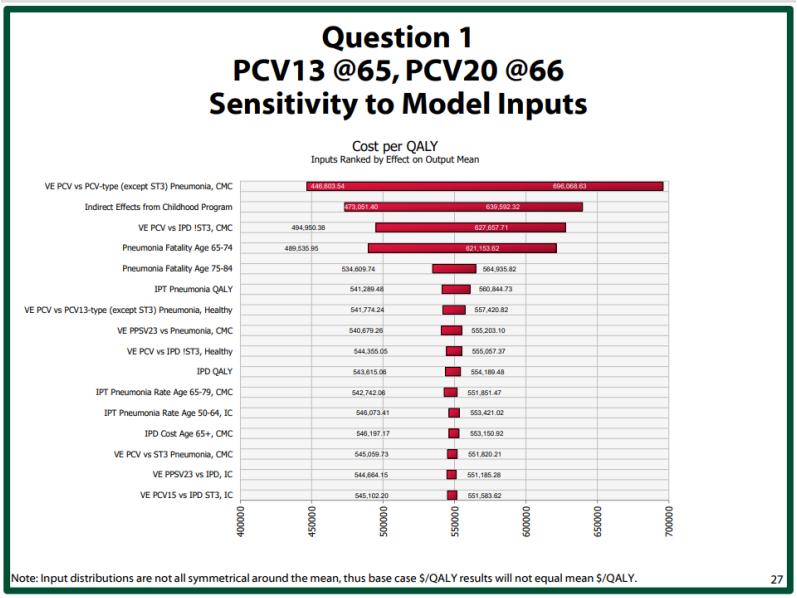
[8] Mangen et al. 2015 Eur Respir J

[9] Patterson S, Webber C, Patton M, Drews W, Huijts SM, Bolkenbaas M, et al. A post hoc assessment of duration of protection in CAPiTA (Community Acquired Pneumonia immunization Trial in Adults). Trials in Vaccinology. 2016;5.:92-96; by assumption; van Werkhoven CH, Huijts SM, Bolkenbaas M, Grobbee DE, Bonten MJ. The Impact of Age on the Efficacy of 13-valent Pneumococcal

[10] Fry AM, Zell ER, Schuchat A, Butler JC, Whitney CG. Comparing Potential Benefits of New Pneumococcal Vaccines with the Current Polysaccharide Vaccine in the Elderly. Vaccine 2002;21:303-311.

[11] PCV13, PCV20, PPSV23: Medicare maximum allowable reimbursement

[12] Medicare reimbursement for immunization administration (HCPCS code 90471) plus travel cost from Maciosek MV, Solberg LI, Coffield AB, Edwards; NM, Goodman MJ. Influenza vaccination health impact and cost effectiveness among adults aged 50 to 64 and 65 and older. Am J Prev Med 2006;31(1):72-9.



Dr. Stoecker noted that he was going to present only one of the tornado diagrams, but that they all look very similar. The most important thing is generally either the indirect effects from the childhood program or the effectiveness PCV vaccines against non-invasive disease in the CMC population. In terms of the CDF, none of the runs for Question 1 were below $300,000 per QALY. About 35% of the runs were below $500,000 per QALY and about 70% of the runs were below $600,000 per QALY. The provides some sense of what the numbers could be. Given that there is uncertainty around all of the inputs, this is a simple way to aggregate all of that uncertainty.

In terms of Question 2 (adults aged 19–64 years with an immunocompromising condition, CSF, or cochlear implant who previously received both PCV13 and PPSV23), Dr. Stoecker highlighted the PCV13 @42, PPSV @42, PCV20 @47 representative run. In the base case, 3 cases of IPD and 11 hospitalized pneumonia cases would be prevented. These numbers are smaller than the previous ones because the cohort is smaller at about 12,000 people versus about 422,000 people. The cost-effectiveness ratio for the Question 2 group in this run is $254,555 per QALY for the base case, with a range of $179,473 to $493,296 per QALY for the 5th and 95th percentiles. Similar to the representative run for Question 1, the CDF shows that none of the runs cost below $100,000 per QALY and about 50% of the runs are below $300,000 per QALY. The distribution for Question 2 looks more cost-effective than the previous one because it costs less to pick up QALY for Question 2. Still, about 20% of the runs for Question 2 cost more than $400,000 per QALY.

For Question 3 (≥65 years who previously received both PCV13 and PPSV23), Dr. Stoecker highlighted the PCV13 @65, PPSV23 @66, PCV20 @71 representative runs. In the base case, approximately 115 IPD cases and 870 hospitalized pneumonia cases would be prevented. The ratio of how much it would cost to pick up an extra QALY would be $414,166 with 5th and 95th percentiles of $281,250 to $872,758. Regarding the CDF, none of the runs cost below $200,000 per QALY. About 7% of the runs are below $300,000 per QALY, about 50% are below $500,000 per QALY, and about 20% are more than $800,000 per QALY.

A number of 1-way sensitivity analyses also were performed in which assumptions are turned off and on. The 2 assumptions turned off and on here were zero herd effects from the childhood program and PCVs having zero effectiveness against Serotype 3. In the 1-way sensitivity run for all schedules, the base case was somewhat North of $100,000 per QALY. Assuming no VE against Serotype 3, the cost per QALY increased slightly. Assuming no herd effects, the cost per QALY decreased slightly. Thus, the 1-way sensitivities for these 2 assumptions do not matter very much. With the same runs but highlighting the schedules having a 1-year delay versus a 5- or 10-year delay, the 1-year delay schedules are the range so it is a little more complicated than whether it is a 1- or 5-year delay. In the same runs highlighting the schedules that have PCV20 after age 65, adding in age 66 a year after receiving PCV20 or age 71 that are more expensive, the schedules where PCV20 is not recommended until age 75 lines up better with the disease profile and those tend to be somewhat cheaper.

To summarize, the limitations are that there is substantial uncertainty around the effects from the childhood program and there is uncertainty around VE against non-invasive disease. None of the policies or model simulations are below $126,640 per QALY. It is important to put that into context. While ACIP does not use a threshold for cost-effectiveness ratios, it is helpful to think about what other institutions use. One frequently cited threshold in the literature in America is $100,000 per QALY to be considered effective. At the top end is the statistical value of a life year of about $500,000 per QALY, which is about what people would pay to get an extra year of life and marginal safety improvements. For Question 1, Adults 19+ who previously received PCV13 only, the cost-effectiveness ratios for the base case ranged from approximately $137,000 to $557,000 per QALY. For Question 2, IC adults 19-64 who previously received PCV13+PPSV23, the base case ranged from approximately $255,000 to $341,000 per QALY. For Question 3, Adults 65+ who previously received PCV13+PPSV23, the base case ranged from $188,000 to $874,000 per QALY for the base case. To bring these into context with recent PCV modeling for adults at ≥65 years of age, ACIP recently voted on replacing PPSV23 for all + PCV13 (shared clinical decision-making) with PCV20 for all, which was cost-saving or replacing that pair of PSCV23 and PCV13 with PCV15 + PPSV23 for all, which also was cost-saving. Cost-saving means on net saving on cost and gaining health outcomes in contrast to all of the runs shown during this session in which spending money resulted in better health outcomes. The committee voted not to continue to recommend PCV13 for all in 2019, which was based at least in part on a cost per QALY of approximately $562,000.

Discussion Summary

Dr. Shah requested confirmation with respect to the Conceptual Model on Slide 11. In the comparator scenarios in the model as displayed, one could get the impression that the comparator at Node 1 was between someone on a schedule who received either PCV20 or no vaccination when, in fact, irrespective of ACIP's recommendation in terms of voting or not in favor of PCV20, that individual would not receive no vaccination but rather something adjunct such as PCV13. He wanted to get a sense of whether in the model the comparator was the person who received no vaccination or whether that person hypothetically would receive something else. The question on the table pertained to comparing the marginal benefit of PCV20 versus whatever the status quo would be. He suspected in practice the status quo would not be no vaccine but rather whatever the standard of care is currently that the infectious disease experts likely would confirm to be something akin to PCV13. He wanted to ensure that the analysis was setting up the answer to the right question of the comparison of the marginal benefit of PCV20 not to no vaccine but rather to the current status quo standard of care.

Dr. Stoecker confirmed that everyone in this model received PCV13 at a minimum and several received PCV13 + PPSV23, which was Schedule A versus Schedule B in the Conceptual Model on Slide 11. After receiving Schedule A, they either could comply with the schedule (about 60% to 70% of the people who get vaccinated with PCV20) or not comply with the schedule and receive no vaccine. Everyone in the model already has a fair amount of protection. He emphasized that the current standard of care is somewhat unclear. Referring to Slide 19, he pointed out that there were people in each category. Some people receive PCV13 only and some get PCV13+PPSV23. Some people get PCV13 only even though they are recommended to get PCV13+PPSV23. The model looks at what people actually received, PCV13 or PCV13+PPSV23, and what it would do to add PCV20 to those particular populations. It is the marginal effect of adding PCV20 over a population who already has some protection. Everyone in the model has received at least PCV13 and some have and some have not completed their series.

Dr. Loehr requested an example of a healthy person under 65 years of age who would have received either PCV13 only or PCV13+PPSV23. The original Policy Question 1 include adults ≥19 years of age who previously received PCV13, which was confusing.

Dr. Stoecker responded that this was why those were missing from the table under 42+ where only a dot was shown because there were no healthy people under 65 years of age.

Dr. Kobayashi indicated that the adults ≥19 years of age who previously received PCV13 only included immunocompromised adults 19–65 years of age or adults ≥65 years of age. That was referring to those who were previously recommended to receive PCV13 and PPSV23. To clarify, no adult groups were recommended to receive PCV13 only. They were recommended to receive PCV13 in series with PPSV23. The group who only received PCV13 is comprised of people in between the recommended series—they have not completed the series. They were included because even as of now, there are people who have received only PCV13.

Dr. Lee pointed out that it was helpful for her to understand from Slide 19 that the proportion of people who are actually getting pneumococcal vaccine is extremely low, so it seemed like there was a lot of work to do to get people vaccinated—period. The presentation estimated that about 12,000 individuals each would be effective for Policy Options 1 and 2 and about 500,000 for Policy Option 3.

Dr. Stoecker clarified that it was about 500,000 for Options 1 and 3 and about 12,000 for Option 2, because Option 2 is immunocompromised.

Dr. Poehling highlighted that this is a time-limited period because as the transition occurred, this would go away. The question regarded how to handle the transition.

WG's Interpretation of the EtR and Proposed Recommendations

Miwako Kobayashi, MD, MPH (CDC/NCIRD) presented a summary of the Pneumococcal WG's interpretation of the EtR Framework for use of PCV20 use among adults who previously received PCV13. As a reminder, the vaccines contain the follow serotypes:

- PCV15: PCV13 serotypes and 22F and 33F
- PCV20: PCV13 serotypes and 22F, 33F, 8, 10A, 11A, 12F, and 15B
- PPSV23 non-PCV20: serotypes 2, 9N, 17F, and 20

She also reviewed the previous recommendations and policy questions described by Dr. Poehling in the overview for this session; the pneumococcal vaccine timing for adults as of April 1, 2022[13]; the EtR Framework domains and questions; and the recommended groups, who are as follows:

- ❑ Group 1: US adults aged ≥19 years who previously received PCV13 only
- ❑ Group 2: US adults aged 19–64 years with an IC condition, CSF, or cochlear implant who previously received both PCV13 and PPSV23
- ❑ Group 3: US adults aged ≥65 years who previously received both PCV13 and PPSV23

The recommended number of PPSV23 doses and the recommended interval for these adults varied depending upon their age and underlying conditions. Once a dose of PPSV23 is given at or after 65 years of age, no additional pneumococcal vaccine doses are currently recommended. Therefore, Group 3 is comprised of adults ≥65 years of age who completed their vaccine series under current recommendations.

As a reminder, the EtR Domains include: Public Health Problem, Benefits and Harms, Values, Acceptability, Feasibility, Resource Use, and Equity. In terms of the Public Health Domain question regarding whether the problem is of public health importance for adults who previously received PCV13, the characteristics of the target population are that there are approximately 27 million adults aged ≥65 years in the total population size of 54.1 million[14]. Approximately 50% of adults have received ≥1 dose of PCV13[15]. Approximately 5% or 0.4 million adults aged 19–64 years have immunocompromising conditions within a population size of 7.7 million[16]. Approximately 4% of eligible adults received ≥1 PCV13 dose[17].

In adults, pneumococcal pneumonia is the most common form of pneumococcal disease. IPD, defined as an illness with pneumococcus identified in a normally sterile place such as blood CSF, is a less frequent but severe form of pneumococcal disease. In 2018-2019, the case fatality ratio from IPD among adults aged ≥65 years was 14%[18]. Younger adults have lower incidence of pneumococcal disease, but the risk is higher among those with IC. This table shows the estimated incidence of hospitalized IPD and pneumococcal pneumonia by age group and risk group from an analysis using US healthcare claims data[19]:

	Rate per 100,000 person-years, 2013–2015		
	Healthy[1]	**High-risk[2]**	**Rate Ratio**
18–49 years			
Hospitalized IPD	0.6 (0.5, 0.7)	8.6 (6.7, 11.2)	**15.4 (11.3, 20.9)**
Hospitalized pneumococcal pneumonia	1.2 (1.1, 1.3)	21.1 (17.9, 24.9)	**17.6 (14.4, 21.5)**
50–64 years			
Hospitalized IPD	1.9 (1.6, 2.1)	16.4 (14.4, 18.7)	**8.8 (7.4, 10.6)**
Hospitalized pneumococcal pneumonia	3.9 (3.5, 4.2)	43.0 (39.7, 46.6)	**11.1 (9.9, 12.6)**

[13] https://www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf
[14] United States Census Bureau
[15] Hoehner et al. https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/pubs-resources/pcv13-medicare-beneficiaries-2010-2019.html
[16] Estimated from census data and Pelton et al. CID 2019 to estimate the proportion with immunocompromising conditions
[17] Deb et al. Expert Review of Vaccines 2021
[18] CDC ABCs, 2018–2019
[19] Reference: Pelton et al. CID 2019; 1. Adults without any conditions with risk-based pneumococcal vaccine indications; 2. Adults with immunocompromising condition or with cochlear implant

Based on the rate ratios shown in the far right column of the table, adults with IC have approximately 9 to 18 times higher incidence of pneumococcal disease compared with adults without underlying conditions/

Regarding the impact of PCV13 use against pneumococcal disease in adults, CDC ABCs data from 2017-2019 show that the PCV13-type IPD incidence among adults aged ≥65 years decreased after introduction of PCV13 use in children in 2010. Notably, Serotype 6C was assessed together with PCV13 serotypes due to the cross-protection from Serotype 6A. No additional declines in PCV13-type IPD were observed after routine PCV13 use was recommended for adults ≥65 years of age in late 2014. This trend continued through 2019. IPV caused by serotypes not contained in PCV13 have been stable.

Looking at trends of specific serotypes contained in PCV13 during 2011-2019, among the PCV13 serotypes, the incidence of IPV caused by Serotype 3 remained stable. In 2018-2019, Serotype 3 caused more than 60% of the remaining IPD among adults ≥65 years of age caused by PCV13 serotypes. That is the reason Dr. Stoecker's model used some different estimates for VE against Serotype 3. Looking at the proportion of IPV for vaccine type for IC adults 19—64 years of age and all adults ≥65 years of age during 2018-2019, pneumococcal serotypes contained in PCV20 but not in PCV13 caused 27% of IPD in adults.

From 2013-2014 before routine PCV13 was recommended for adults ≥65 years of age, hospitalized non-invasive pneumococcal pneumonia incidence decreased in all adult age groups. However, no further reductions were observed after 2014, including among adults ≥65 years of age.[20] Reduction in the incidence of hospitalized PCV13-type pneumococcal pneumonia was observed after routine PCV13 use among a cohort of adults aged ≥65 years in the Louisville cohort study in 2014-2016 in which there was a 31.5% reduction (95% CI: 8.3, 48.9) in PCV13-type hospitalized pneumococcal pneumonia.[21] From October 2013 through September 2016, additional serotypes contained in PCV20 but not in PCV13 caused 3% to 4% of all-cause hospitalized community-acquired pneumonia (CAP) in adults.[22]

Regarding the impact of the COVID-19 pandemic on pneumococcal disease incidence, overall IPD incidence decreased in both adults and children early during the COVID-19 pandemic. Among children <5 years of age, there was a 57% decline in overall IPD in 2020 and a 30% increase in 2021. Among adults ≥65 years of age, there was a 50% decline in overall IPD in 2020 and an additional 25% decline in 2021 but not yet at the pre-pandemic baseline.[23] In an ongoing study of adults hospitalized with pneumonia,[24] one hospital in Nashville collected data before and during the pandemic. While there was increase in the incidence of all-cause hospitalized pneumonia early in the pandemic, the incidence of pneumococcal pneumonia estimates decreased.

The WG determined that pneumococcal disease is of public health importance in adults who received PCV13. Vaccine-preventable pneumococcal disease burden remains, especially for pneumonia. Reduction in pneumococcal disease incidence due to COVID-19 is likely time-limited.[25] Adults in Group 1 who have received PCV13 only have protection against limited serotype coverage. Adults in Group 2 aged 19–64 years with immunocompromising conditions

[20] Gierke et al. IDweek 2020. CDC's Surveillance for NonInvasive Pneumococcal Pneumonia (SNiPP), 2013–2017
[21] Swerdlow Jun 2018 ACIP meeting presentation
[22] Isturiz et al. CID 2021
[23] CDC Active Bacterial Core surveillance unpublished data
[24] Self et al. ISPPD 2022, study funded by Merck
[25] Perniciaro et al. CID 2022

may have limited protection from PPSV23. The population size of Group 3 adults aged ≥65 years is substantial compared to other groups. Although some WG members believe that the significance depends upon factors that determine the risk of pneumococcal disease, such as time since last pneumococcal vaccination, underlying conditions, or age.

Moving the Benefits and Harms Domain, PCV13, PCV15, and PCV20 are conjugate vaccines with capsular polysaccharides conjugated to CRM_{197} carrier protein. This allows the conjugate vaccine to induce a T-cell dependent response, which confers immunity in young infants who did not respond well to polysaccharide vaccines. A T-cell dependent response also results in Memory B-cell production. As a result, conjugate vaccines are expected to have longer duration of protection than polysaccharide vaccines.[26] Effectiveness against IPV is supported by clinical data for both conjugate and vaccines, although limited effectiveness of PPSV23 has been reported in adults with IC conditions.[27] PCV13 efficacy against vaccine-type non-invasive pneumococcal pneumonia was supported by a clinical trial.[28] Data on PPSV23 effectiveness against this outcome has been variable.[29]

According to CMS unpublished data, in June 2022, the median time since last PCV13 vaccination without PPSV23 among Medicare beneficiaries ≥65 years of age was 5.6 years, ranging from 0 to 8.5 years. The median time since last PPSV23 vaccination among adults who received PCV13 followed by PPSV23 was 3.1 years with a range of 0 to 8.4 years.

For GRADE (Grading of Recommendation Assessment, Development and Evaluation), the population was US adults aged 19–64 years with an IC, cerebrospinal fluid leak, or cochlear implant or US adults aged ≥65 years who previously received PCV13. The intervention was 1 dose of PCV20. The comparison was u\Use of PPSV23 based on the currently recommended dosing and schedule. The critical outcomes included vaccine type IPD (VT-IPD), VT-nonbacteremic pneumococcal pneumonia, VT-pneumococcal disease mortality, and serious adverse events (SAEs) following vaccination.

PubMed was searched to identify any published data on PCV20 efficacy, effectiveness, immunogenicity, or safety. In addition, clinicaltrials.gov was searched to identify additional PCV20 clinical trials. There were no PCV20 efficacy or effectiveness data. After excluding studies that targeted pneumococcal vaccine-naïve adults and studies that did not include the outcomes of interest, 2 immunogenicity studies were identified. One of them reported data on safety by previous pneumococcal vaccination status.

To summarize the 2 included studies, both were from Phase 3 clinical trials among adults aged ≥65 years without IC. The first study by Cannon et al. 2021 (safety and immunogenicity)[30] assessed safety and immunogenicity of PCV20 use among adults who previously received PCV13 alone, PPSV23 alone, or PCV13 followed by PPSV23. The study did not compare the immunogenicity of PCV20 with PPSV23. Safety after PCV20 use compared with PPSV23 use was assessed in adults who previously received PCV13 only. The second study, B7471004,[31] was a post-hoc analysis of a Phase 3 clinical trial that assessed co-administration of PCV20 with a quadrivalent inactivated influenza (QIV) vaccine. Response to PCV20 stratified by

[26] Patterson et al. Trials in Vaccinology 2016.
[27] World Health Organization. Strategic Advisory Group of Experts on Immunization 5-7 October 2020. https://terrance.who.int/mediacentre/data/sage/SAGE_eYB_October_2020.pdf?ua=1
[28] Bonten et al. NEJM 2015
[29] Farrar et al. https://www.medrxiv.org/content/10.1101/2022.10.06.22280772v1.full
[30] Cannon et al. Vaccine 2021. Funded by Pfizer.
[31] Safety and Immunogenicity of 20vPnC Coadministered With SIIV in Adults ≥65 Years of Age - Full Text View - ClinicalTrials.gov Funded by Pfizer https://classic.clinicaltrials.gov/ct2/show/NCT04526574

previous pneumococcal vaccination status. Since there was no comparison of PCV20 and PPSV23 immunogenicity among previously vaccinated adults, the immunogenicity of PCV20 was compared based on previous vaccination status. Opsonophagocytic activity (OPA) geometric mean titers (GMTs), which is a measure of functional antibody activity, 1 month after PCV20 vaccination were numerically higher among adults who previously received PCV13 only compared with those who received PPSV23 only. Similar trends were observed among those who previously received PCV13 followed by PPSV23 compared with those who received PPSV23 only. The percent of seroresponders, defined as percentage of participants with a ≥4-fold rise in OPA titers from before to 1 month after vaccination, was numerically higher among adults who previously received PCV13 only compared with adults who received PPSV23 only for most serotypes. For adults who previously received PCV13+PPSV23 compared with previous PPSV23 only, percent seroresponders were numerically higher for only a few PCV20 serotypes. However, adults who previously received both PCV13 and PPSV23 tended to have higher titers at baseline compared with adults who received PPSV23 only.

In terms of GRADE summary findings for safety,[32] the proportion of adults reporting SAEs through 6 months after vaccination was similar across groups. Among adults who previously received PCV13, SAEs 6 months after vaccination were similar across all group: PCV13 + PCV20 (n=246) vs. PCV13 + PPSV23 (n=127) was 2.4% vs 1.6%. PCV13 + PPSV23 + PCV20 (n=325, no comparator group) was 1.6%. No vaccine-related SAEs or deaths were reported.

The WG determined that the desirable anticipated effects of PCV20 use were moderate for Groups 1 and 2 and small to moderate for Group 3. The WG's interpretation for Groups 1 and 2 was based on the understanding of immunologic benefits of conjugate vaccines compared with polysaccharide vaccines since either of these was currently recommended to complete their series with PPSV23. For the adults in Group 1, some WG members believed that the benefits depend on the type of underlying risk of disease. For adults in Group 3 who have completed the recommended series with both PCV13 and PPSV23, more WG members believed that the incremental benefits of PCV20 use will be smaller compared to the first 2 groups. Some WG members believed that these adults would still benefit from added serotype coverage by a conjugate vaccine, while others believed that the benefits would depend on factors such as time since vaccination, age of patient, presence of underlying medical conditions, or indirect effects of pediatric PCV20 vaccination. The undesirable anticipated effects of using PCV20 among previously vaccinated adults were considered to be minimal. The WG believed that the desirable effects from PCV20 use outweigh the undesirable effects, given the minimal anticipated undesirable effects.

The certainty of evidence was determined to be low for both effectiveness and safety for Groups 1 and 2 and moderate for Group 3. For adults aged ≥65 years, indirectness was downgraded once to "serious" for evidence of effectiveness since there are only immunogenicity studies and correlates of protection have not been established for the critical outcomes. Imprecision was downgraded once for safety to serious because of the very small size of the study population. For immunocompromised adults aged 19–64 years, certainty for evidence of safety and effectiveness was further downgraded for indirectness because the included studies enrolled adults aged ≥65 years without ICs.

[32] Cannon et al. Vaccine 2021. Funded by Pfizer

In terms of the Values Domain, the WG's interpretation was "probably yes" for the first question, "Do adults who previously received PCV13 (with or without PPSV23) feel that the desirable effects from PCV20 vaccination are large relative to undesirable effects?" No research evidence was identified for this question. Since these are previously vaccinated adults, the WG believed that they are likely to have some understanding of the importance of receiving pneumococcal vaccine. Some WG members felt that there is not enough information to make the decision or that interpretation will vary among the target population. For the second question, "Is there important uncertainty about, or variability in, how much adults value the main outcomes?" the WG's interpretation was "probably not important uncertainty or variability" for Groups 1 and 2 since these are previously vaccinated adults. The WG's interpretation for Group 3 was variable. Since these are adults who have completed the vaccine series, some WG members believed that there could be uncertainty or variability depending on factors such as their age, life expectancy, time since last vaccination, or perceived severity of pneumococcal disease.

Regarding the Acceptability Domain, the WG reviewed data from 2 healthcare provider (HCP) web-based surveys for this domain. The first survey by Pfizer[33] showed that ≥65% of respondents agreed to the use of a higher-valent PCV for prior PCV13 recipients. In the second survey by the University of Iowa,[34] respondents were asked whether providers agreed with providing PCV20 for previously vaccinated adults. Respondents agreed the most to administering PCV20 for IC adults aged 19–64 years who previously received PCV13 only and the least for adults aged ≥65 years who received both PCV13 and PPSV23. The WG's interpretation of acceptability was "probably yes" for all 3 groups.

Evidence for the Resource Use Domain was based on cost-effectiveness analyses conducted by 3 modeling groups at CDC, Merck, and Pfizer. The summaries presented during this session were based on the work by Dr. Andrew Leidner in CDC's Immunization Services Division (ISD). In terms of the size of the population by age and previous vaccination status,[35] adults ≥65 years of age without ICs who previously received both PCV13 and PPSV23 had the largest population size. Therefore, the comparison focused on assessment of PCV20 use among adults ≥65 years of age without ICs who previously received both PCV13 and PPSV23 and, therefore, completed the recommended vaccination series. This table summarizes the differences in key assumptions across the model that can impact Incremental Cost Effectiveness Ratios (ICERs):

Model characteristics	CDC	Pfizer	Merck
Indirect effects from pediatric vaccination	Yes[a]	Yes[a]	**No**
PCV VE vs. serotype 3 disease	9-26%[b]	**60-75%[b]**	5-26%[b]
PPSV23 VE vs NBP	7-20%[c]	**0%**	3-67%[c]
Inpatient NBP case fatality ratios among 65+	3-5%[d]	3-11%[d]	**7-12%[d]**
QALY loss for IPD and inpatient NBP	0.071[e]	**0.130[e]**	0.071[e]

[33] Pfizer HCP preference survey 2021
[34] University of Iowa HCP preference survey 2022. Respondents were asked if they "Strongly disagree," "Disagree, "Neither agree or disagree," "Agree," or "Strongly agree" with administering PCV20 for adults who were previously vaccinated.
[35] Population levels by year of age come from US Census, 2021 projections. Portions of population in a risk status (Healthy, CMC, IC) by year of age come from the Pfizer model report. Portions of population with a past pneumococcal vaccinations come from the CDC model report.

CDC's and Pfizer's models considered the indirect effects from pediatric vaccination, but Merck's model did not. Not assuming indirect effects can decrease ICERs because indirect effects decrease vaccine-preventable disease burden among adults. Pfizer's model assumed higher effectiveness of PCV against remaining Serotype 3 disease compared to the other 2 models and assumed that PPSV23 has no effectiveness against non-bacteremic pneumococcal pneumonia (NBP). These assumptions can decrease ICERs compared with the other models. Assuming more severe outcomes from pneumococcal disease, such as higher case fatality ratios from inpatient NBP that was used in the Merck model, or assuming a larger QALY losses from disease as assumed in the Pfizer model can decrease the ICERs.

This table summarizes the averted disease burden of PCV20 use among adults ≥65 years of age who received both PCV13 and PPSV23 compared with no additional vaccine:

	CDC	Pfizer[b]	Merck[c]
Age of PCV20 vaccination	71 years	72 years	73 years
Time since last vaccination	5 years	7 years	5 years
QALYs gained	375	876	584
Deaths averted	65	293[b]	131
Hospitalization averted	1,252	3,318[b]	1,444
Cases averted	2,628	6,269[b]	3,143

To make these data comparable, all findings are from single cohort models of adults 71 to 73 years of age. The time since last vaccination ranges from 5 to 7 years. All models show that health outcomes improved with PCV20 use versus no vaccination. Estimated deaths, hospitalizations, and cases averted in the Pfizer model were not discounted. Differences in estimated health outcomes are likely due to differences in model assumptions for VE, CFRs, QALY loss, discounting, and population size.

In terms of the range of cost per QALY gained in the 3 models, CDC's model estimates include results from a cohort who received PCV20 at 71 years of age and 81 years of age. Pfizer's model resulted in the lowest estimates and Merck's model resulted within the range of the CDC estimates as shown in this table:

	CDC[a]	Pfizer[b]	Merck[c]
Age of PCV20 vaccination	71 and 81 years	72 years	73 years
Time since last vaccination	5 years	7 years	5 years
$/QALYs	**153,000 to 414,000**	**81,000 to 159,000**	**217,000**

To put this into context, cost-effectiveness ratios for previous policy questions among adults aged ≥65 years continuing routine PCV13 + PPSV23 use in 2019 were $562,000 per QALY for the base case in the CDC model and $199,000 per QALY in the Pfizer model.[36] The use of

[36] Leidner February 2019 ACIP meeting presentation

PCV20 only or PCV15 + PPSV23 versus the previous recommendations were shown to be cost-saving in most scenarios when the policy options were discussed in 2021.[37]

For Group 1, the most frequently selected responses by the WG was "Yes." However, some members selected "Probably No" and "No." WG members believed that the benefits of recommending PCV20 still outweigh the cost for adults who have received PCV13 only, while some WG members believed that the cost-effectiveness analysis findings do not justify the use of resources except for the immunocompromised. For adults who received both PCV20 and PPSV23, the WG's interpretation varied. For Group 2, similar numbers of WG members responded "Probably No," "Probably Yes," or "Yes." For Group 3, the most frequently selected response was "Probably No," but there were similar numbers who responded "Yes/Probably Yes" combined. Those who responded "Yes" or "Probably Yes" valued the anticipated benefits from PCV20 use over cost. Those who responded "Probably No" believed that the anticipated added benefits from recommending PCV20 instead of PPSV23 for adults who have already received PCV13 and PPSV23 are not large enough to justify the use of resources. Some WG members thought that the interpretation would vary depending upon time since the last vaccination, age, and underlying conditions.

With respect to the Equity Domain, ABCs data pertaining to US IPV incidence in Black and White adults from 2008-2019 shows that since PCV13 was introduced in children, IVP incidence due to all serotypes decreased in all age groups. Racial disparities in PCV13-type IPD incidence in Black versus White adults was reduced in all age groups. Although the incidence due to non-PCV13 serotypes remained fairly stable, Black adults continued to have higher incidence compared with White adults. This table summarizes any pneumococcal vaccine coverage among adults 19–64 years of age with risk-based pneumococcal vaccine indications:

	Sample size	%	(95% CI)
Overall	5,202	23.9	(22.4-25.3)
White	3,514	26.3	(24.5-28.1)
Black	699	23.3	(19.5-27.7)
Hispanic	624	16.7	(13.4-20.6)*
Asian	179	13.8	(8.8-21.2)*
Other	186	23.5	(16.8-31.7)

*p<0.05 for comparisons with White as the reference

The proportion receiving any pneumococcal vaccine was significantly lower among Hispanics and Asians compared with Whites among adults aged 19–64 years of with risk-based pneumococcal vaccine indications. This includes adults without immunocompromising conditions such as diabetes, chronic heart/lung disease, or smokers who were not previously recommended to receive pneumococcal conjugate vaccine.[38] Hispanic and Asian adults had significantly lower vaccine coverage compared with White adults. Compared to White adults, PCV13 and PCV13 + PPSV23 coverage were lower in other racial/ethnic groups among Medicare Part A and B beneficiaries aged ≥65 years.[39]

[37] Leidner September 2021 ACIP meeting presentation
[38] https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/pubs-resources/vaccination-coverage-adults-2019-2020.html
[39] https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/pubs-resources/pcv13-medicare-beneficiaries-20102019.html

The WG's interpretation of health equity varied for all 3 groups and was divided between "Probably Reduced" and "Probably No Impact." WG members who believed that PCV20 use would increase health equity felt that conditions that increased the risk of pneumococcal disease are more prevalent in non-White populations, that PCV20 use will decrease remaining disparities in pneumococcal disease burden, and that access to vaccines is likely better for minority populations compared with access to care for the disease. WG members who felt that PCV20 use probably would have no impact on health equity felt that vaccine access and utilization are likely to follow existing patterns, that there would be limited impact at the population level due to the small number of adults aged 19–64 years with IC who received both PCV13 and PPSV23, and that there would be small incremental benefits of PCV20 among adults who already received PCV13 and PPSV23. WG members who thought there probably would be reduced health equity felt that the PCV20 uptake likely will be higher among those with good access to care and could worsen existing disparities.

Regarding the Feasibility Domain, the WG interpretation of the potential for feasibility was "Yes" for Groups 1 and 2. Currently, the number of recommended PPSV23 doses and the recommended intervals for these adults vary. If a single dose of PCV20 can be used to complete the vaccine series, this may simplify the recommendations and may reduce the need to determine the patient's vaccination status. It also may reduce the need to stock multiple types of vaccines. For Group 3, the WG's interpretation was "Probably Yes." These are adults who have completed the recommended vaccine series, so some WG members believed that adding a dose of PCV20 may complicate the recommendation and that compliance with the recommendation may be an issue.

Additional feasibility considerations include access to PCV20. According to a poll among members of the Association of Immunization Managers (AIM) members in September 2022,[40] members from 7 of 22 jurisdictions currently offer PCV20 through their adult immunization program. Under the Affordable Care Act (ACA),[41] new ACIP recommendations are required to be covered starting 1 year after the date of a recommendation is issued without cost-sharing, so PCV20 doses may not be covered right away.

To summarize the WG interpretation of the EtR domains, for the 2 groups who have not completed the vaccine series, more WG members believed that the added benefit of PCV20 would be greater compared with adults in Group 3 who have completed the recommended vaccine series. Also, more WG members believed that the intervention would be feasible for Groups 1 and 2. There was more variability in the WG's interpretation regarding PCV20 use for Group 3. The WG believed that the added benefit would depend on factors that increase Group 3's risk of pneumococcal disease such as time since last vaccination, age, and underlying conditions. Regarding resource use, more WG members believed that PCV20 use in adults who previously received PCV13 only would be a good use of resources. However, the WG's interpretation was variable for the 2 groups who received both PCV13 and PPSV23. Overall, the WG believed that the desirable consequences probably outweigh the undesirable consequences in most settings.

[40] Members are primarily state, local, and territorial immunization program managers/directors
[41] https://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs12

In closing, Dr. Kobayashi presented the following proposed Policy Options for ACIP's consideration:

- **Option 1: Adults who received PCV13 only and have not completed the recommended vaccine series:**

  *Adults who have received PCV13 only **are recommended to** receive **a dose of PCV20 at least 1 year** after the PCV13 dose or PPSV23 as previously recommended to complete their pneumococcal vaccine series.*

- **Option 2: Adults with immunocompromising conditions who received both PCV13 and PPSV23 before age 65 years with incomplete vaccination status:**

  *Adults with an immunocompromising condition, cochlear implant, or cerebrospinal fluid leak who have received both PCV13 and PPSC23 before age 65 years with incomplete vaccination status are recommended to receive **a dose of** PCV20 at least 5 years after the last pneumococcal vaccine dose or PPSV23 as previously recommended to complete their pneumococcal vaccine series.*

- **Option 3: Adults aged ≥65 years who have completed their vaccine series with both PCV13 and PPSV23:**

  *Shared clinical decision-making is recommended regarding administration of PCV20 for adults aged ≥65 years who completed their vaccine series with both PCV13 and PPSV23. If a decision to administer PCV20 is made, a dose of PCV20 is recommended **at least 5 years after the last pneumococcal vaccine dose.***

Merck Statement

Richard M. Haupt, MD, MPH (Medical Affairs, Merck & Co., Inc.) thanked the ACIP for letting him address the ACIP. He expressed Merck's appreciation for the commitment to the thorough evidence-based evaluation of available policy options for use of the new conjugate vaccines for adults. Based on the day's discussions, it is a challenging question that underscored the importance of considering the public health value of recommendations for new PCVs as an option for adults who previously have been vaccinated with PCV13 and/or PPSV23. He thought the evaluation demonstrated that there are some health benefits afforded by what he referred to as "catch up" vaccination. While these potential benefits come at a high cost and would require significant investment in resources, it is important to consider the value of such an investment. It was noted earlier that given that adult vaccination rates remain below optimal levels in general, perhaps a more effective use of resources should be applied to increase the proportion of unvaccinated adults, particularly in the socioeconomic groups that have disparities. It is important to note that PPSV23 remains the pneumococcal vaccine with the broadest serotype coverage, with demonstrated effectiveness against both IPD and NBP. Revcaccination with PPSV23 is immunogenic, well-tolerated, and results in long-term antibody levels similar to those achieved after primary vaccination. Thus, in this rapidly changing adult pneumococcal vaccination ecosystem, PPSV23 remains a good option to complete a series in those who received PCV13. Considering only PCV20 in this policy scenario potentially will lead to some unintentional bias and creates potential de facto preferential recommendations for PCV20. Merck appreciated that the policy options consider PPSV23 as well as an option. That is very important because preferential recommendations typically require very strong clinical benefit profile and strong clinical evidence demonstrating significant impact on disease burden. Those

were relevant a year ago when the recommendation for use of PCV20 or PCV15 + PPSV23 in adults ≥65 years of age was considered. All those considerations are still relevant in this discussion.

Discussion Points

Dr. Talbot was glad that this was being considered and loves seeing adults receive the most up-to-date care possible. This has been a major question about which she has received many emails and appreciated the feedback. She emphasized that she would like to keep the pneumococcal vaccine recommendations as simple as possible, efficient, and up-to-date to provide the best care possible to older adults. In her mind, someone who has not received a higher valent conjugate vaccine should be recommended to receive a higher valent pneumococcal vaccine. It should not be a shared clinical decision. That will make it easier for the providers.

Dr. Loehr found it helpful to go patient-by-patient, so he was trying to work through in his head who would be receiving these vaccines. In this transition, it came down to whether PCV20 should be changed over for PPSV23. This raised a question regarding how much better PCV20 is than PPSV23. It seemed that PCV20 is marginally better and there are benefits, but it also is fairly costly and that was the tradeoff he was wrestling with in his own mind and helped him think about which direction he was leaning in terms of a vote.

While Dr. Brooks agreed with Dr. Talbot about making the recommendations simple, it could be beyond the pale of this particular vaccine or the questions. Referring to Slide 74, he requested clarity about whether the graph was saying that African Americans were more likely to be hospitalized with non-PCV13 serotypes and if so, whether it would be better to have a vaccine with more serotypes. The greatest effect on IPV was when children were vaccinated. A vaccine for PCV15 or PCV20 potentially would be brought on for children in the next year two. Perhaps that is where the real effect would occur. In the cost-effectiveness slides, he recalled that there was a $500,000 cost per QALY for PCV13 in 2019 that was voted down. That seemed to him like a baseline for considering QALY. For this particular vaccine, QALY seemed more important than any other vaccine he has evaluated thus far. On balance, he was not sure how to put this together. It was almost like they needed a summary of the summary. While there were many angles to this, the 3 questions seemed like a good way to break it down in terms of what ACIP would be voting on.

In terms of the epidemiological equity data, Dr. Kobayashi said that unfortunately there have been differences in the IPV incidence looking at the data by race. The differences seen in the PCV13 types decreased. As a result, the remaining differences are driven largely by the serotypes not included in PCV13.

Dr. Long noted that as a member of this WG, she said for the first 18 or 20 meetings she had a terrible headache at the end of the meetings because this is difficult. She emphasized how amazing it was that all of these nuances were picked up and expressed gratitude for the wonderful analyses and the way the information was presented. This provided the clearest picture there is. While it is very unusual for a WG to not settle on a single answer, this WG rarely settled on a single answer. It was not because this was a problematic WG. It was because the problem is real and the answer is not clear. The practitioners on the WG continuously emphasized the importance of making it simple. It certainly would be simple to say that everyone over 65 years of age should receive a high-valent pneumococcal conjugate vaccine. However, she thought the differences of opinion came down to what someone brings to

the table and how willing they are to spend other people's money and resources for the relatively small benefit for adults ≥65 years of age. The WG considered shorter than 5 years, which was outrageously not cost-effective.

Dr. Kotton spoke in favor of the additional vaccine for IC patients. It is definitely known that IC patients are 9 to 18 times more likely to have IPD and waning immunity over time. Therefore, she thought additional doses of vaccine seemed likely to be protective and well-tolerated. With respect to Dr. Talbot's point about enhanced clarity, targeted education of different groups would be useful for clinicians who take care of IC patients. She found it very disappointing that even after decades of pneumococcal vaccine being available how few American adults are vaccinated with a well-tolerated vaccine against a common illness. She appreciated the attention to the IC hosts who remain excessively vulnerable.

Dr. Shah observed that in connection with Dr. Talbot's points about simplification, with which he completely concurred, another benefit with respect to simplification is that clinicians and office practices would be having to stock only 1 vaccine. Inventory management would be much easier. The same would apply to the state health departments that include pneumococcal vaccine as part of their adult vaccine programs. Inventory management becomes much more streamlined. Much like Dr. Loehr, throughout the morning he was trying to assess the marginal epidemiological benefit of PCV20. He noted that in Dr. Kobayashi's presentation, Slides 21 and 24 purported to account for the percentage of pneumonia that is accounted for by Serotypes contained in PCV20 but not PCV13, which illustrated roughly the marginal epidemiological benefit of PCV20 versus PCV13.

Dr. Loehr asked whether along with these new proposals, ACIP still would be recommending PPSV23 for adults 19─64 years of age with CMCs but not ICs. If that was true, he would still need to stock extra vaccines. He saw nods of agreement about this.

Regarding the use of PCV20 to complete a series that otherwise would include the polysaccharide vaccine, Dr. Lee personally thought this had the potential of resulting in hyporesponsiveness to subsequent vaccines and durability of immunity offered a reasonable rationale to move forward regardless of the cost-effectiveness estimates that they saw. In addition, this would affect a small proportion of individuals at about 12,000 people. From that perspective, the total cost is actually much lower and the cost-effectiveness was not as relevant to her. She thought there would be benefit for the IC population in getting a conjugate vaccine. The simplicity argument also took precedence. Regarding the 3 policy options, she was struggling with whether revaccination or "catch up" vaccination should be offered to those who are not recommended to receive an additional set of vaccines. She was trying to understand whether this was an access, acceptability, or complexity of recommendations question. Given that these vaccines have been available for many years, it seemed to rest with the complexity of the current recommendations. Based on the data presented during this session, the benefits are fairly limited from a population-level perspective as Dr. Shah pointed out. The cost-effectiveness work was done with pre-pandemic disease incidence data, which meant that the cost-effectiveness would look worse in this context. Overall, she would say the most impactful thing they could do would be to think about vaccinating children. The impact of herd immunity was huge when pneumococcal conjugate vaccines were introduced, while the direct recommendation for older adults has not had as substantial an impact. While she wanted to provide access, she was concerned that this would be a transient benefit that might increase complexity for providers trying to vaccinate against COVID and influenza in the coming season.

Dr. Talbot commented that cost-effectiveness models assess hospitalizations and clinical visits, but do not assess older adults who have been hospitalized for pneumonia who never make it back home, or who make it back home but require a large amount of support from home health and family members. They do not take into consideration the amount of time and money that family members must put in to take care of loved ones. It is very important to understand that cost-effectiveness models are good but limited. In older adults, the desire is to compress the time of disability. Even if these vaccines provide only marginal benefit, can reduce that time of disability and provide improved life, which cannot be captured in cost-effectiveness models. Providing up-to-date care limits that kind of disability and provides meaningful life to large numbers of American adults.

Dr. Lee wholeheartedly agreed that a very robust and comprehensive program is needed, especially to protect older adults and IC populations against viral and bacterial respiratory infections. However, she was still struggling with whether this would be the answer that would solve the problem.

In anticipation of recommendations for children, Dr. Long pointed out that PCV13 had much less indirect effect on adults than PCV7 and it is unknown what PCV20 would do. Since they could only deal with the vaccines in front of them, if there is a dramatic effect of immunizing children on adults, ACIP could reconsider these recommendations. However, she did not think they should consider that at this point.

Dr. Poehling thanked everyone for the very thoughtful questions and comments, recognizing that this is hard and also very important. In response to Drs. Loehr and Shah, she pointed out that all of the proposed recommendation language included either PCV20 or PPSV23. That is very important because people could be holding PCV15 and PPSV23 in their clinics, or they could have PCV20. That way, everyone has an ability to participate if this is approved without having to hold yet another vaccine. The goal for the IC and CMC populations was to try to simplify and make them more similar than different for the ease of providers.

It seemed to Dr. Long that before they got to a motion for a vote, they should engage in further discussion about “may” versus “should.” She thought “may” influenced the equity question somewhat because it was thought that “may” would allow the more affluent population to get PCV20. She thought using “should” for everybody would be less likely to decrease equity or increase inequity.

As a practicing physician purchasing these vaccines, Dr. Loehr emphasized that the rule is that the insurance companies do not have to pay for it for a year after ACIP approval. His office still cannot give PCV15 to many children because the insurance companies will not pay for it. This also must be taken into account.

Dr. Gluckman (AHIP) complemented the committee on the robust nature of the conversation throughout the day regarding this complex issue. He stressed that as they consider this, ACIP should recognize how much power they have due to the mandate, such that when decisions are made, they have significant implications for what must be administered and the cost of those. They have seen examples in which the pharmaceutical industry was compelled to lower costs based on ICER recommendations. An example would be proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors for lowering cholesterol. He wondered whether there would be consideration for ACIP to do an ICER-like analysis to determine what the cost of the product should be to meet a reasonable cost-effectiveness threshold to put the appropriate pressures on the pharmaceutical industry to have rational pricing. That type of power does make effective and

efficient use of resources possible. Medicare resources are limited. One thing they are seeing in the community is the complexity among providers with regard to choosing between PCV20 versus PCV15 + PPSV23. The 2-vaccine combination raises the complexity because people need to return in a year. He did not recall from previous conversations whether anyone had ever assessed the cost-effectiveness comparisons between PCV20 and PCV15 + PPSV23. From a raw cost perspective, the combination is quite a bit more expensive. Turning to the power of the mandate, insurance is forced to potentially cover a vaccine schedule that is more complex and more costly versus one that might be simpler. The current recommendation does add complexity and probable significant cost. In terms of uptake, they are seeing mostly PCV20 being used in the community.

Regarding the question about direct comparison of PCV20 to PCV15, Dr. Kobayashi indicated that when they reviewed the evidence last year, they did not do any direct comparisons. They reviewed the use of both vaccines compared to the previous recommendation. That was because there were limited data that provided direct comparison of PCV15 versus PPSV23 and there were no immunogenicity studies that provided direct comparison, so the WG decided to review evidence separately for those 2 vaccines. Therefore, there is an option for the use of both vaccines currently.

Dr. Gluckman (AHIP) suggested that it might be reasonable to revisit this at a later date as more data become available just as ACIP revisited the PCV13 recommendation for older adults at a later date, which relates to the power of ACIP mandates.

Dr. Goldman (ACP) said he struggled with this as well on the WG, but he always goes by the patient in front of him. While it is so important to consider cost to public health, his concern as a practicing physician regards what is best for his patient. To Dr. Talbot's point, he tended to look at this as a catch-up vaccine for those who have not received a higher valent conjugate vaccine that seems to be more effective than a lower valent immunogenically. He would err on the side of giving a patient the PCV20 to ensure that they have the appropriate coverage. To Dr. Shah's point, inventory management also is important. As a practicing physician, it is extremely expensive to purchase these vaccines up front. There is not an adult vaccine program like the Vaccines For Children (VFC) program, so adult physicians have to pre-purchase and stock vaccines. To simplify to giving one vaccine as opposed to multiple types of vaccines for the same disease makes it much easier when using one simplified recommendation. That said, it is unconscionable to him that the insurance companies are posting billions of dollars in profit, yet they cannot implement these recommendations timely within 1 year. Some begin coverage earlier, but some wait. It puts physicians in the community at extreme financial risk and decreases access because they cannot get vaccines to patients in a timely manner with assurance of reimbursement to make sure they can be covered and paid for. To him, the simplification of carrying 1 vaccine to be stocked to benefit the patients and reduce harm when there is minimal risk is the simplest option to choose from the WG's proposed recommendations.

Regarding the shared decision-making recommendation for PCV20 administration to older adults who have completed both PCV13 and PPSV23, Dr. Schmader (AGS) indicated that AGS wanted to go on record that this share decision-making recommendation is problematic. It is simply not pragmatic in clinical settings with older adults. In clinical settings with older adults, patients have multiple chronic conditions, there are competing demands, and caregivers often have to make the decisions. A shared clinical decision-making recommendation did not work before for PCV13. AGS agreed completely with the suggestions to simplify the recommendations.

Speaking as practicing physician, Dr. Fryhofer (AMA) emphasized that the complexity of a pneumococcal vaccination is certainly a problem for practicing physicians. As mentioned by several others, having to stock several types of pneumococcal vaccine in stock in order to appropriately vaccinate patients is very expensive, difficult, and especially puts a strain on small practices. That said, she commended the presenters for this session for doing such a fabulous job of explaining the difference between the conjugate and polysaccharide vaccines. She is very sensitive to increasing coverage by the various serotypes and appreciated that there now is a conjugate vaccine that covers more serotypes. However, the 3 proposed recommendations that were put up for a vote did not make this vaccination recommendation simpler. Instead, they added complexity and confusion. Like others, she looks forward to seeing data in which children are vaccinated with the higher valent vaccines to see what effect that has on adults. If they start vaccinating adults now, it may not be possible to know this.

Dr. Hogue (APhA) thanked the speakers for the fascinating presentations and expressed appreciation for the tremendous effort and work that was put into the details. He noted that he is a pharmacist and was speaking on behalf of the American Pharmacists Association (APhA). The APhA also found significant problems with the proposed recommendation relative to shared clinical decision-making among people who are ≥65 years of age. Increasingly during the pandemic and now thinking ahead, American adults are getting their vaccines in pharmacies. Unfortunately, insufficient access in many community pharmacies due to the complexity and incomplete medical records of patients makes it somewhat difficult and very time-consuming to engage in conversations with patients about which vaccines they may need when a shared clinical decision-making recommendation is made. All HCP are faced with the ethical dilemma of the individual patient in front of them. If the patient could be given a vaccine that would provide at least some more protection against a few more serotypes in the years when they are likely to be most vulnerable against these infections, how could someone deny giving that person a vaccine? While he understood the population-level cost-effectiveness data and the potential marginal benefits, it seemed difficult to put HCP in the position of trying to make a shared clinical decision-making recommendation. He thought shared clinical decision-making could contribute to worsening health equity issues because shared clinical decision-making decisions, as occurred previously with pneumococcal recommendations from a few years ago, tended to cause providers to do nothing. Immunization rates did not go up and, in fact, there was increased vaccine hesitancy. If providers are confused about the recommendations, patients will be as well. Dr. Hogue urged the ACIP voting members to simplify the shared recommendation. He had less problems with the other 2 proposed recommendations.

Dr. Young said she has had the unfortunate encounter dealing with this issue as a consumer. At 69 years of age, she presented to her local pharmacy. She has coverage with Blue Cross and Medicare, both of which battled over who should cover it and eventually refused to cover it. Therefore, she had to pay the $247 out-of-pocket or defer. She was stunned. She took PCV20 because she wanted the conjugate vaccine because it is longer lasting and she had only received PCV13 many years ago. From a health equity standpoint, she wondered how others who have less resources are going to deal with this when insurance companies have the authority to deny coverage of vaccine for such a serious condition.

Proposed Updates to Clinical Guidance on Pneumococcal Vaccine Use among Adults

Dr. Kobayashi (CDC/NCIRD) shared the proposed changes to the current pneumococcal recommendations[42] to provide clarification and to address existing gaps for feedback from the committee, which she pointed out would not be part of the vote. As a reminder, the current recommendations that ACIP approved last year are as follows:

- **Adults aged ≥65 years***. Adults aged ≥65 years* who have not previously received **PCV** or whose previous vaccination history is unknown **should** receive 1 dose of PCV (either PCV20 or PCV15). When PCV15 is used, it should be followed by a dose of PPSV23.

- **Adults with previous PPSV23 only**. Adults who have only received PPSV23 **may** receive a PCV (either PCV20 or PCV15) ≥1 year after their last PPSV23 dose. When PCV15 is used in those with history of PPSV23 receipt, it need not be followed by another dose of PPSV23.

*Same recommendations for adults aged 19–64 years with certain underlying medical conditions or other risk factors.

The question received over the past few months related to these recommendations included the following:

- Does "who have not previously received PCV" include adults who have previously received PCV7?

- Wouldn't adults who received PPSV23 only be part of adults "who have not previously received PCV or whose vaccination history is unknown?"

