MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

OCTOBER 25-26, 2023
MEETING SUMMARY

CONTENTS

WEDNESDAY: OCTOBER 25, 2023

WELCOME AND INTRODUCTIONS

Dr. Grace Lee (ACIP Chair) called to order and presided over the October 25-26, 2023 Advisory Committee on Immunization Practices (ACIP) meeting. She conducted a roll call each day, which established that a quorum was present. A list of Members, *Ex Officios*, and Liaison Representatives is included in the appendixes at the end of this summary document. No conflicts of interest (COIs) were identified during this meeting and quorum was maintained throughout both days.

Dr. Melinda Wharton (ACIP Executive Secretary, CDC) noted that copies of the slides for the meeting were available on the ACIP website and were made available through a ShareLink™ file for ACIP Voting, *Ex Officios*, and Liaisons Members. She provided housekeeping instructions and explained that 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, which were scheduled for approximately 12:50 PM Eastern Time (ET) on October 25, 2023 and at approximately 10:00 AM on October 26, 2023. To create a fair and more efficient process, individuals interested in making an oral comment were asked to submit a request online in advance of the meeting. Priority is given to advance requests. If more people make requests than can be accommodated in the allotted time, speakers are selected through a blind lottery. The 14 speakers selected by lottery for this meeting were notified in advance of the meeting. Members of the public also had the opportunity to submit written comments on issues coming before the ACIP via https://www.regulations.gov using Docket Number ID CDC-2023-0079. More information on the written public comment process can be found on the ACIP website.

As noted in the ACIP Policies and Procedures manual, ACIP members agree to forgo participation in certain activities related to vaccines during their tenure on the committee. For certain other interests that potentially enhance a member's expertise 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 day of each meeting.

MENINGOCOCCAL VACCINES

Introduction

Katherine Poehling, MD, MPH (ACIP, WG Chair) introduced the Meningococcal Vaccine Work Group (WG). She reminded everyone of the 3 policy topics under consideration by the WG (pertaining to the Pfizer pentavalent vaccine):

1. Should pentavalent vaccine be included as an option for MenACWY/MenB vaccination in people currently recommended to receive both vaccines?

2. Should pentavalent vaccine be included as an option for people currently recommended to receive MenACWY only?

3. Should pentavalent vaccine be included as an option for people currently recommended to receive MenB only?

In February 2023, the WG discussed the epidemiology of meningococcal disease in the United States (US), Pfizer's MenABCWY vaccine clinical trials data, and the WG's interpretation of those data. In June 2023, the WG introduced the CDC's cost-effectiveness model and provided a summary of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) and Evidence to Recommendation (EtR) Framework.

Between June and October 2023, the WG received feedback during the June ACIP meeting. A review of the meningococcal schedule has been postponed to allow for consideration of GSK's forthcoming pentavalent vaccine and availability of data about post-COVID meningococcal epidemiology. The WG also reviewed comparisons of the cost-effectiveness models. The CDC cost-effectiveness model has been updated with new price estimates. The price for pentavalent vaccine was $40 to $90 more than MenB but is now similar, so there has been an adjustment. The WG also discussed 3 potential recommendation options based on the concerns raised by ACIP members in June and the new cost-effectiveness assessments.

To summarize where the WG is, there is strong consensus among the WG members for the first policy question regarding whether pentavalent vaccine should be included as an option for MenACWY/MenB vaccination in people currently recommended to receive both vaccines, which pertains to persons 16 to 18 years of age; it typically happens around 16 years. There was strong consensus among the WG members regarding the second policy question that the pentavalent vaccine should not be included as an option for people currently recommended to receive the quadrivalent vaccine only, which pertains to the 7th grade dose. There was limited consensus among WG members about the third question that perhaps pentavalent vaccine should be included as an option for people currently recommended to receive MenB only. This is the dose that typically is given just before college entrance or military service.

During this session, presentations were provided on the plan for revisiting the adolescent schedule for meningococcal vaccines, a comparison of the Pfizer and CDC cost-effectiveness analyses for Pfizer's MenABCWY vaccine, a summary of the EtR Framework and proposed recommendations for Pfizer's MenABCWY vaccine, and a vote and the Vaccines for Children (VFC) Resolution.

Plan for Revisiting Adolescent Schedule for Meningococcal Vaccines

Lucy McNamara, PhD, MS (CDC/NCIRD) provided a brief update on the meningococcal vaccine WG's plans for revisiting the adolescent schedule for meningococcal vaccines over the next year. As mentioned earlier, a great deal of interest was expressed during the June 2023 ACIP meeting in revisiting the current meningococcal vaccine schedule for adolescents. Some of the questions that were raised regarded whether the dose of MenACWY at 11 to 12 years of age is still needed, especially given recent epidemiology of very low disease burden among those 11–15 years of age. There also were some questions around the shared clinical decision-making recommendation for B vaccines. It was noted that the availability of pentavalent meningococcal vaccines may complicate the shared clinical decision-making discussion for providers and that some nuances, such as the projected short duration of serogroup B

protection may be lost, when it is possible to give a single injection covering all 5 serogroups. It also was highlighted that opportunities to reduce the total number of vaccines given, by leveraging pentavalent vaccines for instance, would be appealing if it is possible to still maintain a high level of protection. The WG considered this feedback and decided to incorporate revisiting the adolescent schedule into its work plan over about the next 15 months.

There are a number of reasons that the WG is planning to spread this evaluation out over that timeframe rather than trying to push to accomplish it more quickly. The WG would like to ensure that there is adequate time to complete and fully evaluate the necessary GRADE and EtR assessments, including addressing questions about cost-effectiveness and the importance of the booster response for what currently is the second dose of MenACWY vaccines for protecting older adolescents. The WG anticipates being able to assess the extended interval data for pentavalent vaccines administered more than a year apart at some point during 2024, which will open new options for spacing of meningococcal vaccine doses. The WG wants to make sure that there is plenty of time to integrate the recommended changes into the overall Child and Adolescent Immunization Schedule in a way that will be clear to clinicians. In addition, the WG wants to ensure that they can fully consider an additional year of post-COVID epidemiology, which they feel is particularly important in light of the new meningococcal strains in the US that are primarily affecting Black and Hispanic populations and have substantial implications for health equity.

While there are many ways the adolescent schedule for meningococcal vaccines could be altered, the WG plans to focus on the following core questions based on the input from the last ACIP meeting:

1. Should the MenACWY series recommendations be changed to begin at an older age than currently recommended at 11—12 years of age, to eliminate the dose recommended at 11—12 years of age of MenACWY entirely, or to revise the recommendation to shared clinical decision-making?

2. Should the MenB series recommendations be changed to alter the recommended ages or dosing interval to provide better protection for individuals 18—19 years of age, or should the shared clinical decision-making recommendation be revisited for some or all adolescents(e.g., those planning to attend college)?

3. Are there ways to better integrate the MenACWY and MenB vaccine schedules to streamline administration and increase feasibility for providers?