- If an adult inadvertently received PPSV23 first instead of PCV15, is it a "may" or "should" for a person to complete the series with PCV15?

- If an adult aged <65 years with indications receives both PCV15 and PPSV23, does the person need another dose of PPSV23 in the future?

- What should we do if we do not have access to PCV15 or PCV20?

To address these questions, the proposed clarifications were made to the existing language (proposed clarifications shown in red):

- **Adults aged ≥65 years*.** Adults aged ≥65 years* who have not previously received **PCV13, PCV15, or PCV20** or whose previous vaccination history is unknown **are recommended** to receive 1 dose of PCV20 or PCV15. When PCV15 is used, it should be followed by a dose of PPSV23 **to complete the recommended vaccine series. If PPSV23 is inadvertently given before PCV15, a dose of PCV15 or PCV20 should be given at least 1 year later.**

  Footnote: If PCV15 or PCV20 is not available, a dose of PCV13 may be given followed by a dose of PPSV23 as previously recommended.

[42] Kobayashi et al. MMWR 2022. https://www.cdc.gov/mmwr/volumes/71/wr/mm7104a1.htm

- **Adults who received PPSV23 only.** Adults who have only received PPSV23 **are recommended to receive a dose of either PCV20 or PCV15** ≥1 year after their last PPSV23 dose. When PCV15 is used in those with history of PPSV23 receipt, it need not be followed by another dose of PPSV23.

*Same recommendations for adults aged 19 –64 years with certain underlying medical conditions or other risk factors.

In terms of the rationale for recommending new PCVs for adults who previously received PCV7, it has been at least 10 years since PCV7 was available in the US. The new PCVs cover ≥8 more pneumococcal serotypes. The WG is currently proposing consideration of use of PCV20 for adults who previously received PCV13. The rationale for the WG not recommending additional doses of PPSV23 for adults who receive PCV15 followed by PPSV23, HCPs have been confused by the recommendations of repeat PPSV23 doses. Reported coverage of PCV13 and PPSV23 among adults aged 19–64 years with IC has been very low.[43] The impact of new PCV use among children is unknown. New pneumococcal vaccines are in advanced stages of development.

Regarding the rationale for recommending PCV15 or PCV20 for adults who inadvertently received PPSV23 first for the PCV15–PPSV23 series, there was a suggestion to avoid the use of "should" vs "may." Also, it will allow for the harmonization of the recommendation for adults who received only PPSV23. There also are similar recommendations for PCV13 and PPSV23 series. The rationale for recommending either PCV15 or PCV20 for adults who have received PPSV23 only is that under the new recommendations, all adults with indications for pneumococcal vaccines are recommended to receive a PCV. In addition, the interval of "at least 1 year" is consistent with the PPSV23–PCV13 sequence that was previously recommended.

In terms of the proposed changes to address gaps in the current adult pneumococcal vaccine recommendations, adults who received hematopoietic stem cell transplant (HCST) are currently not included as part of the pneumococcal risk conditions. There is existing guidance in CDC's *General Best Practice Guideline for Immunization* that has the following language:

- ***Sequential administration of 3 doses of pneumococcal conjugate vaccine** is recommended, beginning 3-6 months after the transplant, **followed by a dose of PPSV23.***

- *Some sources state a 4-week interval between these doses as reasonable with the dose of PPSV23 being replaced by a dose of PCV13 in the context of graft-versus-host disease. Other sources support 3 doses of PCV13 at 8-week intervals, with a dose of PPSV23 recommended 8 weeks after the last dose of PCV13 and 12 months after the HSCT.*

[43] Deb et al. Expert Rev Vaccines 2021.

In addition, the Infectious Disease Society of America (IDSA) *Clinical Practice Guideline for Vaccination of the Immunocompromised Host* includes the following:

- ***Three doses of PCV13** should be administered to adults and children starting at 3–6 months after HSCT (strong, low). **At 12 months after HSCT, 1 dose of PPSV23 should be given** provided the patient does not have chronic GVHD (strong, low). For patients with chronic GVHD, a fourth dose of PCV13 can be given at 12 months after HSCT (weak, very low).*

To address this gap, the following language was proposed that recommends PCV use in adults who are HSCT recipients:

- *Adults who are hematopoietic stem cell transplant (HSCT) recipients are recommended to receive three doses of PCV20 4 weeks apart starting 3 months after HSCT. This should be followed by a fourth PCV20 dose at least 6 months after the 3rd PCV20 dose, or at least 12 months after HSCT, whichever is later.*

- *HSCT recipients who have started their pneumococcal vaccine series with PCV13 or PCV15 may complete their 4-dose pneumococcal vaccine series with PCV20.*

- *If PCV20 is not available, three doses of PCV15 4 weeks apart, followed by a dose of PPSV23 at least 12 months after HSCT may be given. For patients with chronic graft-versus-host disease, a fourth dose of PCV15 can be given in place of PPSV23.*

Regarding the rationale for use of PCV20 among HSCT recipients, HCST recipients have poor immune response to PPSV23 when given during the first year of transplantation or longer, especially in those with chronic graft versus host disease (GVHD)[44]. PCV20 currently has the broadest serotype coverage among available PCVs. In this high-risk population, a regimen that provides broad pneumococcal serotype coverage early on is warranted.

In terms of the evidence for use of 4 doses of PCV among HSCT recipients, there are no PCV20 studies among HSCT recipients but there are 2 studies[45] that assessed the use of 4 PCV13 doses. Both studies used 3 PCV13 doses given 1 month apart followed by a booster dose 6 months after the 3rd PCV dose + a dose of PPSV23 either 1 or 2 months after the final 4th PCV dose. Immune responses against the PCV13 serotypes increased from baseline to after the 3rd PCV13 dose, and from after the 3rd dose to after the 4th dose. In one study, local and systemic reactions occurred more frequently after the 4th PCV13 dose, compared with after 1st–3rd dose of PCV13, but most were mild to moderate reactions.[46]

There is evidence on PCV15 use among HSCT recipients, in a Phase 3 randomized controlled trial (RCT) among HSCT recipients,[47] participants received 3 doses of PCV (either PCV13 or PCV15) followed by a dose of PPSV23 at 12 months (or a dose of PCV13 or PCV15 in those who developed GVHD) showed that between those who received PCV13 or PCV15, immunogenicity was generally comparable for the 13 shared PCV13 serotypes. PCV15 recipients had higher immunogenicity for 2 additional serotypes not included in PCV13.

[44] Hammarström V, et al. Support Care Cancer. 1993; Tomblyn M. et al. Bone Marrow Transplant. 2009.
[45] Cordonnier C, et al. Clin Infect Dis. 2015; Garcia Garrido HM, et al. Am J Hematol. 2022
[46] Cordonnier C, et al. Clin Infect Dis. 2015
[47] A Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Allogeneic Hematopoietic Stem Cell Transplant Recipients (V114-022/PNEU-STEM) https://ClinicalTrials.gov/show/NCT03565900

Injection-site adverse events and solicited systemic events were reported more frequently among those who received PCV15, but most were mild to moderate.

Discussion Points

Dr. Kotton thought the proposed changes to the clinical guidance for PCV use in adults who are HSCT recipients would be extremely helpful to the stem cell transplant community. This treats them as a homogeneous population, but people who undergo HSCT could have either auto or allogeneic and allogeneic, may or may not have GVHD, may not be on immunosuppression, and would be at higher risk for infection. Starting fairly soon after transplant may not be so useful for some people. Starting 3 months after transplant could be quite quick, although it might be appropriate for an auto but not allogenic. She thought adding the phrase that is in the COVID-19 recommendations reading, "A patient's clinical team is best-positioned to determine the degree of immunocompromise, need for vaccination, and appropriate timing of vaccination" might be useful for clinicians. She has received a lot of feedback about the 3-month timing. Often at 3 months, people are not having a robust immune response to vaccination. Changing the language to "starting 6 months after transplants" to provide the vaccines would offer some clinician decision-making that would not be in the shared decision-making.

Proposed Recommendations: Policy Options 1, 2, and 3 for PCV20 Use in Adults

Dr. Kobayashi (CDC/NCIRD) presented the proposed recommendations for Policy Option 1, 2, and 3:

> **Policy Option 1**
> *Adults who have received PCV13 only **are recommended** to **receive a dose of PCV20 at least 1 year after** the PCV13 dose or PPSV23 as previously recommended to complete their pneumococcal vaccine series.*
>
> **Policy Option 2**
> *Adults with an immunocompromising condition, cochlear implant, or cerebrospinal fluid leak who have received both PCV13 and PPSC23 before age 65 years with incomplete vaccination status are recommended to receive **a dose of PCV20 at least 5 years** after the last pneumococcal vaccine dose or PPSV23 as previously recommended to complete their pneumococcal vaccine series.*
>
> **Policy Option 3**
> *Shared clinical decision-making is recommended regarding administration of PCV20 for adults aged ≥65 years who completed their vaccine series with both PCV13 and PPSV23. If a decision to administer PCV20 is made, a dose of PCV20 is recommended **at least 5 years after the last pneumococcal vaccine dose.***

Discussion Points

Dr. Loehr suggested splitting this recommendation into 2 groups: 1) ≥65 years of age; and 2) immunocompromised. He would put some of this under Policy Option 2 and some of this as adults ≥65 years of age who have only received PCV13. He would vote differently on those 2 categories.

Dr. Kobayashi said that what she presented covered different groups, but either way, adults who received PCV13 only and received no doses of PPSV23 have the lease serotype coverage. The intent of the vote was to offer an option to receive PCV20 to complete their recommended series.

Dr. Loehr said that he recognized that, but personally would vote differently for someone ≥65 years of age versus immunocompromised.

Dr. Lee noted that the recommendation could not be amended until there was a motion on the table according to Robert's Rules of Order. She called on Dr. Kobayashi to respond about the intent of this recommendation so that everyone would be clear about what they would be voting on. The following motions were made so the discussion could continue:

- ❑ Dr. Brooks motioned to accept the language for Policy Option 1 as proposed. Dr. Kotton seconded the motion.

- ❑ Dr. Loehr made a motion to accept the language as proposed for Policy Option 2. Dr. Long seconded the motion.

- ❑ Dr. Long made a motion to accept the language as proposed for Policy Option 3. Dr. Talbot seconded the motion.

Proposed Recommendation: Policy Option 1 for Adults Who have Received PCV20 Only

Dr. Kobayashi (CDC/NCIRD) presented the revised language for Policy Option 1 for the vote based on the discussion, which was as follows:

Revised Policy Option 1
Adults who have received PCV13 only are recommended to complete their pneumococcal vaccine series by receiving either a dose of PCV20 at least 1 year after the PCV13 dose or PPSV23 as previously recommended.

Accompanying Text
- Adults aged 19–64 years with an immunocompromising condition, cochlear implant, or cerebrospinal fluid (CSF) leak
- Adults ≥65 years of age

Discussion Points

Dr. Talbot asked whether persons with diabetes or who smoke would be eligible to receive PCV20. It was her understanding when ACIP voted for PCV15 and PCV20, they combined all of the high-risk groups under 65 years of age and that included those with diabetes and smokers. She was concerned that now these groups were being pulled out and making it more confusing.

Dr. Kobayashi clarified that individuals under 65 years of age who are diabetic were not recommended to receive PCV13 previously. Those groups were previously recommended to receive PPSV23, so PCV20 or PCV15 is recommended for those adults. Adults who are vaccine-naïve are recommended to get PCV20 or PCV15, including those who are diabetic or have chronic heart/lung disease. The proposed recommendation addressed only those who received PCV13 based on the previous recommendation.

Dr. Long thought keeping PPSV23 in the recommendation was somewhat confusing because it would mean that those who took that option would then need to get an additional dose of PCV20 at 65 years of age.

Dr. Kobayashi clarified that it was PPSV23 as previously recommended. These individuals would continue to get PPSV23 based on what is currently recommended. That would include repeat dosing and 1 final PPSV23 at 65 years of age if they select that option.

Dr. Brooks requested confirmation that they were not adding a new vaccine to the guidance and instead were replacing one with another.

Dr. Kobayashi clarified that he was correct. Currently, these people are recommended to receive PPSV23. The recommendation was saying that alternatively, they could get 1 dose of PCV20 and then complete their recommended series.

For clarification, Dr. Talbot suggested that it might be easier to indicated that everyone who previously received PCV13 would be eligible to receive PCV20.

Dr. Poehling indicated that this was exactly what the revised language was stating, and then it indicated the people who most likely would fall into that category. The WG was trying to keep this broad because some practices are not carrying PCV20 and they want to ensure that people get coverage in whatever way is available.

Dr. Daley expressed concern about defining people by what vaccine they received as opposed to their age and their presence or absences of a chronic condition. Even though he understood the intent because it was referring to a specific group, it ran the risk of causing confusion.

Regarding the discussion earlier in the morning about administrative simplification, Dr. Shah asked whether it was the case that the view of a provider or state health department from an inventory management perspective could be simplified here because they need not carry both PPSV23 and PCV20. They could stop carrying PPSV23 and still provide the recommended care for their patients.

Dr. Kobayashi responded that this was raised during a WG discussion in terms of inventory management in that context. Some providers do not carry the polysaccharide vaccine in which case, they can complete for adults who started the series with PCV13 with a dose of PCV20. That is the intent of the recommendation.

It was not clear to Dr. Shah how much the decision hinged on the cost-effectiveness analysis presented earlier in the day because it also made a strong epidemiological case for the benefits of PCV20 versus PCV13. That said, he had the impression that the cost-effectiveness analysis presented a scenario in which the patient contemplated here (e.g., an adult who received PCV13) would get nothing rather than PPSV23. He was not sure whether that was correct or the extent to which it altered the ultimate decision here because of the strength of the epidemiological data.

Dr. Kobayashi clarified that there were multiple models, some of which looked at PCV13 + PCV23 versus no additional vaccines. There also were models that looked at PCV13 plus PCV20 versus PCV13 and PPSV23. All of this was considered, but was not all presented during this session.

Dr. Talbot appreciated Dr. Daley's comment and hoped that he could provide language he thought would be better.

Dr. Kotton observed that the language did not seem to be accurate. She takes care of IC patients and if they receive PCV13, they are supposed to get PPSV23 8 weeks later.

Dr. Kobayashi confirmed that for PPSV23, it is 8 weeks later. That is why they put "or PPSV23 as previously recommended after PCV20 at least 1 year later." PPSV23 as previously recommended includes multiple groups.

Dr. Kotton said she did not think this would work in a clinical scenario because people would not understand that. From her experience at her large academic hospital, people do not know where to find the information and will not understand how to get this. In addition, they are very busy in clinic and will not have time to look this up. It cannot be that many steps. She interpreted this to mean PPSV23 a year later based on the wording.

Dr. Bell emphasized that they should not further confuse themselves. Thinking about the proposed recommendation for Policy Option 3 with clinical decision-making versus a recommendation, it was not clear whether they were adding to the group to which that would be applied by what they were saying about people ≥65. It seemed like additional confusion.

Dr. Kobayashi clarified that in the case of adults 65 years of age and older who got PCV13 and a dose of PPSV23, they would be considered complete with the recommended vaccination.

Dr. Daley suggested that they could take an approach of identifying those who are recommended for pneumococcal vaccination and then talk about a first and second dose. In this case, the second dose could be PCV20. Potentially, they could combine all 3 recommendations.

Dr. Loehr said his sense was that this would be a transitional vote that probably would be good for a year and hopefully no one would fall into this category anymore. He respectfully disagreed with Dr. Daley in that he would not lump these 3 policies because the third policy in his mind was a very separate policy that required a totally different discussion.

Dr. Kotton asked the WG what data supported the 1-year gap between PCV13 and PCV20 and what would happen if they were given 3 or 6 months apart.

Dr. Kobayashi indicated that only immunogenicity data are available. The shortest interval they saw was 6 months between PCV13 and PCV20. There reasons they settled with at least 1 year was because there is an immunogenicity study of a PCV13 series that showed that after the second dose of PCV13 given 1 year and later, the immune response was lower for some serotypes compared to after the first dose of PCV13. There is some concern about interference of antibodies. Therefore, the WG was comfortable with 1 year for everybody.

Dr. Poehling added that part of the goal was to keep this similar to the current recommendation, which is that someone can get PPSV23 and try to keep that on the same timeframe.

Ms. McNally said she understood the need for this recommendation, but it is very complex and she was concerned about what Dr. Kotton pointed out about implementation. She wondered if it would be possible prior to the vote to see a visual aid that would be prepared for vaccinators and the public so they can understand this issue. Others agreed.

Ms. Bahta suggested that in the language, they could include those who previously started a pneumococcal vaccination series with PCV13 before the new recommendations and finish it with the third dose. In the previous recommendation for adults ≥65 years of age, the recommendation for PCV13 + PPSV23 was removed. She wondered if they were reinstating that.

Dr. Kobayashi clarified that it is an interim recommendation in that the whole purpose of the proposed options was for those who started their series with PCV13. While ACIP no longer recommends PCV13 for people who are pneumococcal vaccine naïve, but they acknowledge that there were some people who were vaccinated based on the previous recommendation. They are trying to explore whether the new higher valent conjugate vaccines can be offered to these people.

Dr. Lee acknowledge that the point of the recommendation was to help simplify and clarify that completing a vaccine series with other available products is a very reasonable thing to do. However, she still found the original recommendations ACIP made years ago to be confusing. She felt like a visual would be beneficial.

Dr. Loehr suggested that the recommendation should state, “If you started under the old rules, you may complete under the new rules.” This all relates to whether someone started under the old rules regardless of whether they were IC or over 65 years of age.

Dr. Daley thought they would need to find a way to merge the 3 policy options. While he understood the intent, he remained concerned about defining people by what vaccine they received and all that that implied. He would feel more comfortable with age and condition, but he was not sure that would work because then the recommendation would have to say “and did or did not get a PCV13.” He was having a challenge with how much one would have to know about the old rules to do this right.

Dr. Hahn (CSTE) agreed that of all of the recommendations ACIP has made over the years, these are so complex and confusing. This would benefit from a visual decision tool of some sort. Without that, providers will continue to be extremely confused.

Dr. Long asked whether it might be helpful to try to address Policy Option 3, in which case there could be an overriding principle (e.g., everybody needs to have PCV20 when they are 65 years of age) and people who have not completed their series before that age can complete their series with PCV20. Nobody knows why some of these people received PCV13 (e.g., mistake, wanted it).

Dr. Bell said that to her, Policy Option 3 was a relative big policy issue in terms of whether they were going to say that everybody over 65 years of age for whom some sort of pneumococcal vaccine is recommended should all get boosted with PCV20. That seemed like a much bigger issue than how they phrased cleaning up this group, which is an interim group, for whom it is unknown who they are and why they got PCV13. How to do it is very complicated because these are all very complicated, but she did not think that this would be as controversial an issue as what they think about everybody over 65 getting a dose of PCV20. In terms of the ordering of these questions for the discussion, she was not clear whether they would end up having to revisit things because they were waiting to address the larger policy issue until the end of the discussion.

Dr. Goldman (ACP) pointed out that from the primary care perspective, people with CMCs would not have received PCV13 based on the previous recommendations. In his mind, it is more of a do over. There is now PCV20, which has a good immunological response. This answers the question that whether someone got PCV13 or not, whether they should or should not have been given it with CMCs, they could move past that, get the PCV20, and move on to continue the recommendation. He was surprised that this proposed recommendation was engendering as much discussion.

Dr. Talbot said that she also assumed that if someone had received PCV13 and then received the polysaccharide vaccine, they should still be eligible for a higher level of a conjugate vaccine. She thought one of the reasons she was having trouble with the Policy Option 1 vote was because anyone who has received PCV13, regardless of whether they received PPSV23, should be eligible for a new conjugate vaccine.

In the interest of time, Dr. Lee indicated that ACIP would take the opportunity to revisit the vote later in the meeting and would reconsider the order of the vote options, beginning with Policy Option 3 and then moving to Options 1 and 2, in the hope of achieving a cleaner set of recommendations and decisions. Therefore, the pneumococcal discussion was tabled until the second day of the meeting to give the WG time to make revisions. The discussion and votes from the second day of the meeting are included here with the presentations and discussions from the first day of the meeting for ease of reading.

Background for Proposed Policy Options

Dr. Kobayashi (CDC/NCIRD) presented additional background information on the second day of the meeting. Previously, PCV 13 was recommended for high-risk adults. In 2021, ACIP recommended use of PCV15 or PCV20 for certain high-risk adults who ***"have not previously received PCV*** *or whose previous vaccination history is unknown."* Adults who received PCV13 are currently recommended to complete the series with PPSV23. It is known that conjugate vaccines have immunologic advantages over polysaccharide vaccines. PCV20 currently provides the broadest serotype coverage among available conjugate vaccines. The proposed recommendations address 2 questions from the current recommendations:

1. Should we add PCV20 as an option to PPSV23 or adults who received PCV13 but have not completed their series?

2. Should we add PCV20 for adults 65 and older who completed their series with both PCV13 and PPSV23 for added protection?

In the current recommendation, use of PCV20 alone or PCV14 in series with PPSV23 is recommended for high-risk adults who have not previously received PCV or whose previous vaccination history is unknown. This includes adults ≥65 years of age and younger adults with certain risk conditions. Adults who have not received any pneumococcal vaccination are not recommended to receive PCV13 anymore under the current recommendations. Adults who started the series with PCV13 before the update are currently recommended to complete the series with PPSV23.

Dr. Kobayashi reviewed each of the 3 groups under consideration, pointing out that the order of the groups was changed from the previous day to the following:

- **Group 1:** Adults 19–64 years of age with an IC condition, CSF leak, or cochlear implant who received PCV13 + PPSV23 but have not completed their recommended series. The estimated size of this group is approximately 0.2 million based on vaccine coverage data. The proposed policy option is to add an option of PCV20 for pneumococcal vaccine series completion.

- **Group 2:** Adults ≥65 years of age who completed the series with PCV13 + PPSV23, meaning that they have completed their series under the current recommendations. The estimated size of this group is approximately 17 million based on vaccine coverage data. The proposed policy option for this group regards whether to add another dose of PCV20.

- **Group 3:** Adults who started the series with PCV13 under the previous recommendation but have not received PPSV23. The estimated size of this group is approximately 9 million adults ≥65 years of age and approximately 0.2 million adults 19–64 years of age. The proposed policy option for this group regards whether to add an option of PCV20 for the pneumococcal conjugate vaccine series.

Vote 1: Proposed Policy Option 1 for Adults with IC, Cochlear Implant, or CSF

Dr. Kobayashi (CDC/NCIRD) presented the following proposed Policy Option 1 for discussion and a vote, which the previous day was Policy Option 2:

> *Adults with an immunocompromising condition, cochlear implant, or cerebrospinal fluid leak who have received both PCV13 and PPSC23 before age 65 years with incomplete vaccination status are recommended to receive a dose of PCV20 at least 5 years after the last pneumococcal vaccine dose or PPSV23 as previously recommended to complete their pneumococcal vaccine series.*

Discussion Points

Given the significant amount of time in discussion the previous day about the pneumococcal votes, Dr. Lee requested that the committee keep this discussion focused on clarifying questions regarding what Dr. Kobayashi just presented or any new key issues that would impact the decisions in front of them.

Dr. Kotton emphasized that while the proposed policy option did not indicate any additional vaccine after 5 years, it is known that immunity wanes significantly in this population.

Dr. Kobayashi pointed out that this was to try to be as consistent as possible as the current recommendation, which is that adults who are IC and have CMCs are recommended to receive 1 dose of PCV20. As of now, there are no repeat vaccine recommendations for this group. In part, this is because there are some uncertainties about how the future would look with new higher valent vaccines in advanced stages of development. It is anticipated that PCV20 will be used in children in the near future, so it is possible that the WG and ACIP will be revisiting the recommendations.

Dr. Talbot questioned why the decision was made to wait for 5 years for PCV20 for these individuals if they could be provided with better protection. It seems like this high-risk population would benefit from getting this about 1 year after receiving the previous vaccine.

Dr. Kobayashi indicated that this was based on the current understanding of the duration of protection of these vaccines plus the economic analysis to understand the timing that would maximize protection and also would make sense from the economic perspective.

Dr. Poehling added that the third reasons was a strong sense from practicing clinicians that it was important to have the same timeframe for whichever vaccine is being used in an effort to simplify.

Dr. Long thought it would be clearer not to say “before age 65 years” because then it seems that the interpretation is when someone becomes 65 years of age, they would need something else. Instead, it should say “19–64 years of age who are more than 5 years out from their PPSV23 vaccine and have not yet received such.” Then everybody would understand who exactly these people are. They are not really incomplete. They need a booster if they are more than 5 years out.

Dr. Lee thought what Dr. Long was saying was consistent with the vote language just presented by Dr. Kobayashi. If clarifications were needed, she thought they could defer to the WG to ensure that the intent is as clear as possible.

Dr. Talbot made a motion to amend Proposed Policy Option 1 “at least 1 year after the last pneumococcal vaccine dose or PPSV23 as previously recommended to complete their pneumococcal vaccine series” because it was not clear why polysaccharide would be used at all in the IC group. Dr. Kotton seconded the motion.

Dr. Long emphasized that the WG looked at this very carefully. If one has received both a conjugate vaccine and a PPSV23, they are well-protected for 5 years. It adds very little to give them another vaccine right after that.

Dr. Kotton said she assumed that was based on serologic not clinical data, so they do not actually know about protection.

Dr. Kobayashi pointed out that the cost-effectiveness analysis assumed lower VE specifically for ICs.

Dr. Poehling added that one of the perspectives she wanted to share from the WG was that not only do the infectious disease physicians need to be treating and vaccinating the IC population, but also primary care physicians need to be doing this. One of the important principles that has been used to guide the WG is simplifying the recommendations. The perspective shared from physicians was using the same regimen for the same groups would enhance coverage, which would be beneficial because the coverage in this group is known to be very low.

Dr. Lee also endorsed remaining consistent with the current recommendations, in part because if they start to change this for this small group, it will become very confusing for most clinicians. While she understood the point made about 5 years versus 1 year, she felt like they have to make it easier for people to use this as an opportunity.

Dr. Kotton emphasized that approximately 3% of the US population is immunocompromised and as shown in the presentation slides are at 9 to 18 times greater risk for IPD. Many of the decision-making analyses are run by computer with alerts. In the area of many people using electronic medical records (EMRs), this could be of assistance. She did not think they needed to make a decision that is likely to be less protective to a highly vulnerable population just to make the recommendation "one-size-fits-all."

Dr. Lee requested that they put the amended Proposed Policy Option 1, reordered from Policy Option 2 the previous day and with the change from 5 years to 1 year, to a vote.

Motion/Vote Policy Option 1 Amended:
PCV20 Vaccine for Adults Who Adults with IC, Cochlear Implant, or CSF

Dr. Talbot made a motion to amend the proposed Policy Option 1 recommendation to read, "Adults with an immunocompromising condition, cochlear implant, or cerebrospinal fluid leak who have received both PCV13 and PPSC23 before age 65 years with incomplete vaccination status are recommended to receive a dose of PCV20 at least 1 year after the last pneumococcal vaccine dose or PPSV23 as previously recommended to complete their pneumococcal vaccine series." Dr. Kotton seconded the motion. No COIs were declared. The motion did not carry with 2 affirmative votes, 13 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Dr. Lee requested that they put the original Proposed Policy Option 1, reordered from Policy Option 2 the previous day, to a vote.

Motion/Vote Policy Option 1 As Proposed:
PCV20 Vaccine for Adults Who Adults with IC, Cochlear Implant, or CSF

Dr. Loehr made a motion to approve the proposed Policy Option 1 recommendation to read, "Adults with an immunocompromising condition, cochlear implant, or cerebrospinal fluid leak who have received both PCV13 and PPSC23 before age 65 years with incomplete vaccination status are recommended to receive a dose of PCV20 at least 5 years after the last pneumococcal vaccine dose or PPSV23 as previously recommended to complete their pneumococcal vaccine series." Dr. Long seconded the motion. No COIs were declared. The motion caried with 14 affirmative votes, 1 negative vote, and 0 abstentions. The disposition of the vote was as follows:

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

Vote 2: Proposed Policy Option 2 for Adults ≥65 Years Who Completed Their Vaccine Series with both PCV13 and PPSV23

Dr. Kobayashi (CDC/NCIRD) presented the following proposed Policy Option 2, which the previous day was Policy Option 3, for discussion and a vote:

> *Shared clinical decision-making is recommended regarding administration of PCV20 for adults aged ≥65 years who completed their vaccine series with both PCV13 and PPSV23. If a decision to administer PCV20 is made, a dose of PCV20 is recommended at least 5 years after the last pneumococcal vaccine dose.*

Discussion Points

As a reminder, the previous day, Dr. Long made a motion and Dr. Talbot seconded the motion to accept the above recommendation as proposed.

Dr. Talbot made a motion to amend Proposed Policy Option 2 to remove "shared clinical decision-making so the recommendation would read, "PCV20 is recommended for adults aged ≥65 years who completed their vaccine series with both PCV13 and PPSV23 at least 5 years after the last pneumococcal vaccine dose." While she wanted to make an amendment from 5 years to 1, she refrained from doing so. Dr. Kotton seconded the motion along with the full remarks of Dr. Talbot.

Dr. Long asked Dr. Kobayashi or Dr. Poehling to tell ACIP what the affected numbers and dollars would be if ACIP approved this amended recommendation versus shared clinical decision-making.

Dr. Kobayashi indicated that the cost per QALY depended upon the model. The one that was in the middle of the 3 models was the estimate by Merck, which was approximately $227,000. Depending on the assumptions used, the higher range of the CDC model was around $440,000 per QALY gained. The lowest estimate was from Pfizer. The population is approximately 17 million adults ≥65 years of age who completed their vaccine series with both PCV13 and PPSV23 based on vaccine coverage data.

Dr. Bell voiced her opinion that she would not support the amendment. While they all wanted to save as many lives as possible, she also feels like she has to consider the big picture. This is a change that has a small incremental benefit. The idea of boosting, or essentially revaccinating, with a new vaccine that provides small incremental benefit for a very large population is not prudent. While she does not make her decisions based only on cost-effectiveness, she did not feel like it is a good idea to endorse something that involves essentially revaccinating a very large number of people for a very small incremental benefit. Although she does not love shared clinical decision-making as a way to communicate an idea that this could be done, there is not a better way to do this. Being a member of this group herself, this is a very heterogeneous population. There may be some people who do not feel like it is worth it to get another dose of vaccine, while other people might feel it is very important. The original proposed language offers that option.

Dr. Talbot reminded everyone that the cost-effectiveness analyses greatly under-estimated the impact on children and older adults. In addition, the polysaccharide vaccine is a B-cell vaccine that has waned at 5 years. This is not only boosting to improve the polysaccharide vaccine, but also to offer people extra protection. Therefore, she thought this would offer a huge rather than

an incremental benefit. Many older adults are still working and should be able to continue to contribute.

Dr. Brooks found this to be a dilemma. The cost-effectiveness data are compelling and this is the largest population under discussion. He also recalled from the data the previous day that the higher rate of pneumococcal disease in African Americans with the types not in PCV13 is of concern. He also thought that the concept of shared clinical decision-making would not necessarily serve that particular population well. While he could see both sides of this, he leaned more toward the proposed amended language due to his impression of what communities and what populations would be mostly served by this additional vaccine.

Ms. McNally requested that they hear from the American Geriatric Society (AGS) and any other liaisons interested in weighing in on this issue.

Dr. Schmader (AGS) fully supported Dr. Talbot's position. The AGS believes that shared decision-making is simply not pragmatic and agrees with all of the other arguments Dr. Talbot made.

Dr. Goldman (ACP) added support for Dr. Talbot's amendment and 1 year. As a practicing physician, he thinks it is extremely important not to look only at cost-effectiveness but also to consider the effect on the individual. Therefore, he absolutely supported making this a stronger recommendation.

Dr. Lee pointed out that the ACIP deliberates not only the recommendations themselves, but also has a fiscal responsibility. Therefore, they must be aware of the fact that they are tied to insurance requirements and the VFC program. While this targets the older adult population, it does have impact on Medicare. She requested that they put the amended Proposed Policy Option 2, reordered from Policy Option 3 the previous day, to a vote.

Motion/Vote Policy Option 2 Amended:
PCV20 in Adults Aged ≥65 Years who Completed Vaccine Series with PCV13 & PPSV23

Dr. Talbot made a motion to amend the proposed Policy Option 2 recommendation to read, "Adults aged ≥65 years who completed their vaccine series with both PCV13 and PPSV23 are recommended to receive a dose of PCV20 at least 5 years after the last pneumococcal vaccine. Dr. Kotton seconded the motion. No COIs were declared. The motion did not carry with 6 affirmative votes, 9 negative votes, and 0 abstentions. The disposition of the vote was as follows:

6 Favored: Brooks, Chen, Cineas, McNally, Shah, Talbot
9 Opposed: Bahta, Bell, Daley, Kotton, Lee, Loehr, Long, Poehling, Shanchez
0 Abstained: N/A

Dr. Lee requested that they put the original Proposed Policy Option 2, reordered from Policy Option 3 the previous day, to a vote.

Motion/Vote Policy Option 2 As Proposed:
PCV20 in Adults Aged ≥65 Years who Completed Vaccine Series with PCV13 & PPSV23

Dr. Long made a motion to approve Policy Option 2 as proposed, "Shared clinical decision-making is recommended regarding administration of PCV20 for adults aged ≥65 years who completed their vaccine series with both PCV13 and PPSV23. If a decision to administer PCV20 is made, a dose of PCV20 is recommended at least 5 years after the last pneumococcal vaccine dose." Dr. Talbot seconded the motion. No COIs were declared. The motion caried with 13 affirmative votes, 2 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Vote 3: Proposed Policy Option 3 for PCV20 Vaccine in Adults Who Received PCV13 Only

Dr. Kobayashi (CDC/NCIRD) presented the following proposed Policy Option 3, which the previous day was Policy Option 1, for discussion and a vote:

> *Adults who have received PCV13 only are recommended to receive a dose of PCV20 at least 1 year after the PCV13 dose or PPSV23 as previously recommended to complete their pneumococcal vaccine series.*

Discussion Points

As a reminder, the previous day Dr. Brooks motioned to accept the language for Policy Option 3, which was reordered from Policy Option 1, as proposed. Dr. Kotton seconded the motion.

Dr. Long pointed out that the clarifying language for this recommendation would need to say that if 5 years passes after receipt of PPSV23, another dose of vaccine may be needed because these are people who received PCV13 for a reason.

In the interest of time, Dr. Lee asked that if additional discussion was needed that Drs. Kobayashi and Poehling take it back to the WG.

Motion/Vote Policy Option 1: PCV20 Vaccine for Adults Who Have Received PCV13 Only

Dr. Brooks made a motion for ACIP to adopt the recommendation stating that, "Adults who have received PCV13 only are recommended to complete their pneumococcal vaccine series by receiving either a dose of PCV20 at least 1 year after the PCV13 dose or PPSV23 as previously recommended." Dr. Kotton 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: Bahta, Bell, Brooks, Chen, Cineas, Daley, Kotton, Lee, Loehr, Long, McNally, Poehling, Shah, Sanchez, Talbot
0 Opposed: N/A
0 Abstained: N/A

CHIKUNGUNYA VACCINES

Session Introduction

Beth Bell, MD, MPH (ACIP Chikungunya WG Chair) introduced this session, which focused on chikungunya vaccines. She explained that chikungunya is a mosquito-borne viral disease that is characterized by an acute onset of fever and severe and polyarthralgia that can be debilitating. The Chikungunya Vaccines WG was formed recently. No Chikungunya vaccine has ever been licensed in the US or globally, but there are multiple chikungunya vaccines in development. One manufacturer initiated rolling submission of a Biologics License Application (BLA) to the Food and Drug Administration (FDA) in August 2022 and licensure is possible during 2023, so the WG was formed in May 2022. The purpose of the Chikungunya Vaccines WG is to: 1) review and evaluate data on chikungunya disease, epidemiology, and vaccines; and 2) develop policy options for ACIP's consideration for US persons at risk for chikungunya, including travelers and residents of US territories and states with, or at risk of, transmission. The Terms of Reference (TOR) for the Chikungunya Vaccines WG are as follows:

- ❑ Review information on chikungunya disease, including outcomes
- ❑ Review data on chikungunya epidemiology and burden among US residents, including travelers and persons living in areas at risk for local transmission
- ❑ Review data on safety, immunogenicity, and effectiveness of chikungunya vaccines
- ❑ Provide evidence-based recommendation options for ACIP
- ❑ Identify areas in need of further research for informing potential future vaccine recommendations
- ❑ Publish chikungunya vaccine *Morbidity and Mortality Weekly Report* (*MMWR*) Recommendations and Reports document

This session included an overview of chikungunya disease and vaccines, a presentation on the immunogenicity and safety of Valneva's chikungunya vaccine, and the WG's interpretation of the vaccine data and the WG's plans and timelines.

Overview of Chikungunya and Chikungunya Vaccines

Susan Hills, MBBS, MTH (CDC, NCEZID) explained that chikungunya is a mosquito-borne disease caused by chikungunya virus, which is an alphavirus. The disease is characterized clinically by the acute onset of fever and often service polyarthralgia. The virus has caused large outbreaks with high attack rates. During such outbreaks, from one-third to three-quarters of local populations have been affected. Outbreaks have occurred in most parts of the world, including in Africa, Asia, Europe, the Americas, and islands in the Indian and Pacific Oceans. Chikungunya virus was first identified in Tanzania in the 1950s.[48] The name "chikungunya" is derived from a word in the local language in the area the outbreak occurred and means "that which bends up," which refers to the stooped posture of individuals infected with the virus. Over the next 50 years, cases and outbreaks occurred sporadically in parts of Africa and Asia. Beginning in 2004, there was a large increase in the number of chikungunya cases reported from India and islands in the Indian and Pacific Oceans.[49] Imported cases also resulted in outbreaks in temperate areas of Europe. In late 2013, the first local transmission of chikungunya virus in the Americas was identified.[50] The virus subsequently spread through most of the Americas, with more than 2.6 million cases ultimately reported during the outbreak. In association with this outbreak, there was widespread transmission in the US territories of Puerto Rico (PR) and US Virgin Islands (USVI) and also some limited local transmission in the Continental United States (CONUS), with 13 cases reported in Florida and Texas.

The rapid spread of the virus and recent large outbreaks have essentially driven the development of chikungunya vaccines. Chikungunya cases among US travelers have primarily reflected chikungunya virus transmission patterns in the region of the Americas. Before 2013, chikungunya was not a common travel-related disease. When chikungunya emerged in the Americas, there was a sharp increase in cases, with almost 3,000 traveler cases reported during 2014 alone. In the years since, there has subsequently been a steady decline in cases. Future chikungunya outbreaks are likely to occur, although it is difficult to predict when and where these might be. The greatest risk for travelers will be when these epidemics occur. The mosquitos that spread chikungunya virus to humans are *Aedes* (*Stegomyia*) species mosquitos, primarily *Aedes aegypti* and *Aedes albopictus*. They are active daytime biters with peak activity at dusk and dawn. They lay their eggs in containers that hold water, such as buckets and flowerpots.

In addition to mosquito-borne transmission, other uncommon modes of chikungunya virus transmission that have been documented include intrauterine and intrapartum transmission, blood-borne transmission through needlestick injury, and transmission through aerosol exposure in the laboratory. The clinical symptoms of chikungunya typically develop about 3 to 7 days following the bite from an infected mosquito, with the majority of infected persons developing symptoms. The most common symptoms of disease are a high fever and arthralgia, which is typically severe and can be debilitating. Other symptoms also can occur, such as maculopapular rash, myalgia, and headache. The joint symptoms are usually in multiple joints, and there typically is a bilateral and symmetric pattern. Joint pains occur most commonly in the hands and feet, but they also can affect more proximal joints. There is no specific antiviral treatment for symptoms. The approach to management typically involves rest, fluids, and the use of analgesics and antipyretics. Although rare, serious complications of chikungunya can occur, such as myocarditis; ocular disease, including uveitis or retinitis; hepatitis; acute renal disease; severe bullous lesions in infants; and neurologic disease such as meningoencephalitis,

[48] Robinson MC. Trans Roy Soc Trop Med Hyg 1955
[49] Thiberville SD. Antiviral Res 2013
[50] https://www.cdc.gov/chikungunya/geo/index.htm

Guillain-Barre Syndrome (BGS), myelitis, or cranial nerve palsies. Deaths are very rare but can occur.

Some groups of people have an increased risk for more severe disease. This includes adults older than 65 years of age and people with underlying medical conditions (e.g., hypertension, diabetes, or heart disease). Pregnant women have symptoms and outcomes similar to other people, but intrapartum transmission can result in neonatal complications including neurologic, myocardial, or hemorrhagic symptoms. For many people with chikungunya, symptoms resolve in about 7 to 10 days. However, some have ongoing joint pain and prolonged fatigue for months or years after their acute illness. The exact proportion with persistent symptoms is difficult to define. There are more than 50 studies on the topic, but the study results shows substantial variability related to a variety of factors including the study methodology in terms of whether it was prospective or a retrospective study and whether an uninfected comparison group was included; the duration of follow-up; the means of ascertaining symptoms; and cohort type, such as whether they were drawn from the community, hospitalized patients, or the traveler population; the demographics of the patients included; and other factors. During a future ACIP meeting, the WG will present more information on this topic as sequelae are very important to understanding the potential benefit of vaccination. Factors that appear to be associated with more prolonged symptoms include older age, the severity of acute illness, and the presence of pre-existing joint disease.

At present, the main means of prevention for chikungunya is the use of protective measures against mosquito bites, including insect repellant. There are no licensed chikungunya vaccines either in the US or globally. If a chikungunya vaccine is licensed, it will be a measure to provide additional benefit for some persons. There are many chikungunya vaccines in various stages of development, including the 2 shown in this table that have completed or have in progress Phase III clinical trials and possibly will be licensed in the US:

Manufacturer	Type	Schedule and administration	Status	Notes
Valneva	Live attenuated	1 dose IM	- Phase III in adults ≥18 years completed - Phase III in adolescents (12–17 years) commenced January 2022 - Lot-to-lot consistency completed	CEPI co-funding
Emergent BioSolutions	Virus-like particle	1 dose IM	- Phase III in 12–65 years commenced October 2021 - Phase III in ≥65 years commenced May 2022	

Abbreviations: IM-Intramuscular; BLA-Biologics License Application; FDA-Food & Drug Administration; CEPI-Coalition for Epidemic Preparedness Innovations

Valneva's vaccine, shown in the first row, is the furthest advanced. The vaccine is a live-attenuated vaccine. The schedule is 1 dose administered intramuscularly (IM). A Phase III study in adults 18 years of age and older has been completed. A Phase III study in adolescents 12—17 years of age commenced in January 2022. A lot-to-lot consistency study has also been completed. Emergent BioSolutions also has a chikungunya vaccine in late-stage development, which is shown in the second row. This is a virus-like particle (VLP) vaccine for which the schedule is also 1 dose administered IM. A Phase III trial among adults and adolescents aged 12—65 years of age commenced in October 2021, and the Phase III trial among adults aged 65

years and older commenced in May 2022. Notably, Valneva's vaccine has received co-funding from the Coalition for Epidemic Preparedness Innovations (CEPI).

CEPI is a global partnership working to accelerate the development of vaccines against epidemic diseases. Chikungunya vaccine was selected for prioritization by CEPI in recognition of the disease's public health risk and global economic impact. Valneva's vaccine is one of 3 chikungunya vaccine candidates that CEPI is supporting. The other 2 Chikungunya vaccine candidates that CEPI is supporting are shown on this table:

Manufacturer	Type	Schedule and admin		Status	Notes
Merck	Live attenuated measles-vectored	1 dose + booster	-	Phase II completed	CEPI co-funding
International Vaccine Institute/ Bharat Biotech	Inactivated whole virus	2-dose	-	Phase II/III commenced August 2021	CEPI co-funding

Abbreviations: CEPI - Coalition for Epidemic Preparedness Innovations

The first is the Merck vaccine, originally from Themis Bioscience, which is a live-attenuated measles-vectored vaccine. The schedule is expected to be 1 primary dose and a booster. Phase II trials have been completed for this vaccine. The other vaccine is being developed in a collaboration between the International Vaccine Institute in Korea and Bharat Biotech in India. This is an inactivated whole virus vaccine that is administered in a 2-dose schedule. A Phase II/III trial commenced in August 2021.

In regard to Valneva's vaccine, Valneva initiated a rolling submission of their BLA to FDA in August 2022. That submission is targeted for completion by the end of 2022. FDA has given the vaccine a Breakthrough Therapy designation, which allows a request for a priority review. Vaccine licensure is expected to occur during 2023, with an initial indication for adults aged 18 years of age and older.

In summary, chikungunya is a mosquito-borne disease that can cause large outbreaks, particularly in tropical and subtropical regions. In the US, there have been previous outbreaks in territories and limited local transmission in 2 states. The likelihood and scale of any future outbreaks in areas of the US with the *Aedes* mosquito vectors is unknown, but given the expansion in the area of transmission of many other viruses in recent times, there is clear potential for transmission or outbreaks in the US in the future. For travelers, the greatest risk for infection is during outbreak periods. The clinical presentation of disease is with fever and often severe polyarthralgia, and there is a risk for long-term joint symptoms. Because no chikungunya vaccine has previously been licensed, there are no existing ACIP chikungunya vaccine recommendations. The WG will be discussing potential recommendation options for ACIP's consideration for travelers and residents of US territories and states with, or at risk of, transmission.

Dr. Hills also briefly explained the accelerated approval pathway that will be used for licensure of chikungunya vaccines, given its relevance to Valneva's presentation to follow. Under FDA regulations, several licensure pathways are available for new vaccines. The most appropriate pathway depends upon the type of evidence that can be generated to demonstrate the vaccine's effectiveness. The 3 pathways[51] are Traditional Approval, Accelerated Approval, and the Animal Rule. Traditional approval can occur through an efficacy trial with a disease endpoint, human challenge studies, or immunogenicity studies. Randomized control field efficacy trials would be challenging for chikungunya vaccine because outbreaks are unpredictable, and the duration can be relatively short. As a result, this approach would be logistically very challenging. Clinical development likely would be substantially delayed if this approach was necessary. Human challenge studies can generally be justified in adults when there is assurance that the challenge infection will be self-limited, or complications can be easily managed without sequelae. The main concern with this approach for chikungunya vaccine is that while most cases resolve without complications, some patients get persistent debilitating arthralgia and no treatment is available. Therefore, this approach is unlikely to be ethically justifiable. The third approach, immunogenicity studies, can be used where there is an established correlate of protection from disease. For chikungunya, several animal and human studies have suggested that protection is primarily mediated by chikungunya virus neutralizing antibodies. However, the protective threshold for neutralizing antibody titers has not been definitively established.

FDA can grant accelerated approval for products that are for serious conditions and that fill an unmet medical need. This pathway is designed to bring products for serious conditions to market faster. Demonstration of effectiveness for accelerated approval is based on controlled clinical trials showing that the vaccine has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. This is slightly different from traditional approval where effectiveness is assessed directly. With accelerated approval, there is a post-licensure requirement for controlled trials to confirm the clinical benefit. The approach for accelerated approval of chikungunya vaccines was endorsed at an FDA Vaccines and Related Biological Products Advisory Committee (VRBAC) meeting in November 2019.[52] The marker of protection that can be used for accelerated approval of chikungunya vaccines is based on a neutralizing antibody titer estimated from a validated non-human primate model (NHP). As mentioned earlier with regard to the accelerated approval pathway, effectiveness will need to be confirmed in a Phase IV post-licensure field study.

Discussion Points

Dr. Chen requested clarification on the risk factors for severe disease, given that he noted no mention of immunocompromise, which he presumed would be a risk as well. In addition, he observed that underlying medical conditions could include a wide swath and also asked for more information about this risk.

Dr. Hills responded that there have been various studies that examined more severe disease. Immunocompromise is a risk condition as it is for almost all infections. While it was not mentioned specifically in the presentation, there is some overlap because the disease and some of these underlying medical conditions often occur within the same group. Particularly in terms of disease severity, it is older adults who are also the ones with a variety of underlying medical

[51] Yang et al. Vaccine 2017. Regulatory considerations in development of vaccines to prevent disease caused by chikungunya virus.
[52] Vaccines and Related Biological Products Advisory Committee (VRBAC) meeting, November 8, 2019 (https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-november-8-2019-meeting-announcement)

conditions who are showing up in the studies as being at most risk of severe disease. The other issue is that it is like a U-shaped curve with severity because in addition to those groups, there are neonates. If there is intrapartum transmission, then there is very severe disease among those very young infants and neonates born to mothers who were viremic during pregnancy with myocardial disease, neurologic manifestations, and with hematologic issues that can lead to cerebral hemorrhage. There have been studies that have independently suggested that these underlying medical conditions put people at increased risk of severe chikungunya. A younger person with well-controlled hypertension is probably at far lower risk of severe disease than the older person who has not well-controlled hypertension.

Dr. Brooks asked how outbreaks occur of an arbor-borne or vector-borne infection in terms of whether it is just because there is a large number of people in a population who have it and then the *Aedes* bites them and spreads it to other people.

Dr. Hills replied that this is an interesting question. When the outbreak spread through the Indian and Pacific Oceans in 2004, there was a slight viral mutation that led to increased ability of the *Aedes albopictus* mosquito to transmit. *Aedes albopictus* have more distribution in temperate areas and *Aedes aegypti* tends to stick to tropical and subtropical areas. This means that there is transmission by a vector in areas where people are non-immune. Overall, in terms of outbreaks, a variety of factors can lead to outbreaks. There can be population immunity, a critical point of insufficient population immunity, genetics, environmental conditions, and a variety of other factors, which is why it is difficult to predict specifically when and where the next outbreak may occur.

VLA1553 Chikungunya Vaccine Candidate

Katrin Dubischar (VP, Program Director Chikungunya Vaccine at Valneva) introduced Valneva's vaccine candidate, VLA1553; summarized the evidence supporting the serological endpoint that Valneva defined together with the FDA for this vaccine candidate; and provided and overview of the clinical study in terms of key immunogenicity and safety data. VLA1553 is a live-attenuated vaccine candidate used in a single dose in IM immunization that comes in a lyophilized presentation. The vaccine candidate is based on the La Reunion strain of the East Central South African genotype of chikungunya virus. Its attenuation has been achieved through reverse genetics, resulting in a 60 amino acids deletion in the non-structural protein 3 (nsP3) protein that reduces its replication capacity against the virus. The target populations and geographic reach anticipated for this vaccine are travelers, the military, and outbreak preparedness in countries like the US, Europe, and/or Canada. There is also a major burden in low- and middle-income countries where chikungunya virus is endemic. Valneva is partnering with CEPI and they work together with Instituto Butantan from Brazil to make the vaccine affordable.

To summarize the evidence generated in support of the serological endpoint used in the Phase III clinical trial program,[53] Valneva investigators transferred human post-vaccination sera from its Phase I clinical study to NHPs at varying titer levels and then challenged these animals with a wild-type chikungunya virus. Following the challenge, the NHPs have been monitored for the development of fever and viremia. The protocol for this study was agreed to with the FDA and the results have been published. In terms of the results in the group that has received human post-vaccination serum, no fever has developed in any of the NHPs. Fever typically develops in the NHPs that receive non-immune serum. No live replicating virus has been detected in any of

[53] Roques P, et al. JCI Insight. 2022;7(14):e160173. doi: 10.1172/jci.insight.160173.

the NHPs. All of the animals had strongly reduced viral load and some animals even had undetectable viral RNA load, depending on the titer before the wild-type virus challenge.

With these data, it was possible to determine a pre-challenge titer that resulted in sterilizing immunity in the NHPs. This was selected to meet the definition of "seroresponse." Taking a conservative approach, seroresponse was defined as a titer of ≥150 in a micro-Plaque Reduction Neutralization Test ($\mu PRNT_{50}$). In addition to this evidence coming from the NHP model, there is some supportive evidence from a prospective seroepidemiological study conducted in the Philippines. That trial was following up its cohort to monitor them for acute febrile illness. In that trial, the neutralizing antibody titer of 10 in a micro-$PRNT_{80}$ assay was associated with protection from development of chikungunya virus fever. Valneva was able to get a panel from that trial. The titer they have observed in that study would translate to a micro-$PRNT_{50}$ of about 50 in the Valneva assay system, also supporting the selected response titer of ≥150.

In terms of Valneva's clinical study program, 3 clinical trials provided data for the initial licensure. The first is a Phase I clinical study[54] conducted in 120 adults aged 18–45 years that evaluated 3 dose levels of the vaccine and included re-vaccination as a homologous viral challenge. This study generated safety, immunogenicity, and viremia data.[55] Second was a Phase III clinical trial comparing VLA1553 to placebo among a total of 4,115 participants. This pivotal Phase III study generated safety and immunogenicity data. The third study was a lot-to-lot consistency study in 408 participants aged 18–45 years of age. This RCT compared 3 lots of VLA1553.

To further describe the study design for the Phase I clinical trial, 120 healthy volunteers aged 18–45 years were immunized with 3 approximate dose levels of the vaccine: $3x10^3$ $TCID_{50}$ (Low), $3x10^4$ (Medium), $3x10^5$ (High) $TCID_{50}$. The low- and medium-dose groups contained 30 participants each and the high-dose group consisted of 60 participants. All of these groups were immunized on study Day 0. Development for viremia was monitored on Days 3, 7, and 14 post-vaccination. Further study visits took place on Day 29 and out to follow-up until Month 12. Half of the high-dose group received another dose of the vaccine at Month 6, and all other study participants received another dose at Month 12. Those immunizations were with the live vaccine as equaling an intrinsic viral challenge.