The WG established a tentative timeline for addressing these questions over the next 4 ACIP meetings. In February 2024, the plan is to return to the committee, recognizing that there may be a number of new members at that time, with more detailed terms of reference (TORs) for addressing the schedule change. In June 2024, the WG hopes to present epidemiologic analysis that are relevant to possible schedule changes, including understanding the burden of disease currently averted by the MenACWY dose at 11—12 years of age; assessment of racial and ethnic differences in disease burden among adolescents; an analysis of the risk factors for serogroup B meningococcal disease among college versus non-college students; an update on breakthrough meningococcal disease cases in vaccinated individuals to inform the thinking around duration of protection of the vaccines; and tentatively extended interval data for administering 2 doses of pentavalent vaccines several years apart if they are available by that point. In October 2024, the WG plans to cover the GRADE and EtR assessments for proposed changes to the adolescent schedule and a cost-effectiveness analysis for changes to the

MenACWY and MenB adolescent schedules. The WG hopes to have votes during February 2025. In addition, the WG also anticipates addressing upcoming policy questions related to an additional pentavalent vaccine for which there is not yet a set timeline. The hope is to remain somewhat flexible to ensure that the WG can appropriately integrate, review, and discuss the additional pentavalent vaccine within the broader schedule change discussion.

Discussion Points

Dr. Daley inquired as to whether there is an ability to assess competing priorities. The increasing complexity of the schedule can have negative side effects, such as challenges for providers in terms of knowing what to stock. For instance, a family medicine practice will be immunizing birth to older ages. Consideration will have to be given to number of products to stock, whether switches can be made from one product to another, how decisions will be made about who should be vaccinated in an environment with clinical decision support versus one without, whether larger refrigerators will be needed to stock the various vaccine products, et cetera. There could be benefits to simplification that would then translate to other vaccine-preventable diseases.

To Dr. McNamara, this would fall under the “feasibility” component of the EtR Framework and definitely could be considered in the WG deliberations. She invited suggestions and resources for data or evidence relevant to any proposed strategies in terms of how changes in the meningococcal vaccine schedule could affect overall feasibility in the clinical setting.

Dr. Talbot said she felt like they were doing this out of order. It seemed peculiar to vote for a new vaccine, re-evaluate this in a few months, change the schedule, and then vote again. If they wait to re-evaluate the vaccine, when to administer it, how much is needed, et cetera, the decisions would be clearer and less complicated for primary vaccinators. It will not help vaccination rates to make a decision during this meeting only to change it in 3 months. She suggested not voting on this vaccine until they know what schedule will be recommended. Given that there currently are vaccines to cover these pathogens, there is no hurry to do this. This differs from the hurry during COVID when people were dying and hospitals did not have enough staff, rooms, and ventilators. Therefore, she did not see the hurry for voting during this session.

Dr. McNamara agreed with this point and explained that this is a big part of why the WG framed the PICO questions the way they did for the pentavalent vaccine. The intent pertained to whether the pentavalent vaccine could be swapped in basically as a part of the existing recommendations, not to change any of the existing recommendations for ACWY or B vaccines. At this juncture, the point is to let people know whether they can use the pentavalent vaccine in lieu of already recommended doses. The pentavalent vaccine was recently licensed and typically, ACIP evaluates vaccines after they are licensed. She deferred to the ACIP Secretariat to discuss whether there truly is a hurry. The vaccine was licensed last week.

Dr. Wharton indicated that it would be up to ACIP about whether there would be a vote. A motion and second would have to be made in order to move forward on a vote. As Dr. McNamara commented, the intent of this proposal was to provide a recommendation for use of a licensed vaccine in the context of the current schedule upon which ACIP would vote the next day. A potential change in the current recommendations would clearly be a longer conversation. In the meantime, an ACIP vote would allow providers to use this recently licensed product within the context of the current schedule.

Ms. Arthur (BIO) reminded the committee that because of the 21st Century Cures Act (Cures Act) that was passed a few years ago, there is a statutory obligation that newly licensed vaccines be evaluated and voted upon relatively close to their licensure at the nearest ACIP meeting.

Dr. Kimberlin (AAP Redbook) said that in his personal view, he thought it was good that the WG would be evaluating the meningococcal schedule over the next 18 months. He thinks it is always good to look for ways that things that have evolved over many years could be streamlined and perhaps improved upon based upon current data. His recommendation would be to try to avoid shared clinical decision-making recommendations. Increasingly, he is hearing from providers in the field that these do not really help. If, after 18 months, the WG cannot make a decision, it is unclear how a private practice pediatrician is supposed to do the same with much less information and much less time to do the deep dive than the expert ACIP members were able to do.

Ms. Howell (AIM) acknowledged that while the ACIP does not determine immunization requirements for schools, many states have 7th grade requirements or requirements around meningococcal vaccine for children 11—12 years of age. If this change is made, states probably would have to change legislation or rules. She expressed her hope that the WG would take this into consideration.

Dr. Long agreed with Dr. Talbot that it would be difficult for the ACIP to talk about the current vaccine, because everything would be flavored by what they think about the schedule and the use of meningococcal vaccines. Perhaps they should table this discussion until at least they hear the cost-effectiveness data because that may alter what they want to do.

Dr. Poehling emphasized that the WG has really spent a lot of time thinking about what the most cogent and efficient way to move forward would be. The question regards whether they have all of the information they need or would like. She said she would like to make the argument that they had enough information to make a decision during this meeting and that with the FDA's approval of this vaccine, no recommendation would mean that people would have to make decisions with no guidance. In her opinion, it would be better to have ACIP guidance.

Dr. Fryhofer (AMA) noted that her comment was triggered by Dr. Daley's comment about competing priorities, complexity, and storage challenges. As increasingly more vaccines are recommended, she encouraged pharmaceutical companies to make small quantities of vaccines available for purchase rather than making a minimum of tens, hundreds, or thousands of doses. That would increase access to vaccination.

Comparison of Pfizer and CDC Cost-Effectiveness Analyses

Ismael R. Ortega-Sanchez, PhD (Senior Health Economist, CDC/NCIRD) discussed the economics of the potential pentavalent meningococcal conjugate vaccine, comparing and summarizing key elements and findings of 2 economic models (Pfizer and CDC) on the use of pentavalent vaccine for the prevention of invasive meningococcal disease (IMD) among US adolescents. In the previous 8 to 9 months, the 2 models were updated several times. They also were discussed extensively with the ACIP Meningococcal WG. For full disclosure, Dr. Ortega-Sanchez indicated that he led the team conducting the CDC model.

The 3 policy questions centered on analysis by both models are listed here:

1. Should the pentavalent vaccine (MenABCWY) be considered as an option for MenACWY/MenB vaccination in people currently recommended to receive both vaccines? (PICO 1)

2. Should the pentavalent vaccine (MenABCWY) be included as an option for people currently recommended to receive MenACWY only? (PICO 2)

3. Should the pentavalent vaccine (MenABCWY) be included as an option for people currently recommended to receive MenB only? (PICO 3)

In general, the goal is to answer whether the new pentavalent vaccine should be considered as an option for the quadrivalent and MenB vaccination in people currently recommended to receive both vaccines. The starting point of the 2 economic models are the policy questions regarding potential recommendations for the use of pentavalent vaccine in adolescents. To consider the economics of each policy question is to consider simultaneously the health benefits and cost of vaccination by answering the question, "Is vaccinating adolescents with the pentavalent (MenABCWY) vaccine series to prevent invasive meningococcal disease in adolescents cost-effective relative to the use of quadrivalent and MenB vaccines?" To address this question, the 2 models used the same comparator (e.g., the current standard of care). The current standard of care and the hypothetical vaccines and vaccination strategies (interventions) in the model are labeled using the initials of the vaccine and serogroups contained in the dose, which are as follows:

Standard of Care (SoC)		
First dose	**Second dose**	**Key Label**
At 11-12 yrs old with MenACWY	At 16 yrs old with MenACWY	**Q-Q**
At 16 yrs old with MenB	At 16.5 yrs old with MenB	**B-B**

Potential vaccination strategies			
First dose	**Second dose**	**Third dose**	**Key Label**
At 11-12 yrs old with MenACWY	At 16 yrs old with MenABCWY	At 16.5 yrs old with MenB	**Q-P-B**
At 11-12 yrs old with MenABCWY	At 16 yrs old with MenABCWY	None (N)	**P-P-N**
At 11-12 yrs old with MenACWY	At 16 yrs old with MenABCWY	At 16.5 yrs old with MenABCWY	**Q-P-P**

SoC= Standard of care (current vaccination programs: **Q-Q** and **B-B**)
MenABCWY = Potential pentavalent vaccine (**P**) with serogroups A, B, C W Y
MenACWY = currently recommended quadrivalent vaccine (**Q**) for serogroups A, C, W, Y,
MenB =currently recommended monovalent vaccine for serogroup **B**

5

To have a visual about the comparisons of the Pfizer and CDC incremental analysis included in the 2 models being compared, the table below describe the alignment of this incremental cost-effective analysis with the policy questions to be answered. An important and recurring detail in this presentation is the price of a dose of pentavalent used as input in the specific incremental analysis:

Policy question	Incremental analysis	*Pfizer*	CDC	Vaccine Price used for Pentavalent **
PICO #1	Q-P-B **vs** SoC	Included*	Included	$250 (private) / $187.5 (public)
PICO #2	P-P-N **vs** Q-Q	Included	Included	$210 (private) / $157.5 (public)
PICO #3	Q-P-P **vs** SoC	Included	Included	$210 (private) / $157.5 (public)

SoC = Standard of care (current vaccination programs: Q-Q and B-B)
* Included in *Pfizer* technical report updates until August 2023, not included in the *Pfizer* technical report update of October 2023
** The price of $250 (private) / $187.5 (public) is for strategies using a single dose of pentavalent and the price of $210 (private) / $157.5 (public) for strategies using ≥2 doses of pentavalent

The policy questions have important implications for the 3 groups of elements included in the models. The comparison of the 2 economic models focuses on how appropriate the selection of the modeling approach is, the inputs, and the assumptions—especially those that are strong influential assumptions. In general, the 2 models follow similar designs with the use of a static analytical decision-making approach, reliance on probabilistic or deterministic sensitivity analysis to manage the various data uncertainties, a hypothetical cohort of adolescents ≥11 years of age in the US, a timeframe of the first 15 years after 11 years of age to account for the vaccination schedules, loss of income associated with temporary productivity loss and premature mortality associated with meningococcal disease.

Once the modeling strategies were set, the 2 models were fed with different types of input data (e.g., epidemiologic, vaccine characteristics, healthcare resource utilization (HCRU) and cost, indirect cost quality of life, and other parameters). Across models, the sources, specific values, and assumptions of the parameters have some overlaps, but they were marked as different as well. In the boxes are the standard outcomes estimated and reported by the 2 models, though the presentation focused primarily on the cost per quality-adjusted life year (QALY) saved or the incremental cost-effectiveness ratio (ICER):

	Pfizer	CDC
Prevention of:		
• IMD cases	✓	✓
• IMD-associated sequelae	✓	✓
• IMD-associated deaths	✓	✓
QALYs saved	✓	✓
$/QALY saved	✓	✓
Number needed to vaccinate (NNV) to avert an:		
• IMD case		✓
• IMD death		✓

Selected inputs for this comparison focused on the cost of the vaccine and vaccine administration, IMD incidence for the pre-vaccine and in vaccine era, initial vaccine effectiveness (VE) and waning over time, IMD-associated permanent sequalae, age and serogroup-specific Case Fatality Rate (CFR), and acute IMD QALY scores and unitary direct costs.

From March 2023 to June 2023, Pfizer submitted various technical reports using the pentavalent vaccine price of $240 with a range of $230 to $250 per dose. In August 2023, Pfizer submitted a new technical report updating the pentavalent price to $250 for the private cost per dose and $187.50 for the public price. In October 2023, Pfizer submitted a newer technical report updating the pentavalent prices for the strategies using 2 doses for pentavalent of $210 for the private sector and $157.50 for the public sector. For the strategies with a single dose of pentavalent, the price remained at $250. This distinction is very important in terms of analyzing the specific outcomes estimated in each of the models. Regarding the various components of the vaccination program beyond the price per dose, vaccine costs were differentiated based on the 2023 public and private sector prices and vaccine administration settings for vaccines already available in the vaccination schedule. Ranges were estimated from public and private vaccine prices and the cost of administration by site. Pentavalent was calculated using the hypothetical range of prices as released by Pfizer for the pentavalent vaccine in August and in October 2023. Although not included in these costs, in the CDC model, rates of moderate and severe adverse events (AEs) were taken into account using publications in the literature. Only the CDC model considers vaccine wastage for open vial, mishandling, or outdated shelf life. Another significant component in the total estimation is vaccination program costs.

In terms of the average annual incidence in vaccine serogroups BCYW by age per 100,000 used in the models based on ABC Core Surveillance and the National Notifiable Diseases Surveillance System (NNDSS), rates of IMD remained relatively higher in late adolescents. But in general, rates have been declining for all ages. Overall, the incidence rates are 1/6 of those from the recent pre-vaccine era. In terms of the marked differences in the models, the CDC model used age by year IMD incidence data showing the peak in the late adolescent years, while the Pfizer model used only 4-year averages. Moreover, Pfizer extrapolated the average rates from late adolescents to the early 20s. This approach may underestimate the incidence in 10 years and overestimate the incidence in early 20 years.

The initial VE by vaccine dose and serogroup are critical data inputs to assess the vaccination impact of the strategies. Value and assumptions on initial protection are based on value sources.[1] The pentavalent is based on the Phase 3 noninferiority initial VE by a single dose at 11 to 12 years of age and a second dose at 16 years of age of pentavalent vaccine as reported by Pfizer. For quadrivalent and MenB, the initial VE was based on effectiveness surveillance.

One of the key assumptions following initial VE was related to the duration of protection. This assumption was differentiated by serogroups containing the vaccine. Assumptions on vaccine protection were more conservative in the CDC model. There was a fast decline in waning of vaccine protection in the CDC model for both the quadrivalent and MenB vaccines. For the Pfizer model, there was an assumption based on vaccine protection as being persistent to about 4 to 5 years for a single dose of pentavalent based on the hSBA from the Pfizer clinical trial report. In the CDC model, the duration of protection for pentavalent vaccine was assumed to follow quadrivalent vaccine, while the duration of protection for MenB for a single dose and 2-dose and for the pentavalent was assumed to be following the MenB vaccine. There was

[1] Phase 3 noninferiority initial vaccine efficacy by single dose (at 11-12yrs) and second-dose (16yrs) of pentavalent (Men ABCWY) vaccine as reported by Pfizer (data on file); Updated Pfizer Technical reports on Cost-effectiveness of the Pentavalent Meningococcal Vaccine (MenABCWY) in the US; Cohn AC, MacNeil JR, Harrison LH, et al. Active Bacterial Core Surveillance (ABCs) Team and MeningNet Surveillance Partners. Effectiveness and Duration of Protection of One Dose of a Meningococcal Conjugate Vaccine. Pediatrics. 2017 Feb;139(2):e20162193. doi: 10.1542/peds.2016-2193. PMID: 28100689; PMCID: PMC8353579; *The range for VE efficacy for first dose of MenB is from Castilla et al. NEJM 2023 https://www.nejm.org/doi/full/10.1056/nejmoa2206433

uncertainty of the waning assumption beyond available surveillance of Phase 3 data. The CDC model tried to minimize the inclusion of that uncertainty into the model, whereas the Pfizer model still showed substantial protection that also influenced the estimates in the end of the cost-effective analysis.