To briefly summarize the results of the Phase 1 clinical trial, there was an excellent immunogenicity profile in all dose groups after a single dose. The medium dose was selected for further development based on the study. Seroconversion was observed in all individuals in the trial in all dose groups when the seroresponse threshold was applied. There was 100% seroresponse at Day 14 in all groups. Neutralizing antibodies were retained in all participants at Month 12. After re-vaccinations were administered either at Month 6 or at Month 12, there was no anamnestic neutralizing antibody response, which showed that the single dose was sufficient to induce a sustained high titer of neutralizing antibodies and another vaccination was not needed. The study also showed that there was no vaccine-induced viremia after the re-vaccination. No associated clinical symptoms or reactogenicity were experienced after the re-vaccinations, which was taken as an early indication that the antibodies induced to the immunization at Day 0 efficiently neutralized the vaccine virus upon revaccination. With those data, it was possible to skip a Phase II study, it was not necessary to generate further dose and schedule data, and it was possible to advance immediately into Phase III clinical trials.

[54] Wressnigg et al. 2020; Lancet Infect Dis 20:1193-1203
[55] Viremia tested by RT-qPCR, readout: CHIKV genome copy equivalents (GCE) detected per 1mL of initial specimen

To provide more details regarding the pivotal clinical study design (VLA1553-301), this was a multicenter randomized placebo-controlled trial conducted in the US that enrolled 4,115 adults aged 18 years and above with no upper age limit. The primary endpoint was the portion of participants with seroresponse for individuals who were negative at baseline for chikungunya virus neutralizing antibodies. The threshold agreed to with the FDA for acceptance of the data from that study was that the lower bound of the 95% confidence interval for the seroresponse rate needed to exceed 70% for the study to meet its endpoint. In terms of safety, unsolicited AEs were captured for 6 months and solicited adverse events were captured for 10 days following vaccination. Recruitment was stratified by age into 2 groups: Younger Adults (18–64 years, N=3,652) and Older Adults (≥65 years, N=463). The randomization scheme was 3:1 for the VLA1553 and placebo groups. The first 462 participants constituted the immunogenicity subset. Immunizations took place on Day 1. Study visits occurred on Days 8 and 29 for the primary endpoint. The last follow-up visit was at Month 6. Demographic characteristics were similar between the VLA1553 and the placebo groups with about 55% females and a good diversity of racial distribution. The mean age was about 45 years.

To briefly summarize the results, the pivotal study met the primary endpoint. The seroresponse rate over time on Day 29, which was the time point for determining the primary endpoint, was seen in 99% or 263/266 individuals versus no seroresponse in the placebo group. A high seroresponse rate also was maintained at the Month 6 visit, with 96% of individuals still showing seroresponse. In terms of the kinetics of the neutralizing antibody response, there was no impact by age. VLA1553 was equally immunogenic in the 2 age strata of 18–64 and ≥65 years of age. The titers peaked at Day 29 and then declined over time. However, they stayed well above the threshold for seroresponse.

Briefly summarizing the results from the lot-to-lot consistency study (VLA1553-302) conducted in 408 adults 18–45 years of age, the primary endpoint was the GMT for neutralizing antibodies on Day 29 post-vaccination. The study met its primary endpoint, lot-to-lot consistency was demonstrated, and seroresponse was seen in 98% of participants on Day 28 and 96% at Day 180. Therefore, the immunogenicity profile seen in those individuals is consistent with the pivotal study.

Moving to safety data for the pivotal study, VLA1553-301, about 62% of individuals reported any AEs in the 6 months following administration of VLA1553 compared to about 45% for the placebo group. Related AEs were observed in 51% of the VLA1553 group. Severe adverse events (SAEs) were reported by 3.4% of the individuals, and 2% of individuals reported related SAEs in this trial. Based on the solicited local AE profile observed for 10 days after vaccination, about 15% overall developed local AEs. The majority of these events were mild to moderate. About 11% in the placebo group developed local AEs. The most common local AE was tenderness. Overall, about 50% of individuals developed systemic AEs events. The most common were headache, fatigue, and myalgia. Those were observed in more than 20% of the VLA1553-301 group, and the majority of the systemic reactions were mild or moderate. About 70% developed arthralgia. A number of severe reactions were observed, most of which were fever.

Because chikungunya virus is associated with arthralgia, post-vaccination arthralgia was examined in more depth. In the VLA1553 group, about 17% reported any arthralgia. About 0.5% of these individuals, or 15 individuals, reported arthralgia with a duration exceeding 11 days. The longest duration was 180 days. Contrasting that with findings from the placebo group, about 5% developed any arthralgia, but also 0.5% of the placebo group reported an arthralgia with a

duration exceeding 11 days. The longest duration here was 180 days. In terms of the relative frequency of arthralgia by duration for the VLA1553 group and the placebo group, the relative frequency of longer-lasting arthralgia did not increase with VLA1553 in comparison to placebo.

In the pivotal Phase 3 study, about 1.5% of the VLA1553 group versus 0.8% in the placebo group reported any SAEs. There were 2 related SAEs reported with VLA1553. The first case was an event of myalgia in a 58-year-old female study participant. The onset of this event was one day after her vaccination. She was hospitalized for a couple of days for diagnostic procedures. The outcome of myalgia was that she recovered about a month later. The participant has a history of fibromyalgia. During the work-up of this case, no other trigger for the myalgia could be identified. The second case was in a 66-year-old male who developed a syndrome of inappropriate antidiuretic hormone secretion (SIADH) 10 days after immunization with VLA1553. That individual was also hospitalized and made a full recovery. The assessment was that the syndrome of SIADH may have been related to prolonged fever symptoms post-vaccination. To breakdown AEs by age in the Pivotal Phase III study, about 63% of VLA1553 recipients reported any AEs in the 2 age strata. The rates of related AEs, related SAEs, and related SAEs were comparable in the 2 age groups, though somewhat lower in the individuals aged 65 years and above.

For the lot-to-lot consistency data, VLA1553-302, the safety profile also has been consistent with what has been observed in the pivotal Phase III study. Among the 408 subjects aged 18─45 years, 63% experienced any AEs. There were no significant differences between lots. About 61% reported solicited AEs, 19% reported local AEs, and 57% reported systemic AEs. AEs were mostly mild or moderate. No related SAEs were observed in this clinical trial.

In summary, VLA1553 met its primary endpoint in a pivotal immunogenicity Phase III study. The serological endpoint, μPRNT50 titer ≥150, was agreed by the FDA to support an accelerated approval pathway. A single dose induced seroresponse in 99% of participants at Day 29, and seroresponse was sustained in 96% of individuals at Day 180. Similar GMTs were observed in seroresponse rates in older and younger adults. VLA1553 was generally well-tolerated across the age groups. An independent DSMB did not identify any safety concerns. The majority of AEs were mild or moderate and resolved within 3 days, with 2.1% reporting severe solicited AEs, the most common of which was fever. The safety profile is comparable with other licensed vaccines. Valneva has initiated the BLA submission to the FDA.

Discussion Points

Dr. Poehling asked for clarification regarding whether the VLA1553 trial included persons with medical conditions.

Dr. Dubischar responded that the requirements of the protocol in terms of exclusion criteria were that the individuals had to be generally healthy based on their medical history, physical examination, and screening laboratory tests. They allowed individuals to have had a chronic illness or chronic condition like hypertension, diabetes, or hyperlipidemia if that condition was stable and well-controlled on therapy for the past 6 months.

Dr. Chen requested additional information about how deeply the studies looked into age effects and if there could be an understanding of the immune response among others who have chronic medical conditions who are immunocompromised. It also did not appear that any studies had been done in pregnant women, which is another target population of interest.

Regarding the age span, Dr. Dubischar indicated that the oldest individual in the Pivotal Phase III trial who received VLA1553 was 88 years of age. Overall, there were a couple of hundred people in this age stratum. They have a full breakdown of the underlying medical conditions that individuals had. For example, about 19% of the individuals in that study had a medical history of hypertension. They are in the process of looking at data further stratified by individuals who take any immune-modifying medications. No pregnant women were included in the clinical trial. They had an exclusion criterion relating to pregnancy. Given that this was the first large study of this vaccine candidate, they felt that it would have been too early to study pregnant women at this stage. In terms of the development of post-marketing, Dr. Hills explained the difficulties and the logistical boundaries of implementing effectiveness or efficacy of a Phase III-type of clinical trial, but they are in the process of determining, together with the FDA and other regulatory agencies, what the best way of demonstrating VE effectiveness is. Most likely, this will be in an observational study setting in an area where the virus circulates, so in endemic areas.

Dr. Daley observed that the persistence of the antibody titers seemed longer than he would expect and he wondered whether that suggested anything about replication of the virus or persistence of the virus after a single dose. In addition, he requested further information about the 17% arthralgia in the vaccinated population in terms of how bad, how long, et cetera.

Dr. Dubischar replied that they have seen that with other live-attenuated vaccines where there is a precedence of very long-lasting immunity after immunization. Natural infection with chikungunya virus is considered to confer life-long immunity. They also have looked at viremia and saw a complete resolution at Day 14, so there are no concerns in terms of that perspective. The majority of arthralgia cases were mild, with 14% of individuals reporting mild arthralgia, 3% reporting moderate arthralgia, and 0.3% reporting severe arthralgia. Severe would have included the inability to perform the daily chores. The mean duration of arthralgia observed in the VLA1553 participants was 5 days. In placebo recipients, the mean duration of those with arthralgia was 8.8 days.

Ms. Bahta asked whether the live-attenuated strain used was specific or if there was any cross-protection to other strains.

Dr. Dubischar responded that chikungunya in general is believed to be present as one serotype even though there are multiple genotypes of the virus. The data they have been able to generate so far are heterologous neutralizations. They see that the vaccine-induced antibodies also neutralize viruses from other chikungunya genotypes.

Recognizing that pregnancy was an exclusion criterion, Dr. Sanchez asked whether any of the women enrolled in the study became pregnant during the study and whether any of the animal models included the use of live-attenuated vaccine in pregnant animals. In addition, he thought 17% arthralgia seemed high and he wondered whether there was any frank arthritis.

Dr. Dubischar indicated that pregnancies were reported during the study. There were some miscarriages and some healthy babies. They have looked at the percentages, which are not really very different from what would be observed in the general population. The animal studies have included pre- and post-natal toxicity studies, which did not show any alarming signals. In terms of the question regarding arthritis, one individual reported arthralgia and arthritis. She had a genetic predisposition marker for the development of arthritis. Most of the events were solicited AE arthralgias. In terms of whether 17% is high, it is also seen with other non-live vaccines.

Dr. Sanchez asked whether there was any attempt to determine whether the vaccine virus actually got into the fetus during any of the episodes.

Dr. Dubischar responded that this was not attempted. This included pregnancies that were conceived a while after the immunization, so there are very little data at the moment regarding use in pregnancy.

Dr. Talbot applaud Valneva for including older adults as many times there is intent to use vaccines in older adults and they do not actually test the vaccine in older adults. She asked the median age of those over 65 years of age as she was trying to figure out how many were much older. In addition, she requested additional information about the frailty of the individuals in this age group.

Dr. Dubischar indicated that 70.3 years was the mean age of the older age group in the trial. In terms of frailty, there were individuals who had multiple conditions who were well enough to participate in the study. Only those who were stable and did not have progressive diseases were included. It would be a fair summary to say that it is a healthy older adult population, but not necessarily a very frail population.

Dr. Talbot clarified that frailty does not depend just on medical issues, so it would be helpful in the future to measure the level of frailty in these folks.

Dr. Poehling emphasized that pregnancy is a very high-risk condition for this illness. One of the challenges is that the pregnant population usually gets studied really late in the process. She encouraged Valneva to conduct some NHP studies to assess administration of the vaccine during pregnancy.

WG Interpretation of the Vaccine Data and Activities

Susan Hills, MBBS, MTH (CDC, NCEZID) indicated that the WG conducted an initial review of the immunogenicity and safety data and will be reviewing the data in far more depth as they move ahead. During this session, she provided a brief review of the key aspects of the vaccine data and a summary of the WG's initial conclusions. Beginning with the immunogenicity data, the Pivotal Phase III study was a randomized placebo control double-blind trial in adults aged 18 years and older. Subjects were seronegative at baseline (i.e., no detectable chikungunya virus neutralizing antibodies). Seroresponse was defined as chikungunya virus neutralizing antibody titer of ≥150 by 50% micro-plaque reduction neutralization test ($\mu PRNT_{50}$), which was based on the value from the validated NHP model. For the immunogenicity component, 462 subjects were enrolled overall. However, the immunogenicity analysis was based on the per protocol population who were subjects with no major protocol deviations. There were 362 subjects or 78% of all enrolled subjects in the analysis, including 266 vaccine recipients and 96 placebo recipients. The trial was conducted during the COVID-19 pandemic, and more than half of the protocol deviations were related to attendance at study visits.

The key overall results were that the seroresponse at 28 days was 99% with a GMT of 3,362. At 6 months after vaccination, 96% a seroresponse and the GMT was 752. When seroresponse rates were compared between younger adults aged 18–64 years and older adults ≥65 years of age, at 28 days the seroresponse rates were 99% and 100% for the two groups, respectively. At 6 months, the rates were 97% and 95%. The GMTs were similar in the 2 age groups at both time points. The other phase III study was a lot-to-lot consistency study, which gathered immunogenicity from data from approximately 350 adults aged 18–45 years. In this study, the

key results were that the seroresponse rate at 28 days was 98% and at 6 months was 96%. The key points the WG noted from the review of the data are that there is a total of 622 adults with immunogenicity data in the 2 Phase III trials. The seroresponse rates at 28 days post-vaccination were high at 98% or higher, and at 6 months remained high at 96%. There were similar seroresponse rates in older and younger adults, although the data among older subjects are limited as they are based on only 59 individuals.

In terms of the WG's interpretation of the safety data, the key study was the Pivotal Phase III study that was a randomized placebo controlled double-blind trial in adults. The placebo was phosphate buffered saline. Recruitment was in a 3:1 ratio, with 3,082 adults receiving vaccine and 1,033 receiving placebo. All of these subjects were included in the safety population. Overall, 89% of subjects were aged 18─64 years and the remaining 11%, or about 346 participants, were aged 65 years and older. Overall, 62% of vaccine recipients reported any AEs compared with 45% of placebo recipients. About 51% of events were considered by study investigators to be related AEs. About 2% of vaccinated subjects had a related SAE. In all of these categories, the rates among the vaccine group were significantly higher than the rates among the placebo group. In regard to solicited local reactions within 10 days after vaccination, any reported local AE occurred in 15% of vaccine recipients, which was similar to the rate of 11% among placebo recipients. Tenderness was the most commonly reported event, reported by 11% of subjects. Other reactions (e.g., pain, erythema, induration, and swelling) were reported by 6% or fewer vaccine recipients. Regarding the solicited systemic reactions reported within 10 days after vaccination, 50% of vaccine recipients reported an AE compared with 27% of placebo recipients. The rate of severe systemic AEs was 2% in vaccine recipients, with no severe events reported among placebo recipients. The most common systemic AEs among placebo recipients were headache, fatigue, and myalgia. All of these were reported at rates of about 25 to 30%.

One of the AEs that the WG was particularly interested in is arthralgia. As Dr. Dubischar noted, that is a key feature of chikungunya disease and this is a live-attenuated vaccine, so it is an event in which the WG is particularly interested. Overall, arthralgia was reported by 17%, or 514 vaccine recipients, compared with 5% of placebo recipients. The severity of arthralgia among these 514 subjects was mild in 83%, moderate in 16%, and severe in 2%. The duration until resolution of arthralgia after vaccination was 1 to 5 days in 85%, 6 to 15 days in 13%, and more than 15 days in 2%. The maximum duration for one individual was 182 days. For SAEs, overall the rate was 1% in both the vaccine and placebo groups. However, among vaccine recipients, 0.1%, or 2 of the events, were considered related compared with 9 in the placebo recipients.

The key points the WG noted from the initial review of the data are that there are a total of approximately 3,500 adults with data from 2 Phase III trials, including the Pivotal Phase III study and the lot-to-lot consistency study that had similar results in terms of rates of AEs. Overall, AEs and SAEs occurred at significantly higher rates in vaccine recipients compared with placebo recipients. In regard to reactogenicity, local reactions were reported at low rates by 15% of vaccinated subjects in the Pivotal Phase III trial, with rates of individual events almost all being lower than 6%. However, solicited systemic reactions were reported by 50% of subjects, which was about twice the rate reported among placebo recipients. Arthralgia is an AE of interest in chikungunya vaccine and was reported by 17% of vaccine recipients. SAEs events were uncommon, but there were an insufficient number of subjects in the trial to detect rare SAEs.

The WG has been forming in recent months, so the members have only had the chance for a preliminary review of these data. The plan is for the WG to review the data in far more depth during the GRADE assessment. In association with the vaccine's likely licensure during 2023, the WG plans to present the EtR Framework during the October 2023 ACIP meeting, with a vote anticipated during the following February 2024 meeting. This session included a broad introduction to chikungunya and the Valneva vaccine, the first chikungunya vaccine likely to be licensed in the US. However, there are a number of other important topics that the WG plans to present during future ACIP meetings as they are important to the consideration of vaccine recommendations. The WG will present more detailed information on the epidemiology of chikungunya among travelers and among residents of the US areas with past transmission of chikungunya virus, as well as more in-depth information on acute disease and disease burden from sequelae of infection. The WG also plans to review the vaccine immunogenicity and safety data comprehensively as part of the GRADE assessment and anticipates that over time, there will be additional data on use of Valneva's vaccine among younger age groups and potentially additional chikungunya vaccines submitted for licensure in the US. The WG will be presenting those data as they become available.

Discussion Points

Dr. Kotton asked whether there eventually would be studies conducted to assess concomitant vaccines in the travel clinic and military settings, such as coadministration of yellow fever (YF) vaccine with this live viral vaccine and if there are insights, thoughts, or concerns about that.

Dr. Dubischar responded that this is, indeed, a topic of consideration for Valneva though they have not solidified their plans yet. They are aware that such data may be useful within the travel vaccine setting.

Dr. Long asked whether the WG had thought about the 2 viruses occurring in the same areas where people may have had preceding infections with dengue before they get this vaccine and whether there may be cross-reactivity in enzyme immunoassays, but probably not neutralization assays. That is, she wondered whether the WG is concerned about the performance of the vaccine in those who previously have had dengue or chikungunya in terms of enhancement of disease, detrimental response to vaccine, or AEs.

Dr. Hills responded that because dengue is a flavivirus and chikungunya is an alphavirus, they are not concerned about that interaction. However, one of the questions of relevance to this question is thinking about response in people who have had previous chikungunya or perhaps other alphavirus infections. Moving forward, the WG will take this into consideration.

Dr. Kotton asked whether the use of the vaccine will be considered among immunocompromised patients. She understood the hesitancy in pregnant women to give a live viral vaccine, but immunocompromised is different.

Dr. Hills said she believed immunocompromised would be a contraindication to vaccination, but called on Valneva to comment on that further.

Dr. Dubischar added that Valneva expects that severe immunocompromisation will be a contraindication to receiving the live vaccine, given that it is a replicating virus vaccine. However, there also are considerations that the use of this vaccine may be prudent in some subgroups, such as HIV-positive individuals. There may be studies on those topics in the future.

Dr. Lee asked for clarification on where the WG is headed in terms of vaccines that serve unique populations with uncertain exposures and whether perhaps the WG would consider discussion around clearly defining risk-based groups and/or whether shared clinical decision-making makes sense in this case.

Dr. Hills indicated that the WG definitely could take that into consideration.

COVID-19 VACCINES 10-19-23

FDA Statement

Rebecca Reindel, MD (Medical Officer, FDA) announced that earlier in the morning, the FDA authorized the Novavax COVID-19 Vaccine, Adjuvanted for use under EUA as a first booster dose for individuals ≥18 years of age for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate and for ≥18 years of age who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted because they otherwise would not receive a booster dose of COVID-19 vaccine. For these individuals, this booster dose may be administered at least 6 months after completion of a primary vaccination with an authorized or approved COVID-19 vaccine.

CDC Statement

Evelyn Twentyman, MD, MPH (CDC/NCIRD) reported that CDC signed off on recommending the use of the Novavax monovalent COVID-19 vaccine as a single booster dose in those ≥18 years of age as outlined in the authorization from the FDA. CDC's Interim Clinical Considerations for Use of Authorized and Approved COVID-19 Vaccines will be updated along with all accompanying schedules and clinical guidance materials.

Session Introduction

Matthew F. Daley, MD (Chair, COVID-19 Vaccine WG) introduced the COVID-19 Vaccines Session. In terms of updates, he reported that bivalent booster authorizations were extended down to children ≥5 years of age. October 12, 2022, FDA granted EUA for the use of Moderna bivalent COVID-19 vaccine boosters in children ages 6–17 years and use of Pfizer-BioNTech bivalent COVID-19 vaccine boosters in children ages 5–11 years. Also on October 12, 2022, CDC signed off on and recommended use of updated bivalent COVID-19 boosters in people ≥5 years of age.

To review the COVID-19 Vaccines WG's activities for the months of September and October 2022, the WG has reviewed and discussed vaccine safety and immunogenicity data for monovalent Moderna COVID-19 vaccine boosters for children 6—17 years of age; vaccine safety and immunogenicity data for the Novavax COVID-19 vaccine booster for adults ≥18 years of age; COVID-19 epidemiology and outcomes among people who are pregnant; COVID-19 epidemiology and outcomes among infants; vaccine safety and effectiveness data pertaining to the use of COVID-19 vaccines during pregnancy; and the proposed integration of COVID-19 vaccines into the Vaccines for Children (VFC) program.

The agenda for this session included presentations on COVID-19 in pregnant people and infants 0—5 months of age; COVID-19 vaccine safety during pregnancy; the effectiveness of maternal COVID-19 vaccination in pregnant people and infants; the evidence regarding COVID-

19 vaccine use in children; and implications for the VFC Program. Dr. Daley indicated that following the public comment period, the ACIP would vote on COVID-19 vaccines for the VFC Program.

COVID-19 in Pregnant People and Infants 0–5 Months of Age

Sascha Ellington, PhD, MSPH, CPH (DRH, NCCDPHP, CDC) presented background information regarding what is known about COVID-19 in pregnant people. Assessing risk of COVID-19 in pregnancy typically focuses on determining: 1) whether pregnancy is a risk factor for severe illness by comparison to a non-pregnant group, usually women of reproductive age; 2) if COVID-19 is associated with increased risks for maternal complications and adverse pregnancy outcome compared to pregnant people without disease; and 3) whether infants born to people with COVID-19 during pregnancy are at risk for severe outcomes.

A recent updated Living Systematic Review and Meta-Analysis by colleagues in the United Kingdom (UK) assessed pregnancy as a risk factor for severe illness.[56] So, comparing people with COVID-19 by pregnancy status. Among all the outcomes examined, the odds of ICU admission and invasive ventilation were increased in pregnant people compared to non-pregnant women of reproductive age. However, an important consideration is that the meta-analysis does not adjust for potential confounders and likely underestimates the risks observed in US data that pregnant women and people with COVID-19 are younger and have less underlying health conditions than non-pregnant people with COVID-19. The US closely monitored cases of COVID-19 in pregnancy using CDC's National COVID-19 Case Surveillance data, which includes a pregnancy variable from June 2020–July 2022. During this timeframe, a total of 226,263 infections in pregnant people were reported. Case counts peaked in December 2021 and January 2022. There were 738 ICU admissions and 329 deaths reported among pregnant people. ICU admissions and deaths both peaked in August 2021 when Delta was the predominant variant.

In terms of risks of maternal fetal and infant adverse outcomes among pregnant people with COVID-19 compared to those without COVID-19, data from the Allotey systematic review and meta-analysis showed that all maternal and perinatal outcomes assessed were significantly higher in pregnant people. The odds of all-cause mortality was 6 times as high for pregnant people with COVID-19 and ICU admissions were 5.4 times as high. There was a 57% increase in the odds of preterm birth and an 81% increase in the odds of stillbirth. Additionally, the odds of neonatal death and admission to the Neonatal Intensive Care Unit (NICU) were more than twice as high for infants born to pregnant people with COVID-19 during pregnancy than those born to pregnant people without COVID-19. Data from the Surveillance for Emerging Threats Network (SET-NET)[57] for pregnancy and infant outcomes assessing outcomes among pregnant people with COVID-19 during pregnancy from January 25, 2020–December 31, 2020 demonstrate that the risks also vary by trimester infection, with third trimester infections associated with the greatest risks of preterm birth, NICU admission, and infants being born small for gestational age.

[56] Allotey, J et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020. Updated 7-May 2022 https://doi.org/10.1136/bmj.m3320
[57] https://onlinelibrary.wiley.com/doi/10.1002/bdr2.2081

To briefly describe COVID-19 vaccination coverage among pregnant people, 2 data sources were used. Self-reported survey data from the National Immunization Survey (NIS)[58] estimated that 77% of pregnant people received the primary series and that of those who received the primary series, 48% received the first booster. These data are weighted to be nationally representative. Data from the Vaccine Safety Datalink (VSD),[59] which uses electronic health data from 9 healthcare organizations, found that 72% of pregnant people received a primary series and that 60% of those received a booster. Overwhelmingly, most pregnant people received the primary series before they became pregnant. VSD data also showed that 43% of pregnant people received both their primary series and their monovalent booster, indicating that more than half of the population of pregnant people are likely unvaccinated or under-vaccinated currently.

In terms the epidemiology of COVID-19 among infants from birth through 5 months of age, data from COVID-NET[60] for the period from March 1, 2020—September 10, 2022 show that pandemic rates have been highest among adults ≥65 years of age. Older adults are known to be at the highest risk of severe disease with COVID-19. However, rates among infants 0—5 months of age increased relative to other age groups during the Omicron periods, surpassed rates in those 50—64 years of age, and now are approaching the rates of those ≥65 years of age.

A comparison of hospitalization burden for COVID-19 and influenza, which has long been recognized to cause severe respiratory disease in infants 0—5 months, during October 2020—September 2021, showed that the cumulative COVID-19-associated hospitalization rate was similar to influenza associated hospitalization rates during the pre-pandemic influenza seasons from 2017—2020. During October 2021—April 2022, the preliminary cumulative COVID-19-associated hospitalization rate shown was higher than influenza-associated hospitalization rates during the same pre-pandemic influenza seasons. These data indicate that COVID-19 can cause a similar higher burden of hospitalization as influenza in infants 0—5 months of age.[61]

Among infants 0—5 months of age with COVID-19-associated hospitalizations, 84% had COVID-19 symptoms (including 97% of those >1 month of age), 24% had an underlying health condition with prematurity being most frequent, and 18% were admitted to the ICU.[62] Regarding disparities in this age group, the cumulative COVID-19-associated hospitalization rates are highest in infants 0—5 months of age who are non-Hispanic, American Indian, Alaskan Native, Hispanic, and non-Hispanic Black.[63] COVID-19 has exposed long-standing inequities that have systematically undermined the health of racial and ethnic minority populations, putting them at higher risk for infection, severe illness, and death. Unfortunately, these disparities also affect infants. Tragically, COVID-19 has caused deaths among infants 0—5 months of age. According to death certificate data from January 2020—October of 2022, a total of 265 deaths due to COVID-19 have been reported, accounting for 0.5% of all-cause deaths in this age group.[64]

[58] NIS-ACM: National Immunization Survey-Adult COVID-19 Module. https://www.cdc.gov/vaccines/imzmanagers/coverage/covidvaxview/interactive/adults.html Accessed 10/5/2022
[59] VSD: Vaccine Safety Datalink. https://covid.cdc.gov/covid-data-tracker/#vaccinations-pregnant-women. Accessed 10/5/2022
[60] COVID-NET, https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html. Accessed October 1, 2022.
[61] Source: 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.
[62] March 20 – August 31, 2022. Data source: Coronavirus Disease 2019–Associated Hospitalization Surveillance Network. Accessed October 10, 2022.
[63] Data source: Coronavirus Disease 2019–Associated Hospitalization Surveillance Network. Accessed September 28, 2022.
[64] Source: https://data.cdc.gov/NCHS/Provisional-COVID-19-Death-Counts-by-Age-in-Years-/3apk-4u4f/data. Accessed 10/12/2022.

Updates on COVID-19 Vaccine Safety in Pregnancy from the VSD

Elyse O. Kharbanda, MD, MPH (HealthPartners Institute) provided an overview of present analyses on spontaneous abortion (SAB) and ongoing pregnancy surveillance following COVID-19 booster vaccination, and a summary of VSD studies on COVID-19 vaccine safety and pregnancy. Of the 9 VSD sites, 8 sites contributed data for these analyses. For the case-control surveillance, the primary objective was to conduct monthly surveillance of SAB (cases) and ongoing pregnancy (controls) in order to estimate the odds ratio for receiving a third mRNA COVID-19 vaccine dose in the 28 days prior to the SAB. Secondary objectives were to evaluate the odds ratios for receiving a third mRNA vaccine dose in a 42-day window and the odds for receiving any COVID-19 vaccine booster in a 28-day or 42-day window.

"Booster dose" was defined as a COVID-19 vaccine dose administered at least 28 days after completion of the primary series.[65] Primary analyses focused on a third mRNA COVID-19 vaccine dose after 2 prior mRNA COVID-19 vaccine doses, given that this was the most common booster type in the population. Secondary analyses evaluated any booster dose type of either a second Janssen/J&J, mRNA vaccine after Janssen/J&J, or fourth or subsequent mRNA vaccine dose. These analyses preceded availability of the bivalent vaccine.

In terms of the approach for the primary analyses, a validated algorithm was used to identify SABs and ongoing pregnancies of 6—19 weeks gestation. The cases were assigned to a 28-day surveillance period based on the pregnancy outcome date. Exposures to a third mRNA COVID-19 vaccine dose in a 28-day window prior to the SABs were then identified. Ongoing pregnancies of 6—19 weeks gestation were assigned to 1 or more 28-day surveillance periods. Within a single 28-day surveillance period, the midpoint was assigned as the index date and exposures were identified in a 28-day window prior to the index date. For the primary analyses using generalized estimating equations, the odds of exposure to a third mRNA COVID-19 vaccine dose in the 28 days prior to SAB were calculated compared to the odds of exposure to a third mRNA COVID-19 vaccine dose among ongoing pregnancies in the 28 days prior to an index date. Secondary analyses were performed applying a 42-day exposure window and changing the exposure to any COVID-19 vaccine booster.

The primary analyses population included 112,718 unique pregnancies from November 1, 2021 through June 12, 2022. Of these, 14,226 ended in a SAB. Among ongoing pregnancies, 10.6% receive a third mRNA COVID-19 vaccine dose before 20 weeks gestation, and 6% of pregnancies ending in the SAB received a third mRNA COVID-19 vaccine dose while pregnant. The adjusted odds ratios for a third mRNA COVID-19 vaccine in the 28 days prior to SAB, overall and by vaccine type, are shown in this table:

	***aOR (95% CI)**
Primary analyses **3rd mRNA COVID-19 vaccine in 28-day window**	0.94 (0.86-1.03)
By vaccine type	
mRNA-1273, Moderna	0.93 (0.81–1.07)
BNT162b2, Pfizer-BioNTech	0.95 (0.84–1.07)

[65] Primary vaccine series: 2 mRNA COVID vaccine doses or 1 Janssen/J&J dose mRNA COVID-19 vaccines are mRNA-1273, Moderna or BNT162b2, Pfizer-BioNTech

For the primary analyses, receiving a third mRNA vaccine dose in a 28-day window was not associated with SAB. The adjusted odds ratio was 0.94 and the 95% confidence interval was 0.86 to 1.03. Results were similar when stratified by vaccine type. In terms of the adjusted odds ratios and 95% confidence intervals for the primary and secondary analyses, adjusting the exposure window from 28 to 42 days or expanding the booster definition from a third mRNA vaccine dose to any COVID-19 vaccine booster dose did not substantially change the findings.

The analyses presented on SAB and COVID-19 booster vaccines are part of a large portfolio of VSD work monitoring COVID-19 vaccine safety and pregnancy. This table offers an overview of the many ongoing VSD studies of this area and the status of this work:

Short title	Exposure	Outcome(s)	Status (as of 9/21/22)
Spontaneous abortion case-control surveillance	Primary vaccine series	Spontaneous abortion – based on automated data	Published in JAMA 9/2021 Presented at ACIP 9/2021
	Booster vaccination*		*Topic of presentation today*
Stillbirth and Spontaneous abortion case-control study	Primary vaccine series	Spontaneous abortion and stillbirth – based on chart review and expert adjudication	Chart reviews and expert adjudication of cases ongoing
Acute maternal outcomes (within 42 days of vaccination)	Primary vaccine series	Fever and other acute local and systemic reactions	Published in NEJM 7/2022
	Booster vaccination*		Analyses ongoing
Pregnancy complications and birth outcomes	Primary vaccine series	Gestational diabetes, hypertensive disorders of pregnancy	Analyses ongoing
		Small-for-gestational age, preterm birth	Published in MMWR 1/2022
		Birth defects, infant infections	Analyses ongoing
		Growth and developmental outcomes	Planning analyses – awaiting infants to reach 2 years of age

*Monovalent booster vaccines; bivalent booster vaccines can be evaluated in the future

Some of the studies have been disseminated previously through presentation or publication. For others, the analyses are ongoing or are awaiting infants to reach a critical age. The safety of the primary vaccine series of the monovalent boosters is currently being evaluated. Additional outcomes include stillbirth, fever and other local and systemic reactions, small for gestational age and preterm birth, pregnancy complications, major structural birth defects, and growth and developmental outcomes.

In summary, COVID-19 booster vaccination in early pregnancy was not associated with increased risk for SAB. The VSD is continuing comprehensive surveillance of COVID-19 vaccine safety and pregnancy. To date, no safety signals have been identified. Future studies will evaluate long-term outcomes and newer COVID-19 vaccines.

Updates on COVID-19 Vaccine Safety in Pregnancy from v-safe[sm]

Christine Olson MD, MPH (CDC/NCIRD) presented data from the v-safe[sm] COVID-19 Vaccine Pregnancy Registry, including describing the registry participant cohort and presenting preliminary data on pregnancy and infant outcomes. People who voluntarily enrolled in CDC's v-safe[sm] After Vaccination Health Checker indicated whether they were pregnant at the time they received a vaccine, or if they became pregnant after vaccination at later check-in points. Individuals reporting pregnancy were then called and screened for eligibility for the pregnancy registry. Eligibility was based on when they reported that pregnancy into v-safe[sm], meeting the age criteria of being ≥18 years of age, whether they were an English or Spanish speaker, and whether they were either pregnant at the time of vaccination or were vaccinated in a peri-

conceptional period (≤ 30 days before the first day of the last menstrual period before pregnancy). Eligible individuals were then consented for pregnancy registry enrollment and interviewed by phone at designated time periods over the course of their pregnancies, postpartum, and after the infant reached 3 months of age. Not all participants were interviewed during all trimesters of pregnancy, and they may have entered the registry at any point in this continuum. Some initial interviews were conducted after delivery occurred. Participants were also asked if they would consent to obtain medical records for the pregnancy and infants through 3 months of age. Pregnancy registry interviews began in January 2021 and were completed in August 2022. Medical record requests and reviews for select outcomes and conditions are still ongoing.

Over 65,000 participants reported a pregnancy into the v-safe[sm] After Vaccination Health Tracker during the eligibility period of December 2020—June 2021. Attempts were made to reach all potential participants, with about 60% being unreachable. Overall, 36% of potential participants were contacted and determined to be eligible for enrollment. Of these, 98% enrolled. In total, there are 22,953 participants enrolled and 15 participants contributed more than 1 eligible pregnancy. The distribution of vaccine type was 3% J&J, 39% Moderna, and 58% Pfizer BioNTech. This demonstrates that the majority of participants received one of the mRNA vaccines. This was due to the timing of the rollout of the vaccines and the lower uptake of the J&J vaccine. The mean age of participants is 33.9 years, with 45% reporting that they worked in healthcare and 79% describing themselves as non-Hispanic White. Among registered participants, the timing of the COVID vaccine that made the participants eligible for the registry is reasonably distributed across all pregnancy time periods. About 10% (N=2,245) of participants were vaccinated in the peri-conceptional period, about 28% (N=6,352) were vaccinated in the first trimester, about 40% (N=9,074) were vaccinated in the second trimester, and about 23% (N=5,192) were vaccinated in the third trimester.

To provide an overview of outcomes for the completed registry cohort, pregnancy outcomes are self-reported by registered participants with the exception of stillbirth. Self-reported stillbirths have been adjudicated and reclassified if needed based on medical records when available. Overall, the proportions of live births and fetal losses were similar by vaccine type. The proportion of registry participants reporting stillbirth was 2.45 per 1,000 live and stillbirths. This is lower than the background rate from the US National Vital Statistics System (NVSS) in which the stillbirth rate is 5.89 overall, of which 4.89 are among the non-Hispanic White population that is most similar to the v-safe[sm] cohort. To summarize the incidence of self-reported medical conditions, pregnancy complications, and infant outcomes by vaccine type, the incidence observed in the pregnancy registry was similar to or below available background rates. An analysis presented during a previous ACIP meeting identified no increased risk of SABs or miscarriage before 20 weeks of gestation among the registry participants.[66]

In an analysis of the first half of the registry cohort, major birth defects were reported for 429 or 3.5% of fetuses or infants. There was no statistical difference between those vaccinated in the first trimester and those vaccinated later in pregnancy after 20 weeks. All of the prevalence estimates fall within the 3% to 5% expected prevalence for major birth defects as reported in the literature. In an analysis of over 20,000 registered participants with pregnancies ending after 20 weeks of gestation, a comparison was made of the prevalence of multiple outcomes of interest (e.g., stillbirth, preterm birth, gestational hypertension, NICU admission, and maternal ICU admission) between registry participants who reported no SARS-CoV-2 infection during

[66] Lauren H Zauche, Bailey Wallace, Ashley N Smoots, Christine K Olson Titilope Oduyebo, Shin Y Kim, Emily E Petersen, Jun Ju, Jennifer Beauregard, Allen J Wilcox, Charles E Rose, Dana M Meaney-Delman, Sascha R Ellington, CDC v-safe Covid-19 Pregnancy Registry Team; 2021 Oct 14;385(16):1533-1535. doi: 10.1056/NEJMc2113891.

pregnancy with those participants who reported SARS-CoV-2 infection after being fully vaccinated. Other studies have reported an increased risk of poor pregnancy outcomes among unvaccinated pregnant people infected with SARS-CoV-2. Although the pregnancy registry does not include an unvaccinated control group, infection after full vaccination was not associated with an increased risk of those outcomes compared to those who are vaccinated and had no reported SARS-CoV-2 infection.

In conclusion, the VCF COVID-19 vaccine pregnancy registry adds to the accumulating evidence on the safety of COVID-19 vaccination during pregnancy. To date, the pregnancy registry has not identified any concerning safety signals, including any increased risks of adverse pregnancy-related outcomes for either the registry participant or the infant or any disproportionate outcomes by vaccine type or timing. Several findings reported during this session are from early analyses while data collection was ongoing. While early analyses will be replicated with the final full cohort of registered participants, there is no reason to expect that associations will change over time. For select participant and infant outcomes and conditions, the acquisition abstraction of medical records is still in progress. This effort, which takes additional time and care, will aid in confirming and or identifying conditions such as birth defects in cases where participant-reported information may have been insufficient in detail to make an accurate determination. CDC will continue to monitor the safety of COVID-19 vaccination during pregnancy, with an extended follow-up period through 15 months post-delivery or end of pregnancy. Follow-up calls are scheduled to begin in November 2022. Dr. Olson thanked the registry participants for generously sharing their time and information, as well as the many people who support the registry.

Effectiveness of Maternal COVID-19 Vaccination among Pregnant People and Infants

Katherine E. Fleming-Dutra, MD (NCIRD, CDC) presented an update on the effectiveness of maternal COVID-19 vaccination among pregnant people and infants. And as a reminder, CDC recommends that everyone stay up to date with COVID-19 vaccination, including all primary series doses and the most recent booster dose recommended for them by CDC. People ≥5 years of age are recommended to receive 1 updated bivalent mRNA booster dose. Staying up to date with COVID-19 vaccinations is recommended for everyone, including people who are pregnant, trying to get pregnant or who might become pregnant in the future, and people who are breastfeeding.

In terms of the composition of monovalent and bivalent COVID-19 mRNA vaccines, monovalent mRNA vaccines contain mRNA encoding for spike protein from the ancestral or original SARS-CoV-2 virus, while bivalent vaccines contain mRNA encoding for spike protein for both the ancestral strain and the Omicron BA.4/BA.5 variants. Because bivalent vaccines were first recommended on September 1, 2022, there has not yet been time to assess the effectiveness of bivalent boosters among pregnant people and infants. Therefore, the data shown during this session reflected monovalent vaccines.

The VISION Vaccine Effectiveness (VE) Network uses a test-negative design. This analysis assessed monovalent mRNA VE against COVID-19-associated ED and urgent care visits and hospitalizations.[67] Looking at monovalent VE for ED and urgent care visits occurring among pregnant people and non-pregnant women 18–45 years of age, Delta VE among pregnant people was high at 78% or above for 2 and 3 doses. Among non-pregnant women, the power

[67] Schrag et al. Estimation of COVID-19 mRNA Vaccine Effectiveness Against Medically Attended COVID-19 in Pregnancy During Periods of Delta and Omicron Variant Predominance in the United States JAMA Netw Open. 2022;5(9):e2233273. doi:10.1001/jamanetworkopen.2022.33273

was higher as evidenced by narrower confidence intervals. But the VE estimates and patterns are the same. Effectiveness was high, waned a little after 150 days after Dose 2, and was restored by a third dose. It is known that the Omicron variant can evade monovalent vaccine-induced immunity more than prior variants did. These estimates reflect the mismatch between the monovalent vaccine and the Omicron variant. As expected, VE for ED and urgent care visits was lower during Omicron predominance than it was during Delta predominance. Among pregnant people, effectiveness waned to non-significant or not different than 0 by 150 days after Dose 2, but was restored by a third dose. Similar patterns are observed among non-pregnant women with waning over time after Dose 2, restoration of effectiveness after a third dose, but then waning again over time after Dose 3. Looking at VE against hospitalization, VE was very high during Delta predominance at 98% to 99% among pregnant people and 90% and above among non-pregnant women. During Omicron predominance, the study had more limited power due to lower numbers of hospitalizations. Among pregnant people, VE at 7 to 119 days after Dose 3 was 94%. Among non-pregnant people, VE was 50% to 73%.

These data indicate that VE of monovalent mRNA vaccines for COVID-19-associated ED and urgent care visits and hospitalizations is similar among pregnant people and non-pregnant women. In the published paper by Schrag et al, VE also was similar when stratified by doses given during pregnancy to that of doses given before or during pregnancy. Thus, time since last dose likely affects VE for these outcomes more than whether vaccine doses were given before or during pregnancy. VE is lower during Omicron predominance compared to Delta predominance in both pregnant and non-pregnant people. This is likely due to a combination of factors, including mismatch between monovalent vaccine and the variant.

Transitioning to the effectiveness of maternal monovalent mRNA vaccination in prevention of hospitalization among infants 0─5 months of age, these data come from the “Overcoming COVID-19” platform that assesses the VE of maternal monovalent mRNA primary series given during pregnancy and prevention of hospitalization for COVID-19 infants ages 0─5 months of age. VE estimates are stratified by variant time period of Delta and Omicron predominance. The estimates are stratified by timing of the second vaccine dose at any time during pregnancy in the first 20 weeks or after 20 weeks. Most importantly, maternal COVID-19 primary series vaccination protected infants 0─5 months of age from hospitalization for COVID-19. Overall, protection was lower during Omicron predominance than during Delta. When VE was stratified by timing of vaccination during Delta, effectiveness estimates for hospitalizations were not significantly different. However, during Omicron predominance, vaccine given in the first 20 weeks did not show effectiveness in infants, but it did give protection if given after 20 weeks.

In summary, COVID-19 can cause severe disease in pregnant people and infants. COVID-19 vaccination of pregnant people is safe for pregnant people and infants. Maternal monovalent mRNA COVID-19 vaccination protects pregnant people and infants 0─5 months of age from COVID-19, including from severe disease and hospitalization. Monovalent VE was lower during Omicron predominance when there was a mismatch between the vaccine and the predominant circulating variant. Thus, bivalent vaccines have the potential to improve protection against circulating new Omicron variants. This is why CDC recommends that everyone, including people who are pregnant, trying to become pregnant, may become pregnant, and who are breastfeeding should stay up to date with COVID-19 vaccines and get the recommended updated bivalent booster when eligible. As a reminder, CDC’s guidance on staying up to date with COVID-19 vaccines and co-administration of vaccines applies to everyone, including pregnant people. COVID-19 vaccines may be administered without regard to timing of other vaccines. This includes simultaneous administration of COVID-19 vaccine and other vaccines,

such as influenza, and Tdap (pertussis) vaccine on the same day. There are additional considerations if administering an orthopoxvirus vaccine that can be found on CDC's website.

Discussion Points (Ellington, Kharbanda, Olson, Fleming-Dutra)

Dr. Sanchez inquired as to whether any data on monoclonal use during pregnancy have been captured in the VSD or v-safe[sm].

Dr. Kharbanda responded that there are no data on this in the VSD vaccine safety evaluations. Dr. Olson replied that this information is not being collected in v-safe[sm], which has been focused on COVID-19 vaccines.

Regarding v-safe[sm], Dr. Cineas asked whether there are any subgroup analyses of outcomes for the 45% of participants who were healthcare workers compared to participants who were non-healthcare workers.

Dr. Olson indicated that this has not yet been assessed, but they are still working on the further data evaluation of Phase 1 of the registry. This includes the interviews that were conducted during pregnancy and the 3 to 4 months following pregnancy. Subgroup analyses have not been done and it is not clear whether there will be adequate numbers to be able to report out in a manner that will be helpful. However, they have always been aware that a relatively large proportion of participants came from the healthcare field due to their early access to the vaccines based on the staged rollout. Over time, that has steadily declined and the cohort has become more diverse. HCP are still over-represented within the cohort.

Dr. Poehling summarized that her understanding was that under Omicron predominance, the rates of COVID-19 in children 0–5 months of age was getting close to those ≥65 years of age and three quarters of them are healthy. Moms who get COVID-19 during pregnancy have an increased risk of being admitted to the ICU themselves. There is an increased risk of stillbirth, preterm delivery, and neonatal death. It is safe for moms to get the vaccine during pregnancy and the outcomes are much better than for moms who get COVID-19. There is protection for the mom and infant.

Regarding Slide 26 in Dr. Kharbanda's presentation, Dr. Daley emphasized that these are complicated decisions for pregnant women among many other things they are considering. What he has heard from speaking with women is that they are most concerned with risk and safety. At 2.5 years into the pandemic, it is important to be able to say that safety is being exhaustively studied and the results are very reassuring. He would hope that would provide reinsurance and increased vaccination rates. He found these data compelling, but wondered how it could be communicated more broadly in order to increase coverage.

Dr. Long pointed out that there are limited therapeutics for children 0–5 months of age who have coronavirus infection. These data should be very helpful in promoting vaccines as the best way to protect babies from death due to coronavirus. She expressed an interest in knowing what percentage of mothers of the children 0–5 months of age with hospitalization, ICU, and death were vaccinated.

Dr. Sanchez stressed that there is still a lot of work to be done with only 48% of women having received the primary series. He asked whether any data were captured on multisystem inflammatory syndrome in children (MIS-C), which he thinks should be included in terms of pregnancy and neonatal outcomes. He was not surprised about the increase during the

Omicron era, because there also was higher transmission to normal newborns during the summer when Omicron was circulating. Transmission previously had been only from mother to normal newborn or in the first few days had been only 1% and went up to 5% or 6% in these babies.

Regarding MIS-C, Dr. Olson clarified that the death counts came from NVSS. If COVID-19 was listed as a potential cause of death on the death certificate, that was captured in the death counts. CDC separately conducts surveillance for MIS-C. While the MIS-C can occur in this age group, the MIS-C experts were unable to join this session but can follow up with numbers specific to that group after the meeting.

Referring to Slide 13, Dr. Long noted that the words "had COVID-19 symptoms" were used specifically to mean COVID lower respiratory tract-like symptoms. When she thinks of adult COVID disease, she thinks of sepsis, fever, hypothermia, apnea, or multi-system inflammatory syndrome. She has never seen this on the pediatric age group.

Dr. Ellington replied that a number of symptoms are captured in that particular group of COVID-19 symptoms.

Dr. Hamid confirmed that there is a very long list of symptoms and nonspecific symptoms but noted that she did not have it with her.

In an effort to connect what is known about the VE of vaccinating mothers for protection of children 0—5 months of age, Dr. Daley referred to Slide 62 showing 265 deaths among children 0—5 months of age involving COVID-19, which represents 0.5% of all deaths in this age group. Without going too far beyond what the studies show, it seemed to him that there is at least high potential for these neonatal deaths to be vaccine-preventable.

Ms. Hayes (ACNM) pointed out that anytime adverse pregnancy outcomes are discussed, it is very important to provide the background in order to keep the data relevant. She thought Dr. Brooks' question about whether this vaccine is protective against stillbirth and other adverse outcomes was a great question. Referring to Slide 9 from Dr. Ellington's presentation, Ms. Hayes said her experience was that 77% of pregnant people are not vaccinated, so she was curious about how this survey was done in terms of how it was sent out and to whom.

Dr. Ellington clarified that 2 data sources were provided to corroborate the 2 rates. The first survey was the NIS-ACM adult COVID module within which there are questions that are stratified by whether the woman is pregnant, recently pregnant, trying to become pregnant, or not in those categories. The exact methods on how the NIS-ACM is implemented can be found at https://www.cdc.gov/vaccines/imz-managers/coverage/covidvaxview/interactive/adults.html. It is a survey implemented among the adult population that is weighted to be nationally representative. The second data source is through electronic health systems. These are 2 different ways to ascertain what is thought to be the current overall estimated coverage of vaccination in pregnancy. While the sources are not the same, they are similar in terms of their estimates. Certainly, there are things that affect these estimates with the first data source such as response rates. Those who were unvaccinated may be less likely to respond to surveys, so there could be some bias in the estimate. The second data source supports that overall, receipt of the primary series among pregnant people is quite high and it is not necessarily that they received the vaccination during pregnancy. Overwhelmingly, these people all were vaccinated before they became pregnant. The additional datapoint is the number of persons who received the primary series. Multiplying the number who completed the primary series (72%) by the

number of people who were boosted (60%) resulted in the 43% of pregnant people who have received primary series plus a monovalent booster. There certainly are limitations to both data sources in terms of representativeness and what the response rate might be for the survey.

Ms. Hayes (ACNM) expressed interest in knowing the percent of public and private insurances in this population. She has worked largely with pregnant people on Medicaid. Given that they are highly unvaccinated, she found these data to be somewhat questionable.

Dr. Ellington indicated that there are several publications with these data that provide the breakdown of the insurance coverage for the participants, which they could provide.

Dr. Meaney-Delman added that CDC has been trending this over time and saw during the Delta period, especially when CDC released the HAN and ACOG, Society for Maternal-Fetal Medicine (SMFM), and CDC promoted vaccines in a highly targeted way during the Delta period, there was an increase. Therefore, maternal immunization appears to have trended in the right direction. She agreed that there is still a lot of work to do to promote maternal immunization with vaccines that are known to be safe. In addition, she thought Dr. Daley's point was well taken in terms of vaccine-preventable deaths among children in addition to women. In August 2021, a large number of pregnant people were admitted to the ICU and many of them died. There certainly are vaccine-preventable deaths for mothers, which is supported by good data. Nevertheless, it is still very difficult to promote acceptance in this population. Hopefully, this will help to galvanize more support. There are significant differences in terms of various factors, such as insurance coverage, race, and ethnicity. Both data sources allow for estimation by different race and ethnicity groups and there are significant disparities.

Dr. Young asked whether the infant outcome data were stratified by whether an infant was breastfed and if so, whether any difference was seen. If not, she suggested asking this question.

Speaking to the VE study in Overcoming COVID, Dr. Fleming-Dutra indicated that there was a lot of missing information for the infants on breastfeeding, so it was not possible to control for this variable. From the VSD, there is one study that will include breastfeeding information. That study is following up infant infections after maternal vaccination.

Dr. Romero emphasized the importance of CDC prioritizing pregnant people to receive their immunizations and boosters. There are data to show that this is safe, effective, and protective for the mother and infant. As Secretary of Health for his state, he heard of many cases of women who wound up in the ED on a ventilator for long periods of time and some of them died. This can be prevented.

Ms. McNally requested that someone identify the best time to get vaccinated during pregnancy.

Dr. Fleming-Dutra emphasized that pregnant people and everyone else should stay up to date with COVID-19 vaccinations. The best time to get vaccinated with the bivalent booster is when one is eligible. As shown by the data, VE during Omicron was lower than it was with previous variants. This likely had to do with mismatch of the monovalent vaccine for the circulating variants.

Dr. Meaney-Delman added that it also is important to remember that a healthy mother is needed in order to have a healthy baby.

Referring to Slide 49 showing the protective effects to the infant during the first 5 months of life, Dr. Long asked whether these women were immunized during pregnancy.

Dr. Fleming-Dutra confirmed that these were pregnant people. These mothers were immunized during pregnancy. VE estimates were stratified by the timing of the second dose during pregnancy in terms of whether it was before or after 20 weeks of gestation.

Dr. Long raised this question to the WG to think about, given that vaccine protection is not thought to be long-lived in the population and there will need to be consideration of boosting during pregnancy.