As in previous analyses, the models used percent of survival cases with specific sequelae as reported in the literature. The Pfizer model reports a larger number of long-term sequelae, though there were some with zero value or close to zero probabilities. Over the range of survivors with sequelae, approximately 28% suffered some long-term sequelae in the Pfizer model. The CDC model focused on the most common long-term sequelae among survivors of meningococcal disease infection for which there was a smaller probability of survivors with sequela of approximately 21.6%. However, the CFR was very close at 12.5% in the Pfizer model and the 12.3% in the CDC model. There was differentiation by age group in the Pfizer model. The difference in the methodology was that in the Pfizer model included life years lost at the end of life for those with sequelae who were included in the Pfizer model, which means that for a specific sequela, multiple amputations, there was a reduction in life expectancy that was accounted as the life years saved by the vaccination program.

Regarding medical cost and quality scores, Pfizer medical cost differentiated the type of IMD. On average, medical costs could be twice as much as the costs used by the CDC model. Regarding QALY scores, because meningococcal disease follows a rapid clinical course, both models estimated decrease in QALYs associated with the acute illness for survivors of IMD and specifically for the cases without permanent sequelae. These values are different in magnitude. In the CDC model, the quality adjusted life days (QALD) was approximately 46.26 days during the acute phase of the disease, which is only 1/3 to 1/4 of those used for a Pfizer model for the same acute phase during the acute phase of IMD. After the acute phase in cases without permanent sequelae, the equivalent QALD was approximately 14 to 15 days in the CDC model, which was approximately 1/6 the value used by the Pfizer model during the acute phase of the IMD. In the CDC model, the values are more conservative than used by Pfizer.

In terms of a comparison of the outcomes reported by both models for each of the policy questions, among the main results were the total net cost impact and incremental cost-effectiveness of vaccination studies (e.g., incremental health impact in terms of cases, deaths, life years, and QALYs saved) and ICERs. In terms of PICO 1, the incremental effectiveness and cost-effectiveness of vaccinating healthy adolescents 11-12 and 16 years old with pentavalent vaccine relative to using MenACWY and MenB vaccines, a very important clarification is that to make fair comparison, for the total net cost estimates, cost-saving, and cost per QALY saved, the analysis used $250 per private dose administered versus $187.50 for the public sector. The cumulative probability of ICER per QALY saved for the CDC model, the 5^{th} and 95^{th} percentiles showed that the probability of being cost-saving is very high. CDC and Pfizer aimed to answer PICO 2, the incremental effectiveness and cost-effectiveness of vaccinating healthy adolescents 11-12 and 16 years old with pentavalent vaccine relative to using MenACWY only, using the updated lower price per dose for the private sector of $210 and public sector of $157.50 for the pentavalent vaccine. This analysis showed that the most important variables explaining the variability between the models were related to disutilities and long-term sequelae. The CDC model showed that the ICER also was costly at a higher level at more than twice that of the incremental cost per QALY as reported by the Pfizer analysis. The incremental cost being incrementally costly was correlated by the cumulative probability of simulations in the CDC model, specifically in that both the 5^{th} and the 95^{th} percentiles were positive. In other words, the probability is quite high that in this strategy with 2 doses, the P-P-N is costly relative to the standard of care.

Both models attempted to answer PICO 3 regarding the incremental effectiveness and cost-effectiveness of vaccinating healthy adolescents ≥16 years old with Pentavalent vaccine relative to using MenB vaccine only. The estimates of both the incremental health outcomes and net cost were compared to be similar relative to the standard of care and coincide in pointing that the Q-P-P would be cost-saving. This fact was corroborated by the cumulative probability of simulations in the CDC model in that the 5th and 85th percentile were negative, meaning that they are cost-saving. These estimates used the updated vaccine price of $210 for the private sector and $157.50 for the public sector.

Among the limitations are first that factors not considered in the Pfizer and CDC models may result in overestimating the ICER or underestimating the cost-effectiveness of the pentavalent vaccine. In the base-case, both models assumed no protection against non-IMD and no indirect protection against IMD of unvaccinated individuals because they used only a discrete model not a dynamic model with high immunity components or indirect effects. Productivity losses incurred by caregivers for long-term specific sequelae were based on assumptions and were partially included. Second, differences in key inputs among the Pfizer and CDC models and the uncertainty in input data may explain some of the difference in the results, although it is very interesting to see that there are coincidences as well. The most important elements that drive the difference among these 2 models is the duration of vaccine protection, medical costs, variability in IMD incidence and CFR data, inclusion of different sequalae, and QALY score for IMD cases without permanent sequelae. Third, the pentavalent price for Q-P-B is uncertain. The price used in this analysis was the minimum expected cost as reported by Pfizer. Higher prices will increase total net cost and ICERs.

In conclusion, in both models, pentavalent vaccine would reduce the IMD burden in adolescents. In both models, strategies with 1 or more doses of the pentavalent vaccine would save more or an equal number of IMD cases. For PICO 1, Q-P-B could be incrementally cost-saving relative to the standard of care, remembering that in this strategy, a dose of pentavalent would be substituted for the second dose of the quadrivalent and the first dose of MenB. For PICO 2, the strategy that includes 2 doses of pentavalent and nothing else, is incrementally costly, not cost-saving, relative to the standard of care of 2 doses of quadrivalent. For PICO 3, the model with a quadrivalent followed by pentavalent at 16 years of age and another dose 6 months after pentavalent, is likely cost-saving relative to the standard of care. About 96% of iterations in the CDC model simulation have an ICER less than zero. Reasonable pentavalent prices and duration of protection combined with careful design of vaccination interventions with pentavalent will determine the cost and cost saving value of the pentavalent vaccine among adolescents ≥11 year of age.

Discussion Points

Referring to Slide 12 regarding the cost of the pentavalent vaccine for the 2-dose option versus the single dose option, Dr. Loehr noted that the single dose option, Q-P-B, would be $250 and a 2-dose option (P-P-N and Q-P-P), would be $210. It seemed odd to him as a practicing physician that Pfizer would charge a different amount based on what they decide. He would be purchasing vaccine for his office at a certain price, but they would not know how he is giving it.

Dr. Palumbo (Pfizer) responded that a simplified meningococcal vaccine schedule like Q-P-P would improve vaccination administration and simplify stocking. Pfizer commits to a list price of $210 for a Q-P-P dosing schedule for any combination that includes a 2-dose schedule for the Pfizer pentavalent vaccine as aligned with the label. In the scenario of a Q-P-B in isolation,

given that this does not align with the FDA-approved 2-dose schedule, Prizer cannot commit to a price at this time. The previously shared prices of $250 for private and $187.50 for public per dose shared in Dr. Ortega-Sanchez's cost-effectiveness model was a minimal price for the purposes of economic modeling.

Dr. Talbot observed that this would mean that if the ACIP voted for a Q-P-B strategy, this would mean an off-label recommendation for the P and the B because B is 2 doses.

Dr. McNamara responded that a Q-P-B schedule would be off-label for pentavalent and for B because those are both licensed as a 2-dose series. However, as pointed out earlier, there is no interchangeability between manufacturers of B components. The pentavalent and Trumenba® contain the same component and should be able to be used interchangeably in terms of the immune response, but it is off-label.

Dr. Poehling emphasized that cost-effectiveness is very important in thinking about this. She asked Pfizer for clarification about how many doses are in a bottle and whether she was understanding correctly that the price of the vaccine would vary if it could be used with both Bs, and it could be used for 2 doses only if the ACIP said it could be used when both vaccines are recommended.

Dr. Palumbo (Pfizer) responded that bottles contain a single dose and that in any Q-P-P scenario or any combination where a Q-P-P is an option, the price will be $210 a dose. The problem with the Q-P-B as already stated is that it is not aligned with the label, so Pfizer has not considered or finalized pricing for that scenario. For any combination that includes Q-P-P the price is $210 per dose.

Dr. Poehling requested that since the ACIP was planning to vote during this meeting, she asked the group to convene to come up with a price in case the vote goes a different way, because that is an important determination.

Dr. Cineas asked whether the standard of care used in both analyses, Q-Q and B-B, takes into account the current B uptake in terms of the cost analysis since that is a shared clinical decision-making recommendation.

Dr. Ortega-Sanchez replied that the 2 models used a static model, which means that only direct impacts of vaccination were taken into account. In order to align both models, a single similar uptake of the vaccines was used so that variation was not included in the base-case analysis. They can definitely include variations in uptake to determine whether that would be mute to the incremental cost ratios, because whatever is saved in terms of not giving doses also is not saved in terms of disease prevented and they cancel in the ICER.

Dr. Talbot asked the current price for 1 dose of B, even if giving 2 doses, when the vaccine is purchased. In addition, she asked whether Pfizer was insinuating that if the ACIP changes the recommendation to Q-P-B that they would change the price of B.

Dr. Palumbo (Pfizer) reiterated that the Q-P-B scenario does not align with Pfizer’s label, so they would need to consider what the price would be given that. However, if there is an option of Q-P-P or any combination where 2 doses of the pentavalent vaccine is an option in which case the price would be $210 per dose.

Dr. Talbot clarified that her question regarded the current cost of 1 dose and whether Pfizer would consider changing the price of MenB with a Q-P-B scenario.

Dr. Palumbo (Pfizer) replied that the current cost for Pfizer's MenB vaccine is $178 for private and $130.77 public and that the current price for MenB vaccine would not change.

Dr. Lee said that in this instance, she appreciates the manufacturer's approach in terms of being transparent about the 2-dose pricing and recognizing that if it is not as it was originally licensed for use, Pfizer would need to reconsider the pricing strategy. She also noted that while she typically is not empathetic, she is empathetic in this instance. Nevertheless, this makes it very difficult to make a decision. She thought the tension Pfizer was hearing was more about the fact that the ACIP has to consider cost-effectiveness in any of its decision-making. The uncertainty around the price makes it difficult to assess that, even though there are some ranges and some sensitivity analyses.

Dr. Goode (APhA) asked why the P-P-N, which is no extra intervention, would be more costly than a Q-P-P.

Dr. Ortega-Sanchez indicated that for PICO 2, the Pfizer analysis includes the number of cases incrementally of IMD cases saved, IMD deaths saved, and life years saved, but the cost is basically due to the new pentavalent vaccine price compared to the cost of the standard of care (P-P-N versus Q-Q). When only pentavalent and nothing else is used against the standard of care of 2 doses of quadrivalent vaccine, it becomes costly. In the CDC model for PICO 2, the same analysis was used with the same assumptions and data, but the total per QALY saved was higher ($4.7 million) than the one provided for Pfizer ($1.94 million). All simulations, regardless of which ones are positive, means that it will be costly.

Dr. Talbot observed that if P-P-N is used currently with the recommendation of 11 and 12 years of age, her understanding was that it would not provide B protection in college. However, if P-P is given starting at 16 years of age, that would cover college. Her questions regarded whether P-P-N is cost-effective, but not for B when one gets to college because a B booster would be required at that time.

Dr. Ortega-Sanchez indicated that because the effectiveness of P-P starting at 11 years of age, because of the cost the pentavalent vaccine and because they look very similar in terms of effectiveness, the strategy of substituting the quadrivalent with the pentavalent is more costly, not cost-effective. If that is switched to give the 2 pentavalent doses at 16 years of age, that is a different question that was not analyzed in these strategies. It was one of the analyses they were thinking of doing, but that is a different type of question.

Dr. Long asked what percentage of older adolescents currently get B vaccine under shared clinical decision-making and said she assumed the majority of them are college students.

Dr. McNamara indicated that the last data show that about 30% of those 17 years of age are getting at least 1 dose of serogroup B vaccine. Other data sources show that a little more than 50% of those complete the series. Unfortunately, there are not good ways to assess whether the majority are college students.

Dr. Long emphasized that doctors do not like to have to stock many different kinds of vaccines, so the least difficult would be to use the combination vaccine. She asked whether the cost-effectiveness model took into account that there potentially would be a much higher percentage of MenACWY uptake at this age.

Dr. McNamara indicated that the current MenACWY uptake is in the high 80% range for dose given to adolescents at 11 to 12 years of age and about 60% for completion of the 2-dose series. There are some data from administrative claim sources that have demonstrated that the actual proportion of those 16 to 18 years of age who are current with catch-up recommendations is significantly higher than that as some people don't get the 11-12 year old dose but get it later.

Dr. Long asked whether the cost-effectiveness model figured in that since the default position would be much less shared clinical decision-making and a much higher percent getting the combination vaccine.

Dr. Ortega-Sanchez reiterated that these are static models that include only direct impact of vaccination. In this this type of analysis, uptake is mute in terms of impact on the cost-effectiveness ratio. While not giving the vaccine saves dollars, this also does not save the disease. Therefore, both of those values, one in the denominator and one in the numerator, cancel and that is why the ICERs and cost per QALY saved remain unchanged and are not influenced by the coverage or the uptake of the vaccination.

Dr. Long emphasized that the unintended consequences of not preventing disease would be extremely costly.

Dr. Lee added that the implication would be that the total cost would be higher, but that does not necessarily impact the cost-effectiveness. She reminded everyone that the ACIP Charter specifically states that the committee consider cost-effectiveness and not necessarily total cost in its decision-making.

Ms. McNally asked whether Pfizer could discuss how a shared clinical decision-making recommendation may impact their pricing decision, if at all.

Dr. Palumbo (Pfizer) indicated that this would not impact their pricing decision and reiterated that when she talks about "in combination," if a Q-P-P and a Q-P-B are recommended, the price would be $210 per dose. It is the Q-P-P in isolation that does not align with the label, which they would need to reconsider.

Pfizer Statement

Dr. Luis Jodar (Chief Medical Officer for Pfizer Vaccines/Antivirals and Evidence Generation) emphasized that to be clear so that there are no misunderstandings, when talking about Q-P-P, this is a licensed 2-pentavalent product administered 6 months apart. Once the licensed option is included, other options that include a pentavalent followed by a monovalent B are at the same price. It is only the situation in which there is a mixed schedule that is not in the label, which is a pentavalent and monovalent B, is exclusively recommended when the price needs to be reassessed. To highlight the advantages of a recommendation with the quadrivalent at 11 years of age followed by 2 doses of the pentavalent (PENBRAYA™) at 16 years of age given 6 months apart identified as Q-P-P, Pfizer developed PENBRAYA™ in line

with the CDC's *General Best Practice Guidelines for Immunization*.[2] In general, he said he thought they all could agree that licensed combination vaccines can improve vaccine uptake, vaccine compliance, and reduce the number of injections individuals receive. Recommending 2 doses of PENBRAYA™, the Q-P-P strategy, would simplify the current standard of care by reducing the number of injections from 4 to 3 to help protect adolescents and young adults against all 5 serogroups. This strategy can be accomplished by stocking only 2 vaccines, whereas the mixed Q-P-B strategy would require healthcare providers (HCPs) to stock 3 vaccines (e.g., quadrivalent, pentavalent, and monovalent B vaccines). This would add complexity, costs, and the potential for errors.