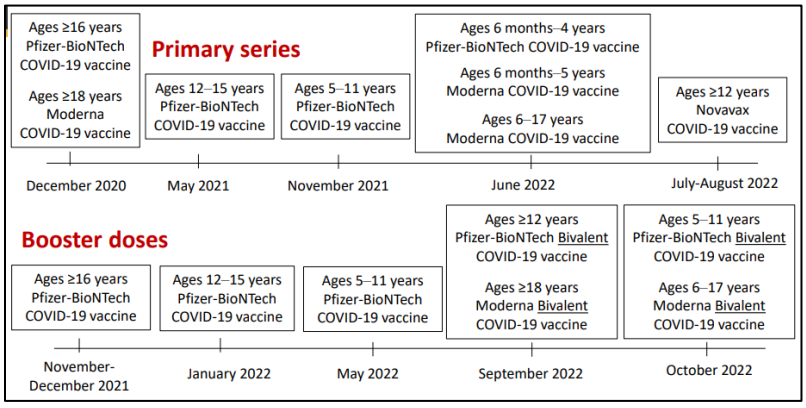
Dr. Oliver indicated that continuing to assess the safety and effectiveness data during pregnancy and among infants is a top priority of the WG. They wanted to get this information out to make everyone aware that COVID is a preventable disease in pregnant people and infants right now. It is important to do what they can with the vaccines and authorizations currently in place. There is still a long list of topics the WG would like to discuss in terms of ways to optimize vaccine recommendations in the future.

On behalf of ACOG, Dr. Eckert reported that ACOG continues to work, and will work even harder, to get the message out to all of its providers that only half of pregnant individuals are vaccinated and to stress the benefit to the mom and the baby. Many practitioners have cared for these women in ICUs and have had to make the hard choices of delivery early, et cetera. She expressed gratitude for shining the spotlight on these data.

Dr. Lee reiterated that with full confidence as a provider, she felt that she could strongly recommend this vaccine to her pregnant patients who are about to have children.

COVID-19 Vaccines in Children

Sara Oliver, MD MSPH (NCIRD, CDC) provided an update on COVID-19 vaccines in children. Since the past winter's peak Omicron surge and throughout 2022, children 6 months–4 years of age have had the highest hospitalization rates.[68] Notably, these pediatric age groups are vaccine-eligible. The following graphic provides a timeline of recommendations for pediatric COVID-19 vaccines and depicts how vaccine policy has evolved over time:



[68] COVID-NET, https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html. Accessed 10/12/2022

Dr. Oliver recapped booster dose recommendations for children that have been discussed during previous ACIP meetings. These included recommendations for monovalent Pfizer-BioNTech COVID-19 vaccine for adolescents 12–15 years of age that were informed by safety data from Israel, waning antibody titers, and VE after a primary series in the setting of Omicron and during the peak of the winter Omicron surge.[69] Recommendations for children 5–11 years of age were based on a clinical trial for booster doses in this age group and post-authorization safety data for the primary series.[70] The booster doses in children 5—11 years of age achieved antibody levels higher than what was seen after the primary series. The reactogenicity after a booster dose was similar to what was seen after a primary series. The rates of myocarditis after a primary series in children 5—11 years of age were considerably lower than rates seen in adolescents.

For the monovalent Moderna COVID-19 vaccines, the booster dose was studied in approximately 2,600 children adolescents with a 50mcg booster studied in 1,349 adolescents 12–17 years of age and a 25mcg booster dose in 1,294 children ages 5–11 years. There was one SAE in a child in the 5–11 years of age group that was unrelated to the vaccine and there were no SAEs in the adolescents 12–17 years of age group. Reactogenicity symptoms were similar to what was seen for booster doses in other age groups. Antibody levels after the booster dose were 4 to 5 times higher than what was seen after the primary series. Based on these data, the FDA authorized and CDC recommended Moderna boosters for children 6—17 years of age.

As discussed during the September 1, 2022 ACIP meeting, data were reviewed to inform the bivalent mRNA COVID-19 vaccines for all individuals ≥5 years of age who were previously recommended to receive a monovalent booster dose. This included post-authorization VE and safety data from over 600 million mRNA vaccine doses that were administered; clinical data from the bivalent COVID-19 vaccines in over 1,700 people, including antibody studies and antigenic cartography data; and modeling data.[71] The ACIP has discussed myocarditis and COVID-19 vaccines numerous times. The risk of myocarditis and pericarditis has been identified after mRNA COVID-19 vaccines. The risk is rare and is primarily observed in adolescent and young adult males within the first week after receiving the second dose of a primary series or the booster dose of the mRNA COVID-19 vaccine. It is known from data previously presented to ACIP that most individuals with myocarditis have fully recovered at follow-up.[72] The risk of adverse cardiac events were 1.8 to 5.6 times higher after SARS-CoV-2 infections than after the mRNA COVID-19 vaccine among males 12—17 years of age.[73] It also is known that an interval of 8 weeks between the vaccine doses may further lower the myocarditis risk.

Understanding the balance of benefits and risks to inform vaccine policy is critical. It is important to make sure that vaccine policy decisions always take the entirety of the data into account, including the benefits of the vaccine and the risk that the infection poses.

ACIP has reviewed the balance of benefits and risks regularly as follows:

- ❑ Primary series for adolescents and young adults: June 23, 2021
- ❑ Primary series for individuals 16-29 years: August 30, 2021
- ❑ Booster doses for individuals ≥18 years: September 23, 2021

[69] https://www.cdc.gov/vaccines/acip/meetings/slides-2022-01-05.html
[70] https://www.cdc.gov/vaccines/acip/meetings/slides-2022-05-19.html
[71] https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-09-01/08-COVID-Oliver-508.pdf
[72] https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-02-04/04-COVID-Kracalic-508.pdf
[73] https://www.cdc.gov/mmwr/volumes/71/wr/mm7114e1.htm?s_cid=mm7114e1_w

- ❑ Booster doses for adolescents 12-15 years: January 5, 2022
- ❑ Booster doses for children 5-11 years: May 19, 2022
- ❑ Bivalent booster doses for individuals ≥5 years: September 1, 2022

Each time ACIP has evaluated the benefits and risks of these mRNA COVID-19 vaccines, ACIP has determined that the benefits outweigh the risks.

CDC and FDA have conducted rigorous post-authorization monitoring for COVID-19 vaccines since authorization starting in January 2021. There have been 22 ACIP meetings focused on COVID vaccines. VE data have been presented during 11 of those meetings and safety data has been presented during 21 ACIP meetings. CDC evaluates VE through multiple observational studies, employing various methods and using information collected through different surveillance platforms, EHRs, or prospective studies. COVID-19 vaccines continue to undergo the most comprehensive and intense safety monitoring in US history. These data are routinely presented to ACIP, currently averaging at least 1 ACIP meeting a month during which both safety and effectiveness data are presented and discussed. For example, data for the monovalent COVID vaccines were presented in September 2022 for the VE data for EDs visits in pediatric age groups.[74] Post-authorization VE for the bivalent vaccines will be presented during upcoming ACIP meetings.

During the September 1, 2022 ACIP meeting, data were presented for mRNA COVID-19 vaccine safety of primary series vaccination in children 6 months–5 years of age. Initial safety findings of both mRNA COVID-19 vaccines (Pfizer-BioNTech and Moderna) are consistent with those observed in the clinical trials. Systemic and local reactions are commonly reported AEs. Vaccination errors are also being reported to VAERS. There have been no unexpected safety findings to date and there is no evidence of an increased risk for myocarditis following mRNA COVID-19 vaccination in children 6 months–5 years of age. Overall, this is a reassuring safety profile.[75]

In terms of COVID-19 vaccine uptake[76] among children and adolescents, 1.4 million children 6 months─4 years of age have had at least 1 COVID vaccine. That is under 7% of children in this age group. Among children 5─11 years, 11 million first doses have been administered. This represents 38.6% of children in this age group. A total of 1.4 million booster doses have been administered, with 15.6% of children in this age group with a primary series. Among adolescents 12–17 years of age, 18 million (71.1%) have received a first dose and 4.5 million (29.3%) have received a booster dose. To put vaccine coverage in the context of other age groups, overall vaccine coverage is the lowest among the pediatric age groups.

To summarize the existing COVID-19 vaccine recommendations that have been discussed during previous ACIP meetings, people ages 6 months and older are recommended to receive a primary series of any age-appropriate FDA-approved or FDA-authorized monovalent COVID-19 vaccine. People ages 5 years and older are recommended to receive 1 bivalent mRNA booster dose after completion of any FDA-approved or FDA-authorized monovalent primary series or previously received monovalent booster dose(s). Monovalent mRNA vaccines are no longer authorized as booster doses. As mentioned earlier in the day, Novavax is now allowed in some populations for a booster dose. Homologous (the same) and heterologous (mix and match) booster doses are allowed. There is no preference provided that the vaccine is age-appropriate.

[74] CDC, preliminary unpublished data. Individuals with prior infections excluded.
[75] https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-09-01/05-COVID-Shimabukuro-508.pd
[76] CDC COVID Data Tracker, https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends Accessed 10/18/2022

For children 5 years of age, only the Pfizer bivalent booster is authorized. For everyone ≥6 years of age, both Pfizer and Moderna bivalent booster doses are options.

Looking in more detail at the schedule for children and adolescents who are not moderate to severely immunocompromised, children 6 months–4 years are recommended to receive either a 2-dose Moderna primary series separated by 4 to 8 weeks or a 3-dose Pfizer-BioNTech primary series with Doses 1 and 2 separated by 3 to 8 weeks and Dose 2 and 3 separated by at least 8 weeks. Children ages 5–11 years are recommended to receive either a 2-dose Moderna or Pfizer-BioNTech primary dose, with doses separated by 4 to 8 weeks if Moderna and 3 to 8 weeks if Pfizer. A bivalent booster dose is recommended at least 2 months after completion of the primary series or the last monovalent booster given. For children 5 years of age, only a Pfizer-BioNTech booster can be given. For those 6–11 years of age, either Pfizer or Moderna can be given. Adolescents 12–17 years of age are recommended to receive a 2-dose primary series of either Moderna, Pfizer, or Novavax. The primary series is separated by 4 to 8 weeks if Moderna and 3 to 8 weeks if Novavax or Pfizer. Regardless of the primary series, either a Pfizer or Moderna bivalent booster is recommended at least 2 months after completion of the primary series or the last monovalent booster.

In terms of more details regarding the vaccine schedule for children and adolescents who are moderate to severely immunocompromised, children 6 months–4 years of age are recommended to receive a 3-dose Moderna primary series for which Doses 1 and 2 are separated by 4 weeks and Doses 2 and 3 separated by at least 4 weeks, or a 3-dose Pfizer-BioNTech primary series for which Doses 1 and 2 are separated by 3 weeks and Doses 2 and 3 separated by at least 8 weeks. Children 5–11 years of age are recommended to receive a 3-dose Moderna or Pfizer primary series in which Doses 1 and 2 are separated by 3 weeks of receiving Pfizer or 4 weeks for Moderna and Doses 2 and 3 separated by at least 4 weeks for both. The bivalent booster recommendations are the same for non-immunocompromised children, with a bivalent booster recommended at least 2 months later. For children 5 years of age, only Pfizer is recommended. Adolescents 12–17 years of age are recommended to receive either a 3-dose Moderna or Pfizer primary series. Doses 1 and 2 are to be separated by 3 weeks if Pfizer or 4 weeks for Moderna. Doses 2 and 3 are to be separated by at least 4 weeks and the 2-dose Novavax primary series should be separated by 3 weeks. A bivalent booster is recommended at least 2 months after completion of the primary series or prior monovalent booster dose.

These tables that include authorized dose type, vials/labels/cap colors, composition, and dose highlight the complexity of pediatric COVID-19 vaccines and the need for continued work to streamline the COVID program and support frontline vaccine providers who are engaged in the monumental effort of vaccinating children and adolescents:

Pfizer-BioNTech COVID-19 vaccines	Ages 6 months–4 years	Ages 5–11 years (monovalent)	Ages 5-11 years (bivalent)	Ages ≥12 years (monovalent)	Ages ≥12 years (bivalent)
Authorized dose type	Primary	Primary	Booster	Primary	Booster
Vial cap color	Maroon	Orange	Orange	Gray	Gray
Composition	Monovalent	Monovalent	Bivalent	Monovalent	Bivalent
Dose	3 mcg	10 mcg	10 mcg	30 mcg	30 mcg

Moderna COVID-19 vaccines	Ages 6 months–5 years	Ages 6–11 years	Ages ≥6 years	Ages ≥12 years
Authorized dose type	Primary	Primary	Booster	Primary
Vial cap color	Dark blue	Dark blue	Dark Blue	Red
Label border color	Magenta	Purple	Gray	Light blue
Composition	Monovalent	Monovalent	Bivalent	Monovalent
Dose	25 mcg	50 mcg	6–11 years: 25 mcg ≥12 years: 50 mcg	100 mcg

In summary, COVID-19 vaccination is the single best way to protect people from serious COVID-19 illness. COVID-19 vaccines continue to be effective in reducing the risk of severe disease, hospitalization, and death, including against the currently circulating Omicron variants. However, many children have not yet initiated a COVID-19 vaccine primary series. Work continues to ensure that all eligible children are able to get vaccinated. The benefits of COVID-19 vaccination outweigh the known and potential risks, including the very small risk of myocarditis or pericarditis. Over 30 million children and adolescents have received at least 1 COVID-19 vaccine dose. While that is great progress, there is still much work to do to increase coverage among children. Incorporation of COVID-19 vaccines in the Immunization Schedule and the VFC Program is an important step toward inclusion of COVID-19 vaccines in a routine vaccination program. Details of implementation for the COVID-19 vaccine VFC program will require ongoing work, but the ACIP vote allows the progress to begin. While it is not the finish line—it is a start. The VFC vote will allow uninsured and underinsured children to have access to COVID-19 vaccines at a time in the future when the vaccine transitions to a commercial market. Now and in the future, equitable access to COVID-19 vaccines for all ages and populations remains critically important.

Discussion Points

Dr. Kotton observed that while children ≥12 years of age who are basically receiving full-dose vaccines and the immunocompromised are supposed to get 3 doses of mRNA in the primary series, it recently came to her attention that many pharmacies no longer have monovalent mRNA vaccine and that some of them in her region have shipped monovalent vaccine back. Given that, she inquired as to what the recommendation would be in order to give a full primary series if monovalent is not available and only bivalent vaccine is available.

Dr. Oliver clarified that at this time, the primary series is only authorized to be a monovalent product. CDC is aware that this is an emerging issue with the transition to the bivalent supply. The agency is working with vaccine deliverers, including pharmacies and health departments, to make sure that there are not pockets where there is no monovalent vaccine. Those who run into an issue potentially should contact the health department or local pharmacy. CDC is conveying to jurisdictions to keep some supply of the monovalent in stock because there are people who still need that product at this point.

Dr. Long acknowledged that there are a lot of strategies being considered for the next generation of vaccines, but wondered whether it was anticipated that there would be a bivalent primary series and if so, what the timeline would be. Although fewer adults are getting immunized initially, all children are, so it seems that a bivalent dose would be beneficial.

Dr. Oliver said that while there is not a specific timeline, studies are ongoing. This topic is on the list of presentations and discussions. As soon as data are available, they will be presented to the ACIP.

Dr. Lee emphasized that according to the slides, barely 5% of children ≤5 years of age have received their primary series. This means that there is an opportunity to provide 95% with a potential bivalent primary series. Her hope is that this will continue to be prioritized because it is a great opportunity right now that has passed for most adults.

Dr. Long stressed that Omicron has changed the landscape for pediatric hospitalizations and deaths. Unfortunately, the safety issue in the very young arose and got a lot of legs from misinformation that she thinks has made people decide they will "wait and see" for their children. They will take the risk for themselves, but they will not take the risk for small children. It is important to get the message out that it is not just the saving of a couple of days of a cold, but that COVID is a serious illness in children and there is an available vaccine and they should have it.

Dr. Daley added that he has been tremendously worried about the complexity of the program, including at the primary care and immunization clinic delivery sites. Even though he is actively involved in the WG, it is difficult to know the timeframe. It is important to work closely with the FDA and vaccine manufacturers to stress that in order to improve and simplify the schedule, it is important to understand what requires primary clinical trials data versus what can be inferred. This is not simply about the need for more education of frontline providers. In his mind, that is the wrong answer. Even though that is a part of the solution, there needs to be a way not to have a special row in every table for children 5 years of age. If moving toward a bivalent primary series and a clinical trial is needed, he asked whether those studies are or will be done. He emphasized the necessity to be specific about what clinical trials data are needed, who is or will be conducting those studies, and when the results will be presented to the FDA for review and the ACIP for deliberation.

VFC Vote: Vaccines to Prevent COVID-19 Resolution

Dr. Jeanne Santoli (CDC/NCIRD) reminded everyone that on November 2, 2021, CDC endorsed the recommendation for the vaccination of children 5—11 years of age. This was the first pediatric COVID-19 vaccination for younger children. It has been 351 days since that event, or just less than a year. On June 21, 2022, there was a rollout of COVID-19 vaccine for children less than 5—6years of age. It has been 120 days since that rollout. Dr. Santoli emphasized that the world was moving at lightning speed because of ACIP's work. She indicated that the purpose of this resolution was to add vaccines for the prevention of COVID-19 to the VFC program, that the eligible groups include all children aged 6 months through 18 years, and that the recommended schedule, dosage, intervals, contraindications, and precautions are as follows:

Recommended Schedule, Dosage, and Intervals
COVID-19 vaccines are either authorized under Emergency Use Authorization (EUA) or approved under a Biologics License Application (BLA) are to be administered according to the most recent age- and vaccine-appropriate schedule included in CDC's Interim Clinical Considerations for COVID-19 vaccines (https://www.cdc.gov/vaccines/covid-19/ clinical-considerations/covid-19-vaccines-us.html).

Recommended Dosage
Dosage information is available online at: COVID-19 Vaccines | FDA.

Contraindications and Precautions
Contraindications and precautions are available in CDC's Interim Clinical Considerations for COVID-19 vaccines (https://www.cdc.gov/vaccines/covid-19/clinical- considerations/covid-19-vaccines-us.html).

Dr. Santoli emphasized that it is very important to make sure that everyone is aware of what this VFC resolution is for and how it is timed somewhat differently than VFC resolutions usually are. COVID-19 vaccines will not be available through the VFC program immediately following the passage of this resolution because they remain available for all Americans under the US Government (USG) National COVID-19 Response. Following the passage of this resolution, CDC will begin some additional necessary steps to award contracts for COVID-19 vaccines. Once COVID-19 vaccines are commercialized and no longer available under the USG's National COVID-19 Response, VFC providers will be able to order vaccines through the VFC program. The timeline for commercialization of COVID-19 vaccines in the US has not been finalized. She then presented the following language for ACIP discussion and a vote:

Approve the Vaccines for Children (VFC) resolution for COVID-19 vaccines.

Discussion Points

Dr. Romero stressed that this is not a policy change, nor is it a mandate for the use of the vaccine. Instead, it is a way to ensure access to this vaccine for children who do not have insurance. CDC does not make recommendations for school attendance. It is a state prerogative to determine which vaccines are required for school attendance, which is completely separate from the VFC Program.

Dr. Kotton asked whether there are vaccines that are currently recommended for children that are not covered by the VFC.

Dr. Wharton indicated that travel vaccines are not routinely included in the VFC Program.

ACIP recently voted for the cholera vaccine for children who were traveling to areas with active cholera transmission, and there was not a VFC vote for this vaccine.

Ms. McNally asked whether availability of COVID-19 vaccine through the VFC Program would still be covered under the Countermeasures Injury Compensation Program (CICP) or of it would move to coverage under the Vaccine Injury Compensation Program (VICP).

Dr. Wharton indicated that the VFC vote would not impact inclusion in the CICP. In addition, specific steps must be followed for a vaccine to be added to the VICP. Inclusion in VFC is not part of that process.

Dr. Hogue (APhA) asked whether there was a rough idea of when most of the monovalent pediatric approved vaccine currently available in the marketplace would expire and if there were any insights into when the commercial program would begin. Uptake has slowed and manufacturers are going to have to have some incentive to produce primary series vaccine.

Dr. Meyer from CDC's Immunization Services Division (ISD) indicated that a large proportion of monovalent mRNA vaccine stock is expected to expire over the next couple of months. However, there are some unknowns in terms of the availability of bivalent mRNA vaccines for primary series, whether the expiration dates could be extended, and several other issues. These are expected to be worked out over the next couple of months. There is still a sufficient supply of monovalent mRNA vaccines. While CDC is aware that some locations have less supplies of these vaccines, the vast majority of people in the US live within 5 miles of a site that carries the mRNA vaccine.

Dr. Hogue (APhA) expressed concern that as COVID vaccines for children and adolescents move to the commercial market, less than 150 pharmacies are approved VFC providers across the US. From a policy standpoint, CDC and state departments of health should take this into consideration going forward. This raises concerns about adolescent patients perhaps not getting immunized. Pharmacies offer a good option for getting vaccinated and pharmacists can advocate with patients and parents for their need for a primary care wellness visit from a PCP at the time they get the immunization.

Dr. Duchin reminded everyone that in June 2021, the National Vaccine Advisory Committee (NVAC) produced a report with recommendations for advancing immunization equity. That report recognizes that immunization equity is a long-standing and persistent barrier to immunization uptake for almost all of the recommended vaccines. Underlying systemic barriers and biases in the immunization system exist and need to be removed to create a truly optimal health-for-all system. A recent publication in "Health Affairs" is a reminder that since its enactment, the VFC has lifted immunization rates across all children, significantly reducing financial and racial inequities in childhood immunization rates. Its successes have been measured not only in health care access, but also in health outcomes in terms of the prevention of millions of cases of serious diseases, including hospitalizations and deaths. Net savings to insurers have been estimated in the billions of dollars, while societal savings from the reduced impact of preventable disease are in the trillions of dollars. Black, Hispanic, and Asian community members who are adults have lower vaccination rates than Whites for all recommended adult vaccines. For example, adults with health insurance have vaccination rates 2 to 5 times higher than people without health insurance for influenza, shingles, HPV, and other diseases. With respect to this session's discussion about the VFC program for COVID-19 vaccines, he wanted to highlight the NVAC recommendation and the fact that a vaccines-for-all program is needed for children and adults. A vaccines-for-all programs should be created and operated in parallel with the VFC Program that could provide vaccines at no cost to the recipient regardless of their age so that financial barriers to both COVID-19 vaccines and all other ACIP-recommended routine vaccines are removed.

Dr. Loehr strongly second Dr. Duchin's recommendation, which he thought was a wonderful idea.

Motion/Vote: COVID-19 Vaccines for Children VFC Resolution

Dr. Poeling made a motion for ACIP to approve the Vaccines for Children (VFC) resolution for COVID-19 vaccines as written. 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:	Bahta, Bell, Brooks, Chen, Cineas, Daley, Kotton, Lee, Loehr, Long, McNally, Poehling, Sanchez, Shah, Talbot
0 Opposed:	N/A
0 Abstained:	N/A

PUBLIC COMMENTS

Overview

The floor was opened for public comment on October 19, 2022 at 3:30 PM ET. Given that many more individuals registered to make oral public comments than could be accommodated during this meeting, selection was made randomly via a lottery. Dr. Lee provided a gentle reminder that the ACIP appreciates diverse viewpoints that are respectful in nature and issue-focused. The comments made during the meeting are included in this document. Members of the public also were invited to submit written public comments to ACIP through the Federal eRulemaking Portal under Docket Number ID CDC-2022-0111. Visit http://www.regulations.gov for access to the docket or to submit comments or read background documents and comments received. While public comments were heard prior to the pneumococcal and COVID vaccine votes, the votes were included with the session presentations for ease of reading.

Public Comments

Dr. David Wiseman
Synechion

Thank you very much. CDC's and FDA's extension of the bivalent boosters to young children without VRBPAC or ACIP votes exudes regulatory steamrolling that avoids questions about extrapolations from data described by FDA as preliminary, imprecise, and potentially unstable. The use of non-scientifically established immunobridging data per FDA, the relevance of extinct Wuhan and BA.1 strains, and BA.4/5 data are based on as few as 8 mice. CDC asserts the FDA says that these vaccines are safe and effective. No. The EUA standard is "may be effective," which FDA has lowered further. FDA has introduced a 2-month boost interval, likely due to evidence of negative efficacy, by 3 months. Does this signify immunological harm? ACIP's efforts to revise this interval were rebuffed despite other examples of CDC modifying FDA decisions. mRNA vaccines are not flu vaccines, which are not gene therapies that turn your body into a factory for a toxic spike protein. Questions asked by VRBPAC's Dr. Portnoy and ACIP's Dr. Sanchez about the locus and duration of spike production and crossing the placenta have been repeatedly evaded. FDA's guidance on variant vaccines applies to monovalents made by a prototype process. Bivalent production raises significant QA, safety, and efficacy implications. At the last ACIP meeting, Moderna revealed that the 2 mRNAs in their bivalent product generate heterotrimers. Is their vaccine tetravalent with 2 homotrimers and 2 novel heterotrimers with unstudied pharmacology and toxicology? To date, pregnancy discussion spotlights CDC's recommendations that circumvent manufacturer's off-label claims outside of FDA-approved instructions stating that the data are insufficient to inform vaccine risk in pregnancy. If the data are robust, let FDA modify the label. More concerning are 2 VSD studies, 1346 and 1345, including some of today's presenters, which stated pertinently now that pregnancy is not a contraindication, there is an urgent need to monitor the safety of these vaccines during pregnancy. You cannot recommend a product saying it is safe without informing patients of the urgent need to study its safety and seek to waive the requirements for informed consent. Alarmingly, since the conditions appear to have been created, where not only pregnant women participated in the study without their knowledge, they may have been coerced to do so by federal and other mandates. Along with CDC's ignoring a safety signal study by NIH, scientific standards have been eroded beyond recognition and ethical standards may have gone the same way. A more robust discussion of the safety and efficacy of these products must

occur, including before they are added to the VFC program. ACIP members, please demand answers. Thank you for your work.

Ms. Katherine Falk
Parent and Vaccine Advocate

Hi. Good afternoon. I am Katherine Falk, a parent and vaccine advocate in Oakland, California. I see you have a lot of business to get through this week and thank you for all that you do. I would like to focus on a portion of your agenda concerning the Vaccines For Children program. VFC is a valuable tool for ensuring that children have access to vaccines regardless of their family's insurance status or ability to pay. In the disruption of the pandemic and the economic turmoil of rapid inflation, this program is more important than ever. Routine vaccination rates slipped somewhat during the pandemic in the United States, and it's crucial to get back on track, especially now that most pandemic precautions such as masking have been dropped and emergency funding for COVID-related expenses is nearing its end. For these reasons, I strongly support the addition of the COVID-19 vaccine to the list of routine childhood vaccines that VFC will pay for. Learning to live with COVID means ensuring all children are protected from it, and making sure money isn't an obstacle is so important for families. There's no good reason not to add the vaccine, no good reason not to help families afford preventative care for their children, and no good reason to let a single child miss a vaccine because their parents couldn't afford it. As I was sitting down to write this comment, I saw that Tucker Carlson decided to take aim at the VFC and at ACIP and the CDC in one of his tweets. If I could address him directly in 10 words or less, I think I would say, "Shame on you for endangering children and public health." I'm sorry he has made your job that much harder with his fearmongering. The work of combatting misinformation continues. To those misled by Tucker's tweet, no matter what he says, only states can mandate vaccines for school attendance. Thank you.

Bob Runnells, BS, MBA
Informed Choice Washington

Hello. Bob Runnells. I'm a Washington State parent extremely concerned about the health of future generations. This committee has been very successful at injecting children, usually against childhood diseases. The CDC has continued to add to the vaccine schedule since 1986 when liability protection was granted to vaccine makers. Today, families who follow the schedule will have their children injected 54 times with 73 doses of antigens for 16 diseases before they graduate. Since 1986, there has been no commensurate improvement in the overall health of our population. The US ranks poorly in many categories, with very disturbing trends like the unexplained autism epidemic. Now the elephant in the room. COVID is not a childhood disease. COVID vaccines, which I will refer to as COVID shots, are not medically indicated for the young. Their amazing immune systems can be strong if not tampered with. What's more, it's now widely acknowledged that COVID shots don't stop transmission, so it cannot be said that these shots save others from getting infected. The marginal benefits from these shots wane quickly—faster than for any other injection on this schedule. COVID shots are not well-targeted to circulating variants. I don't care how fast trials are conducted, even mRNA technology cannot be fast enough to address a new microbe, except for maybe when using gain-of-function of dual-use research. So many of the public see what's going on. We noticed when the vaccine definition was changed. We noticed when the phrase "vaccine failure" was changed to "breakthrough infection" and "immune escape." It's all vaccine failure. We've seen the death certificate criteria change to favor COVID death rates confounding from and with. We see the huge government-funded efforts to market these products in TV, radio, print, billboards, online.

Shouldn't they sell themselves if they're so good? The majority of parents know their kids are not at measurable risk, yet the public health apparatus tries to convince us otherwise. Parents see and sense that something is wrong. Our radar is pinging. We see other countries like Sweden and Denmark with very clear policy shifts against injecting children. Does the CDC consider how other countries are making their decisions? Yet, there's this rush to recommend "kind of" approved COVID shots for ever-lower ages. We see the ACIP as one of the many government bodies and private interests bending rules to mandate COVID shots. We know the CDC childhood schedule is the "golden goose," granting liability immunity to pharmaceutical companies who, by the way, do all their own testing. You must vote "no" on any new shots to any of these schedules for COVID or other diseases. Our young little pincushions are already exposed to too many attempts at artificial immunity. To reduce risk, the ACIP should be finding safe ways to reduce the childhood schedules as VPDs diminish. Four polio shots? Really? Vote "no" in adding vaccines and shots to any schedule. Be extra critical at the studies and talking points aimed toward you. The data must be overwhelming if the committee adds anything to the already bloated schedules. Vote "no."

Thair Phillips
Seniors Speak Out

Hello. My name is Thair Phillips. I'm the National Spokesperson for Seniors Speak Out, and have been an advocate for older Americans for over 25 years. I appreciate the opportunity to speak today and thank the committee for the extraordinary work and dedication they have provided over these last very difficult 2-plus years. Before I go on, I want to say that I recognize that there have been important discussions this morning that I want to acknowledge and assess. I ask the committee to keep in mind that the clearer, the simpler, and the more direct the language, the better patients will understand and the better the chances will be for higher rates of vaccination. We find ourselves today in a situation so much better than we could have imagined in those early, awful months of the pandemic when fear and lack of both effective treatments and preventive measures took an unimaginable toll on people from all walks of life—especially older Americans. ACIP's prompt action and prioritizing older Americans' access to COVID vaccines saved lives and prevented hospitalizations. How far we have come. But the fact remains that there are still serious public health challenges facing men and women of advancing age. As 2022 nears its end, we worry not only about whether there will be a spike in COVID, but also about the impact of flu and pneumonia, whose persistence carries on decade after decade, with pneumonia remaining one of the top 10 causes of death for older adults. Reports forecast that the flu season is very likely to be bad this year, so it stands to reason that now is the time we must prepare ourselves to do everything we can to prevent these old foes from overwhelming those of us who are the most vulnerable. Before COVID, pneumonia caused approximately 1.5 million annual emergency room visits and nearly 50,000 deaths. Though today we see these statistics through a post-COVID lens, we must not forget they are truly horrific, and it is equally important that we remember that there are ways to change them for the better. We urgently need access to the updated pneumococcal vaccines that FDA approved last year. Older adults who are previously vaccinated with earlier pneumococcal vaccines need to know when and if they can be given the newer versions. This year, this season, we need them more than ever. Please act today so that this effective protection is available before another winter season takes its toll and please, once again, the clearer and the simpler the recommendation, the better for the provider, and the patient, and the outcome. Thank you.

Mr. Mark Gibbons
President & CEO
RetireSafe

Good afternoon. My name is Mark Gibbons. I'm the President and CEO of RetireSafe, an advocacy organization which represents the concerns of middle-aged and older adults. As we navigate a third year of COVID pandemic, healthcare concerns have quickly risen to the top of our priorities. A bright spot in this difficult time is how older Americans have really embraced the protections offered by the innovative COVID-19 vaccines and that 95% of Americans aged 65 and over have received at least 1 dose of the vaccine. While we continue to communicate around the very real threat which COVID-19 poses to the respiratory health of older Americans, we have also remained steadfast in assuring our community understands the risk of other diseases, such as influenza, pneumonia, and RSV. Even before the pandemic, we knew that older Americans were more likely to become seriously ill and die from respiratory disease such as the flu and pneumonia. Today, as we continue to also face the unpredictable COVID virus, older Americans are feeling incredibly vulnerable and are seeking to take advantage of any way they can to protect themselves. This is why we're hopeful that the committee will vote in favor of recommending the use of the new pneumonia vaccines in those Americans aged 65 and older who have already received a previous dose. Our community listens intently to their physicians when it comes to how to best protect their health. Offering a clear and simple recommendation for providers on the use of the new pneumococcal vaccines for older patients will go a long way toward reducing the burden of disease on some of the most vulnerable members of society. Just as older Americans aged 65 and over have embraced protections offered by the COVID-19 vaccine above any other age range, we believe that a vote today to expand access to the new pneumonia vaccines would also be welcomed by this community as another important tool that they can use to support a long, healthy life. We are grateful for the committee's ongoing efforts to protect Americans and especially American seniors. For our part, we will continue to educate and inform our communities on important steps they can take to protect themselves. Thank you.

Mr. Burton Eller, Jr
National Grange

Thank you. We had trouble getting the link out to the country in rural America. My name is Burton Eller and I'm speaking today on behalf of the National Grange, the nation's oldest organization representing agricultural, rural, and small-town American life. Today's discussion of qualified guidance for the use of the pneumonia vaccine hits particularly close to home for us. Our own National Grange President, Betsy Huber, is currently recovering from pneumonia. She's doing very well now, but was very sick, and was very grateful to have had the vaccine so that it wasn't any worse. Suffice it to say, we are very concerned to hear this morning's discussion on the additional assessment on the use of the new broad pneumonia vaccines for individuals 65 years and older who may have already received a dose of the vaccine. In rural states and counties across the country, Americans are living at a risk of serious respiratory illness. Rural Americans are 42% more likely to die from COVID than their urban resident counterparts. Just before COVID, the rates of influenza and pneumonia were higher in rural counties than in urban. Two factors contributing to this are the fact that more Americans living in rural communities are older and access to care is limited. Since 2015, 183 rural hospitals have shut their doors. Nearly half of those still in business face negative operating margins and 1 of every 4 are now at risk of closing. On average, rural Americans live twice as far from a hospital than those living in urban areas. Because of this, we believe vaccines are a critical option for protection of those living in rural communities who are more vulnerable to serious respiratory illness or death. The National Grange recently signed a letter to Dr. Melinda Wharton along with

21 other aging consumer and patient stakeholder organizations expressing our support for clarified, straightforward guidance on the use of the newest pneumonia vaccines. We are grateful to the Pneumonia Working Group for evaluating the need for this clarified guidance. Rural Americans already face so many barriers to care, so we ask that this committee keep in mind that those patients need their physicians to have clear recommendations from the CDC in order to provide as comprehensive care as possible during the limited time they may have with their patients. We are grateful to the committee and hope it will vote in favor of the most straightforward recommendation for these new vaccines, so that these Americans who would most benefit from this added protection are able to do so. We thank the ACIP for your work on these important vaccines and will do our part to make certain rural Americans know what could soon be available to them. Thank you.

POLIOVIRUS AND VACCINATION

Poliovirus, Polio Vaccination, and Polio Epidemiology in the US

Kathleen Dooling MD, MPH (CDC) presented on behalf of the newly constituted ACIP Polio WG. The purpose of this session was to: 1) review poliovirus, polio vaccination, and polio epidemiology in the US and globally; and 2) explain the Terms of Reference (TOR) and membership of the ACIP Polio WG. She explained that poliovirus consists of an RNA genome enclosed in a capsid. There are slightly different capsids that give rise to 3 different serotypes: Type 1, Type 2, and Type 3. Immunity to one of those serotypes does not produce significant immunity to the other serotypes.[77] Poliovirus is highly infectious. Person-to-person spread of poliovirus occurs via the fecal-oral or oral-oral routes. Fecal-oral is the most important transmission pathway in settings with suboptimal hygiene and sanitation. Patients are most infectious in the days immediately before and after onset of symptoms, but viruses may remain present in stool for up to 6 weeks and sometimes even longer. The virus can be shed in individuals with minor symptoms or even no illness at all.[78]

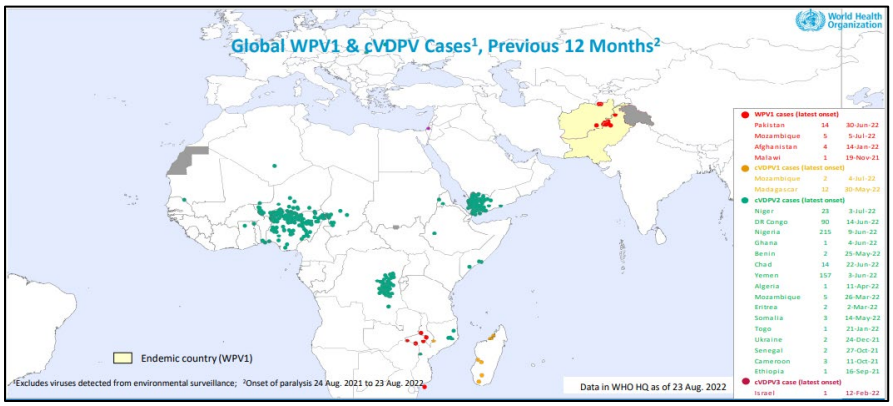
After infection, usually through the oropharynx and potential replication in the small intestine, poliovirus can enter the lymphatic system, then enter the blood system in a viremic phase, and then have AEs on the neural system. It can directly damage motor neurons. If it passes the blood brain barrier (BBB), it can cause meningitis.[79] It is important to remember that most people who get infected with poliovirus do not have any symptoms at all, with 75% of people infected being asymptomatic. Another 25% will have clinical illness, usually diarrhea, but no paralysis. Those who develop paralytic polio represent less than 1% of all infections, which varies slightly by type. If 1 paralytic case of polio is identified, that indicates an outbreak. There could be hundreds or even thousands of people who have been infected.[80]

Moving to the vaccines available to control and mitigate polio infection, the first is inactivated polio vaccine (IPV). IPV contains 3 serotypes of the poliovirus that have been chemically killed. So those viruses cannot replicate, infect, or cause disease. IPV induces highly effective humoral immunity, which means that it is very good at preventing paralysis. About 90% of subjects will have seroprotection after 2 doses and 99% will have seroprotection after 3 doses. IPV induces some nasopharyngeal mucosal immunity but limited intestinal immunity, which means that even people who have had full courses of IPV may still shed poliovirus in their stool if they are

[77] Source: CDC Pink Book, GPEI
[78] Source: CDC Pinkbook, PHIL
[79] Current Topics in Microbiology and Immunology 289:25-56 DOI:10.1007/3-540-27320-4_2
[80] Sources: CDC, Sutter, Kew, Cochi, and Aylward. Poliovirus vaccine-live. Vaccines, 6th Edition, 2013. NB: Other sources cite different percentages.

infected. Since 2000, only IPV has been recommended for use in the US. Oral polio vaccine (OPV) is a live-attenuated vaccine that contains live, weakened polioviruses. It is given orally, replicates in the gut, and is shed in the stool. It prevents paralysis and transmission of poliovirus. It is the vaccine of choice in developing countries or countries that are experiencing polio outbreaks. However, if it is allowed to circulate in under-immunized populations for long enough, attenuated viruses can revert to a form that causes paralysis.

With regard to polio in the US and global eradication efforts, paralytic polio decreased rapidly in the US after introduction of IPV in 1955. Subsequently, OPV was used in 1961 in the US. Shortly thereafter, the US saw its last wild-type case of poliovirus in 1979. By 1994, the Americas were certified polio-free. In 2000, the ACIP voted to use only IPV going forward. In 1988, the Global Polio Eradication Initiative (GPEI) was established based on a vote at the World Health Assembly (WHA). Great progress was made and by 2015, wild poliovirus Type 2 was eradicated. In 2016, the Sabin Type 2 virus component was withdrawn from the OPV in a maneuver that was globally known as “the switch.” By 2019, wild poliovirus Type 3 was eradicated. In 2022, only 2 countries still have endemic wild-type poliovirus Type 1. However, numerous vaccine-derived poliovirus outbreaks are being detected. This World Health Organization (WHO) world map depicts the polio outbreaks that have continued to be identified globally, with 249 laboratory-confirmed cases in 2022:



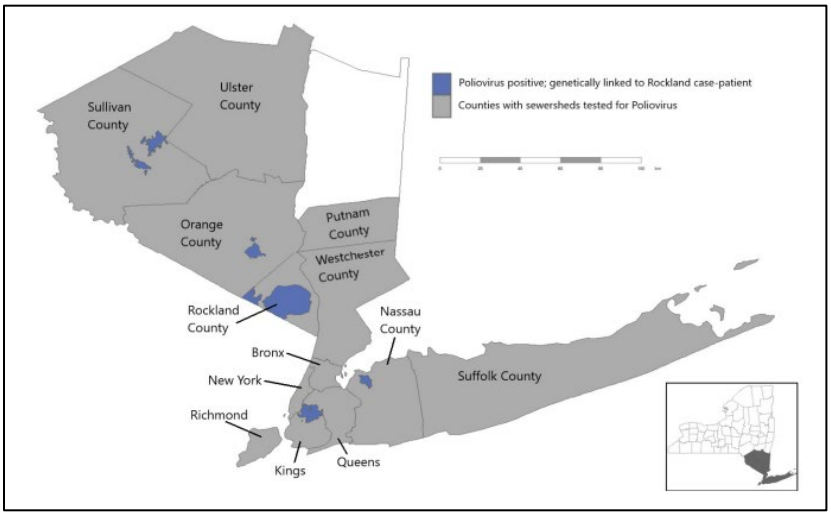
The yellow areas are Pakistan and Afghanistan, which are the 2 countries that still have endemic transmission of Type 1 wild-type poliovirus. However, the green dots illustrate that numerous places have circulating vaccine-derived poliovirus cases.

A case of paralytic polio was identified in New York State (NYS) in 2022. The polio case-patient presentation was in an unimmunized, immunocompetent young adult who developed fever, neck stiffness, back pain, abdominal pain, and constipation. Three days later, this person developed lower extremity weakness. Two days after the weakness began, the patient presented to an emergency department (ED) and was admitted to the hospital with flaccid weakness. As part of the differential diagnosis, this patient was worked up for Acute Flaccid Myelitis (AFM). As part of that work-up, stool, nasopharyngeal swab (NP), oropharyngeal swab (OP), and cerebrospinal fluid (CSF) specimens were submitted for pathogen-specific testing.

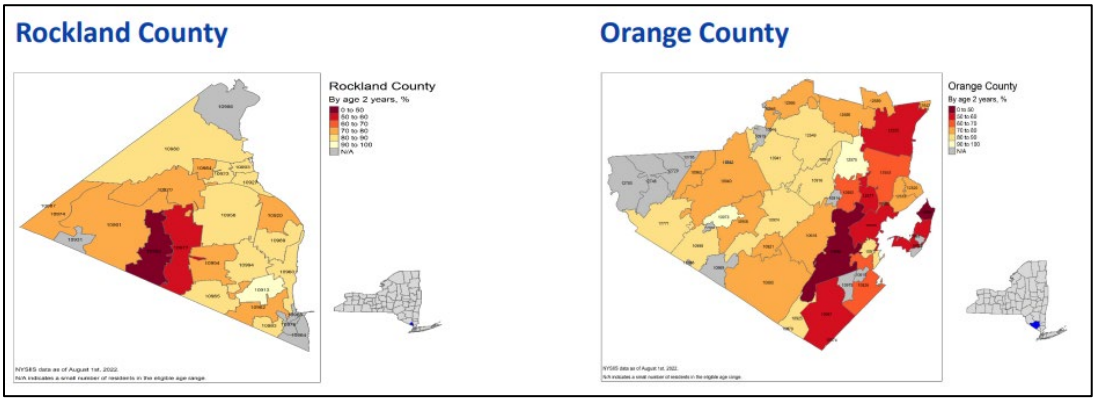
The stool specimen was positive for enterovirus by polymerase chain reaction (PCR). Subsequent sequencing identified vaccine-derived poliovirus Type 2 (VDPV2). This was confirmed by the CDC polio laboratory. The sequence indicated that there were 10 nucleotide changes in the region that encodes the viral capsid protein (VP1) compared to the Sabin 2 strain. This indicates that the virus likely had been circulating for about a year since it was in its

original Sabin form. Again, a single paralytic case implies hundreds and possibly thousands of infections.

This is a depiction of a NYS wastewater polio testing as of October 11, 2022:



In the Southern part of NYS in blue are sewersheds that tested positive for poliovirus Type 2 that are genetically linked to the Rockland case patient. Given that there is transmission in multiple locations in the New York metropolitan region that has persisted over months, this qualifies as a circulating VDPV2 and has been reported as such. Taking a closer look vaccine coverage in the 2 affected counties in NYS, these maps highlight the power of understanding vaccine coverage at the zip code level, which can illuminate heterogeneity even within a county:[81]



As of August 1, 2022, Rockland and Orange Counties had several zip code areas with less than 70% 3-dose polio vaccine coverage among children 2 years of age (dark red colors). NYS and the counties affected have worked extremely hard to catch up and vaccinate their populations. Based on polio vaccine doses administered between July 21, 2022 when the case was first notified in the media through September 25, 2022 compared to that same period in 2021,

[81] Source: NYSIIS data provided by NYSDOH

uptake amongst children increased 42% in Rockland County and 29% in Orange County. While there is still work to be done, progress has been made.[82]

In terms of ACIP recommendations for polio vaccination, the routine childhood schedule in the US consists of 4 IPV doses routinely given at 2 months, 4 months, between 6 to 18 months, and a booster dose at 4 to 6 years. There are numerous polio-containing vaccine products on the market in the US. One is an IPV polio only containing vaccine and the remainder are combination vaccines, which are preferred in most circumstances. This table lists the currently available products:

Vaccine name	Vaccine components	Age indication	Dose in polio series	Injection route
Ipol (SP)	IPV	6 weeks and older, any dose in the series	Any	IM or SC
Pentacel (SP)	DTaP-IPV/Hib	6–4 yrs	1, 2, 3, 4	IM
Vaxelis (Merck)	Dtap-IPV-Hib-HepB	6 wks–4 years	1, 2, 3	IM
Pediarix (GSK)	DTaP-HepB-IPV	6 wks–6 yrs	1, 2, 3	IM
Kinrix (GSK),	DTaP-IPV	4–6 yrs	4	IM
Quadracel (SP)	DTaP-IPV	4–6 yrs	4, 5	IM

IM = Intramuscular; SC = Subcutaneous; All vaccines in the table above are non-live

The safety of IPV vaccine is well-proven, with the only contraindications being severe allergic reactions after a previous dose or a vaccine component precautions, including pregnancy or moderate or severe acute illness with/without fever on the day of vaccination. Local AEs include pain, redness, and swelling appearing in about 3% to 18% of people. Severe reactions are rare. The current guidance for polio immunization for adults on the CDC website has been interpreted from the ACIP Statement that dates back to 2000, which was the last time it was updated:

- ❑ Adults who are unvaccinated or have incomplete vaccination for poliovirus should talk to their doctor about getting vaccinated.
- ❑ Adults at increased risk of exposure to poliovirus may receive 1 lifetime booster dose.
- ❑ Adults at increased risk of exposure:
  - Travelers who are going to countries where there is an increased risk of exposure
  - Laboratory and healthcare workers who handle specimens that might contain polioviruses
  - Healthcare workers/caregivers who have close contact with a person who could be infected with poliovirus
  - Unvaccinated adults whose children will be receiving oral polio vaccine (for example, international adoptees or refugees
  - Unvaccinated adults living or working in a community where poliovirus is circulating

[82] Comparison with 2021 data may have limitations because immunization rates declined markedly during the first years of the COVID-19 pandemic. Source: NYSIIS data provided by NYSDOH

There have been a number of innovations in polio vaccination in recent years that will be points of discussion for the Polio WG, so the WG thought it would be good to highlight these. These first is Novel OPV2 (nOPV2), which was developed to respond to the evolving circulating vaccine-derived poliovirus Type 2 (cVDPV2). nOPV2 is more genetically stable and less likely to be associated with the emergence of cVDPV2. It can provide mucosal immunity to limit the spread, even amongst IPV-vaccinated people. It was approved for use under the WHO Emergency Use Listing (EUL) in November 2020. Safety data on the first 65 million doses of nOPV2 that were used for outbreak response were reviewed by the independent Global Advisory Committee on Vaccine Safety (GACVS), which concluded that there were no obvious red flags or safety concerns. For countries that have eliminated polio and only use IPV, such as the US, the WHO Strategic Advisory Group of Experts (SAGE) recommends vaccine response to cVDPV2 should include routine and catch-up immunization with bOPV or IPV and countries should consider use of nOPV2 if IPV response does not stop cVDPV2. For example, if the outbreak spreads beyond a well-defined population group or geographic area or if transmission persists.[83]

Another innovation is the fractional-dose IPV (fIPV). Many countries now are switching to IPV only schedules. Although the US has a stable and secure supply of IPV, the global IPV shortage has limited the number of doses available. fIPV is administered intradermally using 1/5 of the regular dose, which stretches the limited supplies of IPV.[84,85] The use of fIVP has been recommended by WHO as a response strategy for VDPV2 outbreaks. Currently, fIVP is not recognized as a dose to satisfies immunization requirements in the US.

ACIP Polio WG Terms of Reference

Dr. Oliver Brooks (WG Chair) reported that the ACIP Polio WG had met only once thus far and developed the following TOR policy topics for consideration, for which they invited input from the full ACIP:

1. Whether more specific guidance on adult vaccination, including use of adult booster doses, can be provided in the context of circulating poliovirus.

2. Whether adults who are immunocompromised should be recommended an additional adult booster of a polio-containing vaccine.

3. Whether fractional doses of IPV (fIPV), as prequalified by WHO, should meet polio vaccination requirements, including for people immigrating to the United States.

4. Consider criteria under which novel oral polio vaccine (nOPV) might be used in areas with outbreaks or persistent circulation of poliovirus.

[83] Safety and immunogenicity of two novel type 2 oral poliovirus vaccine candidates compared with a monovalent type 2 oral poliovirus vaccine in healthy adults: two clinical trials: https://doi.org/10.1016/S0140-6736(20)32541-1
[84] Immunogenicity of supplemental doses of poliovirus vaccine for children aged 6–9 months in Moradabad, India: a community-based, randomised controlled trial https://doi.org/10.1016/S1473-3099(11)70190-6
[85] Immune responses after fractional doses of inactivated poliovirus vaccine using newly developed intradermal jet injectors: A randomized controlled trial in Cuba. https://doi.org/10.1016/j.vaccine.2014.11.025

Discussion Points

Dr. Kotton said that this has engendered a lot of questions in her workplace. Adults who are unvaccinated or have incomplete vaccination for polio should talk to their doctor about getting vaccinated. People are asking her, "Well, I'm seeing a 70-year-old person who does not have their vaccine records. Do I need to vaccinate them?" She wondered what the guidance would be in that context for someone who was born, raised, and attended schools in the US. She is concerned that a lot of people may be giving polio vaccine and is worried about supply and whether that is appropriate use. In addition, she inquired about the guidance for those who are immunocompromised.

Dr. Janelle Routh indicated that she is the Team Lead for the Acute Flaccid Myelitis and Domestic Polio Team at CDC. They have received a lot of public inquiries as well about older adults who have lost their vaccination records and cannot remember whether they were vaccinated. In general, CDC says that unless there are specific reasons to believe an adult was not vaccinated as a child, adults who were born and raised in the US likely did receive the polio vaccine as a child, given the fact that vaccination started in the late 1950s and early 1960s. It is reasonable to expect that they were vaccinated because large campaigns were implemented to get all school children vaccinated. Given the safety profile of IPV, people who live or work in an area where poliovirus is circulating could receive an additional booster if they are concerned and have no record or recollection of being vaccinated. However, CDC is not recommending this widely at this time.

Dr. Sanchez pointed out that people who come to the US from other countries may have received OPV and would be shedding virus and asked whether there are any data on this from other communities, such as Boston or California.

Dr. Routh indicated that CDC has been following the global guidance, which suggests that environmental surveillance for poliovirus is best done in connection to a case. While they are not recommending widespread wastewater surveillance at this point, they have been conducting rigorous wastewater surveillance around the case patient in NYS retrospectively from the date of paralysis onset and then moving forward. They found detections of poliovirus linked to the case patient earlier, so prior to the paralysis onset, in May and April. CDC continues to find detections of this poliovirus linked to the case patient's virus moving forward in subsequent months in August and September. The focus has been on communities that might have contact with the NYS community. For instance, additional wastewater testing has been done in New Jersey and Connecticut. All of the specimens to date from these locations have been negative. In New Jersey, testing was not done specifically in the county where communities have ties back to the NYS community but are moving forward to look at that.

Given that Type 2 was removed from OPV, Dr. Sanchez inquired as to where Type 2 is coming from.

Dr. Routh confirmed that now for routine immunization, bivalent OPV is being used that contains only Types 1 and 3. As Dr. Dooling alluded to, that switch was made in 2016. However, because of the ongoing cVDPV outbreaks, the response to those outbreaks has to be with OPV2. In previous years, a monovalent OPV2 was used. It is a "chicken and egg" cycle in which the monovalent OPV, when given to prevent subsequent spread of the outbreak in under-vaccinated communities, can circulate and seed new VDPV outbreaks. That is changing with the nOPV2 coming on board. Over 500 million doses have now been given worldwide. The

hope is that based on the stability of this virus, it will not revert back to neurovirulence quite as often and there will be a decrease in outbreaks moving forward.