Additionally, administration of the monovalent MenB vaccine is not necessarily equitable across the US with adolescents residing in rural areas and Black and Latino adolescents having lower coverage. Pfizer's believes that PENBRAYA™ is a tool that could at least help close these equity gaps. The 2 doses of PENBRAYA™ are given 6 months apart, which is the schedule based on the clinical data and the only one that is aligned with the FDA label. It is estimated that implementation of 2 doses of PENBRAYA could prevent more cases and deaths caused by IMD compared to the current standard of care. The proposed Q-P-P schedule will reduce costs compared to the current standard of care. PENBRAYA™ will cost approximately 43% less than if the ACWY and B vaccines are administered separately. That was why Pfizer wanted to emphasize this price. In fact, Pfizer is committed to making the vaccine available at a similar price to an individual MenB vaccine, thus ensuring that the FDA indicated use of 2 doses is the most cost-saving option for the meningococcal vaccine program.

Dr. Jodar respectfully urged the ACIP to take up this policy and make recommendations of the use of the pentavalent meningococcal vaccine during this meeting. HCP around the country look to the ACIP as experts that set the standards of practice. Silence from ACIP until 2025 will have negative effects on vaccine confidence and avoid information where suboptimal practices can emerge. Recommendations from ACIP should ensure on-label use of the vaccine and will result in better real-world safety and effectiveness data over the next year that the ACIP campaign used to revisit recommendation on the entire meningococcal platform. He thanked the committee for these complex deliberations to optimize the meningococcal vaccine platform and expressed hope that the simplicity, advantages, and cost savings of the Q-P-P strategy can translate into public health benefit and accessibility to everyone.

Dr. Kimberlin (AAP Redbook) asked if on slide 18, is SOC in the table Q-Q + B-B? And on slide 21, what is SOC?

Dr. Ortega-Sanchez indicated on slide 18, it is Q-Q+B-B, and on slide 21 it is Q-Q+B-B.

Summary of EtR and Proposed Recommendations for Pfizer's MenABCWY Vaccine

Dr. Jennifer Collins (CDC/NCIRD) presented a summary of the EtR framework and the proposed recommendation for Pfizer's MenABCWY vaccine. As a reminder, current ACIP recommendations for meningococcal vaccines are as follows:

Routine Schedule

- ❑ MenACWY: dose 1 at age 11–12 years, booster dose at age 16 years
- ❑ MenB (shared clinical decision-making): 2 doses at age 16–23 years (preferred age 16–18 years)

[2] https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html

Special Situations

Indication		MenACWY (age ≥2 months)	MenB (age ≥10 years)
Medical conditions	Asplenia	X	X
	Complement Deficiency	X	X
	Complement inhibitor use	X	X
	HIV infection	X	
Other	Some microbiologists	X	X
	Exposure during an outbreak	X	X
	Travel to hyperendemic areas	X	
	First-year college students	X	
	Military recruits	X	

Meningococcal vaccines that are licensed and available in the US are interchangeable and include:

Vaccine	Trade Name	Manufacturer	Minimum age
MenACWY-CRM	Menveo	GSK	2 months
MenACWY-TT	MenQuadfi	Sanofi Pasteur	2 years

MenB vaccines are not interchangeable, and include:

Vaccine	Trade Name	Manufacturer	Minimum age
MenB-4C	Bexsero	GSK	10 years
MenB-FHbp	Trumenba	Pfizer	10 years

Pfizer's pentavalent MenABCWY vaccine is now licensed as a 2-dose series with a 6-month interval for individuals aged 10–25 years. As a reminder, the pentavalent vaccine is comprised of Trumenba™, Pfizer's MenB vaccine that is currently licensed and available in the US, and Nimenrix™, Pfizer's MenACWY vaccine that is not licensed in the US, but has been used extensively in Europe and elsewhere for more than a decade.

The Meningococcal WG addressed 3 policy questions for the following PICOs:

1. Should the pentavalent vaccine be included as an option for MenACWY/MenB vaccination in people currently recommended to receive both vaccines? (PICO 1)

2. Should the pentavalent vaccine be included as an option for people currently recommended to receive MenACWY only? (PICO 2)

3. Should the pentavalent vaccine be included as an option for people currently recommended to receive MenB only? (PICO 3)

The population is individuals aged 10 years or older currently recommended to receive MenACWY+MenB, MenACWY, or MenB vaccine. The intervention is vaccination with Pfizer's pentavalent vaccine. The comparison varies by the policy question. The 6 outcomes that were assessed through the GRADE process include:

1. Meningococcal disease caused by serogroups A, B, C, W, and Y (as appropriate by PICO)
2. Short-term immunity
3. Persistent immunity
4. Interference with other recommended vaccines administered concurrently
5. Serious adverse events (SAEs)
6. Non-serious AEs

This table shows how the PICOs were translated into schedule options for healthy adolescents for the purposes of the GRADE assessment and the economic analysis. As a reminder, Q stands for the quadrivalent vaccine (MenACWY), B for MenB, and P for the pentavalent vaccine:

Options	11–12 year old dose	16 year old dose #1	16 year old dose #2
Standard of care (MenACWY only)	Q	Q	–
Standard of care (MenACWY + MenB)	Q	Q+B	B
PICO 1 (MenABCWY as option for MenACWY + MenB)	Q	P	B
PICO 2 (MenABCWY as option for MenACWY)	P	P	±B
PICO 3 (MenABCWY as option for MenB)	Q	P	P
Combination of all 3 PICOs	P	P	P

Recall that these options assumed that vaccinations were given first at ages 11—12 years when the first quadrivalent dose is recommended, with subsequent vaccinations at age 16 years when the second quadrivalent dose is recommended. However, as discussed during the June ACIP meeting and earlier during this meeting, 16 years of age often is not optimal timing for the MenB component. To summarize the WG consensus presented during the June 2023 ACIP meeting, the WG was in favor of PICO 1 or Q-P-B. The WG was not in favor of PICO 2 or P-P-B. The WG was divided regarding PICO 3 or Q-P-P. Since that time, the WG refined the EtR framework and further considered possible implications of each PICO, especially PICO 3, based on concerns raised by ACIP members during the June 2023 meeting regarding the following:

- ❑ Cost-effectiveness concerns about all options, including the current schedule
- ❑ Concerns about increasing exposure to B component vaccines related to reactogenicity, low burden of disease, and limitations to protection
- ❑ The concern that the optimal timing of B component is often not age 16 years
- ❑ Fidelity to clinical trial data, licensure, and stocking concerns
- ❑ Stocking and administration considerations

As presented earlier, the cost-effectiveness analysis was revised to reflect updates to the quoted price of the pentavalent vaccine and to incorporate refinements to the CDC model.

To summarize the updated EtR, for the public health problem domain, members noted that the incidence of meningococcal disease is low and decreasing, but that it causes very severe disease and poor outcomes even with treatment. The case fatality rate is 10% to 15% and 10% to 20% of survivors have permanent sequelae. The WG interpretation for public health problem for all three PICOs was that yes, meningococcal disease is a problem of public health importance.