Dr. Shah pointed out that this has been a frequent topic of conversation among State Health Officials. One observation on the communications front, given the complexity of poliovirus, particularly with terms like “vaccine-derived,” there is a notion that polio just happens sometimes or it is perhaps tethered to vaccination. It is important to be very clear in communications that the occurrence of polio in Rockland County and elsewhere is directly related to the under-vaccination. That fact sometimes gets lost, so it is important to underscore that for everyone. There are certainly outstanding questions around the pros and cons of greater use of wastewater testing. While that is not within the purview of the WG, a frequent question that comes up amongst State Health Officials regards why not switch to the nOPV given its mucosal benefits.

Dr. Talbot indicated that she lives in a pocket of the US where there was and still is a lot of disparity in healthcare. They have cases of older, Black women who get tetanus because they were never vaccinated, but their male counterparts were because they served in the military. She asked whether there are any data on polio vaccination in non-White groups to provide some idea about that population.

Dr. Routh indicated that they do assess vaccination by race and ethnicity in children and doses that are reported into Immunization Information Systems (IIS) across jurisdictions but did not know whether that information is captured for adults.

Dr. Brooks added that race and ethnicity likely was not collected 30 years ago on vaccine administration in adults.

Dr. Romero pointed out that it is important to keep in mind the epidemiology of wild-type disease prior to 1955 when the vaccine was introduced. Prior to that, this was a widely circulating virus to which most individuals were exposed during childhood. Most individuals of that age group probably have natural immunity to wild-type poliovirus and they were boosted with the vaccine. He will determine whether CDC can provide some numbers for ACIP.

Dr. Daley asked how what ACIP decides as a committee fits with the global strategy in the context of the use of OPV outside of the US and in terms of risk.

Dr. Routh indicated that CDC has been talking to global immunization colleagues about that very question. The questions for them are, “What does eradication actually mean now in the context of these ongoing cVDPV outbreaks now that we have found this in the US. Does eradication mean no paralysis versus actually eliminating the virus from the environment across the world?” This is good to consider moving forward with nNOPV discussions in the US. She thinks it will be an important factor to understand how colleagues are viewing eradication and that probably will lend itself to how CDC and ACIP might think about using it.

Dr. Daley asked what the metric of success is in terms of management of this as an outbreak. While he said he did not know enough about circulation through wastewater as it relates to cases, an unvaccinated 20-year-old is clearly at risk. Does part of success mean no more cases of paralysis? Vaccination should lead to that, but does vaccination also lead to decreased circulation in wastewater and over what timeframe? What are the metrics as an immunization program for success as policy decisions are made about vaccination?

Dr. Routh indicated that these are really good questions that CDC has been discussing internally in terms of the response. Absolutely, success means no more cases of paralysis. It also means elimination of the circulating virus in wastewater. As long as there are wastewater detections of this circulating virus linked back to the case patient's virus, there is ongoing transmission in the community even without paralysis. They certainly can talk about the dynamics of transmission in the US, which for the most part has good sanitation and hygiene. Transmission of poliovirus is more oral-oral than it is fecal-oral. It is known that IPV provides some nasopharyngeal mucosal immunity. Recent global deliberations have said continued use of IPV for outbreak response is recommended in countries that only use IPV in their routine immunizations. CDC is certainly following that guidance. As Dr. Dooling alluded to, if this virus is observed to be breeding out of its current geography and population, other methods should be considered. To her, the metric of seeing this outbreak end is seeing no more virus detections in wastewater. That will take time. Globally, testing is recommended for an additional 6 months after the last positive detection in wastewater.

Dr. Romero emphasized that as a global society, people move very quickly from parts of the world that use OPV and bring it in. It is important to keep in mind that to say something has "broken out of its environment where it is being seen," it is important to sequence and understand this. Finding the virus in a city does not mean that they are at risk or not. For instance, Chicago is a travel hub but that does not mean it came from New York and there is spread or breaking out of the virus. It is very important for the public to understand that also. It also is important to understand that the ability to surveille for this virus currently outstrips the ability to understand how this virus is traveling around the world. These are important points to keep in mind.

With the enormous increase in the number of clinical detections of enterovirus/rhinovirus now that BioFire identifies together and does not separate, Dr. Long asked whether CDC is looking at data for lesser diseases than Acute Flaccid Paralysis (AFP) to determine whether there are any circulating strains in the US. For clinicians, an enterovirus is an enterovirus and a poliovirus is an enterovirus and that is all they would hear and would not look unless there is something special about a case that is neurologic.

Dr. Routh indicated that CDC has data from the platform probably has been shared widely with ACIP, the New Vaccine Surveillance Network (NVSN), which is a system of 7 pediatric centers across the country that test for a number of respiratory viruses, including enterovirus/rhinovirus (EV/RV). The only rapid assay they have to distinguish further is for EV-D68. The sites across the network test EV/RV specimens for EV-D68, but any additional typing of those specimens would need to be done through sequencing. Some of that is done at those sites and others come to CDC for sequencing. For the most part, CDC has most data pertaining to EV-D68, which is likely responsible for the every-other-year pattern of outbreaks of AFM until 2018. Interestingly this year, even though there was an uptick in EV/RV respiratory illness over the summer that at many sites that was due to EV-D68, there was not a concurrent upswing in AFM cases. While this brought a lot of relief, it also raised additional questions.

Dr. Zahn (NACCHO) noted that in the era of COVID, there has been wastewater monitoring and there has been assistance from sanitation districts. Of course, they are not going to work under public health and that is an "extra" task for them. Very often, testing wastewater is not a priority for them and it takes time to get them on board. He requested additional information about the experience in New York. While polio raises a different level of concern, he wondered how quickly wastewater monitoring can be set up in a community and how easy it is to maintain over time.

Dr. Routh stressed that CDC adheres to the global guidance that in countries that have eliminated polio, the maintenance of polio elimination revolves around good surveillance for AFP, that the US has with AFM, and strong vaccination coverage. It is known that there are pockets of under-vaccination, but there is good IPV3 vaccination in the majority of the US. What wastewater testing should be used judiciously to understand the size and scope of an outbreak of a polio case. A number of critical considerations are needed to think about before rolling out wastewater testing. First and foremost is containment issues. Poliovirus Type 2 is under containment. If it is found in the wastewater, there is a series of requirements that go into place, not just with wastewater samples, but with all samples that potentially could contain poliovirus (e.g., clinical specimens like stool, respiratory swabs, et cetera). The second issue is response. If a poliovirus of public health importance is detected in wastewater, it behooves the jurisdiction to roll into response. This essentially means improving vaccination coverage in those areas, which is an effort that takes resources, acquiring vaccine, and mobilization of access points to get vaccines into arms. Communication around potential detections of poliovirus in wastewater and how to communicate that to communities is challenging. There are many worried-well who are hearing about the detection of poliovirus in wastewater, which can spur them to want vaccination, which might not be the best use of resources. It is important to think critically about how to communicate the right messages. Reflecting on something Dr. Mark Pallansch often says to which Dr. Routh has been trying to adhere is that even in the absence of poliovirus detections in wastewater, efforts should be made to improve vaccination coverage across the US. It is very important to identify communities with under-vaccination, determine the barriers and challenges to getting vaccines into arms, and then work to provide strategies to improve vaccination coverage.

THURSDAY: OCTOBER 20, 2022

AGENCY UPDATES

Centers for Disease Control and Prevention

Dr. José Romero began with current efforts in maintaining childhood vaccination coverage, reporting that during the 2020-2021 school year, national vaccination coverage among kindergartners dropped compared to the pre-SARS-CoV-2 pandemic period. CDC is working to recover ground lost during the pandemic and is working with HCP and families to get children caught up on recommended childhood vaccines through its “Back-To-School Call to Action” that outlines steps to encourage catch-up vaccination, as well as its “Let’s Play Catch-Up” communication campaign that encourages parents to prioritize the need to bring their children up-to-date on routine childhood vaccination.

In the area of seasonal influenza, the National Foundation for Infectious Diseases (NFID) and CDC hosted a joint Influenza/Pneumococcal Conference at the National Press Club in October 2022 in DC to kick off the 2022-2023 influenza season. CDC has partnered with the Ad Council and the AMA for their annual “Get My Flu Shot” campaign, which also has been translated into Spanish. This campaign, with an emphasis on Black and Hispanic audiences, encourages the American public to get vaccinated against influenza for the coming season. The first weekly FluView report for this season was published on October 14, 2022. Early increases in influenza activity were reported in most of the US, with the highest level of activity occurring in the Southeast and South-Central parts of the country. This may portend a significant influenza season. While no pediatric deaths had been reported to the CDC for the current season, the

previous week the CDC received reports of 2 new pediatric deaths from the previous influenza season, brining that season's total to 43 deaths and reminding everyone about the significance of this disease for children. Based on current claims data for persons 18 years of age and older, approximately 12 million doses of influenza vaccine had been administered in pharmacies and physician offices as of the week of September 24, 2022.

In terms of the recent polio outbreak, CDC has been actively involved with the NYS Department of Health leading the response. CDC is supporting them and has been working at the local, state, and international levels to control this outbreak. CDC has deployed staff to NYS since August 4, 2022 in efforts to assist in investigation and vaccination efforts in Rockland and Orange Counties. Among CDC's many actions are conducting testing of poliovirus in wastewater samples in NYS and neighboring states;, providing confirmatory testing for clinical specimens; collaborating with Israel, the United Kingdom (UK), and the World Health Organization (WHO) to understand the origins and relatedness of this virus to those found in those countries; ensuring safe and secure handling and transport of potentially infectious materials through the National Authority of Containment; and facilitating procurement of polio vaccine for the affected areas. The latest wastewater report is anticipated to be published at the end of October 2022 in the *MMWR*.

The Acute Flaccid Myelitis (AFM) Patients Under Investigation (PUI) reports declined over the last 4 weeks, indicating that the expected surge in AFM cases failed to materialize this year. This is now the 5th or 6th year that a large increase has not been seen.

Concerning meningococcal disease, Florida is experiencing an outbreak of Serotype C meningococcal disease primarily among men who have sex with men (MSM) since December 2021. This is one of the largest meningococcal outbreaks among MSM in US history. There were 35 cases as of October 18, 2022, including 7 non-MSM cases and 7 deaths. MSM living in Florida are recommended to receive a meningococcal vaccination. MSM who are traveling to Florida are recommended to talk to their HCP about getting MenACWY vaccine. CDC has been responding to this outbreak with laboratory, epidemiology, and communications support and using multiple channels to provide vaccination.

Regarding measles, as of October 18, 2022, provisional data indicated that there have been 29 cases of measles in the US. Five jurisdictions have been involved: Arizona, Minnesota, Ohio, Virginia, and Washington State. All cases have occurred in unvaccinated individuals and all but 1 case occurred in individuals less than 20 years of age. All confirmed cases were associated with importation by individuals who had traveled to Kenya, Somalia, and Tanzania where measles outbreaks are ongoing. This highlights the importance of pre-travel vaccination for children.

With regard to monkeypox, as of the 19th of October, there were 27,635 confirmed cases of monkeypox orthodox cases in the US. A total of 539 new cases were reported between October 13th and October 19th. CDC's mission is to contain this multinational outbreak of monkeypox through containment of this multinational outbreak of monkeypox through preventing the spread of monkeypox; education; medical countermeasures; post-exposure prophylaxis (PEP); expanding laboratory testing availability; coordinating vaccination activities in the US; and monitoring travel-associated cases.

Turning to a success story from the ACIP concerning varicella, in 1995 the ACIP took the scientifically-informed yet bold move to recommend routine immunization with varicella vaccine. The US was the first country to introduce varicella vaccine into a routine childhood vaccination schedule and program in 1995. Over the quarter century of this effort, the US has prevented an estimated 91 million cases of varicella, 238 hospitalizations, 1.1 million hospitalization days, and almost 2000 deaths among those 0─49 years of age. This has led to a life year savings of 118,000 years and a net societal savings of over $23 billion dollars. Dr. Romero congratulated the ACIP on their wise decision.

Centers for Medicare and Medicaid

Ms. Mary Beth Hance provided updates for CMS, reporting that the Inflation Reduction Act of 2022 (IRA) included immunization provision that made changes to adult vaccine coverage and related costs for beneficiaries in Medicare, Medicaid, and the Children's Health Insurance Plan (CHIP). Medicare Part D generally covers commercially available vaccines except for those covered under Part B. Starting in January 2023, Part D plans may not apply a deductible, co-insurance, or other enrollee cost-sharing requirement for Part D-covered adult vaccines recommended by the ACIP. CMS has issued guidance to Medicare Part D sponsors to address this provision. For Medicaid and CHIP, beginning in October 2023, coverage of ACIP-recommended adult vaccines without cost-sharing is mandated for enrollees who receive coverage under traditional Medicaid and for all Medicaid medically needy enrollees in specified states and CHIP enrollees who are 19 years of age or older. CMS anticipates releasing guidance on this provision. Regarding seasonal influenza, CMS has made updates to CMS.gov to provided updated seasonal influenza vaccination and pricing for the 2022-2023 influenza season. In addition, CMS continues to amplify guidance regarding COVID vaccines and is issuing press announcements whenever there are changes pertaining to COVID vaccines.

Health Resources and Services Administration

Ms. Melinda La Salle presented the update for the Health Resources and Services Administration (HRSA), reporting that the National Vaccine Injury Compensation Program (VICP) continues to process an increased number of claims. In FY 2021, petitioners filed 2057 claims with the VICP. Nearly $208.3 million were awarded to petitioners and $36 million were awarded to pay attorney fees and costs for compensated and dismissed cases. In FY 2022, petitioners filed 995 claims with VICP. Nearly $196 million were awarded to petitioners and $34.2 million were awarded to pay attorney fees and costs for compensated and dismissed cases. FY 2023 data collection has now begun. As of October 12, 2022, the Countermeasures Injury Compensation Program (CICP) had a backlog of 1536 claims alleging injury that are awaiting review. As of October 1, 2022, 10,323 claims alleging injuries or deaths from COVID-19 countermeasures have been filed with the CICP. This included 7412 claims alleging injuries from COVID-19 vaccines. Of these, 6 COVID-19 countermeasures claims have been determined eligible for compensation and are pending review of eligible expenses. A total of 48 COVID-19 have been denied compensation because the standard of proof for causation was not met and/or a covered injury was not sustained. In addition to claims alleging injuries or deaths from COVID-19 countermeasures, as of October 1, 2022, the CICP has received 2 claims alleging injuries from monkeypox vaccine. More information about both programs can be found on the HRSA/gov VICP and CICP websites.

Indian Health Service

Dr. Matthew 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 significant impact in Tribal communities. Collaborating with its federal Tribal and Urban Indian Organization partners, the IHS has prioritized equitable access to COVID vaccine throughout Indian Country. To date, participating federal Tribal and Urban facilities within the IHS jurisdiction have administered over 2.3 million COVID vaccines. Following recent regulatory actions by the FDA and CDC, the IHS rapidly communicated information regarding bivalent COVID vaccine booster and anticipates that the majority of its service population will be vaccinated in their IHS medical home and federal Tribal and Urban facilities are now actively engaged in implementation. To date, nearly $40,000 bivalent booster doses have been administered throughout Indian Country. Across its 3 surveillance systems, to date, IHS COVID vaccine safety monitoring has demonstrated a reassuring safety profile 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 American Indian and Alaskan Native (AI/AN) service population. Beginning this past Spring, IHS has been working proactively to ensure access to JYNNEOS® vaccine to mitigate the risk of monkeypox in Tribal communities. Over 10,000 doses of JYNNEOS® have been pre-positioned across IHS's 12 areas. On September 9, 2022, IHS announced a monkeypox pre-exposure prophylaxis (PrEP) initiative to expand eligibility for JYNNEOS® vaccine to include not only PEP and PEP++, but also PrEP for at-risk populations. In collaboration with federal and Tribal partners, IHS also has implemented a simple process for onboarding sites to participate in the national monkeypox Vaccine Equity Pilot Program (VEPP) to further expand access in its vulnerable service population. In the coming weeks, IHS will be rolling out a new national vaccine strategy. The E3 Vaccine Initiative is designed to promote access for every patient at every encounter to every recommended vaccine when clinically indicated. This includes all ACIP-recommended vaccines in all age groups. 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 serviced by the IHS.

National Institutes of Health

Dr. John Beigel presented the National Institutes of Health (NIH) update, reporting that most of the updates were outside of COVID, reflecting the need to continue advancing other vaccines. The NIH updated its "Strategic Plan for NIH Research to Cure Hepatitis B," which is a roadmap that tries to plot a course toward ending the Hepatitis B epidemic that is focused on treatment and vaccination strategies and screening. NIH continues to make advancements for universal influenza vaccines. Another clinical trial started at the NIH Clinical Center for a universal influenza vaccine. Pre-clinical models suggest broad neutralizing responses. NIH continues to worry about pandemic influenza and has begun additional studies for H5 influenza. The most recent trial examined an intranasal H5 influenza vaccine that includes adjuvants as a way to try to improve the antibody response and block pandemic influenza. A novel Lassa fever vaccine Phase 1 study started in Liberia that is called the Partnership for Research on Vaccines and Infectious Diseases in Liberia (PREVAIL), which is a collaboration between the National Institute of Allergy and Infectious Diseases (NIAID), the Liberian Ministry of Health (MoH), and other collaborators. NIH is conducting additional intradermal studies in monkeypox to verify the intradermal and subcutaneous dosing and a lower intradermal dosing. A Nepah vaccine study started at the NIH based on mRNA platform that is done in collaboration with Moderna. Nepah is also one of the diseases NIH worries about in terms of its pandemic potential. Having an immunogenic vaccine will be the first step.

Office of Infectious Disease and HIV/AIDS Policy

Dr. David 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). The National Vaccine Advisory Committee (NVAC) met on September 22-23, 2022. During the meeting, NCAC approved a total of recommendations to sustain and increase confidence in vaccines across the lifespan. The report will be made available on the NVAC website. The next NVAC meeting will be on February 2-3, 2023. Health People 2030 seeks to establish a National Prevention Agenda with evidence-based, measurable targets to be achieved by the end of the decade. The OIDP National Vaccine Program is working with the HHS Office of Disease Prevention and Health Promotion (ODPHP) and CDC to formalize 2 immunization objectives as part of the Healthy People 2030 immunization and infectious diseases core objectives. The first is to increase the proportion of people who receive Tdap during pregnancy, and the second is to increase the proportion of adults 19 years of age and older who have received recommended age-appropriate vaccines. As a reminder of its importance, in Healthy People 2030, the annual influenza vaccination objective is one of 10 leading health indicators for all ages. HHS supports efforts to prevent influenza with the campaign “Boo to the Flu” to drive home the message for people to get the influenza vaccine by the end of October. HHS also has recently launched several audience-specific digital media toolkits on HHS.gov/immunizations to promote the influenza vaccine in racial and ethnic minority populations and, for the first time, small businesses. Now available on HIV.gov is a video series featuring OIDP Director, Kaye Hayes, and the White House National Monkeypox Deputy, Dr. Demetre Daskalakis of CDC. In the videos, the importance of equity and wellness in the federal monkeypox response, monkeypox VE, and vaccine availability are discussed.

COMBINED IMMUNIZATION SCHEDULE

Session Introduction

Sybil Cineas, MD, FAAP, FACP (ACIP Combined Immunization WG Chair) introduced the Combined Immunization Schedule session, reminding everyone that the Combined Immunization Schedule WG updates the child/adolescent and adult immunization schedules annually. The child/adolescent immunization schedule includes recommendations for persons 18 years of age or younger, while the adult immunization schedule includes recommendations for persons 19 years of age or older. The goal of the Combined Immunization Schedule WG is to better harmonize the child/adolescent and adult schedules. New policies are not established in the proposed schedules. Rather, the annual schedules reflect recommendations already approved by ACIP.

As a reminder of why the schedule is presented for a vote every Fall, ACIP approval of the proposed schedules is necessary prior to publication in the *MMWR* in February of the following year. In addition, ACIP approval is necessary before having partners from professional organizations listed in the following table review and approve the schedules:

Child/Adolescent Schedule	Both Schedules	Adult Schedule
• American Academy of Pediatrics (AAP) • National Association of Pediatric Nurse Practitioners (NAPNAP)	• American Academy of Family Physicians (AAFP) • American Academy of Physician Associates (AAPA) • American College of Obstetricians and Gynecologists (ACOG) • American College of Nurse-Midwives (ACNM)	• American College of Physicians (ACP) • Society for Healthcare Epidemiology of America (SHEA) • American Pharmacists Association (APhA)

Of note, this is the first year that the American Pharmacists Association (APhA) will be listed as an approving organization for the adult schedule. ACIP welcomes them and their input.

Presentations on revisions to both schedules may include the use of vaccine trade names. This is for identification purposes only and does not imply endorsement by the CDC. The 2023 schedules presented in the following slides are drafts and are therefore subject to change based on ACIP's discussion and vote. This session included presentations on harmonization between the child/adolescent and adult schedules, edits to all tables, content changes of the notes, and content changes to the appendix listing contraindications and precautions. The proposed edits are intended to incorporate ACIP recommendations and MMWR publications that have occurred since November 2021 and improve the readability and utility of the schedules into language that is easy to interpret by the busy provider.

2023 Child and Adolescent Immunization Schedule

Patricia Wodi, MD (CDC Co-Lead) indicated that the proposed updates to the 2023 Child/Adolescent Immunization Schedule included changes in the following areas:

Changes to Tables	Changes to Vaccination Notes	Changes to Appendix
• Cover Page • Table 1 • Table 2 • Table 3	• COVID-19 • Dengue • Hepatitis B • Influenza • Measles, Mumps and Rubella • Meningococcal A,C,W,Y • Meningococcal B • Pneumococcal • Polio	• Column Header • Influenza • Hepatitis B • Human Papillomavirus • Measles, Mumps, Rubella • Varicella

Beginning with the cover page, in the table with vaccine abbreviations and trade names, the WG proposed 3 edits. The first edit was to add COVID-19 vaccines and review separate abbreviations for the monovalent and bivalent mRNA vaccines, as well as a separate abbreviation for the monovalent protein subunit vaccine. In the Measles, mumps, and rubella vaccine row, Priorix® was added. In the pneumococcal conjugate vaccine row, PCV15 was added.

In Table 1, the Routine Immunization Schedule by age, a row has been added for COVID-19 vaccines and ages 6 months–18 years of age are shaded in yellow, indicating the recommended age for vaccination. Text also was included to review the notes section for more details on the primary and booster vaccination. PCV15 was added in the pneumococcal vaccination row. In the inactivated poliovirus vaccine row, "See Notes" was added for persons ≥18 years of age to prompt providers to look at the notes section for more details. In Table 2, the Catch-up Immunization Schedule for children who have started late or who are more than 1 month behind, there is 1 proposed edit in the pneumococcal conjugate vaccine row for the minimum interval between Doses 3 and 4, which has been revised to indicate when the fourth dose is recommended. In Table 3, Immunization by Medical Indication, a row was added for COVID-19 vaccine. In the columns for HIV infection and immunocompromised persons, "See Notes" was added in the line text.

In terms of edits to the "Notes" section, COVID-19 vaccines were added under "Additional Information" in the injury compensation section with a sentence stating, "COVID-19 vaccines. COVID-19 vaccines that are authorized or approved by the FDA are covered by the Countermeasures Injury Compensation Program (CICP). For more information, see www.hrsa.gov/vaccinecompensation/index.html or https://www.hrsa.gov/cicp." The previous COVID-19 vaccination box was deleted and a new section was added for COVID-19 vaccination. The same format was used as the infographics on the CDC webpage for use of the COVID-19 vaccines. The "Routine Vaccination" section summarizes the recommendations for children, adults, and those who are moderately or severely immunocompromised. The "Primary Series" section is based on the age of the child and includes the dose series and recommended interval between doses for each product. Because booster dose recommendations are still evolving, a link is included to the webpage with the most current recommendations. The "Special Situations" section summarizes the recommendations for children and adults who are moderately or severely immunocompromised. The primary series includes the dose series and recommended minimum intervals for each product. For booster vaccination, a link is included to the webpage. A bullet also was added to remind providers that "pre-exposure prophylaxis may be considered to complement COVID-19 vaccination" in this population. A note was added at the end that reminds providers to "Administer an age-appropriate vaccine product for each dose" that includes links to the COVID-19 schedule and dosage formulations and the EUA indications.

Moving to dengue vaccination, a bullet was added to "Routine Vaccination" stating that, "Dengue vaccine should not be administered to children traveling to or visiting endemic dengue areas."

For hepatitis vaccination, there are no new recommendations. However, the section was revised so that HCP can easily find recommendations based on the mother's hepatitis B antigen titers. There is now a section under "Routine Vaccination" for children whose mothers are HBsAg-positive. Another section is included for children whose mothers are HBsAg-unknown that includes information to remind providers that "If other evidence suggestive of maternal hepatitis B infection exists (e.g., presence of HBV DNA, HBeAg-positive, or mother known to have chronic hepatitis B infection), manage infant as if mother is HBsAg-positive." Under "Catch-Up Vaccination," Heplisav-B® and PreHevbrio® have been added for adolescents aged 18 years or older.

For influenza vaccination, the recommendations were added back for persons with egg allergy with symptoms other than hives. Last year, this information was in the appendix as a precaution. A new bullet was added to the “Special Situations” section stating, “Close contacts (e.g., caregivers, healthcare personnel) of severely immunosuppressed persons who require a protected environment: these persons should not receive LAIV4. If LAIV4 is given, they should avoid contact with/caring for such immunosuppressed persons for 7 days after vaccination.”

Under “Special Situations” for MMR vaccination, a bullet was added that states, “In mumps outbreak settings, for information about additional doses of MMR (including 3rd dose of MMR), see www.cdc.gov/mmwr/volumes/67/wr/mm6701a7.htm.”

Under “Special Situations” for meningococcal serogroups A,C,W,Y vaccination, a sentence was added stating that,“* Menveo has two formulations: One-vial (all liquid) and Two-vial (lyophilized and liquid). Menveo one-vial formulation should NOT be used before age 10 years.” Under “Special Situations” for meningococcal B vaccination, the bullet was revised for anatomic of functional asplenia to include language in parentheses stating that, “(if dose 2 was administered at least 6 months after dose 1, dose 3 not needed; if dose 3 is administered earlier than 4 months after dose 2, a fourth dose should be administered at least 4 months after dose 3).”

Under “Routine, Catch-Up, and Special Situations” for pneumococcal vaccination, PCV15 was added, PCV13 was replaced with PCV, and a note was added that states that “PCV13 and PCV15 can be used interchangeably for children who are healthy or have underlying conditions. No additional PCV15 is indicated for children who have received 4 doses of PCV13 or another age appropriate complete PCV13 series. In addition, the bullet regarding chronic liver disease and alcoholism was deleted because those are not risk factors for invasive pneumococcal disease in children and adults.

A new “Special Situations” was added for poliovirus vaccination to address “Adolescents aged 18 years at increased risk of exposure to poliovirus with: No evidence of a complete polio vaccination series (i.e., at least 3 doses): administer remaining doses (1, 2, or 3 doses) to complete a 3-dose series and evidence of completed polio vaccination series (i.e., at least 3 doses): may administer one lifetime IPV booster. For detailed information, see: www.cdc.gov/vaccines/vpd/polio/hcp/recommendations.html

The appendix was added last year that includes the contraindications and precautions for the vaccines in this schedule. The header was changed from “Contraindications” to “Contraindicated or Not Recommended.” In the Hepatitis B row, a new bullet was added that states that, “Heplisav-B and PreHevbrio are not recommended during pregnancy due to a lack of safety data in pregnant women. Use other hepatitis B vaccines if indicated.” In the footnote, links were added to the pregnancy registries for both vaccines. In the HPV row, a new bullet was added stating, “Pregnancy: HPV vaccination not recommended.” In the MMR row, the MMRV vaccine product was added. In the “Precautions” column, a new bullet was added that states, “For MMRV only: Personal or family (i.e., sibling or parent) history of seizures of any etiology.” In the “Varicella” row, a new bullet was added under “Precautions” stating that, “If using MMRV, see MMR/MMRV for additional precautions.”

Discussion Points

Ms. Bahta pointed out that while ACIP already has recommended COVID-19 vaccination for children, it is still under an EUA. Therefore, she requested clarity on whether it was appropriate to be added under the “Routinely Recommended” schedule.

Dr. Wodi indicated that before they presented this to the WG, CDC had a conversation with the Office of General Council (OGC) and were told that it was okay to add it to the schedule.

Regarding poliovirus vaccine, Dr. Brooks asked whether it was only for adolescents aged 18 years of age or if someone 17 or 19 years of age should be included.

Dr. Wodi explained that the current policy has a routine recommendation for up to 17 years of age. Beginning at 18 years of age, routine vaccination is not recommended. This policy is from 2000. Poliovirus vaccine is recommended for persons who are 18 years of age and older if they are at increased risk of exposure. Those 19 years and older will be reflected in the adult schedule.

Referring to Slide 37, Dr. Lee asked why chronic liver disease was deleted from the pneumococcal conjugate vaccine. While alcoholism makes sense, there are children with chronic liver disease who need liver transplants.

Dr. Wodi said that her understanding was that in the last Policy Note, it was added in error for children and adults. When the new Policy Note for PCV15 was written, that error was corrected.

In the past, chronic liver disease was never listed as a risk condition for the pediatric population. That is reflected in the *MMWR* published in 2010. There was a vote on use of PCV13 in children with immunocompromised conditions among individuals 6─18 years of age. When the *MMWR* was published, it reflected the conditions of use in the adult group. There always has been confusion. It was never the intent to change the table and it was not presented to the ACIP. When the *MMWR* was published, the table for that age group was switched over. With the recent *MMWR* that was published with the PCV15 recommendation, that previous confusion was addressed.

Dr. Poehling indicated that the WG would be addressing PCV20, which would be an easy way to include this issue in the conversation.

In response to public comment received regarding concerns about adding COVID-19 vaccine to the routine childhood schedule, Dr. Daley emphasized that this does not represent new recommendations. Instead, it represents a summary of existing recommendations. He appreciated and acknowledged that there is symbolism in adding COVID-19 vaccine to the schedule, which is that the ACIP views this as routine and that COVID is here to stay. When he thinks about the routine schedule as a practicing pediatrician, he views it as an opportunity to prevent serious disease and death among his patients. If something is added to the schedule, he believes that is because the benefits continue to strongly outweigh the risks. This does not constitute a mandate. While there are mandates, those are largely decisions made by state boards of health. For parents who are concerned that having COVID-19 vaccines on the schedule would turn into a mandate, he would want to turn that conversation in a different direction. He has had parents present to his office to obtain vaccines that are required for their children to attend school. He tells them that he does not vaccinate so their children can go to school and that instead, he is vaccinating to prevent serious illness and death in their children.

While the school mandate helps in that it brings parents into his office, his goal is to prevent serious disease and death. It is important to continue to do better in communicating why the benefits are believed to strongly outweigh the risks.

Dr. Shah clarified that the vote and discussion regarding the addition of COVID-19 vaccines to the recommended immunization schedule was separate and distinct from the previous day's vote in support of a resolution to add COVID-19 to the VFC Program at the point that the vaccines become commercialized. The previous day's vote in effect was a resolution about the coverage of the vaccine for un-insured and under-insured children—not a discussion of what pediatricians ought to be doing in an office setting. The discussion during this session regarding the addition of COVID-19 vaccines to the recommended childhood immunization schedule did not constitute a requirement that any child receive the vaccine. That decision remains where it did before. This is rather a codification of a pre-existing recommendation. The ACIP recognizes that there is concern around this, but moving COVID-19 to the recommended immunization schedule does not impact what vaccines are required for school entrance, if any. Indeed, there are vaccines on the schedule currently that are not required for school attendance in many jurisdictions, such as seasonal influenza. Local control matters and is honored. The decision around school entrance for vaccines rests where it did before, which is at the state, county, and municipal levels if it exists at all. They are the arbiters of what vaccines are required, if any, for school entry. The discussion during this session does not change that.

2023 Adult Immunization Schedule

LCDR Neil Murthy, MD, MPH, MSJ (CDC Co-Lead Combined Immunization Schedule WG) indicated that the proposed updates to the 2023 Adult Immunization Schedule included changes in the following areas:

Changes to Tables	Changes to Vaccination Notes	Changes to Appendix
• Cover Page • Table 1 • Table 2	• COVID-19 • Hepatitis B • Influenza • Measles, Mumps and Rubella • Meningococcal • Pneumococcal • Polio • Tetanus, diphtheria, and pertussis • Zoster	• Column Header • Influenza • Hepatitis B • Human Papillomavirus •

There are 6 main changes on the cover page. The first edit is to the upper righthand corner where the American Pharmacists Association (www.pharmacist.com) was added as a partner organization approving the adult schedule. The next couple of edits are in the list of adult vaccines. For the first time, COVID-19 vaccines have been added to the list of recommended vaccines. The first abbreviation refers to the monovalent mRNA vaccine, the second refers to the bivalent mRNA vaccines, and the third refers to the monovalent protein subunit vaccine. In the hepatitis B row, PreHevbrio® was added to the list. Similarly in the MMR row, Priorix was added to the list®. Compared to the 2022 schedule, the pneumococcal conjugate vaccines PCV15 and PCV20 were combined into 1 row in the table. Under the "Injury Claims" section, information is included about COVID-19 vaccines and the CICP.

There are 3 proposed edits recommended for Table 1 that outlines the age-based recommendations for adult vaccines. The first is the addition of a COVID-19 vaccine row. The entire row is yellow, indicating that COVID-19 vaccination is recommended for adults of all age groups. Guidance regarding the COVID-19 primary series and booster doses is provided in the overlaying text. The second edit is to the MMR row where overlaying text has been added to the ≥65 years of age column. It now refers providers to the notes section for vaccination considerations for HCP who are ≥65 years of age. The third edit is to the Hepatitis A row where the overlaying text now states "2, 3, or 4 doses depending on vaccine" to include the 4-dose accelerated Twinrix® schedule that can be used for Hepatitis A vaccination.

Compared to the 2022 schedule, only 1 major change was made to Table 2 that outlines immunizations by medical condition or other indications. COVID-19 has been added as a row to this table. The HIV and Immunocompromised Conditions columns has overlaying text of "See Notes" since such patients may have different primary series requirements and additional considerations for PrEP to complement COVID-19 vaccination.

In terms of the "Notes" section, a COVID-19 section has been added to Page 1. In the 2023 schedule, COVID-19 is now formally incorporated into the schedule and is no longer in a special call-out box as it was in previous years. The COVID-19 sections begins with a "Routine Vaccination" guidance portion that describes the primary series for mRNA vaccines and the protein subunit vaccine for the general population. Because guidance on booster dose recommendations may change based on evolving data, providers are encouraged to review the latest booster dose recommendations at the website presented in the notes. The "Special Situations" section begins with a brief description of the recommended primary series for persons who are moderately or severely immunocompromised. Again, a hyperlink is provided for providers to refer to the booster dose recommendations for persons who are moderately or severely immunocompromised. The last bullet in this section reminds providers to consider PrEP in addition to COVID-19 vaccination for persons who are moderately or severely immunocompromised. The COVID-19 vaccinations section ends with a note referring providers to additional resources on COVID-19 schedules and EUA indications for these vaccines.

Regarding the Hepatitis B vaccination section, Hepatitis B vaccination is routinely recommended for all adults 19–59 years of age. The descriptions of the 2-, 3-, and 4-dose series are provided in the "Routine Vaccinations" section. Compared to the 2022 schedule, these descriptions have been slightly revised. Any reference to the 4-dose series for persons on hemodialysis have been moved to the "Special Situations" section. PreHevbrio® also was added to the description of the 3-dose series. A note at the end of this section states that, "Heplisav-B® and PreHevbrio® are not recommended in pregnancy due to lack of safety data in pregnant women." The Hepatitis B section continues on into the second page of the notes. Two bullets have been added under "Routine Recommendations" describing the recommendations for persons ≥60 years of age. The first bullet states that "Age 60 years and older with known risk factors for hepatitis B virus infection **should** complete a HepB vaccine series." The second bullet states that "Age 60 years and older without known risk factors for hepatitis B virus infection **may** complete a HepB vaccine series." Risk factors for HepB virus infection are then listed. Minor edits were made in this section to improve clarity in the language. The hepatitis B note section ends with a "Special Situations" section describing the vaccination regimen or patients on hemodialysis.

Moving to the influenza section, a sub-bullet was added to the "Routine Vaccination" section for persons who are ≥65 years of age. This sub-bullet states that "Any one of quadrivalent high-dose inactivated influenza vaccine (HD-IIV4), quadrivalent recombinant influenza vaccine (RIV4), or quadrivalent adjuvanted inactivated influenza vaccine (aIIV4) is preferred. If none of these three vaccines is available, then any other age-appropriate influenza vaccine should be used." A hyperlink was added to the 2022-2023 influenza recommendation and a bullet is included for the 2023-2024 influenza recommendation as well. In the "Special Situations" section, the bullet describing guidance for persons with an egg-allergy who experienced any symptoms other than hives has been modified. This bullet now reads that "Any influenza vaccine appropriate for age and health status may be administered. If using egg-based IIV4 or LAIV4, administer in medical setting under supervision of health care provider who can recognize and manage severe allergic reactions." A bullet was added to the "Special Situations" section describing the guidance for persons who are close contacts to those who are severely immunocompromised. This bullet states that close contacts "Should not receive LAIV4. If LAIV4 is given, they should avoid contact with/caring for such immunosuppressed persons for 7 days after vaccination."

The "MMR Vaccination" section begins on Page 3 of the notes. This section has only 1 major addition this year. A bullet has been added to the "Special Situations" section to refer providers to the guidance that describes administering an additional dose of MMR in the context of a mumps outbreak setting. In the context of the change in the MMR row in Table 1, the "Special Situations" section includes the language stating, "Health care personnel: Born before 1957 with no evidence of immunity to measles, mumps, or rubella: Consider 2-dose series at least 4 weeks apart for measles or mumps or 1 dose for rubella." This is why the overlaying text was added to the MMR row in Table 1.

The only change to the "Meningococcal Vaccination" section this year is the addition of guidance in the "Special Situations for MenB" section states that "If dose 3 is administered earlier than 4 months after dose 2, a fourth dose should be administered at least 4 months after dose 3."

Page 4 of the notes begins with the "Pneumococcal Vaccination" section. Notably, this section does not include the ACIP's vote during this meeting. This vote will be incorporated into this section as soon as possible. A bullet has been added under both "Routine Vaccination" and "Special Situations" that states, "For guidance on determining which pneumococcal vaccines a patient needs and when, please refer to the mobile app which can be downloaded here: www.cdc.gov/vaccines/vpd/pneumo/hcp/pneumoapp.html.

In light of the ongoing polio response that started in the summer, a new "Polio Vaccination" section was added to Page 4 of the notes. Although the "Routine Vaccination" section states that "Routine poliovirus vaccination of adults residing in the United States is not necessary," the "Special Situations" section includes recommendations stating that "Adults at increased risk of exposure to poliovirus with no evidence of a complete polio vaccination series (i.e., at least 3 doses): administer remaining doses (1, 2, or 3 doses) to complete a 3-dose series." "Adults at increased risk of exposure to poliovirus with evidence of completed polio vaccination series (i.e., at lease 3 doses): may administer one lifetime IPV booster dose." Detailed information about these recommendations can be found at the hyperlink provided in this section.

"Tetanus, Diphtheria, and Pertussis Vaccination" is the last section on Page 4 of the notes. Here, minor edits were made in the guidance listed under "Special Situations" to improve the clarity of the language. This language now states that for persons who "Previously did not receive primary vaccination series for tetanus, diphtheria, and pertussis: 1 dose Tdap followed by 1 dose Td or Tdap at least 4r weeks later, and a third dose of Td or Tdap 6–12 months later."

On Page 5 of the notes, a few changes were made to the "Zoster Vaccination" section this year. A noted was added at the end of the "Routine Vaccination" section to provide some background on serologic evidence of prior varicella. This note reads, "Serologic evidence of priori varicella is not necessary for zoster vaccination. However, if serologic evidence of varicella susceptibility becomes available, providers should follow ACIP guidance for varicella vaccination first. RZV is not indicated for the prevention of varicella, and there are limited data on the use of RZV in persons without a history of varicella or varicella vaccination." Language was added under "Special Situations" to clarify the immunocompromising bullet that states, "Immunocompromising conditions (including persons with HIV regardless of CD4 counts)**: 2-dose series recombinant zoster vaccine (RZV, Shingrix) 2-6 months apart (minimum interval 4 weeks; repeat dose if administered too soon). A hyperlink is provided for providers to learn more. A note has been added to the end of the "Special Situations" section to provide some background for persons with immunocompromising conditions who do not have a documented history of prior varicella infection, varicella vaccination, or prior herpes zoster. This note reads, "If there is no documented history of varicella, varicella vaccination, or prior history of herpes zoster, providers should refer to the clinical considerations for use of RZV in immunocompromised adults aged ≥19 years and the ACIP varicella vaccine recommendations for further guidance: www.cdc.gov/mmwr/volumes/71/wr/mm7102a2.htm.

Turning to the "Appendix" section that lists all of the contraindications and precautions to each of the adult vaccines. The first change is to the header of the appendix table to "Contraindicated or Not Recommended." Just like last year's appendix, the first page of the appendix lists all of the contraindications and precautions for the influenza vaccine. The "Precautions" column no longer lists having an egg allergy since any influenza vaccine appropriate for age and health status may be administered to persons with an egg allergy.

The second page of the appendix lists all of the contraindications and precautions to all of the non-influenza vaccines. In the HepB row, the language regarding pregnancy has changed. It now reads that "Heplisav-B® and PreHevbrio® are not recommended due to lack of safety data in pregnant persons. Use other hepatitis B vaccines if HepB is indicated." The language for pregnancy in the HPV row also has changed. It now reads, "Pregnancy: HPV vaccination not recommended."

Discussion Points

Regarding hepatitis A on Table 1, Dr. Lee did not recall an ACIP recommendation for 4 doses of hepatitis A vaccine.

LCDR Murthy indicated that this was just to accommodate for the dosing regimen if Twinrix® is used, which also would confer protection for hepatitis A.
Dr. Lee thought from a recommendation standpoint if would be clearer if they said, "2 or 3, but 4 are acceptable." She did not believe there was a recommendation for 4 doses, though there is a recommendation for the combined vaccine. Since COVID-19 vaccines are on the schedule, she also wondered whether they also should be included in the "Contraindications and Precautions" section.

Dr. Wodi indicated that there has been discussion about adding COVID-19 in the table and appendix. There might be an update before the 2024 schedule, so the decision was made not to make a change at this time.

Regarding Table 2 that states “See Notes” for COVID-19 vaccine immunosuppressed and various HIV populations, Dr. Kotton pointed out that it was flagged to the right of that. She suggested including the same language as Table 1 where it says “2- or 3- dose primary series and booster (See Notes)” for clarification.

Dr. Goldman suggested that perhaps language could be added as in the past that states “anyone seeking protection from hepatitis B” for clarification in the notes for ≥60 years of age for hepatitis B that states “may receive.”

LCDR Murthy indicated that they could speak with the hepatitis B experts about that suggestion.

Recognizing that there are constantly dynamic changes with COVID-19, Dr. Lee suggested linking back to the Clinical Guidance in the schedule so people can look it up and link back to the original.

LCDR Murthy referred to the link in a box at the top of the Appendix that links providers to the contraindications and precautions for COVID-19 vaccinations. The hope is to incorporate that formally as a row in the Appendix once they are able to do so.

Motion/Vote: Combined Immunization Schedules

The following language was proposed for the vote on the combined immunization schedules:

> *Approve the Recommended Child and Adolescent Immunization Schedule, United States, 2023, and the Recommended Adult Immunization Schedule, United States, 2023*

Motion/Vote: Combined Immunization Schedules

Dr. Poeling made a motion for ACIP to approve the Recommended Child and Adolescent Immunization Schedule, United States, 2023, and the Recommended Adult Immunization Schedule, United States, 2023 with the considerations discussed. 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:	Bahta, Bell, Brooks, Chen, Cineas, Daley, Kotton, Lee, Loehr, Long, McNally, Poehling, Sanchez, Shah, Talbot
0 Opposed:	N/A
0 Abstained:	N/A

ADULT RESPIRATORY SYNCYTIAL VIRUS (RSV)

Session Introduction

Camille Kotton, MD (Chair, Adult RSV WG) introduced the adult RSV session. She reminded everyone that the February 2022 session included an introduction to the Adult RSV WG, orientation to the multiple vaccine products in development to prevent RSV disease in adults, an overview of RSV virology and immunology, and an introduction to the seasonality and burden of RSV disease in the US. Recent WG activities have included discussions on the selection of efficacy and safety outcomes for the review of RSV vaccines for older adults, a presentation from GSK on the safety and efficacy of adjuvanted RSVpreF3 vaccine in adults 60 years of age and older, and a presentation from Pfizer on the safety and efficacy of bivalent RSVpreF vaccine in adults 60 years and older. In addition, there have been WG discussions regarding potential barriers to uptake of a novel RSV vaccine for older adults, including lack of patient and provider awareness of the importance of RSV as a pathogen in older adults, concerns about vaccine fatigue given that there have been multiple COVID-19 boosters, the increasing complexity of the adult immunization schedule, and potential public and/or provider hesitancy to co-administer RSV vaccine with other indicated vaccines that could make a vaccine rollout somewhat complicated. The agenda for this session included presentations on the safety and efficacy of RSVpreF3 and RSVpreF and WG considerations.

GSK RSV OA Candidate Vaccine Clinical Development

Bishoy Rizkalla, PhD (GSK Global Medical Affairs) presented the results from the GSK RSV Older Adult Vaccine Clinical Development Program. He pointed out that the journey to a viable vaccine that addresses the significant burden of disease associated with RSV in adults 60 years of age and older and those with underlying comorbidity has been multiple decades long, and that it was with great appreciation to the study participants, site staff, study investigators, GSK scientists, and R&D organization that he was able to present positive results to the ACIP. During this session, he presented key results from 3 of GSK's Phase 3 studies: 1) AReSVi-004 among adults ≥60 years of age to assess safety, reactogenicity, immunogenicity, persistence, and revaccination[86]; 2) AReSVi-006 pivotal efficacy study among older adults ≥60 years of age[87]; and 3) RSV-007 among older adults ≥60 years of age to assess safety, reactogenicity, and immunogenicity when co-administered with FLU-QIV[88].

The final formulation of the vaccine selected and used in the Phase 3 program is an antigen adjuvant combination that is designed to induce a robust humoral and cellular mediated immune response to help protect older adults and those with underlying comorbidities. The vaccine targets the RSV F protein and is engineered to maintain the pre-fusion confirmation of this protein.[89] 120 µg of the RSVPreF3 antigen is combined with GSK's $AS01_E$ adjuvant system to help boost the RSV CD4+ T-cell response in older adults. This is the same adjuvant system that's used in the GSK shingles vaccine.[90] However, the $AS01_E$ that is used in GSK's RSV vaccine contains half the dose of adjuvant.

[86] ClinicalTrials.gov, 2022 NCT04732871. https://clinicaltrials.gov/ct2/show/NCT04732871
[87] ClinicalTrials.gov, 2022. NCT04886596. https://clinicaltrials.gov/ct2/show/NCT04886596
[88] ClinicalTrials.gov, 2022. NCT04841577. https://clinicaltrials.gov/ct2/show/NCT04841577
[89] Graham BS, et al. Curr Opin Immunol. 2015;35:30–38; and Leroux-Roels I, et al. J Infect Dis. 2022:jiac327
[90] Leroux-Roels I, et al. J Infect Dis. 2022:jiac327

AReSVi-004 is an ongoing study that assesses the immunogenicity, safety, reactogenicity, and persistence of a single dose of the RSVPreF3 OA investigational vaccine and different revaccination schedules in adults ≥60 years of age in 3 arms: 1 initial dose with annual revaccination, 1 initial dose with revaccination at Month 24, and 1 dose with no revaccination. The data presented during this session were from 12 months following initial vaccination. There are 3 datasets that denote the immune response by different age strata of 60─69 years of age, 70─79 years of age, and ≥80 years of age. The vaccine induces a robust humoral and polyfunctional CD4+ T-cell response as seen by the peak 30 days following vaccination. This immune response is sustained over the 360 days following a single dose of the vaccine to levels well above those at pre-vaccination in all of the age groups. These data support that the vaccine is able to induce a robust and persistent immune response consistently across the broad spectrum of age in this older adult population.

AReSVi-006 is the Phase 3 pivotal efficacy study. This is an ongoing randomized, placebo-controlled, observer-blind, multi-country study to demonstrate the efficacy of a single dose and annual revaccination doses of GSK's RSVPreF3 OA investigational vaccine in adults ≥60 years of age. This study will evaluate the efficacy and safety of the vaccine over the course of 3 RSV seasons. The data presented during this session were following the first RSV season. In this study, approximately 25,000 study participants ≥60 years of age and older were recruited across 17 countries. Participants were 1:1 and randomized to receive either an RSVPreF3 vaccine or placebo. The primary endpoint of the study is to demonstrate the efficacy of a single dose of the GSK RSV vaccine in the prevention of RSV-associated lower respiratory tract disease (LRTD) in the first RSV season. Through the subsequent 2 seasons of the study, GSK will be able to demonstrate the efficacy of a single dose of this vaccine over the 3 RSV seasons, as well as the efficacy of the GSK vaccine when administered annually.

LRTD is defined in these studies as a participant who experiences at least 2 lower respiratory signs or symptoms, of which at least one must be a lower respiratory sign, or a participant who experiences at least 3 lower respiratory symptoms. All cases of RSV-associated LRTD were adjudicated by an independent external adjudication committee. The demographic characteristics of participants recruited are representative of the older adult population. The subjects recruited from the US represent 28% of the overall study population. Sites across 23 states and 8 HHS Service Regions recruited approximately 7,000 study participants. Importantly, participants with a medically stable chronic condition could participate in the study. Approximately 39% of the overall population had at least 1 pre-existing comorbidity of interest known to increase the risk of severe RSV disease. Participants with chronic obstructive pulmonary disease (COPD), asthma, congestive heart failure, diabetes, and advanced renal or liver disease make up this 39% proportion.

The primary endpoint of a single dose of RSVPreF3 in older adults was met through GSK's Phase 3 program with a demonstrated efficacy of 82.6% in the prevention of RSV-associated LRTD. There is great confidence around this point estimate with the lower bound of the confidence interval being well above the pre-specified criteria for success that has been agreed to with regulatory authorities. Consistently high vaccine efficacy (VE) was demonstrated across the full spectrum of RSV disease, with an observed efficacy of 71.7% in the prevention of RSV-associated ARI. This endpoint casts a wide net to capture upper and lower respiratory symptomatic RSV cases broadly. This is an important result in the context of the millions of symptomatic cases experienced by older adults annually. In terms of the more severe end of the disease spectrum, very high VE of 94.1% was observed in the prevention of severe RSV-associated LRTD. Although a lower frequency of hospitalizations was observed with 2 cases in the first season, this can be expected due to several reasons. The first season of this ongoing

study took place during the COVID-19 pandemic. This is a period when enrolled adults were commonly practicing social distancing and wearing masks, and investigators worldwide reported declines in hospitalizations due to non-COVID respiratory infections. Additionally, this is in the context of the clinical trial setting where there is close follow-up and protocol-defined medically attended visits.

GSK will continue to collect data to demonstrate the impact on hospitalization and other patient-reported outcomes over the upcoming seasons of the study. Importantly, the consistently high efficacy of this vaccine across the full spectrum of RSV disease has the potential to deliver clinically meaningful impact on the significant annual burden of RSV disease in older adults. The high VE against RSV-associated LRTD was observed over the 6.7-month follow-up period. Looking at the cumulative incidence curve, there is clear separation between the RSV and placebo groups very early, which is sustained over the duration of the follow-up period. This supports the efficacy of the vaccine candidate over the course of an entire RSV season. High and consistent efficacy also was observed in the more vulnerable subgroups at 92.9% in the prevention of RSV-associated LRTD in the pre-frail population, 93.8% in those with advancing age of 70─79 years, and 94.6% in those with pre-existing comorbidities of interest that are known to increase the risk of severe RSV-associated disease. Due to too few cases being observed in adults ≥80 years and those considered frail, it was not possible to conclude VE in these subgroups. In this regard, it is important to evaluate the immune response in these specific subgroups.

The immunogenicity data from a subset of participants in this efficacy study by the same age strata demonstrate that the vaccine induces a robust and consistent functional antibody response regardless of the underlying age of the study participant. The same trend is observed in terms of the immune response by baseline frailty status, with the vaccine inducing this consistent immune response regardless of the underlying frailty status of the participants. Looking at the efficacy by RSV subtype, it is important to note that the high efficacy seen in this study was in the context of an RSV-B dominant season with almost two-thirds of all RSV LRTD cases associated with an underlying RSV-B infection. However, the RSV F protein is highly conserved across both RSV-A and RSV-B. The vaccine demonstrates this high efficacy consistently regardless of RSV-A or RSV-B subtype.

Transitioning now to safety, the study evaluated solicited AEs following vaccination through the use of daily diary cards in a subset of study participants. In terms of local and systemic events for the 4 days following vaccination by event severity, the most frequent local event was pain and the most frequent systemic event was fatigue. Most of these events were mild to moderate in severity, with very low frequency of Grade 3 events observed following vaccination. The events were transient with the median duration of the events subsiding between 1 to 2 days. Most unsolicited AEs within 30 days in all participants were mild to moderate in severity, with a low frequency of Grade 3 events seen within 30 days of vaccination. This is the largest and only placebo-controlled study in GSK's Phase 3 program with approximately 25,000 study participants. The rate of SAEs, fatal SAEs, or potential immune-mediated diseases (pIMDs) were balanced between the 2 arms 6 months following vaccination. Of note, there was a single case of GBS observed in a participant in the open-label immunogenicity study presented earlier. who has since recovered. The association was temporal in nature. However, with the evidence available, GSK cannot confirm the diagnosis or exclude an alternative etiology. Importantly, the Independent Data Monitoring Committee (IDMC) overseeing this efficacy study has not identified any safety concerns during the regular reviews of unblinded safety data.

RSV-007 is an open-label, randomized, controlled, multi-country study to evaluate the immune response, safety, and reactogenicity of the RSVPreF3 investigational vaccine when co-administered with seasonal influenza vaccines in adults ≥60 years of age. This is an important feature in the context of the overlapping seasonality of RSV and influenza and potentially may be an important feature to support programmatic flexibility and implementation of RSV vaccination in the future. This study specifically assesses co-administration of GSK's RSV vaccine with inactivated quadrivalent influenza vaccine (FLU-QIV). The primary endpoint of this study is the non-inferiority of the functional immune response of the vaccines when co-administered versus administration of either vaccine alone. A GMT ratio of 1.5 was set as the criteria for success for non-inferiority. The primary endpoint was met with all influenza antigen HI titers and RSV-A and RSV-B laboratory responses not exceeding the GMT ratio 1 month after vaccination. This supports that the GSK vaccine can be co-administered with FLU-QIV without immune interference of either vaccine. In light of the ACIP flu recommendations that were made in June 2022 for older adults, GSK also is conducting 2 additional co-administration studies with high-dose and adjuvanted influenza vaccines. The data for these studies will be presented to ACIP as they become available.

In conclusion, the GSK RSV vaccine candidate for adults ≥60 years of age provides a high and consistent efficacy across the full spectrum of RSV disease regardless of RSV-A or RSV-B subtypes. The vaccine induces a robust and persistent immune response consistently across the broad spectrum of age in this older adult population. Supporting programmatic and implementation flexibility, the vaccine can be co-administered with inactivated quadrivalent influenza vaccines. The vaccine was well-tolerated with a favorable safety profile. In the context of the significant annual burden of disease in older adults and those with underlying co-morbidities, the GSK RSV vaccine candidate has the potential to deliver clinically meaningful impact for older adults and for public health. GSK looks forward to continuing to work with the RSV Adult WG over the coming months. Pending FDA approval, GSK anticipates enabling access to the vaccine ahead of the 2023-2024 RSV season.

Discussion Points

Dr. Talbot expressed her extreme excitement for this vaccine as someone who has conducted RSV research in older adults for a while. She is excited to see the prevention of acute respiratory illness that likely also will have large impacts on hospitalization. A much higher number of individuals ≥70 and ≥80 should have been enrolled in order to assess VE among these groups, given that these are the groups with the highest morbidity and mortality over individuals 60–69 years of age. She requested additional information about the cases of GBS that were reported, including whether they were in the placebo or vaccine group.

Dr. Rizkalla clarified that there was 1 case of GBS throughout the program that was observed in the open-label immunogenicity study. He invited his colleague Peggy Webster, Head of Vaccines Safety at GSK, to make a comment.

Dr. Webster added that the single case of GBS was reported in the open-label RSV004 study, which was the only case observed in the aggregated safety analysis across all of the studies in the RSV Older Adult Program, with data from more than 15,000 exposed participants. For this particular case, the investigator considered that there was a reasonable possibility that the event was associated with the RSV older adult vaccine. Based on the information GSK received, the case met the third level of diagnostic certainty according to the Brighton Collaboration case definition of GBS. It occurred within the risk window for GBS as a vaccine-related reaction. While the clinical signs and serological parameters reported to GSK can be

present in several neurological disorders, a neurological consultation and/or electrophysiologic (EP) testing were not reported. Additionally, it was not reported if alternative causes for the participant's symptoms were investigated. As such, the company concluded that the reported information was not sufficient to either confirm the diagnosis of GBS or exclude possible alternative etiologies. The participant fully recovered.

Dr. Poehling reported that children's hospitals across the US are seeing a significant early RSV season from which there will be considerable important data. She applauded the approach of comparing placebo, a 1-dose, and an annual dose and thinks this will be very important. She asked what placebo was used, if she understood correctly that the adjuvant was the same as that used in the shingles vaccine, and if any trials are planned to compare those who have received the shingles vaccine with those who have not.

Dr. Rizkalla indicated that the placebo is saline and the adjuvant in GSK's RSV vaccine is using the $AS01_E$ adjuvant system, which is distinct from the $AS01_B$ that is used in GSK's shingles vaccine that contains double the amount of adjuvant. The study has not compared those who have/have not received shingles vaccine.

Ms. Bahta requested further information about the criterion of frailty.

Referring to Side 25, Dr. Rizkalla indicated that frailty was assessed using the Gait Speed test, which is one component of the Short Physical Performance Battery (SPPB) measurement. He called upon his colleague Veronica Hulstrom, Clinical R&D Project Lead, to review more of the details.

Dr. Hulstrom added that frailty was assessed by a Gait Speed test that basically allows 2 lengths of a walk of 3 or 4 meters in which the participant walks down the hallway through a 1-meter zone for acceleration, a central 4-meter testing zone, and a 1-meter zone for acceleration. The timing is recorded and reported in the eCRF and further grouped as follows:

- ❑ Frail, participants with a walking speed <0.4 m/s or not able to perform the test (reasons might include: tried but unable, could not walk unassisted, not attempted – study staff or participant felt unsafe, participants unable to understand the instructions)
- ❑ Pre-frail, participants with a walking speed of 0.4–0.99 m/s
- ❑ Fit, participants with a walking speed ≥1 m/s

Dr. Kotton emphasized that this could be a significant vaccine for the immunocompromised host community in that they can suffer from severe life-threatening and deadly RSV infections. While that population was omitted from the initial trials, she expressed hope that they eventually would be included and would benefit from this vaccine. She remains significantly concerned about the case of GBS with respect to the elderly population toward whom this vaccine is focused. Even though the adjuvant is different, GBS also was seen with SHINGRIX. The package insert for SHINGRIX has been amended to include information about GBS, so she wondered whether GSK is doing further work to look at this. It is unfortunate that the individual with presumed GBS did not have a neurologic evaluation, which makes things challenging for everybody. In terms of safety, she asked whether GSK had any thoughts about whether this case could be related to adjuvant in that both the RSV and shingles vaccines are adjuvanted.

Dr. Webster indicated that the findings from a post-marketing observational study among the US Medicare beneficiary population, which was performed to evaluate for an association between vaccination with SHINGRIX and GBS, were published the previous year. The primary analysis, which was claims-based and included all doses, found a slightly increased risk of GBS during the 42 days following vaccination with SHINGRIX, with an estimated 3 excess cases of GBS per million doses administered. The benefit-risk balance remained in favor of vaccination, as SHINGRIX is efficacious in decreasing the risk of herpes zoster and its complications. The analysis that was performed by the CDC, CMS, and FDA was robust and provided new and significant safety information for SHINGRIX about a potential risk that is serious or otherwise clinically significant and therefore has implications for prescribing decisions or for patient management. The company continues to closely monitor reports of GBS associated with SHINGRIX vaccination through proactive enhanced pharmacovigilance. Incident cases of GBS are being measured as one of the objectives of an ongoing targeted safety study. GSK would be happy to follow up with the WG after the meeting to provide a response with additional information regarding the safety profile of SHINGRIX, if desired.

Dr. Kotton thought it would be helpful to have that information. With respect to the trial, she was glad to hear that there will be more RSV disease activity this season to better analyze the vaccine. She also remained concerned that there were overall very small numbers of patients who developed RSV infection in terms of the impact that would have on the data.

Dr. Philip Dormitzer, GSK Global Head of Vaccines R&D, responded that it is important to distinguish between the number of overall cases of RSV illness and severe RSV illness. While there was quite a good number of cases of RSV illness, there were relatively few hospitalizations and cases of severe illness. GSK expects to accumulate much more data over the course of the next 2 seasons.

Dr. Chen congratulated GSK on the positive efficacy signal. It is very exciting for the RSV vaccine field to see a successful candidate. He reiterated that it would be nice to see this kind of efficacy in frailer older adults and to make sure that the efficacy of this vaccine is understood in older adults who have limited independence. Nursing home and homebound populations of older adults continue to be a concerning part of the population who suffer from the burden of RSV disease. Continuing to look at older adults with multiple chronic medical conditions and who are immunocompromised will be very helpful in terms of understanding the efficacy of this vaccine.

Dr. Rizkalla indicated that the frail population, as assessed by the Gait Speed test, represents approximately 1.2% of the recruited population, so GSK has not been able to accrue enough cases to be conclusive on the efficacy in that group. However, efficacy in the pre-frail population was observed to be 92.9% and 94.6% in those with at least 1 pre-existing comorbidity of interest, which gave GSK confidence that this vaccine will infer a protective benefit in these at-risk sub-populations in the older adult population.

Ms. McNally indicated that as ACIP's Consumer Representative, she wondered whether GSK could response to Dr. Kotton's comment that there may be providers who have some reluctance about co-administration of this vaccine with other vaccines.

Dr. Rizkalla indicated that the study demonstrated the immune response with co-administration of the GSK RSV vaccine with inactivated quadrivalent influenza vaccine. There is an extensive program in place that evaluates the co-administration of other vaccines that are used in older adults, starting with a priority dose of influenza vaccine, looking at high-dose influenza and

adjuvanted influenza vaccine. These studies have been posted on clinicaltrials.gov and have initiated recruitment. GSK will present further details to the WG when available. Moving beyond influenza, other co-administration studies in this older adult population will be initiated, including COVID-19 mRNA vaccination, which in an endemic context potentially could be used with overlapping seasonality.

Dr. Sanchez asked whether more severe illness was seen among those who developed RSV who received the vaccine and what the characteristic illness was in those patients. In addition, he inquired as to whether GSK is studying prevention of transmission, any asymptomatic testing, and whether the vaccine will prevent transmission within the household to others. He thinks looking at other modes of transmission would be important.

Dr. Rizkalla pointed out that the trigger for this study is symptomatic ARI disease, both upper and lower respiratory tract disease. GSK has not assessed asymptomatic cases, given that ARI is the trigger. Referring to Slide 32 regarding medical attendance beyond the protocol-defined visits in the study, 29% of participants experiencing an ARI sought additional medical attendance. Of those in the placebo, 40% sought additional medical attendance for an ARI-related diagnosis. For those with LRTD in the vaccine arm, 42.8% sought additional medical attendance compared to 60% in the placebo arm. They also have patient-reported outcomes, which has demonstrated a symptomatic benefit in the cases in the active arm.

Dr. Loehr requested clarification about whether “engineered antigen” means recombinant engineering. Referring to Slide 12, he asked whether the list on the righthand side that has 95 ARIs, 40 LRTDs, and 17 severe were 3 separate categories or the severe subset of the LRTD subset of the ARI. That is, if he counts the placebo groups, he could either have 3 different groups adding up to about 150 or 1 group of 95 and 2 subsets.

Regarding the recombinant engineering question, Dr. Dormitzer responded that this is correct and means that there are mutations in the protein sequence to stabilize it in the pre-fusion conformation. These are the mutations developed at the NIH as part of their prototype for this vaccine.

Responding to the placebo question, Dr. Hulstrom responded that it is a subset. Dr. Rizkalla added that of the 95 cases who experienced symptoms according to the definition of ARI, 40 went on to be classified as LRTD. Of the 40 classified with LRTD, 17 were considered severe.

Dr. Long asked whether GSK has information on all-cause ARI or LRTD to answer the safety question that this is not detrimental or possibly is helpful for other infections and the burden is under-appreciated, and if there was anybody in this group who had coronavirus infection and how they did with this vaccine.

Dr. Hulstrom indicated that no subgroup analyses have been performed in terms of a COVID occurrence group.

Dr. Rizkalla added that the all-cause group met the definition for ARI and went on to be confirmed as RSV-associated by RT-PCR. Other respiratory viruses were not part of the design of the study.

Safety and Efficacy of Bivalent RSV Prefusion F Vaccine in Adults ≥60 Years of Age

Alejandra Gurtman, MD, FIDSA (Pfizer Vaccine Clinical R&D) presented data on the safety and efficacy of Pfizer's bivalent RSVpreF vaccine in adults ≥60 years of age. The Pfizer RSVpreF consists of bivalent stabilized prefusion F proteins based on prefusion F conformations from the contemporary RSV-A and RSV-B strains. RSVpreF elicited high neutralizing titers for both RSV-A and RSV-B in Phase 1/2 studies that initially supported both of Pfizer's targeted indications that included maternal immunization for the prevention of RSV lower respiratory tract illness (LRTI) in infants and active immunization of older adults for the prevention of RSV-associated LRTI.[91] Pfizer's Older Adult Clinical Development Program has been comprehensive and includes adults ≥18 years of age in 6 studies. Pfizer tested 3 dose levels with and without aluminum and also formulations with and without CpG. Early on, studies demonstrated that RSVpreF was immunogenic in a non-adjuvanted formulation and that adding aluminum or CpG conferred no immunological benefit. The final dose selected was 120 µg containing 60 µg of A and 60 µg of B strains and the vaccine is unadjuvanted.

For this session, Dr. Gurtman focused on the results of Pfizer's Phase 3 pivotal efficacy study titled RENOIR (The **R**SV vaccine **E**fficacy study i**N** **O**lder adults **I**mmunized against **R**SV disease), which is the VE study in older adults. The RENOIR study is a global Phase 3 study designed to evaluate the efficacy, immunogenicity, and safety of the bivalent pre-fusion F subunit vaccine in adults. The RENOIR study is being conducted at 240 sites in 7 countries, including the US. The study is targeted to enroll up to 40,000 participants ≥60 years of age. Participants are randomized 1:1 to receive either RSVpreF 120 µg or placebo. Randomization is stratified by the age groups 60–69 years, 70–79 years, and ≥80 years. Participants are eligible if they are healthy or have stable chronic conditions, including stable cardiopulmonary disease, diabetes, asthma, or COPD. Immunocompromised persons or those who have serious chronic disorders are excluded.

Regarding safety monitoring, a subset of participants completed a daily e-diary to monitor local reactions and systemic events for 7 days after vaccination. Unsolicited AEs are captured through 1 month after vaccination in all participants. SAEs and newly diagnosed chronic medical conditions are captured through the end of the study. In addition, all participants undergo active surveillance for ARI by completing a weekly e-diary. If ARI symptoms arise, participants perform a self-nasal swab and contact the investigational site. The site conducts a clinical assessment, capturing details of any ARI symptoms. Depending upon the investigator's judgment, the illness visit may be conducted in person or remotely. When an in-person visit is completed, an additional nasal swab is collected. A subset of participants have blood draws at 3 pre-specified time points to assess immunogenicity, the data for which were not presented during this session.

To describe the key study definitions, ARI is defined as having 1 or more symptoms lasting more than 1 day (e.g., nasal discharge, nasal congestion, sore throat, cough, sputum production, wheezing, or shortness of breath). These are the symptoms for which all participants complete the weekly e-diary surveillance entry, which triggers the self-nasal swab and contact with the investigational site. LRTI is an ARI with 2 or 3 signs or symptoms of new or worsening cough, sputum production, wheezing, shortness of breath, or tachypnea. Severe LRTI (sLRTI) is defined as LRTI plus at least 1 objective criterion (e.g., hospitalization due to

[91] Falsey A., et al. J. Infect Dis 2022;225(12):2056-2066; Walsh E., et al. J. Infect Dis 2022;225(8):1357-1366; and Baber J., et al. J. Infect Dis 2022 May 11;jiac189.

RSV, new or increased oxygen supplementation, and new or increased mechanical ventilation, including CPAP). Dr. Gurtman did not present an analysis on severe illness during this session as they did not accumulate enough severe cases at the time of this analysis. A case definition of RSV-associated ARI or RSV-associated LRTI is made when a participant has at least 2 or 3 symptoms or severe illness and a positive validated RSV PCR test.

For safety, the objective was to describe the safety profile of the RSVpreF vaccine. The primary efficacy objective was to demonstrate the efficacy of RSVpreF in preventing RSV-associated LRTI with at least 2 or at least 3 signs or symptoms in the first RSV season following vaccination. There are several secondary efficacy objectives, including efficacy against RSV-associated ARI and severe RSV-associated LRTI in the first season. Additional objectives include efficacy of the vaccine in the second season and across 2 seasons. The focus of this session's presentation was safety, LRTI, and ARI. As with many VE studies, RENOIR was designed as a fixed event trial. The analysis presented during this session was a per protocol pre-planned interim analysis. The endpoints were considered to be the final analysis. Pfizer has an agreement with regulatory agencies on licensure criteria, including VE with a lower bound of at least 20% and agreement on the case definitions for LRTI, ARI, and sLRTI. The Type 1 error for this interim analysis was adjusted for the interim analysis.

To present the interim analysis results of the study starting with enrollment and demography, a total of 34,284 participants were enrolled, all of whom are included in the safety database. In terms of demographic characteristics, the RSVpreF and placebo groups were balanced in terms of sex, race, ethnicity, and age. About a third of the participants were 70—79 years of age and about 6% in each group were ≥80 years of age. In terms of pre-specified significant conditions, approximately 50% of the participants had 1 medical condition, 15% in each group had at least 1 chronic cardiopulmonary condition, and about 19% in each group had diabetes.

Local reactions within 7 days of vaccination were more frequently reported in the vaccine group than in the placebo group at 12.1% versus 6.6%, respectively. The most frequently reported local reaction was pain at injection site, followed by redness and swelling. Most local reactions were mild, lasted 1 to 2 days, and resolved. The proportion of participants who reported a systemic event within 7 days were similar in the vaccine and the placebo groups at 27.4% and 25.7%, respectively. The most frequently reported systemic events were fatigue, headaches, and muscle pain. These were similar across the groups. There was only 1 Grade 4 event of a fever of 40^0 on the day of vaccination in a participant in the placebo group. Most events were mild or moderate and of short duration. For unsolicited AEs from vaccination through 1-month follow-up, about 9% of participants in each group reported any AE. The frequency of related, immediate, severe, and life-threatening AEs was similar in the vaccine and placebo groups. Newly diagnosed chronic medical conditions also were similar in both groups. There were 3 SAEs deemed by the investigators to be related to the vaccine. AEs leading to withdrawal from the study or leading to death were similar in the vaccine and placebo groups. AEs leading to death were reported in 52 RSVpreF recipients and 49 placebo recipients. The primary causes of death most frequently reported were in the system organ class of cardiac disorders. None of the deaths were assessed as related to the study.

Among the 3 RSVpreF recipients reporting SAEs assessed as related by the investigator, the first was an allergic reaction in a 61-year-old female 7 hours after vaccination that resolved on the same day. It was seen to be a delayed allergic reaction and not anaphylaxis. The second event was a retrospective diagnosis of a Miller Fisher Syndrome (MFS) in a 66-year-old female in Japan with a limited work-up. An anti-GQ1B IgG was negative and no conduction studies were done. This case meets Level 4 of the Brighton Collaboration. The third event was GBS in a

66-year-old male in the US who developed a non-ST elevation myocardial infarction requiring angioplasty 7 days after vaccination, followed by slow progression of lower extremity weakness and ataxia. The conduction study was consistent with acute demyelinating polyneuritis of the lower extremities. This case meets Brighton Collaboration Level 1. All of these cases were evaluated by Pfizer's external DMC who did not identify any safety signals and recommended continued enrollment into the study. At the time of this presentation, more than 20,000 participants had been exposed to the vaccine with no additional unexpected SAEs identified.

Turning to the efficacy of the vaccine, this analysis looked at RSV-associated LRTI defined by at least 2 symptoms. There were 11 cases in the vaccine group and 33 in the placebo, with an observed efficacy of 66.7% and a lower confidence interval of 28.8%. For those who had at least 3 symptoms, there were 2 cases in the vaccine group and 14 cases in the placebo group. This resulted in VE of 85.7% with a lower confidence interval of 32%, indicating an even higher efficacy against more severe disease. In terms of the difference between the 2 groups, among the RSV LRTI cases with 2 or more symptoms, cough and sputum production were the most common symptoms reported. For the cases involving 3 or more LRTI symptoms, wheezing, shortness of breath, and tachypnea were more frequently reported, which is consistent with more severe disease.

Looking at the cumulative case accrual curve from the day of vaccination for RSV-associated LRTI with at least 2 symptoms, VE was shown after Day 15 and persisted for at least 6 months. This is sufficient to cover a typical RSV season. Similarly, the cumulative figure for RSV-LRTI with at least 3 symptoms showed that VE persisted for at least 6 months. VE in those with 2 symptoms or 3 symptoms was consistent across different subgroups, including age and those with pre-specified high-risk conditions. It is important to note that the numbers were small for each subgroup and the confidence intervals were somewhat wider. RSVpreF was efficacious in terms of RSV-associated ARI, with 22 cases in the vaccine group and 58 cases in the placebo group. This resulted in VE of 62% with a lower confidence interval of 37%, which indicates that RSVpreF also protects against less severe disease—primarily upper respiratory disease. Looking at efficacy by subgroups A and B across those with 3 symptoms, 2 symptoms, or just ARI, VE was consistent for both strains as well.

In conclusion, the interim analysis for the RENOIR Phase 3 pivotal trial has demonstrated that RSVpreF is safe and well-tolerated. Local and systemic events were mostly mild to moderate and short-lived, and the AE profile did not suggest any safety concerns for RSVpreF vaccination in adults ≥60 years of age. RSVpreF was highly efficacious in reducing RSV-associated LRTI in adults ≥60 years of age and in reducing RSV-associated ARI in this age group. The study is ongoing, and Pfizer anticipates having additional data in the future. Dr. Gurtman acknowledged and thanked all of those who make this possible, including the clinical trial participants and their families, study sites, investigators, partners, and staffs.

Discussion Points

Dr. Talbot emphasized that while it is great that a vaccine designed for older adults that can prevent ARI and hospitalizations is being tested, the study is underpowered for those ≥70 years of age. It is very important when conducting studies that they be conducted among the adults among whom they are intended to be used. No data were presented on frailty, which is incredibly important to distinguish. VE is higher in those who are not frail and lower in those who are frail, which offers a concept of how well they will be used and how effective they will be. She asked whether the cases of GBS and MFS were in the placebo or active component. In addition, she asked whether any data are available on re-immunization.

Dr. Gurtman indicated that about 30% of the participants are 70─79 years of age and agreed that the number of those ≥80 years of age is not as good as everyone would like. While it is more difficult to enroll those subjects in clinical trials, the study met the numbers targeted per protocol and hopefully, there will be additional data. Pfizer continues to conduct other studies in which it would be good to have more participants who are ≥80 years of age. With respect to the GBS and MFS cases, both were active recipients of the RSVpreF vaccine. The MFS case was a Brighton Collaboration Criteria Level 4. It did not have enough information to document and also has a potential alternative cause, as the subject developed a sore throat and what seemed to be a viral syndrome approximately 7 to 8 days after vaccination. The GBS is confounded by a participant who had a myocardial infarction, which required a procedure immediately after that. He developed back pain that progressed to lower extremity weakness. It also is a complicated case. Both cases have potential additional causes other than the vaccine. In the opinion of the company and evaluation, it is hard to confirm that these cases could have been related to the vaccine. Frailty has not been assessed particularly in this study and Pfizer has data on re-vaccination from the Phase 1 study on subjects who received a different dose with 240 µg who were re-vaccinated a year later. The neutralizing antibody titers increased again. Potential re-vaccination in the study is anticipated depending upon what happens during the second season and the cases that are accumulated.

Dr. Poehling requested clarification about the placebo contents and whether the vaccine has any adjuvants.

Dr. Gurtman replied that the placebo is a lyophilized match that looks identical to the vaccine but does not contain the active ingredients. The vaccine has no adjuvants.

Referring to the primary outcome on Slide 7, Dr. Sanchez noted that he was somewhat confused about the differentiation between the acute and lower respiratory tract symptoms. In addition, he asked whether there has been any enhancement of RSV disease after immunization with the active vaccine.

Dr. Gurtman reminded everyone that the ARI symptoms include nasal discharge, nasal congestion, sore throat, cough, sputum production, wheezing, or shortness of breath lasting more than 1 day. Any of these triggers a swab and a consultation with the investigational site. Once the site is aware that a subject has at least 1 of these lasting more than a day. LRTI is an ARI with ≥2 or ≥3 lower respiratory tract signs/symptoms that are new or worsened. A positive PCR is also required.

Dr. Kotton noted that it was her understanding that MFS is related to GBS and requested further specification as to why this case was called MFS in terms of the timing after vaccine exposure and whether something was different about it or if it could be classified as GBS.

Dr. Maria Maddalena Lino, Safety Risk Lead Director at Pfizer, responded that this case was diagnosed as MFS because it has mainly ocular features and a cranial nerve disorder, primarily deferred cranial nerve. She emphasized that this is a diabetic patient and that this is often seen in diabetic patients. The subject reported fatigue, sore throat, and dizziness 8 days after vaccination, presented 3 weeks later, did not need any therapy, and recuperated completely within a couple of weeks. No diagnostic tests were performed to confirm the GBS. The diagnosis was retrospective and the anti-GQ1b was IgG negative.
Ms. McNally asked about the potential concern providers may have regarding the co-administration of this vaccine with other vaccines.

Dr. Gurtman indicated that an ongoing study has completed and co-administration results are anticipated within the next few months. There are additional plans to evaluate this vaccine with other vaccines that are given to older adults.

Dr. Lee asked whether there are any data on asymptomatic infection or transmissibility, which has been critical for COVID-19 and should be understood for all respiratory vaccines.

Dr. Gurtman indicated that at this time, Pfizer does not have data on asymptomatic infection or transmissibility. Additional studies are planned on co-administration.

ACIP Adult RSV Work Group Considerations

Michael Melgar, MD (CDC Lead, ACIP Adult RSV WG) presented a brief summary of the data reviewed by the WG and current WG considerations. The policy questions being considered by the WG are:

- ❑ Should vaccination with GSK's RSVpreF3 vaccine (120 µg antigen + AS01E adjuvant, 1 dose IM) be recommended for all older adults?

- ❑ Should vaccination with Pfizer RSVpreF vaccine (120 µg antigen, 1 dose IM) be recommended for all older adults?

Potential age thresholds being considered by the WG include, but are not limited to, ≥60 years of age and ≥65 years of age. As seen from both manufacturers, VE was largely invariant to participant age in the trials, provided that there were enough events to evaluate it in each stratum. Therefore, the age threshold for a policy recommendation must be informed by other considerations.

To revisit evidence pertaining to RSV-associated risks by age, Dr. Melgar reviewed seasonal rates of RSV-associated hospitalizations among US adults stratified by age estimated from CDC's RSV Hospitalization Surveillance Network (RSV-NET) during the 4 most recent RSV seasons before the COVID-19 pandemic. RSV-NET provides active, population-based surveillance of laboratory-confirmed RSV-associated hospitalizations at sites in 12 US states. The combined catchment areas are estimated to account for almost 90% of the US population. Hospitalization rates were substantially higher among adults 70–79 years of age and ≥80 years of age compared with younger age groups. Adults 60–64 years of age and 65–69 years of age experienced intermediate rates of hospitalization. Additional evaluation, including number of hospitalizations potentially averted by vaccination, will be shared with the WG and the ACIP before a policy recommendation is brought forward.

Evidence reviewed by the WG to date includes the epidemiology and burden of RSV in US adults, including RSV seasonality and population-based rates of medical visits, hospitalizations, and deaths; basic RSV virology and immunology; and the safety and efficacy data presented by GSK and Pfizer. In terms of the WG's summary and interpretation of the data shared by the manufacturers, both clinical trials showed significant efficacy against RSV LRTD or LRTI, which were the primary endpoint in these trials. The efficacy point estimate exceeded 60%. Notably, efficacy cannot be compared between trials due to differences in outcome definitions. However, in each trial, efficacy estimates were based on fewer than 50 total events of the primary outcome. This table shows the number of events of the primary outcome by trial and by vaccine or placebo arm:

GSK			Pfizer		
Outcome	**n/N, vaccine**	**n/N, placebo**	**Outcome**	**n/N, vaccine**	**n/N, placebo**
RSV LRTD[a]	**7**/12,466	**40**/12,494	RSV LRTI ≥2 symptoms[b]	**11**/16,306	**33**/16,308
			RSV LRTI ≥3 symptoms[b]	**2**/16,306	**14**/16,308

[a] Lower respiratory tract disease: ≥2 lower respiratory symptoms/signs for ≥24 hours including ≥1 lower respiratory sign OR ≥3 lower respiratory symptoms for ≥24 hours
[b] Lower respiratory tract illness: ≥2 or ≥3 lower respiratory signs/symptoms lasting more than 1 day

Incidence of symptomatic RSV infection was low in both trials, given that clinical trials may enroll a healthier population, compared with the general US population. In addition, both trials were conducted during periods of atypical RSV seasonality in the US attributable to the COVID-19 pandemic. To better characterize that, Dr. Melgar showed the monthly number of RSV-associated hospitalizations among adults ≥65 years of age that were reported to RSV-NET during the 3 most recent pre-COVID-19 pandemic RSV seasons and during the COVID-19 pandemic. Importantly, RSV-NET has historically conducted surveillance only during October–April of each season. Continuous surveillance was temporarily established during the COVID-19 pandemic in response to atypical RSV seasonality. Pre-pandemic RSV hospitalizations in this population reliably peaked every January. However, there were almost no RSV hospitalizations in January 2021. There also was an unusual summer rise in hospitalizations, which eventually peaked in December 2021 before dropping quickly. The GSK and Pfizer trial periods coincided with the unusual RSV seasonality.

The WG notes that RSV vaccine trials were underpowered to estimate efficacy against more severe clinical outcomes, such as hospitalization and death. There were fewer than 5 RSV-associated hospitalizations in each trial, and neither trial recorded any RSV-associated deaths. However, it is known that the burden of RSV-associated hospitalizations is high among older adults in the US. This table shows RSV-NET estimates for total RSV-associated hospitalizations among adults ≥60 years of age in the US occurring during the 4 most recent pre-COVID-19 pandemic RSV seasons:

RSV season (October–April)	Estimated U.S. Hospitalizations in adults aged ≥60 years	95% confidence interval
2016-17	**64,428**	**44,382 to 117,495**
2017-18	**80,652**	**58,778 to 128,458**
2018-19	**66,548**	**50,851 to 96,264**
2019-20	**84,941**	**64,105 to 125,848**

CDC unpublished data from RSV-NET (https://www.cdc.gov/rsv/research/rsv-net.html). Note that rates are adjusted for test sensitivity (using 95% for rRT-PCR testing) and undertesting for RSV among patients with acute respiratory illnesses. Data are preliminary and subject to change.

It is important to note that the estimates have wide 95% confidence intervals, but the lower bounds exceed 40,000 hospitalizations during every season. Notably, estimates from the 2 most recent pre-pandemic seasons were presented by Dr. Fiona Havers at the 12th International RSV Symposium in Belfast in September 2022.[92] RSV-NET estimates are conservative compared to published literature. A recent Pfizer-sponsored meta-analysis estimated that there are at least 106,000 annual RSV hospitalizations in the US among adults ≥65 years of age.[93] Although neither trial can provide efficacy against RSV-associated hospitalization, efficacy against more severe clinical outcomes might be expected to be at least as high as efficacy against the primary outcome. This is based on the trend evident in both trials of increasing efficacy with increasing severity of the clinical outcome, with point estimates of efficacy against lower respiratory tract involvement exceeding those against any ARI, and efficacy against more severe lower respiratory tract involvement exceeding that against less severe. Again, efficacy cannot be compared across trials due to different outcome definitions.

The efficacy of either vaccine beyond the first RSV season is unknown. Both trials are ongoing with multiple years of follow-up planned. However, data from only the first year will be available for consideration for these first policy recommendations. There is no established immunologic correlate of protection for RSV, limiting the utility of immunogenicity data in informing duration of protection. The need for re-vaccination and the appropriate time interval are yet to be determined. The WG also noted that cases of GBS were reported after vaccination with both investigational vaccines. GSK reported no cases in their pivotal Phase 3 trial that enrolled almost 25,000 participants. However, they did report 1 case in a different Phase 3 study evaluating the safety and long-term immunogenicity of different re-vaccination intervals with their vaccine. To date, over 1,650 participants in that trial all received only 1 dose of the vaccine. In other words, none have yet been re-vaccinated. The case of GBS occurred 9 days after participant vaccination. In total, GSK reported 1 case of GBS among over 15,000 older adults who received their investigational vaccine across all studies. Pfizer reported 2 cases of GBS, including 1 that was classified as a case of the MFS variant. In their main Phase 3 trial, which was somewhat larger than GSK's, the cases had onset 8 and 11 days after vaccination, respectively. Pfizer did not report any additional cases of GBS in their other trials of this vaccine.

In total, there were 2 cases among approximately 26,000 persons who received their investigational vaccine. All cases had onset during the 42-day risk window post-vaccination used in CDC surveillance. However, the significance of 1 to 2 cases observed in safety databases of 15,000 to 26,000 persons is unclear and the population-based background rates of GBS are known to increase with increasing age.[94] Notably, RSV infection also has been associated with GBS in case reports and case series.[95] However, a causal link has not been established. The WG continues to review and interpret the safety evidence.

[92] Estimates for 2018-19 and 2019-20: Havers et al. Hospitalization rates and outcomes for RSV-associated hospitalizations in adults ≥18 years in the United States during two respiratory seasons, October 2018 - April 2020. Presentation at: 12th International RSV Symposium; 2022 Sep 29 – Oct 2; Belfast, United Kingdom.

[93] McLaughlin JM, et al. Rates of Medically Attended RSV Among US Adults: A Systematic Review and Meta-analysis. Open Forum Infect Dis. 2022 Jun 17;9(7):ofac30

[94] Sejvar JJ, Baughman AL, Matthew Wise, Morgan OW. Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. Neuroepidemiology. 2011;36(2):123-33

[95] Helgeson SA, Heckman AJ, Harris DM. First Reported Case of Respiratory Syncytial Virus Infection Causing Guillain-Barré Syndrome. Indian J Crit Care Med. 2018 Apr;22(4):309-310; and Munayco CV, Gavilan RG, Ramirez G, et al. Large Outbreak of Guillain-Barré Syndrome, Peru, 2019. Emerg Infect Dis. 2020 Nov;26(11):2778-2780

Uptake of a novel RSV vaccine among older adults will depend upon patient and clinician education. The adult immunization schedule, as Dr. Kotton noted, is becoming more complex and includes multiple vaccines with re-vaccination intervals. While RSV is well-known as an important pediatric pathogen, it is likely less well-known as a pathogen in adults compared with influenza and SARS-CoV-2. Therefore, without a dedicated education effort, RSV vaccination has the potential to be deprioritized relative to other vaccines. The WG notes that safety and efficacy of co-administration of influenza, COVID-19, and RSV vaccines must be established. The next steps for the WG are to review the GRADE of the evidence for the GSK and Pfizer investigational vaccines, review analyses on the cost-effectiveness of vaccinating older adults against RSV, review EtR for each investigational vaccine, and determine the final policy questions. The age threshold in the policy question will be informed by each of these pieces of evidence, as well as other considerations.

In closing, the WG posed the following questions for ACIP members' consideration:

- ❑ Are there additional data needed prior to ACIP voting on recommendations for the use of either of these investigational vaccines on older adults?
- ❑ What additional data would ACIP like to see to determine an appropriate age threshold for an adult RSV vaccine recommendation?
- ❑ Are there additional questions that ACIP would like answered regarding an adult RSV vaccination program?

Discussion Points

In thinking about the age threshold for a recommendation, Ms. Bahta asked whether there is a racial and ethnic breakdown of RSV in order to consider the equity aspect of this.

Dr. Lee emphasized the complexity of the vaccination schedule and expressed her hope that they could get to a place with an age-based platform that is more straightforward and focuses on respiratory diseases across the board. Having those data and some type of rates would be helpful, so it would be beneficial to hear absolute numbers and relative rates in another presentation. Having consistency in that presentation would provide a better sense of the relative burden of these infections.

Dr. Poehling stressed the importance of using the same definition of LTRD/LRTI, because the number of symptoms is not as important. It would be beneficial to be able to compare across and to have a breakdown on the safety data by age and background rates.

Dr. Sanchez requested further insight regarding the potential for enhancement of disease after vaccination.

MATERNAL/PEDIATRIC RESPIRATORY SYNCYTIAL VIRUS (RSV)

Session Introduction

Sarah S. Long, MD (Chair, Maternal/Pediatric RSV WG) reminded everyone that RSV is the leading cause of hospitalizations in US infants. It can affect the small airways and lungs, particularly in infants. About 40% of infants who are infected will have LRTD. Most infants (68%) are infected in the first year of life and nearly all (97%) by the age of 2 years.[96] Premature

[96] Glezen et al, Arch Dis Child, 1986 3Langley & Anderson, PIDJ, 2011

infants who are born at ≤30 weeks gestation have hospitalizations that are 3 times higher than term infants and their admission to the ICU and need for ventilation are also increased compared with term infants. Of children hospitalized with RSV, 79% who are <2 years of age have no underlying medical conditions.[97] While risk groups are identified, it is known that all children are susceptible to RSV and LRTD and hospitalization. Approximately 2% to 3% of all infants are hospitalized for RSV.[98] The burden of disease, outcome, and severity of disease are significant.

Previous maternal/pediatric RSV ACIP presentations have focused on the epidemiology and burden of RSV disease in infants in terms of seasonality in the US, outpatient and ED visits, hospitalizations, and death. It is important to note that prior to the pandemic, RSV seasonality was very tight and repetitive but has become slightly different for the last 2 or 3 years, with the worst season and early and more hospitalizations. This has stretched resources throughout the US. The WG also has discussed the virology and immunology of infection. In addition, the WG has discussed the safety and efficacy of nirsevimab. It is important to realize that this is not a vaccine but is instead antibody passive protection.

WG discussions on nirsevimab have focused on the initial results of the pivotal Phase 3 study in infants born nearer term at ≥35 weeks gestation, the Phase 2B study in infants born at 29─34 weeks gestation who would have been candidates for palivizumab, and a Phase 2/3 safety and pharmacokinetic study in high-risk infants with chronic lung disease and congenital heart disease. The Phase 3 study was halted when on hiatus in the middle of the COVID-19 pandemic due to the lack of cases of RSV. For this session, the results of the entire Phase 3 study were available to evaluate in addition to some second-year data on the Phase 3 infants given nirsevimab in the first year of life and Phase 2/3 safety data on infants who have been given 2 doses.

Nirsevimab for the Prevention of RSV in all Infants

Christian Tilen Felter, MD (Associate VP, Global Medical Expert for Nosocomial Vaccines for Sanofi Pasteur) indicated that also joining him were Drs. Tonya Villafana and Amanda Leach representing AstraZeneca. During this session, Dr. Felter provided an update on nirsevimab for the prevention of RSV in all infants that focused on additional data from clinical trials, duration of protection, and implementation. To set the stage, the Nirsevimab Clinical Development Program was set over 3 separate studies: 1) a Phase 3 pivotal study known as MELODY (Prevention of Medically Attended Lower Respiratory Tract Infection Due to Respiratory Syncytial Virus in Healthy Late Preterm and Term Infants) that was conducted in infants ≥35 weeks of gestational age; 2) a pivotal Phase 2B study among infants 29─35 weeks of gestational age; and 3) a Phase 2/3 study in the palivizumab-eligible population. When taken together as a whole, these studies represent a clinical development program across the entire infant population, which is what is being proposed for nirsevimab.

The MELODY study began in 2019 but was impacted severely by the COVID-19 pandemic. RSV circulation disappeared at that time when the non-pharmaceutical measures came into effect. Because the study was intended to run over several seasons, it was put on hold at that point. Sanofi and AstraZeneca entered into discussions with the FDA about the data that they had at that point, and it was decided to move forward with the initial FDA filing based on the primary cohort of the MELODY study—essentially the first half of the MELODY analysis. It is

[97] Hall et al, Pediatrics, 2013
[98] Hall et al, Pediatrics, 2013 and Langley & Anderson, PIDJ, 2011

important to note that the MELODY study was intended to include approximately 3,000 infants born at ≥35 weeks gestational, so approximately half of them were in the primary analysis. MELODY enrollment resumed in 2021 and has since been completed. This session focused on presentation of the results of that further cohort termed the "MELODY All Subjects Analysis," several other important data points from the follow-ups from this study, and the Phase 2/3 study in the palivizumab-eligible population known as MEDLEY.

The MEDLEY Phase 3 pivotal study analysis included 1,490 participants and demonstrated efficacy with the primary endpoint of medically-attended LRTI. The secondary endpoint was hospitalization due to RSV LRTI. Presented during this session were the completion of the MELODY study as it was originally intended in the MELODY All Subjects Analysis with the full cohort of 3,000 participants as designed through Day 151 in terms of efficacy and safety. In addition, the data have now been pooled together from the MELODY All Subjects Analysis and the Phase 2B recommended dose data. As a reminder, the Phase 2B study was conducted originally in infants 29─35 weeks of gestational age with 50 mg given to all subjects entering the Phase 2B study. At the end of the Phase 2B study, infants ≥5 kg did not have a sufficient efficacy response at that dosage. Moving into the Phase 3 study, it was decided that infants ≥5 kg needed a 100 mg dose. Further analyses of the Phase 2B study were performed looking only at those infants ≥5 kg—the ones who would have received the dose that is going to be put forward for FDA approval. That analysis will focus on efficacy through Day 151 by subgroup. There also are data analyzing RSV-A and RSV-B. The follow-up of the primary cohort in the first half of the MELODY study will be assessed into their second year of life. They were dosed in the first year and were followed through their second RSV season. The MEDLEY palivizumab-eligible population who are going into their second RSV season were given nirsevimab again.

In terms of the MELODY All Subjects (e.g., the full MELODY study as it was originally conceived) had 3 main endpoints of efficacy through Day 151 in the ≥35 weeks of gestational age population. In this analysis, there was consistent efficacy across the different endpoints. Efficacy remained consistent and high between approximately 75% and 80% throughout the study, which is to be expected in terms of the mechanism of action of this product. It is a directly protective monoclonal antibody that does not rely on an immune response from the infant who is being protected. Looking across the different endpoints and cohorts, efficacy remained consistent. Definitions used throughout this presentation included medically-attended RSV LRTI (MA RSV LTRI) with or without hospitalization and MA RSV LRTI (very severe), which means hospitalization that required either intravenous fluids or supplemental oxygen.

Looking at an excerpt of the safety data from the FDA filing for the MELODY All Subjects population, AEs of rash, pyrexia, and injection site reaction were uncommon. By definition, that means that they occurred in less than 1 in 100 but more than 1 in 1,000 subjects. There were no SAEs or deaths considered to be related to nirsevimab by the investigator and no anaphylaxis or serious allergic reactions were attributable to nirsevimab. These supplemental safety data are based on MELODY All Subjects (e.g., complete MELODY study).

As noted earlier, all of the subjects from the MELODY All Subjects and Phase 2B recommended dose study were pooled. As a reminder, the Phase 2B subjects that were <5 kilograms and received the 50 mg dose, which is the dose being proposed to be brought forward to assess the efficacy and impact of nirsevimab across the infant population. The Phase 3 MELODY study and the Phase 2B study were complementary and similar in design. This was done purposefully and was intended to be pooled from the beginning. The Phase 3 MELODY study is the follow-up that went into the second RSV season. When these data are pooled together, consistent and high efficacy was seen in the MELODY All Subjects data at 79% for the primary endpoint of MA

RSV LRTI. Another reason consistency is seen across the 3 endpoints is that the MA RSV LRTI definition that was used in this study was looking at clinically important disease. Essentially, it is looking at small variations across the pathophysiology of LRTI, which makes it possible to see consistent results across the different endpoints. Consistent efficacy is seen across the different cohorts regardless of Northern Hemisphere, Southern Hemisphere, age of randomization, male, female, ancestry, weight, and region. Assessing the MELODY All Subjects data for RSV-A and RSV-B, nirsevimab provided similar efficacy across the 2 subtypes of RSV.

Regarding second season RSV incidence after a single dose prior to the first season in the MELODY Primary Cohort (e.g., MELODY subjects who were enrolled prior to the pandemic who were then followed into their second RSV season), a low incidence of RSV LRTI was observed during the second season and there were no hospitalized cases. With regard to duration of protection, primary and secondary endpoints for MELODY evaluated the efficacy of nirsevimab through 150 days. Efficacy did not decline over the time period of this evaluation. There is some evidence that suggests that this protection extends beyond 150 days, although the degree of this protection is yet to be determined. An analysis of the data from the South African cohort, which experienced a delayed RSV season, showed a hazard ratio of 0.491 (95% CI 0.158, 1.523). Neutralizing antibody titers were 7 times higher than baseline at day 361 in nirsevimab-treated subjects and were significantly higher than those with natural infection.

The proposed second season indication that has been submitted and will be discussed with the FDA is for children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. This may include, but is not limited to, chronic lung disease (CLD) and chronic heart disease (CHD) that formed the MEDLEY cohort and some other proposed groups who are believed to remain vulnerable going into their second season. The MEDLEY palivizumab-eligible population going into their second RSV season were dosed again because they remained vulnerable (e.g., the CHD and CLD cohorts going into the second season). It is important to be aware that the MEDLEY study in the palivizumab-eligible population was a comparative safety and pharmacokinetic study comparing palivizumab with nirsevimab. The efficacy from this study was extrapolated based on pharmacokinetic data. In terms of safety for those who were given palivizumab in both seasons, palivizumab followed by nirsevimab, or nirsevimab followed by nirsevimab, it was determined that there is no significant difference between the safety in these populations. These safety data were felt to be acceptable to bring forward for the indication that is sought. Regarding the pharmacokinetic data, the predetermined criteria of success as discussed with the regulatory authorities in Europe was that 80% of the children must be above the efficacy threshold. Significantly more were above the efficacy threshold. It is important to note that since these infants were larger going into the second season, they were given 200 milligrams of nirsevimab.

In conclusion, nirsevimab has shown consistent and high efficacy and good safety across studies and populations that is consistent with the mechanism of action and with the data that have been presented to ACIP previously. The new data confirm the safety and efficacy against MA RSV LRTI and hospitalization across the cohorts that have been presented, including the MELODY All Subjects analysis that demonstrated efficacy against hospitalization endpoints with an efficacy of 76.8% (49.4-89.4). Efficacy does not wane over the 150 days of the primary analysis, which suggests the potential of extended efficacy. Efficacy has been extrapolated into the first and second seasons for the eligible population. The safety profile is favorable, with low levels of reactogenicity. The season two RSV cases were low and balanced between the nirsevimab and placebo groups.

Discussion Points

Dr. Poehling requested clarification on the original MELODY study in terms of the range included for infants ≥35 weeks gestation (e.g., late pre-term) and how many children were enrolled who are ≥37 weeks (e.g., full-term).

Dr. Leach confirmed that MELODY was conducted in children who were late pre-term and full-term. Overall, the enrollment was approximately 85% in the full-term infant population.

Dr. Sanchez requested further explanation of the determination of the level of protection in terms of the pharmacokinetic extrapolation. It seemed that the levels continued to be elevated based on a placebo group beyond 150 days, which has implications for when it can be administered.

Dr. Felter stated that as a framing, this was based on the analysis of the exposure data from the Phase 2B study, which led to the decision of the differing doses of nirsevimab going into the MELODY study based on weight.

Dr. Leach further commented that the clinical trials were designed to capture disease data over a full year of follow-up. The primary endpoint was concluded based on Day 151, which corresponds to the typical length of a season. At this point, there is not a quality protection that allows for accurate prediction of the duration of protection. However, data are being collected on this in terms of pharmacokinetic and neutralizing antibody responses. Whereas there is certainty that efficacy extends beyond Day 151, more work must be done to determine the precise level of protection.

Referring to back-up Slide 27, the clinical efficacy data from the South African cohort, Dr. Felter pointed out that this was in a season that was delayed due to COVID-19 measures that were put into place. RSV did return to South Africa, and there was ongoing protection that seemed to last out to approximately 1 year. That is consistent with the neutralizing antibody data.

Referring to Slide 23, Dr. Lee requested additional details about the Grade 3 severity events that were 10% in the palivizumab/nirsevimab (P/N) cohort, 11% in the nirsevimab/nirsevimab (N/N) cohort, and 2.4% in palivizumab/palivizumab (P/P) cohort.

Dr. Felter indicated that while he did not have the clinical picture pertaining to all of these events readily available, he could provide them to the WG following the meeting.

Regarding Slide 12. Dr. Loehr requested further details about the subsets in the groups for placebo and the treatment arms in terms of whether the 80 LRTIs were subsets of the original 80 or were separate groups.

Dr. Felter indicated that they were subsets of each other, with an increasingly severe definition going down the definition column. Even the baseline or primary endpoint of MA LRTI were clinically important diseases, which is why there is a consistent level of efficacy across these endpoints.

Next Steps for the ACIP Maternal/Pediatric RSV WG

Jefferson Jones, MD, MPH, FAAP, CDR USPHS (Co-lead, Maternal/Pediatric RSV WG) indicated that the following 2 policy questions are being considered by the Maternal/Pediatric WG regarding nirsevimab:

- Should nirsevimab be recommended for all infants <8 months of age entering their first RSV season and all infants born during the RSV season?

- Should nirsevimab be recommended for children <24 months of age entering their second RSV season who remain at increased risk of severe disease?

The previous presentation gave examples of groups of children who might remain at risk of severe disease. However, the WG has yet to review the evidence for this list. The WG has reviewed evidence related to these policies that includes, but is not limited to: 1) the epidemiology and burden of RSV in infants and young children, including RSV seasonality in the US and incidence of RSV illness in outpatient settings, ED visits, hospitalizations, and deaths; 2) the virology and immunology of RSV; and 3) the initial and updated results on the safety and efficacy of nirsevimab, including the Phase 3 study in infants born at ≥35 weeks gestation, the Phase 2B study in infants born at 29─34 weeks gestation, and the Phase 2/3 safety and pharmacokinetic study in infants eligible for palivizumab, including both the first and second RSV seasons.

Evidence to be reviewed by the WG in the future includes a review of: 1) evidence to identify children <24 months of age entering their second RSV season who remain at increased risk of severe disease 2) the GRADE of evidence for both policy questions; 3) the cost-effectiveness analysis; and 4) the EtR Framework in terms of the public health problem, benefits and harms, values, equity, resource use, acceptability, and feasibility domains. The tentative proposed timeline for future ACIP presentations include a summary of GRADE, the cost-effectiveness analysis, and the EtR Framework during the February 2023 ACIP meeting in preparation of a potential vote by ACIP for use of nirsevimab in June 2023 pending licensure of the product. Additional agenda items may be added if additional products become available.

Discussion Points

Dr. Loehr inquired about the feasibility of administering nirsevimab in an outpatient office. It appeared that practitioners would be giving this product to all children born out of season in the month before the season starts. It will be important for the outpatient community to understand how to store it, how difficult it is to store, and the costs.

Dr. Jones indicated that this information is anticipated to be presented during the February 2023 ACIP meeting.

Dr. Poehling expressed an interest in assessing the difference in late preterm and preterm infants in terms of vaccine safety and efficacy.

Dr. Lee added co-administration to the list of topics to consider, given that the timing is going to be tough with the RSV season and the durability of protection throughout the season, particularly given that the RSV seasons are currently different from usual. In addition, information on coverage would be helpful to understand.

Dr. Kotton stated that in general for the ACIP, it is interesting to vote on a monoclonal antibody when this was not done for EVUSHELD for COVID-19 protection in immunocompromised patients. Therefore, she thought there should be clarity and guidance as to what ACIP does and does not vote on.

Dr. Sanchez observed that concomitant vaccines were allowed during the studies, so there are data on the fact that other vaccines could be given at the same time.

Dr. Long requested that CDC clarify whether a product that is not a vaccine could be included in the VFC Program.

Dr. Wharton indicated that this is under discussion.

PUBLIC COMMENTS

Overview

The floor was opened for public comment on October 20, 2022 at 1:02 PM ET. Given that many more individuals registered to make oral public comments than could be accommodated during this meeting, selection was made randomly via a lottery. Dr. Lee provided a gentle reminder that the ACIP appreciates diverse viewpoints that are respectful in nature and issue-focused rather than comments directed at individuals. The comments made during the meeting are included in this document. Members of the public also were invited to submit written public comments to ACIP through the Federal eRulemaking Portal under Docket Number ID CDC-2022-0111. Visit http://www.regulations.gov for access to the docket or to submit comments or read background documents and comments received. While public comments were heard prior to the Combined Immunization Schedule vote, the vote was included with the session presentations for ease of reading.