Regarding benefits and harms, 3 randomized control trials (RCTs) studied the pentavalent vaccine 2 dose intervals (0, 6 months and 0, 12 months) versus MenACWY-CRM 1 dose + MenB-FHbp 2 doses (0, 6 months). The studies were conducted among both ACWY-naïve and ACWY-primed participants. Available data facilitated assessment of select outcomes through GRADE. Other important benefits and harms were not assessed through GRADE but were factored into the WG interpretations. These included increased reactogenicity of MenB relative to MenACWY and limitations to B protection, including that low VE is expected following a single dose, rapidly waning protection following a 2-dose series, and multiple studies demonstrating that MenB vaccination has no effect on meningococcal carriage.

To summarize the GRADE assessment for benefits, no data were available to assess the critical outcome of meningococcal disease caused by serogroups A, B, C, W and Y. For the critical outcome of short-term immunity, data were available from 1 RCT. Serogroup-specific seroresponses 1 month after the first trial dose of ACWY- or B-containing vaccine occurred as often or more often in the pentavalent group compared with the control group. The evidence type was moderate for healthy persons and low for those at increased risk. For the important benefit of persistent immunity, data were available from 2 RCTs. Seroresponse rates by serogroup were similar between groups. The evidence type was low to moderate for healthy individuals depending on serogroup and low for those at increased risk. For the critical outcome of SAEs, data were available from 3 RCTs. Significantly more SAEs occurred in the pentavalent group versus the comparison group, though none were attributed to the vaccine. The evidence type was low for healthy individuals and very low for those at increased risk. For the important outcome of non-serious AEs, data were available from 3 RCTs. Significantly more non-serious AEs occurred in the pentavalent group versus the comparison group. The evidence type was low for healthy individuals and very low for those at increased risk. No data were available to assess the important outcome of interference with other recommended vaccines administered concurrently.

For PICO 1, the WG interpretation was that the desirable and undesirable anticipated effects were small, and they favored the intervention, with overall certainty varying by group. For PICO 2, the WG interpretation was that the desirable anticipated effects were minimal to moderate, undesirable anticipated effects were minimal or small, and the balance favored the intervention, comparison, or both and overall certainty varied by group. For PICO 3, the WG interpretation was that the desirable anticipated effects were minimal, the undesirable anticipated effects were minimal or small, and the balance favored the intervention or comparison. Overall certainty varied by group.

Regarding the values of the target population, limited data were available. The WG noted that among adolescents during 2021, vaccination coverage of at least 1 dose was 89% for MenACWY and 31% for MenB. Limited data were available on vaccine uptake in other individuals recommended to receive MenACWY or MenB vaccine. In general, use of combination vaccines can reduce the number of injections and is generally preferred over

separate injections of the equivalent component vaccines.[3] For the first values domain question regarding whether the target population feels that desirable effects were large relative to undesirable effects, the WG interpretations were “probably yes” for PICOs 1 and 2 and “probably yes” or “don't know” for PICO 3. For the second values domain question regarding whether there is important uncertainty or variability in how much people value the main outcome, the WG interpretation was “probably no” for PICO 1 and “probably yes” for PICOs 2 and 3.

For the acceptability domain, limited data were available. The WG noted that acceptability likely depends on the PICO and balance of stakeholder values. HCP are likely supportive of options that allow stocking fewer vaccines. Pentavalent vaccines have the potential to increase vaccination rates against serogroup B disease and can reduce the number of injections from 4 to 3 for some patients. However, pentavalent vaccines also have the potential to incentivize MenB administration at 16 years of age with waning immunity by the time of peak risk for some patients. Many providers prefer to wait until closer to exposure to congregate settings, such as college or the military. ACIP and WG members also have expressed concerns about increasing exposure to MenB component vaccines, which are more reactogenic than MenACWY vaccines, particularly when the burden of MenB disease is already low despite low vaccine coverage. The WG interpretations for acceptability were “probably yes” or “yes” for PICOs 1 and 2 and “don't know” for PICO 3.

For the resource use domain, ACIP and WG members have noted that all proposed meningococcal vaccine strategies are expensive, including currently recommended options for adolescents. With the new price estimates, Q-P-P is the most cost-effective option when MenB protection is desired. The WG interpretations were “probably yes” or “yes” for PICO 1, “probably no” or “no” for PICO 2, and “probably yes” or “yes” for PICO 3.

For the equity domain, limited data were available. WG members felt that the pentavalent vaccine is not expected to negatively impact equity. It potentially could reduce disparities among those who might be interested in being vaccinated against serogroup B, but who might not otherwise receive clinical care that includes discussion of the MenB vaccine. WG members also discussed the possible risk of clinics not stocking monovalent B vaccines with some policy options, which could affect availability for outbreaks and for people at increased risk of meningococcal disease who are recommended to receive 3 doses of MenB-FHbp. The WG interpretations for equity were “probably no impact” or “varies” for PICO 1, ”probably increased,” varies,” or “don't know” for PICO 2, and “don't know” for PICO 3.

Regarding whether the intervention is feasible to implement, the WG felt challenges with insurance coverage specific to the pentavalent vaccine are not expected. Substantial financial burdens for providers or health systems also are not expected. The pentavalent vaccine would provide an additional option in the current schedule and may reduce the number of doses for some people. However, administration requires reconstitution, which may lead to administration errors. Stocking 3 different meningococcal vaccine types also may be prohibitive for some providers. The lack of B vaccine interchangeability complicates stocking considerations. The WG interpretations for feasibility were “probably yes” or “yes” for all 3 PICOs.

[3] General Best Practice Guidelines for Immunization. Best Practice Guidance of the ACIP. https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf; and American Academy of Pediatrics. Red Book 2018. Report of the Committee on Infectious Diseases. 31st Ed. https://seciss.facmed.unam.mx/wp-content/uploads/2021/02/Red-Book-31th-Edition.pdf

To summarize the EtR domains and WG interpretations for each of the 3 PICOs, for PICO 1 WG judgements were generally supportive, less so for PICO 2 with more uncertainty, and PICO 3 had the most uncertainty. A summary of the WG consensus and debate regarding the PICOs is shown here:

- ❑ Strong consensus in favor of PICO 1: MenABCWY as an option for MenACWY + MenB (QPB)
- ❑ Strong consensus against PICO 2: MenABCWY as an option for MenACWY only (PPB)
- ❑ Limited consensus regarding PICO 3: MenABCWY as an option for MenB only

The options the WG debated for PICO 3 included the following:

- ❑ Option A: Reject PICO 3 outright
- ❑ Option B: Accept PICO 3 with limitations allowing for Q-P-P only
- ❑ Option C: Accept PICO 3 fully, which would allow for Q-P-P and other options

This differentiation between Options B and C is new since June. In terms of the existing recommendations for the routine schedule incorporating shared clinical decision-making, the first dose of quadrivalent vaccine is recommended at 11 to 12 years of age with a second dose at 16 years of age. Shared clinical decision-making may result in no B vaccination, B vaccination at age 16 years, or B vaccination at an age greater than 16 years. Although this is relatively straightforward, introduction of the pentavalent vaccine adds complexity. Option A adds Q-P-B to the existing options. That is, per the consensus in favor of PICO 1, the pentavalent vaccine could be given in lieu of MenACWY and MenB when both vaccines are indicated. Because PICO 3 is rejected with Option A, the pentavalent vaccine would not be used in lieu of MenB only. The remaining MenB vaccine would therefore be monovalent. The difference between the 2 Q-P-B options relates to the interval between the pentavalent vaccine and the subsequent monovalent B vaccine. Notably, neither option is consistent with the licensure for a 2-dose pentavalent or MenB series, and there is a lack of data regarding immunogenicity with extended intervals between B doses. Option B adds Q-P-P to Option A. That is, if an initial dose of pentavalent vaccine was given at age 16 years, a second dose could be given 6 months later within the licensed indications to complete the meningococcal vaccine series. Apart from this limited circumstance, pentavalent vaccine would not be used to replace MenB. Option C adds Q-Q-P-P and Q-Q-P-B to Option B. That is, in accepting PICO 3 fully, the pentavalent vaccine could be given in lieu of MenB even after the MenACWY series has been completed.