Public Comments

Mr. Jack Baker
National Foundation for Infectious Diseases

Good afternoon. I am Jack Baker with the National Foundation for Infectious Diseases, or NFID. On behalf of NFID, as a longstanding partner of CDC, thank you for the opportunity to address ACIP and thank you for your valuable work in guiding US immunization policy and protecting public health. My comments today will address 3 respiratory viruses of concern: Respiratory syncytial virus, or RSV; COVID-19; and influenza. ACIP has reviewed data on the safety and effectiveness of potential new tools to prevent RSV, which can be serious among both children and older adults. In fact, in the US, RSV is the leading cause of hospitalization among infants and is a major cause of hospitalization and mortality for adults aged 65 years and older. Each year in the US, thousands of young children as well as older adults are hospitalized due to RSV. New RSV prevention tools offer the promise of substantially reducing the burden of RSV. NFID issued a report in January 2022 urging a stronger public health focus on RSV, and we thank ACIP for its work in this area. NFID also commends ACIP for voting to include COVID-19 vaccine in the Vaccines for Children, or VFC, Program, which makes free or low-cost vaccines available to uninsured or underinsured children. In the US, thousands of children have been hospitalized and hundreds have died due to COVID-19. Vaccines can help prevent those tragic complications. Adding COVID-19 vaccines to the VFC Program will help to address disparities

in childhood immunization rates. Later today, ACIP will also discuss an update on influenza, or flu. A recent NFID national survey of US adults found that although 69% believe vaccination is the best protection against flu, only 49% plan to get a flu vaccine during the 2022-2023 flu season. Of concern, the NFID survey revealed that nearly 1 in 5 individuals who are at higher risk for flu-related complications, including older adults and those with chronic health conditions, said that they were not planning to get vaccinated this season. Likewise, only 29% of US adults at higher risk for pneumococcal disease said they have been advised by a healthcare professional to receive a pneumococcal vaccine, but of those who have been advised, 74% have been vaccinated against pneumococcal disease. All these data underscore the importance of strong vaccine recommendations by all healthcare professionals. Additional information about the NFID survey and other resources are available at www.nfid.org. With new tools on the horizon, we must work to raise awareness about the burden of disease and the importance of prevention through vaccination. But it is not enough to have safe and effective vaccines. NFID stands ready to work with CDC and other partners to promote vaccine confidence and ensure that vaccines are used as recommended. Thank you for your time and attention and for your tireless and dedicated service.

Robert Edmonds, PhD
Administrator
Tinnitus Adverse Event Forum

Dear committee, my name is Robert Edmonds. I'm an admin of one of the actually smaller tinnitus adverse event-focused support forums for COVID vaccines with nearly 1,000 members. The topic is, of course, of personal interest to me because I developed chronic tinnitus after my COVID vaccination. This adverse event though isn't foreign to this committee. A prior member of yours, Dr. Gregory Poland, continues to experience it as well, along with variability after being rechallenged as he has communicated in new sources, so please excuse this somewhat off-topic diversion to discuss tinnitus—a symptom already mentioned on the label of some other vaccines. Note my following comments are not being made to dissuade vaccination, but to encourage official recognition so as to lead to research and early treatment of tinnitus with COVID vaccination. With that being said, I will now review some important findings to motivate this issue. In a recent WHO pharmaceutical newsletter, we find "the UMC identified hearing loss and tinnitus following COVID-19 vaccination as a preliminary signal." And in *JAMA Oto[laryngology]* about a recent analysis of data from Israel, "This study suggests that Pfizer mRNA COVID-19 vaccine might be associated with increased risk of SSNHL" and "Patients with SSNHL might experience permanent hearing loss and tinnitus." Now while I understand the VSD has not seen a clustering of cases for tinnitus, in *Laryngoscope*, in an analysis of TriNetX analytics network data resulted in a finding that "patients with a predisposition to vaccine-related tinnitus may be more vulnerable after the first dose than after the second dose." And in *Drug and Safety* in another article, but with FDA coauthors, "Investigation enabled us to discover 2 potentially new AEs, herpes zoster and tinnitus, which are yet to be recognized by health authorities, but which have overwhelming statistical support in VAERS and are supported by published case reports and studies." And finally, while prior papers mostly examined mRNA vaccines, in the meeting highlights of EMA's PRAC we have the statement that they "concluded that cases of dizziness and tinnitus are linked to the administration of COVID-19 vaccine Janssen." This is supported in part by a [unclear] 3001 and their later recognition of another COVID vaccine of the same platform having this issue at an uncommon frequency. With these repeated signals for tinnitus, it is beyond time for US federal funding of research into this adverse event for COVID vaccines, and not just to tell us rates, but to investigate mechanisms and treatments. And there may be a treatment for some with quick utilization of corticosteroids after onset, but so many miss out if so. That is why there is urgency for this issue because we

may be able to improve outcomes for others. I, therefore, call on you to advocate for research and recognition. Let us now help those that follow—help them find peace and quiet. Thank you for your time.

Ms. Linda Walsh
COPD Foundation

Good afternoon. My name is Linda Walsh. I thank you for the opportunity to represent the COPD Foundation today. The COPD Foundation is dedicated to preventing COPD, bronchiectasis, and nontuberculous mycobacterial lung disease. We strive to improve the lives of those affected and seek cures. The COPD Foundation represents more than 16 million Americans diagnosed with COPD and countless more at risk. We strongly support the work of the ACIP and are grateful for the critical efforts required from the group. My purpose today is to strongly advocate for a simplified age-based vaccine recommendation for the prevention of pneumococcal disease, including pneumococcal pneumonia in adults. While well-intentioned, the current recommendations, including shared clinical decision-making, has generated confusion. The current guidelines are complex and confusing to both patients and physicians. In addition, under the current recommendations, individuals with chronic underlying conditions, including COPD, under the age of 65 are not addressed. Overall, individuals with COPD have more pneumonia, suffer from more severe episodes of pneumonia, experience more hospitalizations, and have greater burden and worse outcomes compared to those without COPD. The sentiment around pneumonia on our COPD360Social, the Foundation's online community of over 54,000 individuals, highlights the fear of getting pneumonia and the hope that it could be prevented. We understand from the July 2021 ACIP meeting that there has been a demonstrated cost-effectiveness of PCV20 without the pneumococcal polysaccharide vaccine in individuals 50 and over and in individuals 65 and over and data also suggest a demonstrated cost-effectiveness of PCV15 without the pneumococcal polysaccharide vaccine in individuals 65 and over. These data strongly support the COPD Foundation's request that the ACIP implement a simplified age-based pneumococcal vaccine recommendation that also includes a risk-based recommendation for individuals with chronic underlying conditions, including COPD, who do not meet the age requirement of 50 or 65, respectively. Now more than ever, vaccines and protecting lung health is essential. We need to ensure that we equip our community with clear vaccine guidelines that incorporate at-risk populations, including those with COPD and other lung conditions. Thank you for the opportunity to share the impact of your recommendations. We once again stand ready to assist in providing additional information.

Matthew Wojdyla, PharmD
Medical Director
Representing Self

Hello, my name is Matthew Wojdyla, Medical Director for Sobi, Inc. Sobi is the authorized marketer and distributor for palivizumab in the United States, which is indicated for the prevention of serious lower respiratory tract disease caused by RSV in specific high-risk infants, those who were born prematurely at less than or equal to 35 weeks' gestational age or those who have hemodynamically significant congenital heart disease or chronic lung disease of prematurity. Based on the public materials from the June 2022 ACIP meeting, we became aware that the Maternal Pediatric RSV Work Group is evaluating nirsevimab for the prevention of RSV disease in all infants. RSV is the leading cause of hospitalization in infants aged less than one year in the United States, and the burden of RSV disease is disproportionately higher among premature infants and other high-risk infants with congenital heart disease or chronic lung disease. These factors each contribute to increasing an infant's risk of becoming

hospitalized from RSV compared to healthy, full-term children. These risk factors are not mutually exclusive. Infants who have any combination of these risk factors may be at even higher risk of hospitalization and adverse outcomes. If RSV prophylaxis becomes available for all infants, it will be important to consider how to manage this smaller but higher-risk infant population, as all infants are not the same. According to a 2022 review article by Bowser, et al. in the *Journal of Infectious Diseases*, RSV hospitalizations account for two-thirds of all RSV treatment costs, and the hospitalization of an extremely premature infant costs five and a half times more than that of a healthy term infant. Reducing hospitalizations would alleviate the large financial burden on the health system caused by RSV disease. Palivizumab has more than 25 years' worth of diverse global safety, efficacy, and effectiveness data demonstrating reductions in hospitalizations in length and intensity of hospitalizations in these highest-risk patients. At Sobi, we share the ACIP's interest in protecting the health of all infants, particularly those vulnerable infants who are at the highest risk for hospitalization and developing severe adverse health outcomes from RSV disease. We believe that any new guidance should include consideration of differential risk among different groups of infant populations. Palivizumab was approved by the FDA for demonstrated efficacy in reducing hospitalization across those highest risk groups of infants less than or equal to 35 weeks' gestational age, those with hemodynamically significant congenital heart disease, or those with chronic lung disease of prematurity. Existing and emerging data characterize these differential risks and the beneficial impact of palivizumab in reducing hospitalization of these highest-risk infants. As the ACIP evaluates new modalities for the prevention of RSV disease, we believe palivizumab should be referenced within clinical considerations that are published along with any ACIP decision, specifically addressing its use for protecting those highest-risk infants less than or equal to 35 weeks' gestational age, those with hemodynamically significant congenital heart disease, or those with chronic lung disease of prematurity. Thank you for your time, attention, and the opportunity to speak today.

Mr. Noah Louis-Ferdinand
Communications Coordinator
Voices for Vaccines

Thank you. This is Noah Louis-Ferdinand, the Communications Coordinator from Voices for Vaccines. I wanted to talk about the COVID-19 vaccine for kids and the decisions surrounding it. This is a topic that has become mired in a lot of politics, including mandates, which I just want to make clear the CDC is not a jurisdiction, however. But I want to move past that. We all understand that COVID is less of a risk to kids than adults, but that does not mean no risk. We know that somewhere north of 100,000 kids have been put in the hospital by this disease, and the exact number matters less than what that means in the real world. I wanted to give some examples from my local area, Metro Detroit, where I spent much of the pandemic. The City of Detroit has produced data showing parents feel less comfortable going about life than people without children, whether or not they themselves are vaccinated. To quote the report, “this suggests that vaccine hesitancy does not reflect doubts about the seriousness of COVID-19.” In Flint, just North of me, the Public Health Manager has also told me they've had trouble getting kids vaccinated, but here again, that does not mean COVID isn't having an impact. And much to the contrary, their schools were closed for in-person instruction this past winter into February. Now we all agree that's an issue, but it's also not some arbitrary decision. It's the reality that you take a district that has plenty of challenges already and then you add a surge of disease. We have good evidence that says even a case of flu can cost hundreds of dollars in a household with kids in terms of lost productivity, medical costs, and other things. That is not easy to deal with, and COVID is, of course, much more contagious and much more disruptive and costly than flu is. We have hard evidence that it did cause disruption in these cities just from what

happened, so the question we have to ask ourselves is: If we're serious about making things go normal, how do we actually support communities across the country in dealing with COVID going forward, because it's not going away? I think removing barriers to protection and increasing access is a key step, which is exactly what adding the vaccine to the Vaccines for Children Program does. I finally want to address this point that it's not worth vaccinating kids because the risk is low. And when I hear that, I just have to pause and make sure we really have thought through what we're saying. I met a parent just 2 weeks ago who actually lives a few minutes from my house. His name is Zachary Yaksich. He's someone who lost his daughter, Alana, to influenza because she wasn't recommended to get the flu vaccine back in 2003 kind of with that same thinking that she was low risk. Later, the recommendation would expand. Alana's tragic death happened almost 2 decades ago, but that is obviously not something that leaves you as a parent. Zachary has been advocating in my city and others around us for almost 20 years to get other kids vaccinated, so it has clearly had an impact in his life and that of the people around him. These things do matter, right? In real world communities we try to look out for each other. We're not just going to ignore the impact of a disease, and so I think the want to protect ourselves and each other has to take precedence over politics and secondary considerations. I appreciate ACIP's dedication to making the protection more available and more accessible for everyone.

Mrs. Kim Freitas
Concerned Individual

Good afternoon. My name is Kim Freitas, and I spoke about COVID at a meeting exactly 2 years ago. Everything the experts raised as concerns during the meeting was completely ignored, and these avoidable issues have tragically come to fruition: efficacy, transmission, informed consent, viral priming, ADE, transparency with data to name a few. It is a complete shame that you open these meetings up for public comment, yet you never consider what is presented although you claim that is the intent of public comment. What is even more concerning is the amount of safety signal data that has come out of your reporting systems which is being blatantly ignored. At what point does this committee become liable for their negligence? These EUA COVID injections cannot be added to the childhood schedule. First, it is not FDA-approved. Our children should not be receiving them, let alone the adult population. The data clearly has shown that more kids are damaged by the injections than the virus. Myocarditis is not rare nor mild. It's extremely dangerous because the inflammation caused by the injection actually creates scar tissue on the heart that is not repairable. We already know this injection does not prevent infection or transmission, which makes all of us question why it's even being classified as a vaccine or being presented to this committee. This is not a vaccine. The definition of a vaccination is “the act of introducing a vaccine into the body to produce immunity to a specific disease” until of course the CDC changed the definition on its website in 2021. It is time to stop with this morally and ethically wrong approach to a virus with such a high recovery rate. If you did not know it 2 years ago, you certainly do now. It is time for this committee and agency to pivot away from these dangerous and deadly injections and acknowledge that despite the heavy censorship, enough data has been shared and confirms that this injection is the most dangerous and least effective in history—more so than all the others combined. The strong push behind a product that has failed miserably makes us all question the motives behind this committee and agency. I am here today on behalf of all who have already been injured and killed from this injection and for our children, demanding that you obey your Hippocratic Oath and cease from doing any more physical harm and moral harm to all you recommend the pseudo-vaccine to. The VAERS and v-safe data both have confirmed that this injection needs to be pulled off the market immediately. We need autopsies performed on every single person who received the injection and died suddenly, unexpectedly, or with

unknown causes. We need to be forming committees with embalmers, pathologists, and every medical professional who has witnessed the massacre that has taken place since the rollout of this injection. Until then, we will not allow our children or families to be part of the biggest human experiment ever. In closing, I remind this committee of the Nuremberg Trials. There are consequences for crimes committed against humanity.

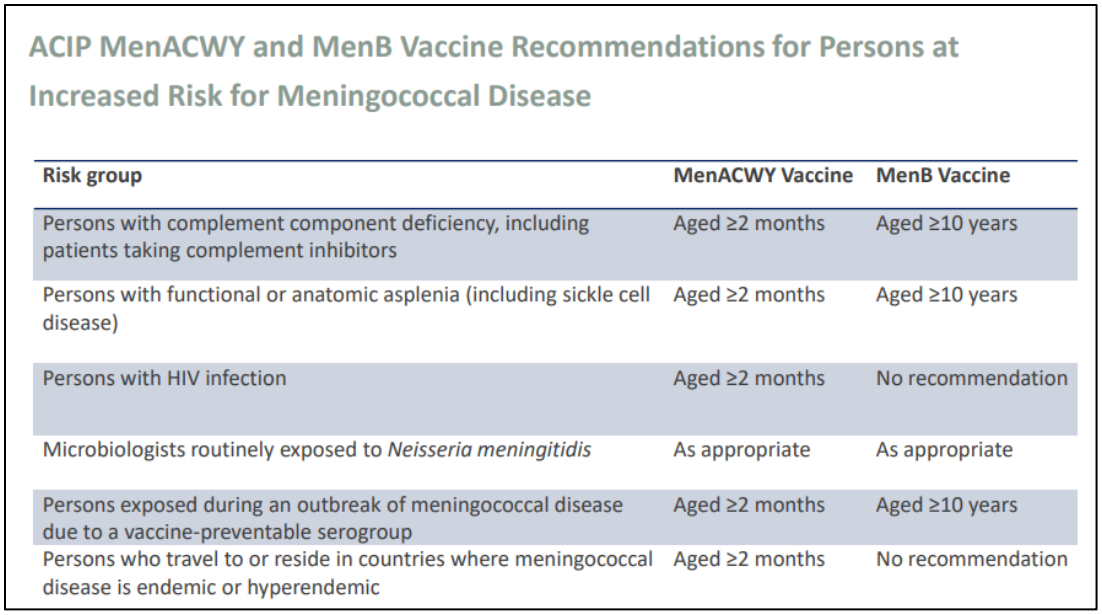
MENINGOCOCCAL VACCINES

Session Introduction

Katherine Poehling, MD, MPH (Work Group Chair) introduced the ACIP meningococcal vaccine WG session, explaining that the main purpose of this WG is to review data on meningococcal vaccines and develop meningococcal vaccine policy options for ACIP consideration. The WG has 4 initial projects, which are to: 1) work with ACIP and VFC leadership to incorporate the Menveo One-Vial into current Menveo recommendations; 2) develop proposed recommendations for the new GSK pentavalent vaccine; 3) develop proposed recommendations for the new Pfizer pentavalent vaccine; and 4) consider whether to recommend meningococcal vaccines for people experiencing homelessness. In terms of the timeline, the WG has made an effort to stagger the projects as much as possible in order to pace themselves so that there are not too many activities occurring simultaneously. While the WG acknowledges that they will be busy, the workload should be manageable.

To frame the discussion for the session, Dr. Poehling briefly described the epidemiology of meningococcal disease in the US. In terms of incidence in the US, there has been a sustained decline from 1996–2019 from 1.3 cases/100,000 to 0.11 cases/100,000 persons in the population. This decline in incidence began prior to the introduction of MenACWY and MenB vaccines. When incidence is broken down by serotype of a group, it has declined for all 3 primary disease-causing serogroups B, C, and Y. That said, the decrease has been less dramatic for serogroup B than for C and Y. Incidence of serogroup W and other serogroups, including disease due to the non-groupable meningococcal bacteria, remained low during this period. Overall, the highest incidence of meningococcal disease was observed in children less than 5 years of age and among young adults aged 19–22 years of age. Serogroup B was the predominant serogroup in children under 5 years of age. In children and young adults 5–22 years of age, serogroup B accounted for approximately half the cases. In adults ≥23 years of age, serogroups C, W, and Y caused the majority of disease.

There are currently 5 meningococcal vaccines licensed and available in the US. Together, these vaccines cover 5 of the 6 serogroups that cause the majority of invasive meningococcal disease in the world and all of the 4 serogroups (B, C, W, and Y) that circulate in the US. Of note, the FDA just licensed a new version of Menveo that consist of 1 vial instead of the traditional 2 vials. MenACWY vaccine is recommended for all adolescents 11–18 years of age, with the first dose at 11–12 years of age and a booster at 16 years of age. MenB vaccine is a 2-dose series that may be administered to adolescents and young adults 16–23 years of age based on shared clinical decision-making. The preferred age for MenB vaccine is 16–18 years of age. The ACIP recommendations for persons at increased risk for meningococcal disease are shown in the following table:

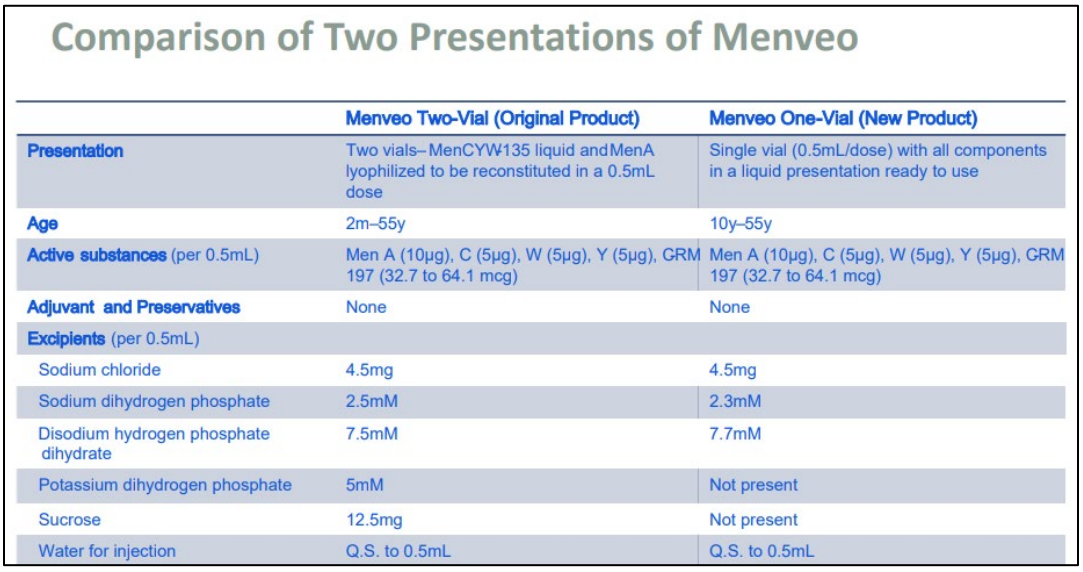


ACIP MenACWY and MenB Vaccine Recommendations for Persons at Increased Risk for Meningococcal Disease

Risk group	MenACWY Vaccine	MenB Vaccine
Persons with complement component deficiency, including patients taking complement inhibitors	Aged ≥2 months	Aged ≥10 years
Persons with functional or anatomic asplenia (including sickle cell disease)	Aged ≥2 months	Aged ≥10 years
Persons with HIV infection	Aged ≥2 months	No recommendation
Microbiologists routinely exposed to *Neisseria meningitidis*	As appropriate	As appropriate
Persons exposed during an outbreak of meningococcal disease due to a vaccine-preventable serogroup	Aged ≥2 months	Aged ≥10 years
Persons who travel to or reside in countries where meningococcal disease is endemic or hyperendemic	Aged ≥2 months	No recommendation

Menveo One-Vial Presentation

Sam Crowe, PhD, MPH (CDC WG Lead) presented an update on GSK's new 1-vial version of Menveo. As a reminder, this is the first main project of the Meningococcal Vaccines WG. This newly licensed product will be available in Spring 2023. The original and new versions of Menveo are nearly identical, so the ACIP Secretariat determined that GRADE and EtR are not required and that ACIP and VFC votes are not needed. The main consideration for this presentation was to explain that the 2 versions of the vaccine are licensed for different age ranges, which raised an important provider communication and vaccine use challenge. This table compares the 2 presentations of Menveo:



Comparison of Two Presentations of Menveo

	Menveo Two-Vial (Original Product)	Menveo One-Vial (New Product)
Presentation	Two vials– MenCYW135 liquid and MenA lyophilized to be reconstituted in a 0.5mL dose	Single vial (0.5mL/dose) with all components in a liquid presentation ready to use
Age	2m–55y	10y–55y
Active substances (per 0.5mL)	Men A (10µg), C (5µg), W (5µg), Y (5µg), CRM 197 (32.7 to 64.1 mcg)	Men A (10µg), C (5µg), W (5µg), Y (5µg), CRM 197 (32.7 to 64.1 mcg)
Adjuvant and Preservatives	None	None
Excipients (per 0.5mL)		
Sodium chloride	4.5mg	4.5mg
Sodium dihydrogen phosphate	2.5mM	2.3mM
Disodium hydrogen phosphate dihydrate	7.5mM	7.7mM
Potassium dihydrogen phosphate	5mM	Not present
Sucrose	12.5mg	Not present
Water for injection	Q.S. to 0.5mL	Q.S. to 0.5mL

Note the difference in age ranges in the second row of the table. Menveo Two-Vial is licensed for individuals 2 months–55 years of age, while Menveo O-Vial is licensed for individuals 10 years–55 years of age. The active ingredients, adjuvant, and preservatives are shown in rows 3 and 4, which are the same between the 2 formulations. There are only a few minor differences in the excipients. The different age ranges for the 2 Menveo presentations will be an important factor when vaccinating very young children who are at high risk for invasive meningococcal disease, particularly when considering the 2 other MenACWY vaccines that are currently licensed in the US, Menactra that is licensed for 9 months–55 years of age that was discontinued as of this past summer, and MenQuadfi that is licensed for persons ≥2 years of age.

After the last Menactra doses are administered, Menveo T-Vial will be the only currently licensed vaccine that can be given to children <2 years of age. GSK plans to maintain a consistent but limited supply of Menveo Two-Vial for children <10 years of age, but the challenge will be to ensure that providers reserve Menveo Two-Vial doses for children <2 years of age. To help address this challenge, GSK will send a letter to clinicians to ensure that they understand the differences between the 2 versions of the vaccine. They also will update their website with new product information and post the provider letter. GSK will provide Menveo Two-Vial through their traditional channels that include VFC, wholesalers, distributors, and GSK Direct.

CDC's ISD is updating the VFC resolution and the 2023 Child and Adolescent Immunization Schedule will include the new vaccine presentation and age ranges. ISD also will conduct outreach with provider groups.

Discussion Points

Dr. Preiss, GSK, emphasized that GSK is pleased that the Menveo One-Vial Presentation has been approved by FDA for individuals 10–55 years of age. This approval means that Menveo will be available as a single vial, giving HCPs a more convenient option. GSK is cognizant that some children under 10 years of age are at increased risk of meningococcal disease and that meningococcal ACWY vaccination is recommended by ACIP for these children. GSK plans to maintain a sufficient supply of Menveo Two-Vial to ensure that HCPs have the option to use an ACWY vaccine that is indicated for young children under 10 years of age down to the existing lower limit of 2 months of age for the indication for the Two-Vial product. GSK will monitor volumes and adjust if required. In addition, a "Dear Healthcare Practitioner" letter will be sent that outlines the differences in the age indication and the vial appearances. The presentation of the carton boxes for the 2 different presentations will be changed to have different color stripes to ensure that they can be distinguished visually as well.

Dr. Talbot pointed out that plenty of adults over 55 years of age are asplenic and would be recommended for a meningococcal vaccination.

Dr. Crowe indicated that Menveo currently has an off-label use for individuals over 55 years of age, which presumably would apply to this new formulation as well.

Dr. Chen asked whether there are any differences in the shelf life between these two products.

Dr. Preiss responded that upon the launch, the shelf life is expected to be 18 months. GSK is submitting data to expand that to 24 months. This will be shorter than the existing Menveo Two-Vial shelf life of 36 months.

Dr. Daley asked whether this is a long- or short-term issue and if there should be concerns if a child under 10 years of age received the One-Vial presentation from a safety or effectiveness standpoint.

Dr. Preiss indicated that they do not have any specific data or an indication in individuals under 10 years of age for this specific formulation or presentation. As noted earlier, the differences in the formulation are limited in terms of no longer having a lyophilized meningococcal A polysaccharide conjugate and instead having that in the liquid. There is not an indication under the age of 10 or any specific data for this presentation.

Dr. Poehling asked whether there are plans to study this product down to 2 months of age and if so, what the timeframe would be.

Dr. Preiss replied that at the moment, GSK has made no determination or decision on whether they will be pursuing further clinical trials to extend the indication under the age of 10. They are currently assessing regulatory feedback and looking at what type of studies would need to be completed to actually achieve that and will make a decision on that at a later date.

Dr. Lee emphasized that the committee prefers simplicity in general.

Dr. Fryhofer (AMA) noted that as a practicing physician, she has had some patients who have needed meningococcal vaccination who are over 55 years of age who, because of their insurance coverage, she had to send to the pharmacy. She has had a hard time getting the pharmacist to administer the vaccine even though she has written a prescription. In fact, she had to take a screenshot of the adult schedule and send it with the patient to show to the pharmacist. She asked whether there is any education to try to make some of these off-label uses known and any suggestions about how that process can be made easier for patients to get the vaccines that they need and that are indicated.

Dr. Crowe noted that MenQuadfi®, 1 of the 3 vaccines currently licensed in the US, is actually for individuals ≥2 years of age. Hopefully, that will be an option regardless. In terms of clarification, this is in the ACIP documentation. He can work with Dr. Poehling and the WG to further investigate this issue.

Dr. Poehling pointed out that while she appreciated that there will be some color-coding differences between the One-Vial and Two-Vial presentations, a portion of the US population is color blind. Therefore, she wondered whether there would be any other indications to make the differences obvious for those who are color blind.

Dr. Preiss reported that there are a number of differences between the 2 presentations to ensure that there are multiple opportunities to visually identify the differences between the presentations. The cartons themselves clearly state whether 1 vial per dose or 2 vials per dose are required. In addition, the color strip down the Two-Vial presentation is purple, whereas the color strip down the One-Vial presentation is a dove gray. In addition, the age indication is clearly stated on the box carton. It also is stated on the Two-Vial that reconstitution is required and on the One-Vial that reconstitution is not required. In terms of the boxes themselves, the two vials for the Two-Vial presentation, the liquid-containing vial has a gray cap and the second vial has an orange cap. That is a white lyophilized powder. The contents of the One-Vial presentation are liquid and the cap is pink. The age indication is on the product in clearly legible writing, along with language about whether the product requires or does not require

reconstitution. The One-Vial presentation also clearly states that this is 1 of 1 and the Two-Vial will have 1 of 2 and 2 of 2 on the respective labels for the vials.

Dr. Crowe added that these materials were included in the ACIP members' background materials with images of what Dr. Preiss described.

Meningococcal Vaccines Work Group Plan for Assessing the MenABCWY Vaccines

Sam Crowe, PhD, MPH (CDC WG Lead) provided an update on MenABCWY vaccines. As a reminder, these assessments are the second and third projects the WG is tackling in the near-term. There are 2 new MenABCWY vaccines currently in clinical trials. One is produced by GSK and the other is a product by Pfizer. Each vaccine is a combination of an existing MenACWY vaccine and an existing MenB vaccine. The Meningococcal Vaccines WG will assess each of these pentavalent vaccines separately in the coming months. The tentative goal is to have votes on these vaccines during the October 2023 ACIP meeting, presuming licensure has occurred.

The GSK vaccine is comprised of Menveo One-Vial (serogroups ACWY) and Bexsero (serogroup B). Both of these vaccines are currently licensed in the US. Clinical trials are assessing a 2-dose schedule at 0 and 6 months. The company is studying the immunogenicity and safety of the vaccine in patients 10─25 years of age in both MenACWY primed and naïve patients. Longer interval studies are underway, but they will not be completed before licensure and an ACIP vote.

The Pfizer vaccine is comprised of Nimenrix™ (serogroups A, C, W, and Y) and Trumenba® (serogroup B). Trumenba® is currently licensed and available in the US. Nimenrix™ is not but is extensively used in Europe and elsewhere. Pfizer's clinical trials are assessing a 2-dose schedule at 0 and 6 months, 0 and 12 months, and another schedule with 2 doses at 11─12 years and a booster at 16 years. They are also assessing a single dose of pentavalent as an alternative to MenACWY vaccine. They are studying the effect of the vaccine on patients aged 10─25 years and in both MenACWY primed and naïve patients. Longer interval studies also are underway, but they will not be completed before licensure or ACIP vote. When tackling these assessments, the WG plans to review the epidemiology of meningococcal disease, immunogenicity, and safety data for each vaccine and the expected public health impact of the vaccines.

The WG will use GRADE and EtR to assess the vaccines. The 3 policy questions the WG decided upon for each pentavalent vaccine are:

1. Should the pentavalent vaccine be included as an option for MenACWY and MenB vaccination in people currently recommended to receive both vaccines? (e.g., individuals 16-years of age are recommended to get MenACWY and can get MenB based on shared clinical decision-making).

2. Should the pentavalent vaccine be included as an option for people currently recommended to receive MenACWY only? (e.g., children 11─12 years of age).

3. Should the pentavalent vaccine be included as an option for people currently recommended to receive MenB only? (e.g., during a serogroup B outbreak).

Of note, the WG decided to add the second and third policy questions because of concern that some providers might not carry MenACWY and MenB vaccines once the pentavalent vaccines become available. The following table includes the outcomes for proposed PICO questions, which are similar for the GSK and Pfizer vaccines:

Outcome	Importance[1]	Included in Evidence Profile
Meningococcal disease caused by serogroups A, B, C, W, and Y	Critical	Yes
Persistent immunity	Important	Yes
Short-term immunity	Critical	Yes
Interference with other recommended vaccines administered concurrently	Important	Yes
Serious adverse events	Critical	Yes
Non-serious adverse events	Important	Yes

This table focuses on the first policy question and asks whether the pentavalent vaccine should be included as an option for MenACWY and MenB vaccination in people currently recommended to receive both vaccines. The PICOs are very similar to one another, so the key differences are highlighted on each slide. The population of each of the PICOs will be all individuals ≥10 years of age currently recommended to receive the licensed vaccines. The intervention will be the pentavalent vaccine under consideration. The comparison will be the currently licensed vaccines, which the WG members rated in terms of the importance of the 6 outcomes listed above. There will be opportunities to revise these assessments later in the process if needed. As mentioned, the WG hopes to complete its review of these 2 vaccines in a year with an anticipated vote in October 2023 presuming the vaccines are licensed by the ACIP meeting date. In February 2023, the WG will present the epidemiology of meningococcal disease in the US and GSK and Pfizer will give the manufacturers' presentations. In June 2023, the WG will present the GRADE and EtR findings and expected public health impact of the vaccines.

Discussion Points

Dr. Chen asked whether the outcomes of immunity were based on a specific cutoff titer for serum bactericidal antibody (SBA), some proportion of seroconversions of 4-fold over baseline, or some other measure.

Dr. McNamara from CDC's Bacterial Meningitis Epidemiology Team (BMET) indicated that typically, SBA is used for the correlate of protection for meningococcal vaccines. The manufacturer might be able to comment on exactly what will be used as the correlate for licensure for these vaccines, but CDC will be looking generally at SBA data for this.

As a member of the WG, Dr. Loehr emphasized that the WG has 3 questions. While initially he thought they needed to answer only one when he started on this WG that they just needed to know if both MenB and MenA could be done in one, there was a strong consideration that some practices would carry only the new pentavalent vaccine. Therefore, the WG thought it was very

important to decide whether that is reasonable to do. That is where the second and third questions came from.

Dr. Long said she thought that the use of a pentavalent vaccine would convert a shared decision-making recommendation to a recommendation, and she would want to have the WG think a lot about the low burden of disease and the trust of the American people in vaccine policies in that they are taking risks, however small, with every vaccine. There is a burden of disease that is considered worth the risk. Immunizing millions of older teenagers with a vaccine with the efficacy as it is or is not for this vaccine and for the very low risk of disease is something she would like to hear a lot more about.

Dr. Poehling thanked Drs. Long and Loehr for their comments in terms of highlighting the purpose of the 3 specific questions. The WG thinks that each one is very important to consider.

Dr. Daley said it felt like there was a precedent for giving a multi-antigen vaccine for an outbreak, such as giving MMR for a mumps outbreak.

Dr. Crowe noted that the ACIP Executive Secretary pointed her to a document that was published in 1999 about this particular issue, which noted that combination vaccines may be used whenever any components of the combination are indicated, its other components are not contraindicated, and the provider might not have other vaccines available or might prefer to use the combination vaccine. It recommends that the benefits and risks to administering the combination vaccine should be considered and compared during the process, which is something the WG will be deliberating.

Ms. McNally said that in trying to understand the policy questions, it seemed that someone who is vaccinated with the 2-dose series against ACWY at 11 or 12 years of age, again at 16 years of age, then chooses to get vaccinated against MenB at 16 years of age but has had only 1 dose could get the pentavalent. If correct, she wondered what harm there might be to the re-vaccination with ACWY, if any.

Dr. Crowe indicated that those are the questions the WG will be deliberating on over the next year. As noted, there is some precedent for having combined vaccines. The approach of the WG at this point is to look at how the pentavalent vaccines can fit within the current ACIP schedule. It changes to that schedule are warranted in the future, the WG will turn to that then.

Dr. Sanchez indicated that he would like to see a re-assessment of the meningococcal vaccine recommendation for adolescents 11—12 years of age to determine whether it is needed. Given the low burden of disease, perhaps they should advocate for the 16-year-old pre-college vaccine.

Dr. Crowe acknowledged that this is an important question and one that the WG has been deliberating. At this point, the intention is to assess the pentavalent vaccines first given the complexity of addressing both vaccines at the same time, but independently from one another. The types of questions are arising throughout the process and likely will over the next year. The WG will be back in touch with the committee as they learn more.

For clarification, Dr. Talbot thought the idea was to create a second vaccine period so that children would come in early adolescence and receive multiple vaccines to facilitate higher vaccination rates. HPV starts at 11 years of age and can start as soon as 9 years of age.

Dr. Lee clarified that the fundamental question is about the platform in terms of whether it needs to remain in the adolescent platform or if a late adolescent platform is needed.

To follow-up on Dr. Long's question about the shared decision-making on MenB after 16 years of age, Dr. Cineas asked whether the current uptake of MenB vaccination is known in that age group.

Dr. Crowe said that around 30% was reported the previous year for a single dose, but did not think they had data for 2 doses, although it might be lower.

Dr. McNamara added that the data they have on the complete 2-dose series for MenB is that usually about half of the people who start a series appear to complete it.

Dr. Balmer, Pfizer, indicated that the Pfizer pentavalent vaccine will be based on licensure criteria that is looking at 4-fold seroresponse of hSBA titers for all 5 serogroups. For the MenB component, they also doing an additional licensure endpoint of a composite hSBA response which is an hSBA titer against all 4 MenB strains being tested.

Dr. Goldman suggested that one thing the manufacturers might want to assess is the dosing schedule. He stocks both types of vaccines in his practice and finds that during many of the pre-college physicals, patients are in a panic to get their vaccines. Having a schedule where the vaccine is administered at 0 and 1 month later would allow them to fit it in in the summertime. At 0 and 6 months, they may not be able to get all of their vaccines in that they want before they get off to college. It would be very helpful to have a pentavalent, but an extended dosing schedule may make it more difficult to implement.

Dr. Lee requested that the WG take that under advisement and she offered Dr. Preiss an opportunity to respond from GSK.

Dr. Preiss indicated that regarding the GSK pentavalent study looking at non-inferiority in terms of MenB responses, a panel of 110 diverse wild-type strains will be used to assess the effect of the antibodies at killing those strains within the context of an endogenous complement assay. The standard assays are used in terms of non-inferiority for ACWY.

Dr. Lee requested that "short-term" be defined, given that it means many different things to many different people. In addition, she emphasized the importance of incorporating equity in the domains.

INFLUENZA VACCINE

Session Introduction

Dr. Keipp Talbott (ACIP, WG Chair) introduced this session. She reported that 2022-2023 influenza vaccination recommendations had been completed and published in the *MMWR Recommendations and Reports* on August 26, 2022. Since the last ACIP meeting, the WG has engaged in discussions of US and Southern Hemisphere seasonal influenza activity, US influenza VE updates from 3 CDC networks, and influenza vaccination in pregnancy. During this session, ACIP heard presentations on a clinical trial to compare safety of recombinant influenza vaccine (RIV4) in pregnancy, an update on influenza activity, and an influenzas VE update.

Influenza Activity Update

Geeta Swamy, MD (Duke University) presented the results from a clinical trial to compare the safety of RIV4 versus quadrivalent inactivated influenza vaccine (IIV4) in pregnancy that was funded by the Clinical Immunization Safety Assessment (CISA) through the CDC. In terms of personal disclosures, Dr. Swamy reported that she serves on DSMBs and has consulted for vaccine companies and clinical trial design, receives funding from the CDC, and chairs various committees for advocacy organizations and federal advisory committees.

In terms of the rationale for the study, ACIP currently recommends influenza vaccine for persons ≥6 months of age, including pregnant women. The goal of the clinical trial was to compare the safety of RIV4 versus IIV4 in pregnancy. Pre-licensure studies for RIV excluded pregnant people. While there is no specific reason to expect that it would be unsafe, there are limited data on the safety of RIV in pregnancy. This rigorous RCT of RIV4 vs. IIV4 in pregnant people was implemented to provide information on the safety of RIV4 during pregnancy, including infant health outcomes.

The primary objective of the study was to compare the proportions of adverse birth outcomes between pregnant women vaccinated with RIV4 vs. IIV4. The research hypothesis was that the proportion of pregnant persons with adverse birth outcomes will be non-inferior, or not higher, after receipt of RIV4 compared to IIV4. The secondary objectives were to compare: 1) proportions of preterm birth after RIV4 versus IIV4 vaccination; 2) proportions of combined fetal and neonatal death after RIV4 versus IIV4 vaccination; 3) proportions of spontaneous abortion after RIV4 versus IIV4 vaccination; and 4) proportions of moderate to severe solicited reactogenicity events in pregnant women vaccinated with RIV4 versus IIV4.

Individuals were enrolled into this prospective, double-blinded, randomized trial in which subjects were randomized 1:1. The study population included 382 pregnant women ≥18 years of age who were less ≤34 weeks gestation who planned to receive RIV or IIV during their current pregnancy. The initial goal was to enroll about 430 participants, but there were issues that curbed the enrollment time period. The reason for enrolling individuals who were less ≤34 weeks gestation was to be able to have adequate time to follow the pregnancy and determine whether there were any impacts on outcomes. Subjects were recruited across 3 sites in the CISA-funded study from Duke University Medical Center, Cincinnati Children's Hospital Medical Center, and Boston Medical Center.

After randomization, participants received study influenza vaccine. Study staff and participants were blinded to RIV4 or IIV4. Solicited local and system reactions were collected during Day 1 (vaccination day) through Day 8 using a memory aid that was provided so that participants could then provide the information back through REDCap electronic data or record that on paper. SAEs and other health outcomes were assessed throughout pregnancy and 90 days following delivery for mothers and infants. Blood samples were collected in pregnant participants before vaccination on Day 1, post-vaccination on Day 29, and at delivery for influenza immunogenicity. Maternal and cord blood samples were collected during the delivery hospitalization whenever feasible.

The primary outcome measure was defined as the proportions of adverse birth outcomes in pregnant women vaccinated with RIV4 versus IIV4 assessed in a modified intention to treat (mITT) population. Adverse birth outcomes was a composite that included preterm birth, spontaneous abortion, fetal death, or neonatal death. Similarly, the secondary outcome measures included preterm birth, a combination of fetal and neonatal death, spontaneous

abortion alone, and local and systemic reactogenicity events. All of the outcome measures were assessed in the mITT population.

In terms of the statistical methods, the mITT population was the primary analysis population who consisted of any participant who was enrolled, randomized into the study, and received study product. The per protocol population was a subset of those that excluded participants who had any serious protocol violations. Statistical testing was done using a noninferiority analysis approach with the upper bound of a stratified Newcombe binomial confidence interval with a Cochran-Mantel-Haenszel (CMH) weighting of the difference. Other objectives included comparisons between the RIV4 group and the IIV4 group using an exact Mantel-Haenszel statistic in a stratified analysis by site.

Regarding enrollment of participants, 430 participants were approached. Of those, 387 were screened, 3 were determined to be ineligible, and none declined. This resulted in a total of 384 who were enrolled and randomized. Of those, 2 were excluded due to eligibility criteria that were identified to be incorrect or not assessed correctly from the start. A total of 190 participants were randomized to the mITT RIV4 (Flublok) group and 192 participants were randomized to the mITT IIV4 (Flulaval) group. Attrition included 2 voluntary withdrawals in the mITT RIV4 group and 5 in the mITT IIV4 group (3 lost to follow-up, 1 delivery in another hospital, and 1 eligibility not met).

The end result was based on 188 participants in the mITT RIV4 (Flublok) group and 187 in the mITT IIV4 (Flulaval) group. The demographic data were fairly consistent between the 2 study groups. About 33% of participants self-reported Black race, about 12% to 13% of participants self-reported Hispanic or Latino ethnicity, and about 34% and 40% in each of the 2 groups were enrolled prior to 20 weeks gestation. As a reminder, individuals were deliberately enrolled early in pregnancy in order to monitor for the spontaneous abortion early pregnancy outcome. The gestation age at enrollment was roughly 22 to 23 weeks.

Looking specifically at the primary outcome of the proportion of adverse birth outcomes based on the composite definition, there were approximately 9% in the mITT RIV4 (Flublok) group and about 11% in the mITT IIV4 (Flulaval) group. The null hypothesis of inferiority was rejected, so the rate of adverse birth outcomes in the recombinant influenza vaccine group is considered not worse or not higher than that of the standard inactivated group. Breaking that down into each of the component outcomes, preterm birth incidence was about 7.5% in the mITT RIV4 (Flublok) group and about 10% in the mITT IIV4 (Flulaval) group, which was not statistically different. Combining fetal and neonatal deaths, it is important to note there were no neonatal deaths. There were 2 fetal deaths in the mITT RIV4 (Flublok) group and none in the mITT IIV4 (Flulaval) group. While not having any events is not estimable from the standpoint of comparison, it would not be any higher than would be expected based on background. Looking at the proportions of spontaneous abortion after RIV4 versus IIV4 vaccination in pregnant women enrolled at <20 weeks gestational age, there was really no difference between the 2 groups.

Regarding moderate to severe reactions amongst the 2 groups, swelling was not identified in any participants. Tenderness was somewhat higher in the IIV4 (Flulaval) group, but it was not statistically different between the 2 groups. In terms of systemic moderate to severe reactions, no fevers were identified. Participants were given a thermometer as part of study procedures and were asked to record their temperatures. Chills were experienced in about 1.5% in each group, with no difference between them. There appears to have been a higher incidence of headache amongst those in the IIV4 group compared to the RIV4 group, but the difference was not statistically significant.

There were some exploratory outcomes as well. For maternal SAEs, there was no difference between the 2 groups. All SAEs were deemed not related to vaccine, as judged by the study investigators. The diagnoses for the majority of participants included antenatal hospitalizations for preeclampsia, preterm labor, preterm premature rupture of membranes, hyperemesis, substance use, end-stage renal disease, vaginal bleeding; and postpartum hospitalizations for preeclampsia, and postoperative infection. For additional exploratory outcomes, there were no differences between groups. These included small-for-gestational age, clinical chorioamnionitis, and preeclampsia or eclampsia. Infant SAEs in the first 90 days of life were deemed not related to vaccination, as judged by the study investigators. There were some other SAEs such as medically attended events like respiratory infection. There was no pattern in congenital malformations beyond the expected number based on background. Congenital malformations in the IIV4 group included renal anomaly x 2, trisomy 21, VSD/renal/absent thyroid, craniosynostosis, short femur, atrial septal defect, anomalous S1 hemivertebra, sagittal synostosis, and ectopic kidney. Congenital malformations in the RIV4 group included cardiac/DiGeorge, extra digit, bilateral pyelectasis, and pyloric stenosis.

In summary, this is the first RCT to compare the safety of RIV4 and IIV4 in pregnant women. This study enrolled 382 participants (89% of goal enrollment). RIV4 was non-inferior to IIV4 for adverse birth outcomes, which is consistent with the study hypothesis. The safety profile of RIV4 and IIV4 is similar for moderate to severe reactogenicity events and maternal and infant health outcomes were assessed. From the standpoint of safety, the study supports the ACIP recommendation to include RIV4 as an option for pregnant persons. The influenza immunogenicity analyses are in progress.

Discussion Summary

Dr. Poehling asked whether any of the infants of the pregnant women who were vaccinated during pregnancy were hospitalized with an influenza illness or had the diagnosis of influenza in the subsequent 6 months.

Dr. Swamy indicated that no active surveillance was conducted for respiratory infection, but there were no hospitalizations specifically for influenza infection.

Ms. Hayes, ACNM, asked whether fetal death was among the congenital anomalies found. If so, it would be beneficial to know whether the fetal death was related to a malformation.

Dr. Swamy indicated that she would check and pass along the information to Dr. Grosskopf to share with ACIP and the WG. The intent is to publish these data.

Dr. Poehling observed that the background rate of each of the outcomes seemed to be in the expected range.

Referring to Slide 13, Ms. McNally asked whether the race and ethnicity representation was what the investigators were hoping to have and whether it was consistent with other vaccination and pregnancy studies.

Dr. Swamy indicated that the investigators did not set a target goal for enrollment by race and ethnicity, but the numbers are proportional to the populations in the clinical sites. For instance, approximately 25% to 40% of patients from Duke identified as being of Black race, depending on variation across its clinics. The site in Boston has a similar demographic and patient profile.

Influenza Surveillance Update

Lynnette Brammer, MPH (CDC/NCIRD) presented on influenza activity in the US over the summer and during the first week of the 2022-2023 influenza season. In terms of virologic surveillance data from clinical laboratories, the percentage of specimens testing positive for influenza was low and continued through summer of last year. There was an increase during the first week of the new influenza season, with 3.3% of all specimens tested and reported to CDC from clinical laboratories being positive for influenza. This varied by HHS region, with a range from 0.2% in Region 8 (Mountain Region) to 10.4% in Region 4 (Southeast). Data from public health laboratories showed predominantly influenza A(H3N2) viruses, but in recent weeks a small increase was seen in influenza A(H1N1) viruses at Week 40.

Regarding outpatient visits for respiratory illness reported by the US Outpatient Influenza-like Illness Surveillance Network (ILINet), the season began above baseline in Week 40 at 2.6% compared to the baseline of 2.5%. It is important to note that this is ILI, not laboratory-confirmed influenza and is a mix of respiratory viruses. ILI activity levels by state seem to correspond pretty well with the areas where higher percentage of specimens are testing positive for influenza.

Data from one of CDC's new surveillance systems that was established during the COVID-19 pandemic showing at least one confirmed influenza positive test among residents of long-term care facilities (LTCF) peaked at 1.4% of facilities having a positive influenza case in a resident. At Week 40, a very slow increase was seen at 0.3% of facilities having influenza positives among residents. A second new surveillance system established during the pandemic monitors reports from all hospitals across the country for the number of admissions for laboratory-confirmed influenza. The peak between October 3, 2021 – October 8, 2022 was in April at 3,481 hospitalizations during Week 16. There was an increase in the week ending October 8th at 1,322. That increase is expected to continue.

While nothing unusual has been observed in terms of all age mortality than would be expected at this time of year, there have been 43 influenza-associated pediatric deaths compared to 1 death in the 2020-2021 season. All of these viruses were influenza A, with the exception of 2 influenza B viruses. The most recent death reported by date of death was for Week 33, which was mid-August.

To summarize, influenza activity in the US remains fairly low overall. However, an increase is being seen—particularly in the Southeast and South Central part of the country. The numbers are small so far, but influenza A(H3N2) viruses are predominant in the US. It is too early to tell which virus will predominate this season. For the Southern Hemisphere vaccine decision, the H1N1 component was updated and is within the same genetic subclade as the US vaccine. At this time, the components selected for the Northern Hemisphere vaccine for 2022-2023 appear to be appropriate for the season.

2022 Southern Hemisphere Influenza Surveillance in Sentinel Countries

Perrine Marcenac, PhD (CDC/NCIRD) presented an update on 2022 Southern Hemisphere influenza surveillance in sentinel countries. The surveillance data came from the WHO's FluNet system, which is comprised primarily of data from influenza sentinel surveillance systems but also includes non-sentinel data. Sequencing data comes from the Global Initiative on Sharing All Influenza Data (GISAID). The data shared for each country showed pre-pandemic historical data of the proportions of specimens testing positive for influenza from 2011–2019; the epidemic threshold above which countries are considered to be experiencing their seasonal epidemic based on 2011–2019 historical data; 2021 data; 2022 data; and 2022 virus data by type and, when available, by subtype and lineage.

Australia's Southern Hemisphere season started and ended earlier than in pre-pandemic seasons, starting in April and ending in Week 35 in August.[99] Type specimens so far have been overwhelmingly influenza A, with H3N2 making up 91.3% of subtype specimens. The dominant clades of circulating influenza viruses are based off of the sequencing of specimens from July 2022. The H1pdm09 dominant clade was the 6B.1A.5A.2. H3 was 3C.2a1b.2a.2 and B Victoria was V1A.3a.2. These dominant clades for H1, H3, and B Victoria are consistent with dominant clades being seen in other Southern Hemisphere countries. Australia's Department of Health and Aged Care issues a biweekly surveillance report that includes antigenic characterization of influenza isolates. Australia's WHO Collaborating Center characterized 2,570 isolates for antigenic similarity to their corresponding vaccine component, which found that 92.4% of influenza A(H1N1), 94.5% of influenza A(H3N2) isolates, and all 6 influenza B/Victoria isolates characterized year-to-date were antigenically similar to corresponding vaccine components. They do not yet have influenza VE estimates but report from preliminary data in 2022 that VE is on the lower end of the moderate range.

Chile experienced an atypical influenza season in 2022,[100] starting with influenza cases increasing during Northern Hemisphere months in January through February, followed by a more traditional Southern Hemisphere season in May through August. The season does not seem to be coming to a close, with the proportion of specimens testing positive increasing as of Week 40. As is the case in Australia, most circulating viruses have been influenza A at 99.9%, with H3 making up over 99.8% of subtype specimens. The dominant clade data was only for H3 as of June 2022. Chile reported the same dominant clade as in Australia and other Southern Hemisphere countries. CDC has been fortunate to work with Chile's Ministry of Health, Institute of Public Health, and the Pan American Health Organization (PAHO) on a summary report of their 2022 season, including influenza VE. By the peak of influenza activity in 2022, Chile had successfully vaccinated 92.5% of persons in their priority groups. Their severe acute respiratory infections (SARI) sentinel data submitted to PAHO's Network for the Evaluation of Vaccine Effectiveness in Latin America and the Caribbean influenza (REVELAC-i were used to estimate this vaccine's effectiveness in preventing influenza hospitalizations, which found that VE against influenza A(H3N2)-associated hospitalizations was 49%.

Unlike Australia and Chile, South Africa has presented a more typical influenza season as compared to historic trends. Their season started in April and has declined in recent weeks. However, unlike Australia and Chile, South Africa has seen high levels of A(H1N1)pdm09 during peak activity, corresponding to over 50% of their subtype specimens. The latter part of their season now seems to be dominated primarily by H3 and B/Victoria. Information on dominant

[99] Data source: https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-ozflu-lucurr.htm Data from 1 January–9 October 2022

[100] Olivares Barraza MF, Fasce RA, et al. (2022) MMWR; provisionally accepted

clades from sequencing data in June and July of 2022 showed the dominant clades to be the same as in other Southern Hemisphere sentinel countries.

To summarize, Southern Hemisphere countries have seen abnormal activity in 2021 and 2022, with shifted timing of the epidemic and changes in the magnitude. However, influenza activity has resumed in new sentinel countries following disruptions in change and transmission during the COVID-19 pandemic. These countries have seen mostly influenza A(H3N2). However, South Africa reported significant circulation of A(H1N1) and B/Victoria viruses.

Discussion Points

Ms. Stinchfield, NAPNAP, expressed gratitude and emphasized that these data are used extensively in the field. She noted that it would be helpful to develop a similar graph for pediatric influenza deaths on data collection related to COVID-19 and potentially for RSV, given that future RSV products are anticipated.

Comparison of Influenza Vaccine Effectiveness against Outpatient and Inpatient Illness in the 2021–2022 Season

Jessie Chung MPH, Samantha Olson MPH, and Nathaniel Lewis PhD (CDC/NCIRD) shared results comparing influenza VE against outpatient and inpatient illness in the 2021–2022 season using data from 3 VE platforms in the outpatient ambulatory ED and inpatient settings to evaluate VE against laboratory-confirmed influenza-associated outpatient visits, ED visits, and hospitalizations.

Ms. Chung began with a presentation of preliminary estimates from the outpatient setting among patients ≥6 months of age from the US Flu VE Network. These estimates were presented preliminarily during the June 2022 ACIP meeting, although representing different age groups during this session for the purposes of comparison with the other 2 networks. The Flu VE Network in the 2021-2022 season included outpatient clinics, including EDs at 7 locations: Kaiser Permanente Washington, Kaiser Permanente Southern California, Marshfield Clinic Research Institute, Vanderbilt University, Baylor Scott & White Health, University of Michigan, and University of Pittsburgh.

As a reminder of the Flu VE Network methods, ambulatory patients ≥6 months of age with acute respiratory illness (ARI) with fever or cough ≤7 days duration were enrolled who presented at outpatient clinics or EDs. Patients were enrolled up to 10 days after illness onset, but this analysis was limited to those who enrolled within 7 days. Enrollment occurred from October 4, 2021–April 30, 2022. A test-negative design was used, with persons who tested positive for SARS-CoV-2 excluded from influenza VE estimates. Vaccination status was defined as receipt of 1 or more doses of any influenza vaccine using documented sources in addition to self-report. The estimates presented during this session were adjusted for study site, age, self-rated general health status, race/ethnicity, and month of onset.

All influenza viruses detected in the Flu VE Network in the 2021-2022 season were influenza A viruses, with nearly all being A(H3N2) viruses. VE against A(H3N2) viruses overall was 36%. By age group, VE among children was 45% and VE among adults was 28%. A very small number of cases were enrolled among persons ≥65 years of age. It was not possible to calculate an adjusted estimate for that age group. Unadjusted VE was 32% for those ≥65 years of age and the estimate was not significant. A subset of A(H3N2) viruses were genetically sequenced, and all of the viruses belonged to a genetic group with antigenic differences from the vaccine strain.

Ms. Olson presented preliminary data from the New Vaccine Surveillance Network (NSVN) from the early stages of calculating VE against influenza-associated ED visits and hospitalizations among children 6 months─17 years of age. The data are being cleaned and it is a top priority for the NSVN to finalize and publish these results. The data are from the same NSVN sites that were included in the last published NVSB Flu VE estimate during the 2019-2020 season. The sites include: Seattle Children's, Cincinnati Children's, Children's Mercy Hospital, Vanderbilt University, Texas Children's Hospital, University of Rochester, and Children's Hospital of Pittsburgh.

To briefly describe the methods, inpatient and ED patients aged 6 months─17 years with acute respiratory illness within 10 days of illness onset were enrolled in the study between November 27, 2021–June 7, 2022. A test-negative design, using both clinical and research testing, was used to compare vaccination odds among influenza-positive cases to influenza-negative controls. Because of the biases mentioned previously, those testing positive for COVID-19 were excluded. To be considered vaccinated, patients received at least 1 dose of any influenza vaccine according to medical records, registries, or self-report. The current sample size was not sufficient to assess 2 doses in the younger children, but this will continue to be assessed before publishing the data. The analysis was adjusted for site, age, and calendar time. VE was calculated to be 30% in the inpatient and ED settings. In terms of those admitted to the ED, a VE of 19% was calculated, with the estimate crossing the null. VE among inpatients was observed to be 31%, with the estimate crossing the null.

Dr. Lewis presented preliminary data from the Investigating Respiratory Viruses in the Acutely Ill (IVY) Network, which focuses specifically on adults who have been admitted to a hospital with ARI. The IVY network consists of over 20 large medical centers, usually associated with academic institutions. This particular analysis focuses on 16 of these sites, including: Intermountain Medical Center, University of Colorado, Baylor Scott & White Health, Hennepin County Medical Center, University of Iowa, Washington University St. Louis, Vanderbilt University, University of Michigan, Ohio State University, University of Miami, Cleveland Clinic, Baystate Medical Center, Beth Israel Deaconess Medical Center, Montefiore Medical Center, Johns Hopkins University, and Wake Forest University.

In terms of the methods used for the analyses in this network, enrollees included hospitalized patients aged ≥18 years with ARI and molecular testing for influenza and SARS-CoV-2 within 10 days of illness onset who were admitted to a hospital within 14 days of illness onset. The dates for this analysis period were well into the middle of the previous influenza season from January 31, 2022–June 15, 2022. This analysis used a test-negative case-control design in which the odds of vaccination were compared among those who tested positive for influenza versus odds of vaccination among those who tested negative for influenza. Vaccination status was determined as receipt of at least 1 dose of any of the seasonal influenza vaccine according to medical records, immunization registries, and/or self-report. If source documentation was not available, self-report alone was used but accounted for less than 5% of participants.

For the analysis, VE was calculated as (1 – adjusted OR) x 100%. Logistic regression models were adjusted for study site, age, sex, race and ethnicity, and calendar time. A familiar trend in low VE against hospitalization was observed overall among everybody ≥18 years of age and when broken down by specific age groups. All of the VE estimates crossed the null, essentially suggesting null to very low VE. However, when immunocompetent adults were specifically broken out, more moderate VE of 50% was observed in adults 18─64 years. This estimate did not cross the null.

Looking at all 3 of these networks in comparison and contrast to one another provides a more robust view of VE during the previous influenza season, this analysis was organized by age group and different settings within each age group. Outpatients were represented by the Flu VE Network, ED and inpatients were represented by NVSN, and inpatients alone were represented by the IVY Network. Assessing estimates across all 3 networks, very low VE was again observed. This is consistent with previous seasons in which H3N2 predominated. Of note, the IVY Network analysis where sequencing was done on 129 specimens also showed that all viruses were A(H3N2) virus. In the IVY network results, immunocompetent patients alone showed VE 50% for persons 18–64 years of age. In contrast to outpatient VE for the US Flu VE Network, this aligns with what might be expected where higher VE is seen for the more severe outcomes. Putting these estimates in opposition to one another allows for teasing out some of the differences.

To summarize, it can be said that influenza vaccination provided low to non-significant protection against influenza in a season where A(H3N2) predominated. This was similar across pediatric ED visits and pediatric hospitalizations. In adult hospitalizations, low to moderate VE was observed in outpatient settings and specifically among immunocompetent hospitalized adults 18–64 years of age. This is similar to previous seasons in which A(H3N2) predominated. Higher VE is seen in outpatient settings. Looking across all 3 networks allows thinking through the differences and why they might exist.

Discussion Points

Dr. Lee asked if the proportion of adults ≥65 years of age received a high-dose vaccine was known.

Dr. Lewis indicated that for the IVY Network, essentially 95% of older adults receive some sort of enhanced vaccine, whether higher dose or adjuvanted. Conversely, about 95% of those under 65 years of age are receiving the standard vaccine.

Ms. Chung added that for the Flu VE Network, about 80% of outpatients ≥65 years of age received high-dose or adjuvanted vaccine. Only 14% of that age group received standard dose IIV4 egg-based vaccine.

Dr. Poehling emphasized the importance of studying influenza every year. She asked whether there were data regarding vaccine coverage by age group in the population in order to understand that perspective.

Ms. Chung indicated that for the Flu VE network, vaccine coverage among controls was what they would look among the enrolled population overall, which was about 60%. Compared to what was observed in the community reported to CDC, it was somewhat higher for adults compared to the community, and perhaps somewhat lower for children in those communities. It is probably similar on average.

Miss Bahta lamented this discouraging data and emphasized that even more discouraging was the lack of efficacy against hospitalization. This suggested the need to take note and somehow send a message that better products are needed.

Dr. Long agreed and observed that VE seemed to be decreasing annually. She wondered whether the WG had considered this notion, with some evidence, that repeated immunizations may be disadvantageous.

Dr. Kotton pointed out that while VE was not what was hoped for, she often views vaccines to be like seatbelts. It is much better to have a vaccine than to not have any vaccine. While these analyses were looking specifically at measured disease incidence and hospitalization, many people have not had influenza for the past few years due to being masked. There are a lot of ramifications of not developing influenza. Even if the risk of disease is not decreased as much as hoped for, there is a positive impact from vaccination. Before pushing forward the idea that repeat influenza vaccine could be dangerous, it is important to make sure that there is robust science behind that.

Dr. Talbot noted that the idea of imprinting is the first influenza one had as a child, presumably because most people are infected fairly early, so it is what one's body responds to the most. The population who is at highest risk for influenza disease now is imprinted with H1N1, which means they are more likely to get sick from H3N2. During H3N2 seasons, much lower VE is typically observed because this population was imprinted with H1N1. That being said, there was a mismatch this year that complicated an already lower VE to an even lower VE. The hope is that the vaccine has the right strains for this year. Tennessee is seeing a mix of H1 and H3 at this point.

Dr. Anderson, PIDS, pointed out that it is very likely that there may have been some waning of the immune response that may have happened for many of these infections that likely occurred in the March and April time period. He wondered about the extent to which that could be adjusted for in the analyses that were performed and how it impacted overall VE.

Ms. Chung responded that to assess this from the Flu VE Network perspective, persons who tested positive for SARS-CoV-2 were removed from midseason estimates, which resulted in a similar estimate to what was observed when the whole time period as assessed. While it is not clear that waning is the biggest factor for lower VE estimates, it is something to consider.

DENGUE VACCINE 10-20-22

Session Introduction

Wilbur Chen, MD, MSc (ACIP WG Chair) introduced this session on behalf of the Dengue Vaccine WG, emphasizing that as humans continue to encroach on natural habitats, there will be the potential for increases in Ebola, monkeypox, malaria, and arboviruses in general. Climate change will increase dengue incidence.

As a reminder, Dengvaxia™ was licensed in 2019 and the ACIP provided recommendations in 2021. This vaccine has a 3-dose regimen given at 0, 6, and 12 months in children 9─16 years of age with laboratory-confirmed previous dengue infection who live in endemic areas with dengue.

The Dengue WG was reactivated on August 30, 2022 and has been reviewing Takeda's TAK-003 candidate dengue vaccine. This vaccine has completed Phase 3 trials. The plan is for the WG to present safety and efficacy data during the February 2023 ACIP meeting. The WG has

reviewed its schedule and has been formulating PICO (population, intervention, comparison, outcomes) questions and reviewing the vaccine's safety and efficacy data.

This session included presentations on dengue epidemiology to reacquaint ACIP with this pathogen and an update on Dengvaxia™ efficacy, safety, and implementation.

Dengue Epidemiology: Globally and in the US

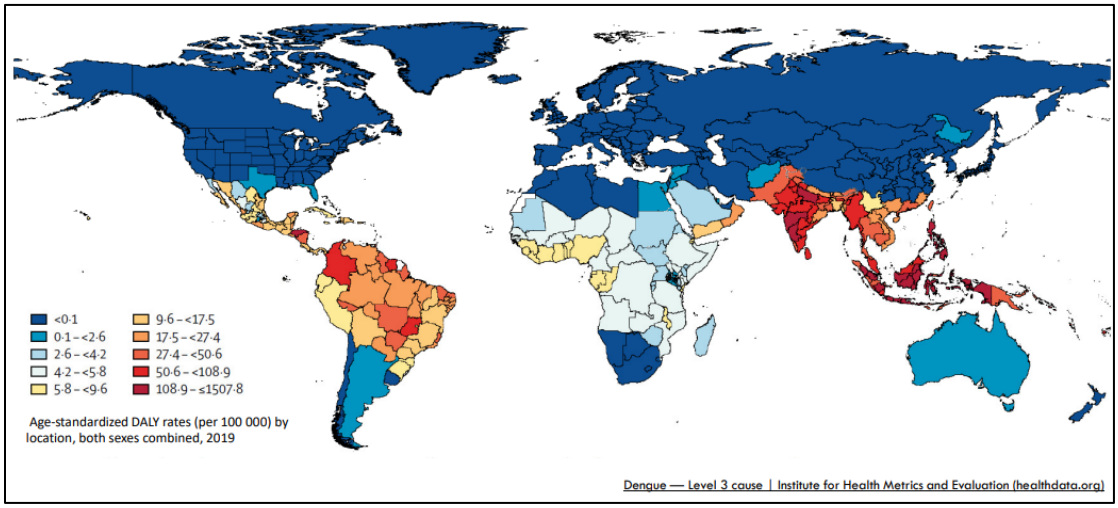
Laura Adams DVM, MPH, DACVPM (CDC/NCEZID) provided a brief background of dengue epidemiology, both globally and in the US, including routes of transmission, clinical spectrum, global burden, and epidemiology in the US in endemic and non-endemic areas. Dengue is caused by dengue viruses (DENV)-1, 2, 3, and 4. Sometimes called "serotypes," all of these types cause disease. Infection with DENV leads to lifelong type-specific immunity against the infecting DENV and short-term cross-protective immunity to the other DENVs, usually for about 1 to 3 years. Dengue is primarily a mosquito-borne disease spread through the saliva of infected mosquito bites. *Aedes aegypti* is the most common vector. However, *aedes albopictus* also can sustain transmission. Other modes of transmission for dengue virus are less common, but include vertical transmission from a mother to a baby; blood transfusion or organ transplantation; needle stick, mucocutaneous exposure, or hospital or laboratory accident; breast milk, and rarely sexual transmission.

In terms of the dengue clinical spectrum, only about 1 in 4 DENV infections are symptomatic, with the majority of infections being asymptomatic or subclinical. Dengue often presents as a mild, undifferentiated febrile illness with common symptoms including fever, aches and pains (eye, muscle, bone, joint), nausea/vomiting, and rash. Mortality among symptomatic dengue cases ranges from <1% if treated appropriately to up to 15% if untreated. Dengue can progress to severe disease in about 1 out of every 20 symptomatic dengue patients and requires close clinical management. Severe dengue is characterized by severe plasma leakage, severe bleeding, and severe organ impairment.

Many factors can affect an individual's risk for severe dengue. There is a known risk by age, with a particularly higher risk among infants born to seropositive mothers and elderly populations. The number of dengue infections and the time between those infections also can play a role. Although severe dengue can occur during any dengue infection, there is a higher risk with the second dengue infection compared to the first, third, or fourth infection. Underlying comorbidities also can be associated with worse outcomes, including asthma, diabetes, obesity, hypertension, sickle cell disease, kidney disease, or anticoagulant therapy.

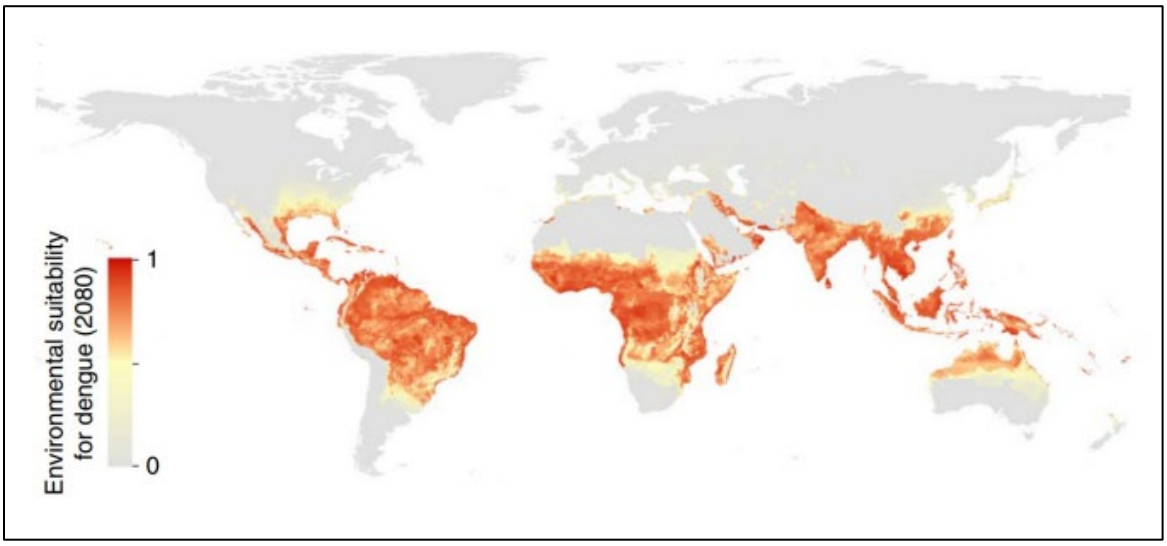
It is important to understand the changing risk for severe dengue during multiple dengue infections. In people naturally infected with dengue, there is a moderate risk for severe disease with the first infection. There is a higher risk with the second infection, which is associated with antibody-dependent enhancement of disease when heterotypic antibodies bind but do not neutralize the dengue virus, leading to higher levels of viremia and vascular leakage. After the second infection, people are at lower risk for severe disease with the third and fourth exposures. The immune response consists of broadly neutralizing antibodies that provide more effective protection. This level of risk also has been associated with dengue antibody titers. Low antibody titers are associated with moderate risk, while mid-range dengue antibody titers have higher risks for dengue hemorrhagic fever and dengue shock syndrome. Higher level antibody titers are associated with lower risk for severe disease.

Dengue is the most common arboviral disease globally and causes significant disability and death. This map shows the age-standardized disability adjusted life years (DALYs) by country, with lower burden shown in darker blue progressing to higher burden in red:

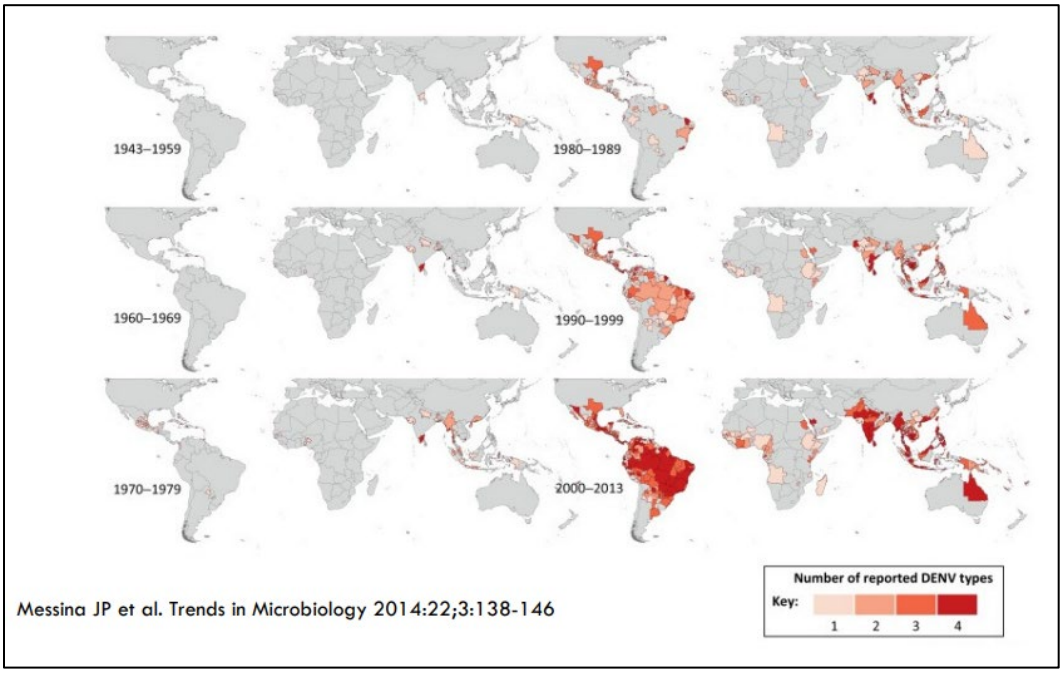


There is generally a high disease burden in tropical and subtropical areas globally, particularly in the Americas and Southeast Asia.

Dengue incidence is likely to increase as the climate warms, both through increased transmission in currently endemic areas and secondarily through expansion of the geographic range of 80 species mosquitoes. This figure shows the areas predicted to have environmental suitability for dengue by 2080, shown in orange and red, and indicates that over 6 billion people will be at risk. This is an increase of more than 2 billion compared to 2015:



Messina and coauthors mapped the global distribution and co-circulation of each DENV type from 1943 to 2013, shown in the panels here:



With the data caveat that serotype diagnostic availability has changed over time, the detection of all virus serotypes has expanded worldwide, together with growing hyperendemicity. Until the 1980s, the majority of areas had only reported 1 or 2 dengue virus serotypes. More recently, all 4 virus serotypes frequently co-circulate.

It would be ideal to have seroprevalence data to assess risk. Because this information is rarely available at the population level and there are differences in case identification and reporting, the Yellow Book criteria are used to group dengue risk levels into 3 broad categories.[101] The first is frequent or continuous risk, which is considered endemic for vaccine recommendation purposes, and includes areas with 10 or more dengue cases in at least 3 distinct years over the most recent 10-year period. The second category is areas with sporadic or uncertain risk that had at least 1 reported, locally acquired dengue case in the past 10 years. The third category is areas with no evidence of risk and no reports of local DENV transmission. Based on using the Yellow Book criteria, dengue is endemic in 6 US territories and Freely Associated States (FAS). These include the FAS of Palau, the Federated States of Micronesia, and the Republic of the Marshall Islands; and the territories of American Samoa, Puerto Rico, and the USVI.

Puerto Rico experienced outbreaks in 2010, 2012, and 2013, with a slight uptick in transmission again in 2020. American Samoa had outbreaks in 2017 to 2018 with high disease rates for the population size. USVI experienced dengue outbreaks in 2012 to 2013 similar to Puerto Rico and with similar case rates, although in a smaller population size. Puerto Rico has the largest population size among the US territories and also reports the most dengue cases, accounting for more than 95% of the dengue cases from endemic areas of the US during 2010 to 2020. Historically, dengue has been endemic in Puerto Rico for many years, with periodic outbreaks occurring approximately every 3 to 5 years.

[101] Jentes et al. Journal of Travel Medicine 2016; 23, 6, 1-5.

In terms of circulating dengue virus serotypes by year in Puerto Rico from 2010 to 2020, all 4 dengue serotypes were detected. However, DENV-4 has been the predominant serotype, particularly during the outbreak years of 2010 to 2013 and in the cases identified in more recent years. The highest burden of dengue cases and hospitalizations by age group in Puerto Rico from 2010–2020 occurred among children 10–19 years of age.[102] This age group experienced higher case rates and hospitalization rates compared to other ages. However, a slightly different trend was seen among fatal dengue cases in the same time period in Puerto Rico, with higher mortality rates occurring among the adult population.[103] While there are limited population-level seroprevalence data, a serosurvey in 2018 assessed previous exposure to dengue and Zika viruses using plaque reduction neutralization assays among about 700 children in Southern Puerto Rico.[104] While exposures to both viruses were frequently identified, testing found that approximately 8% of children 1–8 years of age and 44% of children 9–16 years of age had evidence of previous dengue virus infection.

Moving on to American Samoa, a serosurvey in 2010 among adults found that 96% were seropositive for previous dengue infection.[105] More recently, an outbreak from 2016–2018 identified more than 1,000 confirmed cases.[106] The dengue case rates and hospitalizations in American Samoa were similar to what was seen in Puerto Rico, with the highest rates occurring among children 10–19 years of age.[107]

Dengue also has caused periodic outbreaks in the USVI, which includes St. Croix, St. Thomas, and St. John. Multiple dengue virus serotypes have circulated, with the most recent outbreaks in 2012–2013 consisting of DENV-1 and DENV-4. A school survey in 2012 during these outbreaks found that about 20% of the population had evidence of recent dengue virus infection.[108] The age group with higher dengue case rates in the USVI is also 10–19 years of age. However, the case distribution in USVI also includes a relatively larger proportion of adults compared to the other endemic areas. To assess dengue seroprevalence among children, the USVI Department of Health conducted a serosurvey in 2022 among 372 school children 8–13 years of age. An assessment of prevalence of dengue IgG antibodies by age found that seroprevalence was greater than 40% starting at 9 years of age—the lowest eligible age for vaccination with the Dengvaxia™ dengue vaccine.[109]

In terms of the dengue endemic in FAS in recent years, all 3 jurisdictions have experienced multiyear outbreaks, with large numbers of dengue cases reported. There was a large DENV-3 outbreak that affected all 3 jurisdictions between 2018–2021.[110]

[102] CDC ArboNET, unpublished
[103] CDC ArboNET, unpublished
[104] Communities Organized to Prevent Arboviruses (COPA) seroprevalence study, 2018–2019; unpublished data
[105] Duncombe J, Lau C, Weinstein P, Aaskov J, Rourke M, Grant R, Clements A. Seroprevalence of dengue in American Samoa, 2010. EID. 2013 Feb;19(2):324.
[106] Cotter CJ, Tufa AJ, Johnson S, Matai'a M, Sciulli R, Ryff KR, Hancock WT, Whelen C, Sharp TM, Anesi MS. Outbreak of Dengue Virus Type American Samoa, November 2016–October 2018. Morbidity and Mortality Weekly Report. 2018 Nov 11;67(47):1319.
[107] CDC ArboNET, unpublished
[108] Arbonet, National Arbovirus Surveillance System CDC. *MMWR* 2013;62 (9): 171-172
[109] CDC EpiAid, unpublished data. Data are preliminary and subject to change
[110] https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6228a3.htm; https://www.cdc.gov/mmwr/volumes/69/wr/mm6948a6.htm; https://reliefweb.int/report/marshall-islands/dengue-3-outbreak-republic-marshall-islands-june-25-2019-february-28-2021; and https://www.palauhealth.org/MOHpages/MOHDengueSituation1.aspx

Although dengue is not considered endemic in US states, there is a risk for local transmission of dengue because mosquito vectors are present in multiple states, particularly in the Southern US. Over 94% of dengue cases reported from states during 2010–2022 were associated with travel to endemic areas. However, there are some notable examples of continued local transmission, including outbreaks in Hawaii, Florida, and Texas. Additionally, sporadic dengue cases without a history of travel to an endemic area have been reported from other jurisdictions in California, DC, North Carolina, New York, and West Virginia. More than 8,000 cases were reported from US states to ArboNET during 2010–2022. There was an average of about 665 cases annually, with a large spike in 2019 associated with multiple dengue outbreaks globally. Looking at dengue cases by age group reported from the US, a higher proportion of cases are seen among adults in contrast to the primarily pediatric population in endemic areas. DENV-1 was the most frequently identified serotype among cases with serotype information available. Dengue cases were identified from endemic regions globally, although the most frequently reported locations included the Caribbean and Asia.

In summary, dengue is a public health problem throughout the tropics and subtropics, including the Americas. Dengue is considered endemic in 6 US territories and FAS. In those endemic areas, the highest burden of disease occurs among children and adolescents 10–19 years of age, although many cases and a higher fatality rate occur among adults. In the US states, most cases are associated with travel to endemic areas, although sporadic local DENV transmission has been documented in Florida, Texas, and Hawaii.

Dengvaxia Efficacy, Safety, and Implementation Update

Gabriela Paz-Bailey, MD, PhD, MSc, DTM&H (CDC/NCEZID) presented an update on Dengvaxia™ efficacy, safety, and implementation in Puerto Rico. This topic is important, given that dengue is the most common arbovirus globally and incidence is expected to increase with increasing global temperatures. It also is important to think about the lessons learned with the review, and approval, and implementation of the first dengue vaccine. As a reminder, a person can be infected with dengue multiple times in their lifetime. After a primary dengue infection, the durable protected immune response is directed to serotype-specific epitopes of the infecting virus, leaving individuals susceptible to a second dengue infection with a new serotype. After a second infection with a new serotype, the protective immune response is mainly directed to the epitopes between serotypes. Clinically significant tertiary dengue virus infections are less common. The implication for vaccines is that in those who have experienced a dengue infection before receiving the vaccine, even an imbalanced vaccine dominated by one vaccine serotype is likely to induce cross-protective immunity by activating memory. In dengue-naïve individuals with no immune memory, the protective immune response to each serotype will depend strongly on how well each vaccine component independently performs.

The first dengue vaccine to be approved for use in the US, Dengvaxia™, is a tetravalent live-attenuated vaccine. It is a chimeric viral vaccine on a yellow fever backbone. The vaccine includes gene sequences obtained from each of the 4 DENV serotypes. It is a series of 3 doses separated by 6 months each, which means that a full year is needed to complete the series.[111] In terms of a few events in the history of Dengvaxia™, the Phase 3 trials were published in 2015. The trial results showed increased risk of hospitalization and severe disease among vaccinated children 2–5 years of age. Because of that, the vaccine was recommended by WHO in 2016 for persons ≥9 years of age to be used only in highly endemic areas. Sanofi eventually

[111] For more information, visit: https://www.cdc.gov/dengue/vaccine/hcp/schedule-dosing.html; https://www.cdc.gov/dengue/vaccine/hcp/storage-handling.html

found that the increased risk of severe disease and hospitalization was associated with serostatus, meaning if the child had previous dengue infection or not before receiving the vaccine. Those without previous dengue infection (e.g., naïve) were at higher risk if vaccinated. After this, WHO revised their recommendations to state that the vaccine should be given only to children with laboratory-confirmed evidence of a past infection.

To review VE, Dengvaxia™ protects persons 9─16 years of age with previous dengue virus protection against dengue, hospitalization, and severe disease. VE was 82% for symptomatic disease, 79% for hospitalizations for dengue, and 84% for severe dengue.[112] The vaccine protected against all 4 serotypes in these children, but to different levels. For the outcome of symptomatic dengue, there was higher efficacy of 80% against DENV-3, 89% against DENV-4, and lower efficacy of 67% for DENV-1 and DENV-2.

Regarding safety, post-trial analysis showed higher risk of hospitalization and severe disease following vaccination in seronegative children 9─16 years of age. In seronegative children, the efficacy against symptomatic disease was 39% against hospitalization. It was negative 41% and negative 144% against severe dengue. Please note that this estimate suggests an increased risk, but confidence intervals do cross zero.[113] The most common side effects within 14 days following vaccination include headache, injection site pain, myalgia, malaise, and asthenia. There was no difference between the placebo and the control arms. After FDA approval in 2019, the ACIP reviewed all of these data and unanimously recommended Dengvaxia™ for routine use in June 2021. They noted in the recommendation that it should only be given to children 9─16 years of age who have laboratory confirmation of previous dengue virus infection who live in endemic areas in the US.

Since many dengue infections are asymptomatic or do not result in a medical visit during the acute phase of the illness, most children will need to have laboratory testing done before they receive the vaccine. The test will need to be highly specific to avoid vaccinating a child without previous dengue virus infection. The recommendation from CDC is that the test should have at least 75% sensitivity and 98% specificity. CDC evaluated IgG commercially available tests and found that 2 tests were close but did not quite meet the screening criteria. However, using them in combination achieves specificity of 100%. The current testing recommendation is to use 2 tests in a 2-test algorithm. Positive results are required on both tests for vaccination with Dengvaxia™. The 2 approved tests are:

- ❑ EUROIMMUN Anti-Dengue Virus NS1 Type 1-4 ELISA (IgG)
- ❑ CTK BIOTECH OnSite Dengue IgG Rapid Test

To provide a brief update on dengue vaccine implementation in Puerto Rico, there are 280,000 children who might be eligible for Dengvaxia™. Dengue vaccine acceptance has increased after the availability of COVID-19 vaccines. In an analysis using data from a cohort in Southern Puerto Rico, responses were divided into 2 time periods, pre-COVID and post-COVID. “Pre-COVID” refers to the time before COVID-19 vaccines became available in Puerto Rico and includes interviews conducted from May 2019 to December 14, 2020. “Post-COVID” refers to the time after the COVID vaccines became available in Puerto Rico, which was from December

[112] Sridhar S, Luedtke A, Langevin E, Zhu M, Bonaparte M, Machabert T, et al. Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. New England Journal of Medicine. 2018 2018-07-26;379(4):327-40. Hadinegoro SR, Arredondo-García JL, Capeding MR, Deseda C, Chotpitayasunondh T, Dietze R, et al. Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease. New England Journal of Medicine. 2015 2015-09-24;373(13):1195-206

[113] Sridhar, S, et al. N Engl J Med. 2018 Jul 26; 379(4):327-340

15, 2020 until the end of December of 2021. Approximately 73% of adults intended to get the dengue vaccine, which increased to 85% once COVID-19 vaccines became available. Similarly, when asked their intention to vaccinate their children, the proportion reporting "yes" increased from 76% pre-COVID to 86% post-COVID.

This is one of the first vaccines to require laboratory testing to determine eligibility. The laboratory test requirement has implications for vaccine logistics. Because of this test, multiple visits to the HCP and laboratory will be required before giving the first dose. First, children will have to be evaluated by their pediatrician who will order the pre-vaccination screening test. Next, they will have to go to a laboratory for the test or the test can be conducted in the clinic and the specimen sent to the laboratory. Then they will have to return to their pediatrician to interpret their results and order the vaccine. Finally, children will proceed to the vaccine clinic and receive their first dose and schedule the second and third doses. The process of starting the vaccination can take several weeks, and that the logistics of vaccination are a challenge to vaccine implementation.

Despite these complex logistics, vaccination with Dengvaxia™ has started in Puerto Rico. Dr. Ruiz Cardona is the Principal Medical Official from the Puerto Rico Department of Health, who has presided over the first Dengvaxia™ vaccine administered in Puerto Rico. Currently, Dengvaxia™ and the pre-vaccination screen test is available in 4 clinics on the island. Implementation of the dengue vaccine in Puerto Rico is planned in phases. In Phase 1, the 4 clinics are offering pre-vaccination screening and vaccination. The target date to complete this phase is November 2022, at which time the health department and the immunization program will open up vaccination to all FQHC and their associated satellite clinics. In January 2023, the Puerto Rico Health Department plans to move to Phase 3 during which all private and public providers may offer the dengue vaccine.

There have been several challenges to the implementation of the vaccine. The need for pre-vaccination screening complicates logistics. The tests used are not FDA-approved and are implemented under Clinical Laboratory Improvement Amendments (CLIA) protocols. Puerto Rico has a local regulation that all testing needs to be done by a licensed laboratory technician. Therefore, tests rarely can be implemented as point-of-care. In addition, the public messaging on the vaccine to prevent dengue among those who have had dengue before can be challenging. Insurance coverage for the test has been complicated by lack of a specific billing code, but it was recently resolved. There also have been competing priorities like COVID-19 vaccination.

There is a new dengue vaccine from Takeda, TAK-003, that the WG has started reviewing. TAK-003 is a tetravalent live-attenuated vaccine on a DENV-2 virus backbone expressing E and prM proteins for all 4 dengue serotypes. The schedule includes 2 doses that are administered 3 months apart.[114] On October 13, 2023, the European Medicines Agency (EMA) recommended the approval of Takeda's dengue vaccine for the prevention of dengue disease caused by any serotype in those ≥4 years of age. The review was for European Union (EU) and non-EU countries under an EU-Medicines for all (EU-M4all) procedure. This procedure allows regulators in other countries to rely on the EMA scientific assessment to decide on the use of the vaccine in their countries. The final step in Europe is marketing authorization from the EMA, which is

[114] Wong JM, Adams LE, Durbin AP, Munoz-Jordan JL, Poehling KA, Sanchez-Gonzalez LM, et al. Dengue: A Growing Problem With New Interventions. Pediatrics. 2022 Jun 1;149(6)

expected in the coming months. The vaccine has been approved for use in Indonesia[115] and the company has plans to submit to regulatory agencies in other countries.

In summary, the Dengvaxia™ vaccine has an efficacy of 80% among seropositive children against symptomatic virologically confirmed dengue, hospitalization for dengue, and severe dengue. Implementation has been challenging due to the pre-vaccination screening requirement of a 2-test algorithm and also the reimbursement procedures. The Dengue Vaccine WG has started review of the Takeda TAK-003 dengue vaccine.

Discussion Points

Dr. Kotton asked whether Dengvaxia™ and/or TAK-003 could be used in immunocompromised persons, given that they are live viral vaccines and are replicating.

Dr. Paz-Bailey indicated that the recommendation is that these vaccines can be used among immunocompromised patients with CD4 counts above 200, but not in children who are severely immunocompromised.

Dr. Lee asked whether the testing algorithm would apply to the Takeda TAK-003 vaccine as well.

Dr. Paz-Bailey indicated that this is not yet known, given that the WG has just begun reviewing the Takeda TAK-003 dengue vaccine.

MONKEYPOX UPDATE

Pablo Sanchez, MD (Chair, ACIP Monkeypox WG) presented an update on behalf of the Monkeypox Vaccine WG. As a reminder, monkeypox is a rare but sometimes life-threatening zoonotic infection that is endemic in parts of West and Central Africa. It is caused by the monkeypox virus, which is an orthopoxvirus. It can spread from infected animals to people and then person-to-person through respiratory secretions, skin-to-skin contact with infected body fluids from lesions, and fomites (e.g., shared towels, clothing, and bedding).

In 2021, the ACIP recommended the use of the JYNNEOS orthopoxvirus vaccine that was licensed by the FDA in 2019 for pre-exposure vaccination of people at occupational risk for orthopoxvirus exposures. WG meetings were conducted from 2019–2021, and the recommendations were published on June 3, 2022 in the *MMWR*. The ACIP vote regarding primary vaccine with JYNNEOS was as follows:

- ❑ Use of JYNNEOS as an alternative to ACAM2000 for research laboratory personnel*, clinical laboratory personnel† performing diagnostic testing for orthopoxviruses, and for designated response team members at risk for occupational exposure to orthopoxviruses§.

[115] Takeda Pharmaceutical Company Limited. Takeda's QDENGA®▼ (Dengue Tetravalent Vaccine [Live, Attenuated]) Approved in Indonesia for Use Regardless of Prior Dengue Exposure. 2022 [updated August 22, 2022]; Available from: https://www.takeda.com/newsroom/newsreleases/2022/takedas-qdenga-dengue-tetravalent-vaccine-live-attenuated-approved-in-indonesia-for-use-regardless-of-prior-dengue-exposure/

- ❑ Use of JYNNEOS based on shared clinical decision-making, as an alternative to ACAM2000 for healthcare personnel who administer ACAM2000 or care for patients infected with replication-competent orthopoxviruses.

*Research laboratory personnel are those who directly handle 1) cultures or 2) animals contaminated or infected with replication-competent vaccinia virus, recombinant vaccinia viruses derived from replication-competent vaccinia strains (i.e., those that are capable of causing clinical infection and producing infectious virus in humans), or other orthopoxviruses that infect humans (e.g., monkeypox, cowpox, and variola) †Clinical laboratory personnel who perform routine chemistry, hematology, and urinalysis testing, including for suspected or confirmed patients with orthopoxvirus infections, are not included in this recommendation as their risk for exposure is very low §Public health authorities, at their own discretion, may approve a cohort of healthcare and/or public health personnel to receive primary vaccination against orthopoxviruses for preparedness purposes (e.g., first responders who might participate in a smallpox or monkeypox outbreak).

The JYNNEOS vaccine is an attenuated, non-replicating live virus vaccine produced from the strain Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN). It was licensed by FDA in September 2019 for prevention of smallpox and monkeypox disease in adults ≥18 years of age. It consists of a series of 2 doses administered 28 days apart.[116] The standard administration for JYNNEOS vaccine is subcutaneous administration with a volume of 0.5mL. It was authorized for people aged <18 years under an Emergency Use Authorization (EUA). The currently recommended regimen is intradermal administration with an injection volume of point 0.1mL. This recommendation was based on the results from a clinical study that showed that the lower intradermal dose was immunologically non-inferior to the standard subcutaneous dose. Importantly, it facilitated more people being vaccinated with the JYNNEOS vaccine.

The 2022 outbreak was predominantly associated with men who have sex with men (MSM) and their contacts. The outbreak initially began on May 16, 2022. There were 4 cases in the UK among MSM. The first US case was identified on May 17, 2022. There was then a large global increase in cases, including in countries where monkeypox does not typically occur. The WHO declared monkeypox a Public Health Emergency of International Concern (PHEIC) on July 23, 2022. This was followed on August 4, 2022 by the US declaring a Public Health Emergency (PHE). On August 9, 2022, the US had the peak number of cases in the US. Subsequently, cases have been decreasing but are still occurring. Male-to-male sexual contact (MMSC) has been the most common type of case, but some cases have been reported in women, children, and men who do not report recent MMSC. A demographic shift has occurred from mostly white, non-Hispanic males to many black and Hispanic persons being affected.[117]

The JYNNEOS vaccine was approved for prevention of smallpox and monkeypox disease, this is the primary vaccine being used during the current outbreak, which was recommended by ACIP for primary vaccination and booster doses for certain people at occupational risk for orthopoxvirus infections. ACAM2000 was approved for prevention of smallpox disease, is an alternative to JYNNEOS, and was recommended by ACIP as a primary vaccination and for booster doses for certain people at occupational risk for orthopoxvirus infection. As of October 11, 2022, a total of 906,325 doses of JYNNEOS vaccine doses had been administered and reported to CDC from 54 US jurisdictions. The majority of doses have been provided to white, non-Hispanic persons followed by Hispanic, Black, non-Hispanic, and Asians.

[116] https://www.cdc.gov/poxvirus/monkeypox/interim-considerations/jynneos-vaccine.html
[117] https://www.cdc.gov/poxvirus/monkeypox/response/2022/mpx-trends.html

The components of the US National Monkeypox Vaccine Strategy began as all post-exposure prophylaxis (PEP) and then moved to expanded PEP (PEP++). The current focus has been on pre-exposure prophylaxis (PrEP).[118] The US Government (USG) Interim Recommendations for Monkeypox Vaccine PrEP have centered on: 1) people in certain occupational risk groups; 2) gay, bisexual and other MSM, transgender, or nonbinary people who in the past 6 months have had new diagnosis of one or more national reportable sexually transmitted diseases (STDs) who have had sex with more than one sex partner; 3) people who have had sex in the last 6 months at a commercial sex venue and/or sex in association with large public events in geographic areas where monkeypox transmission is occurring; 4) sexual partners of people with any of the above risk factors; and 5) people who anticipate experiencing the above risks.

Regarding the Monkeypox Vaccine WG's Terms of Reference (TOR), during May 2022, a global monkeypox outbreak began that predominantly was affecting MSM. The WG will review available data to inform monkeypox vaccine policy, including recommendations for use of these vaccines in the US population during the ongoing outbreak. The topics under discussion are to:

- ❑ Review epidemiology of monkeypox virus infection in US
- ❑ Evaluate safety and effectiveness of vaccines licensed to prevent monkeypox
- ❑ Assess risk-benefit balance for use of vaccines during the ongoing outbreak
- ❑ Identify areas where additional data are needed to inform recommendations
- ❑ Develop monkeypox vaccine policy options

The first topic the WG is working on is further consideration of populations for which JYNNEOS monkeypox virus vaccine should be offered as pre-exposure prophylaxis. With the timeline to be determined, the data to be reviewed by the WG include the following:

- ❑ Public health problem
- ❑ Vaccine effectiveness for subcutaneous and intradermal administration
- ❑ Vaccine safety for subcutaneous and intradermal administration
- ❑ Values and acceptability of vaccine to the affected population
- ❑ Feasibility and resource use involved in PrEP expansion
- ❑ Health equity considerations

Discussion Points

Dr. Shah noted that one of the topics states have been discussing is whether moving back to subcutaneous administration ought to be considered. The initial move to intradermal was because of limited vaccine availability. Now that teams are used to intradermal administration and the population most at risk is sensitized to the benefits of vaccine, it would be beneficial to understand whether it is worth it to shift back or better to maintain the status quo.

Dr. Rao indicated that the WG is considering this and has been discussing the VE data that are available, and there will be more VE data and safety data comparing the intradermal and subcutaneous routes. The WG will present to the ACIP on this during a future meeting.

Dr. Chen inquired as to what proportion of the 906,325 doses were given intradermally versus subcutaneously and whether it would be possible to assess the durability of protection by the 2 routes to inform the route of administration in the future.

[118] https://www.cdc.gov/poxvirus/monkeypox/interim-considerations/overview.html

Dr. Rao indicated that the 906,325 doses represents a lot of doses that were given subcutaneously early on in the response, and it reflects a lot of PEP++. Efforts are underway to break it down by how much has been given by each method over time. Regarding duration of immunity from the vaccination, efforts are being made to collaborate with academic partners to evaluate the immune response after someone has monkeypox, the duration of protection, in order to understand when/if they may need to be vaccinated and the duration of the immune response after receiving the JYNNEOS vaccine. From the systematic GRADE review presented previously, it is known that there is an animistic response at least 2 years after completion of the 2-dose series received subcutaneously. Based on the data, the assumption is that the intradermal route is going to be similar, but this will be followed forward beyond the 2-year point to inform guidance in the future.

Dr. Lee asked whether there are any plans to publish and/or present data on the youngest children and the utility or benefit-risk balance of vaccine use dependent on the context of the exposure. It would be helpful to have that as a foundation to understand how to support clinical decision-making.

Dr. Rao indicated that a CDC *MMWR* is planned to be published the first week of November 2022 that characterizes the pediatric and adolescent cases (N=~100 cases) that CDC has been notified of since the beginning of the response through a certain cutoff point. It basically says that the youngest children seem to have acquired it from caregivers through contact and that adolescents seem to be similar to adult MMSC. Transmission is a critical question. The WG has requested an explanation about the cases in women, pregnant women, and children to understand what can be said about the type of exposure that led to some of the cases where MMSC is not believed to be the cause. That is a priority for the response right now. She saw some data earlier in the day that was not yet ready for primetime but will perhaps be presented to the WG in the next week to try to tease this out.

Dr. Sanchez added that it is critical to know more about how many cases have occurred in children ≤5 years of age and ≤12 months of age. From his perspective, it is important to know how many neonates there have been because that is going to dictate what type of care can be offered for the mother/baby dyad at the time of delivery and whether there are any safety concerns.

Dr. Rao indicated that some very young people have been vaccinated and no safety concerns have been identified. Safety is on the radar for the vaccine safety folks. In addition, an effort is being made to understand the location of the lesions. Understandably, it could affect decisions that clinicians make about the delivery. These types of issues are being investigated through special studies. In addition, there is a plan to have a v-safe™ for monkeypox.

CERTIFICATION

Upon reviewing the foregoing version of the October 19-20, 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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AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACA	Affordable Care Act
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
AE	Adverse Event
AESI	Adverse Event of Special Interest
AFM	Acute Flaccid Myelitis
AFP	Acute Flaccid Paralysis
AHIP	America's Health Insurance Plans
AI/AN	American Indian/Alaskan Native
aIIV	Adjuvanted Influenza Vaccine
AIM	Association of Immunization Managers
AIRA	American Immunization Registry Association
AMA	American Medical Association
AOA	American Osteopathic Association
APhA	American Pharmacists Association
AR	Adverse Reaction
ARI	Acute Respiratory Illness
ASTHO	Association of State and Territorial Health Officers
BLA	Biologics License Application
CAP	Community-Acquired Pneumonia
CDC	Centers for Disease Control and Prevention
CDF	Cumulative Distribution Function
CEPI	Coalition for Epidemic Preparedness Innovations
CHD	Chronic Heart Disease
CHIP	Children's Health Insurance Program
CICP	Countermeasures Injury Compensation Program
CLD	Chronic Lung Disease
CMC	Chronic Medical Conditions
CMH	Cochran-Mantel-Haenszel
CMS	Center for Medicare and Medicaid Services
COI	Conflict of Interest
CONUS	Continental United States
COPD	Chronic Obstructive Pulmonary Disease
CPI	Consumer Price Index
CSF	Cerebrospinal Fluid
CSTE	Council of State and Territorial Epidemiologists
cVDPV2	Circulating Vaccine-Derived Poliovirus Type 2
DFO	Designated Federal Official
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DVA	Department of Veterans Affairs

eCRF	Electronic Case Report Form
ED	Emergency Department
EMA	European Medicines Agency
EMR	Electronic Medical Record
ET	Eastern Time
EtR	Evidence to Recommendation
EU	European Union
EUA	Emergency Use Authorization
EUL	Emergency Use Listing
FAS	Freely Associated States
FDA	Food and Drug Administration
FRN	Federal Register Notice
GACVS	Global Advisory Committee on Vaccine Safety
GBS	Guillain-Barré Syndrome
GISAID	Global Initiative on Sharing All Influenza Data
GMT	Geometric Mean Titers
GPEI	Global Polio Eradication Initiative
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GVHD	Graft Versus Host Disease
HCP	Healthcare Personnel / Providers
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
IC	Immunocompromising Conditions
ICERs	Incremental Cost Effectiveness Ratios
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
IDSA	Infectious Disease Society of America
IHS	Indian Health Service
IIS	Immunization Information System
IIV	Inactivated Influenza Vaccine
ILINet	Influenza-like Illness Surveillance Network
IM	Intramuscular
IPD	Invasive Pneumococcal Disease
IPV	Inactivated Polio Vaccine
IRA	Inflation Reduction Act of 2022
ISD	Immunization Services Division
IV	Intravenous
IVY	Investigating Respiratory Viruses in the Acutely Ill
LRTD	Lower Respiratory Tract Disease
LRTI	Lower Respiratory Tract Illness
LTCF	Long-Term Care Facilities
MELODY	Prevention of Medically Attended Lower Respiratory Tract Infection Due to Respiratory Syncytial Virus in Healthy Late Preterm and Term Infants
MFS	Miller Fisher Syndrome
MIS-C	Multisystem Inflammatory Syndrome in Children

mITT	Modified Intention to Treat
MMSC	Male-to-Male Sexual Contact
MMWR	*Morbidity and Mortality Weekly Report*
MoH	Ministry of Health
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	Nonbacteremic Pneumonia
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHS	National Center of Health Statistics
NCIRD	National Center for Immunization and Respiratory Diseases
NFID	National Foundation for Infectious Diseases
NHP	Non-Human Primate
NHSN	National Healthcare Safety Network
NIAID	National Institute of Allergy and Infectious Diseases
NICU	Neonatal Intensive Care Unit
NIH	National Institutes of Health
NIS	National Immunization Survey
NMA	National Medical Association
nOPV2	Novel Oral Polio Vaccine, Type 2
NP	Nasopharyngeal
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
NVSN	New Vaccine Surveillance Network
NVSS	National Vital Statistics System
NYS	New York State
OASH	Office of the Assistant Secretary for Health
ODPHP	Office of Disease Prevention and Health Promotion
OGC	Office of General Council
OIDP	Office of Infectious Disease and HIV/AIDS Policy
OP	Oropharyngeal
OPA	Opsonophagocytic Activity
OPV	Oral Polio Vaccine
PAHO	Pan American Health Organization
PCP	Primary Care Provider/Practitioner
PCR	Polymerase Chain Reaction
PCSK9	Proprotein Convertase Subtilisin/Kexin 9 Inhibitors
PEP	Post-Exposure Prophylaxis
PHAC	Public Health Agency Canada
PHAO	Pan American Health Organization
PHEIC	Public Health Emergency of International Concern
PICO	Population, Intervention, Comparison, Outcomes
PIDS	Pediatric Infectious Disease Society
pIMD	Potential Immune-Mediated Disease
PPSV23	Pneumococcal Polysaccharide Vaccine
PR	Puerto Rico
PRAC	Pharmacovigilance Risk Assessment Committee

PrEP	Pre-Exposure Prophylaxis
PREVAIL	Partnership for Research on Vaccines and Infectious Diseases in Liberia
QALY	Quality-Adjusted Life Year
QIV	Quadrivalent Inactivated Influenza
RCT	Randomized Controlled Trial
RENOIR	RSV vaccine Efficacy study iN Older adults Immunized against RSV disease
RIV	Recombinant Influenza Vaccine
SAB	Spontaneous Abortion
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts
SAHM	Society for Adolescent Health and Medicine
SARI	Severe Acute Respiratory Infections
sBLA	Supplemental Biologics License Application
SD-IIV	Standard-Dose Unadjuvanted Influenza Vaccines
SET-NET	Surveillance for Emerging Threats Network
SHEA	Society for Healthcare Epidemiology of America
SIADH	Syndrome of Inappropriate Antidiuretic Hormone Secretion
SME	Subject Matter Expert
SMFM	Society for Maternal-Fetal Medicine
SNiPP	Surveillance for NonInvasive Pneumococcal Pneumonia
SSNHL	Sudden Sensorineural Hearing Loss
TOR	Terms of Reference
UK	United Kingdom
US	United States
USG	United States Government
USVI	US Virgin Islands
VAERS	Vaccine Adverse Event Reporting System
VDPV2	Vaccine-Derived Poliovirus Type 2
VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VEPP	Vaccine Equity Pilot Program
VFC	Vaccines For Children
VICP	National Vaccine Injury Compensation Program
VLP	Virus-Like Particle
VRBAC	Vaccines and Related Biological Products Advisory Committee
VSD	Vaccine Safety Datalink
VT-IPD	Vaccine-Type IPD
WG	Work Group
WHA	World Health Assembly
WHO	World Health Organization