Option*	Preference for PICO 3	Schedule options incorporating SCDM for MenB
A	Reject outright	**QPB**
B	Accept with limitations	QPB + **QPP**
C	Accept fully	QPB + QPP + **QQPP** + **QQPB**

*All options include a recommendation in favor of PICO 1 and against PICO 2

With this increased flexibility comes a higher cost and a lack of data on safety and immunogenicity of pentavalent vaccines in individuals primed with 2 doses of quadrivalent vaccine. Notably, Q-Q-P-P and Q-Q-P-B options were not assessed through GRADE. In

summary, all 3 options considered by the WG would permit the current standard of care of QQ versus QQBB under shared clinical decision-making. Option A adds QPB, Option B adds QPP on top of that and Option C adds QQPP and QQPB to Option B.

To summarize Options A, B, and C, Option B had the most favorable ratings overall. Option B is best aligned with clinical trial data and proposed licensure and provides only 1 excess dose of MenACWY. It also provides intermediate flexibility to stock 2 vaccines if using the pentavalent vaccine for routine indications, assuming MenB at age 16 years. However, all options would require stocking 3 vaccines for special situations, though 2 vaccines could be stocked regardless if using only MenACWY and MenB. Option B also was the most cost-effective option based on recent price updates from Pfizer. WG members felt there was lower potential for insurance reimbursement issues.

For the balance of consequences for PICO 1, the pentavalent vaccine is an option for MenACWY + MenB. The majority of WG members thought that desirable consequences "probably" or "clearly" outweigh undesirable consequences in most settings. For PICO 1, the majority of WG members favored recommending the intervention. For PICO 2, the pentavalent vaccine as an option for MenACWY only, the majority of WG members thought the undesirable consequences "clearly" or "probably" outweigh the desirable consequences in most settings. For PICO 2, the majority of WG members favored not recommending the intervention. For PICO 3, the pentavalent vaccine is an option for MenB. The WG did not reach a majority consensus on the balance of consequences and were evenly split among the 3 options.

For the WG interpretation of PICO 3, an additional option was added because some WG members favored Q-P-P only. WG members were divided regarding PICO 3. The majority of WG members favored PICO 3 in some form. However, a substantial minority of WG members favored rejecting PICO 3 outright (Option A). The WG agreed to present Option B, Q-P-P, as a compromise to the committee for further deliberation. The combined draft proposal for Option B is as follows:

> Pfizer's MenABCWY vaccine may be used when both MenACWY and MenB are indicated at the same visit. *If MenABCWY is administered in this way, a second dose of MenABCWY may be administered 6 months later to complete the series.

The footnote reads:

> *1) Healthy individuals aged 16–23 years (routine schedule) when shared clinical decision-making favors administration of MenB vaccination, 2) individuals aged 10 years and older at increased risk of meningococcal disease (e.g., due to persistent complement deficiencies, complement inhibitor use, or functional or anatomic asplenia) due for both vaccines.

The WG also wanted to include the following remarks, which are not part of the proposal language:

Remarks:

- For Pfizer's pentavalent vaccine, data are not available regarding safety or immunogenicity of dosing intervals exceeding 12 months.
- The licensed B component vaccines are not interchangeable by manufacturer. Administration of a B component vaccine requires that subsequent B component vaccine (MenB or MenABCWY) doses be from the same manufacturer.

- The minimum interval for Pfizer's MenABCWY vaccine is 6 months. Individuals at increased risk for meningococcal disease who are recommended to receive additional doses of MenACWY and MenB, less than 6 months after a dose of pentavalent meningococcal vaccine should instead receive separate vaccines.

The rationale in favor of the combined draft proposal is that it aligns with clinical trial data and licensure; allows for fewer doses than QQBB; and provides flexibility with vaccine inventory, including for clinics that prefer to stock 2 vaccines for routine indications, assuming MenB at age 16 years. In addition, stocking fewer vaccines may increase equity (e.g., if under-resourced clinics are less likely to stock 3 vaccines). This is the most cost-effective option based on the recent price update from Pfizer. The rational against the combined draft proposal was that it has unnecessary ACWY antigen exposure for the second pentavalent dose in the routine schedule when only MenB is indicated. In addition, there is as much flexibility for providers as in Option 3. General considerations against all options include the potential to incentivize MenB at age 16 years with waning immunity by peak risk for some patients, such as those entering college or the military. There also is uncertainty regarding the cost estimates. If using the pentavalent vaccine, it will be necessary to stock 3 vaccines to cover all indications (routine schedule + special situations), which may be challenging for some vaccine providers.

Discussion Points

Dr. Talbot requested clarification about how clinical decision-making would work if someone receives B through shared clinical decision-making then receives Q as the second dose, whether they would have to have shared clinical decision-making of Q versus P and then would have to have shared clinical decision-making if they decide to receive B, or if they had already decided to do B if they did P. If it is shared clinical decision-making, it seems that all 3 vaccines would need to be stocked (Q, P, and B).

Dr. Poehling said that when she would embark on this conversation would be at the time of the second dose to indicate that there are 2 types, ACWY and B, and then go through which ones would be done. If B will be included, she would explain that it could be done separately or all together. It would be shared clinical decision-making for B regardless. A very small clinic might elect to carry B in the pentavalent vaccine and perhaps refer those who want only B to a health department. A larger organization probably would opt to carry all 3.

Dr. Long emphasized that the ACIP did not decide to make this combination vaccine. Meningococcal disease is the only thing putting them together, and it would be easy to advertise this as the full meningococcal panel. But meningococcal diseases, as uncommon as they are, are also extremely different in that secondary cases occur very quickly with C, W, and Y and it is difficult to recognize if there even is an outbreak of B because it may be 2 cases over 3 months or 3 cases over 18 months. It is a vaccine that is much better targeted for outbreak use because it also has a very short period for which it provides terrific efficacy. Another difficulty is that the existing schedule already is not quite right because the prevention of B starts later than the second dose of CWY. It is difficult for the ACIP to come up with much that would be good utilization of funds and resources if they try to put these together ever. She is very cognizant that not one more antigen should be given than needed. Although this has been done with combination vaccines for small children when they are receiving so many vaccines concurrently, that is not the case here. She inquired about whether there could be an amendment prior to the proposed vote to not vote.

Dr. Kotton said that as an adult provider, she did not want to comment on the pediatric issues, which are complicated. However, she administers many doses of meningococcal vaccine—especially to people who have had splenectomies. She remains astounded at the number of Americans who have had splenectomies who are under-vaccinated. In her experience, she would estimate that well over 80% of people who have had splenectomies are poorly vaccinated. It would be good to offer them an easy option. Furthermore, she sees people who are going to become immunocompromised, who are thinking about starting eculizumab and other similar drugs that greatly increase the risk of meningococcal disease. Although she is excited about the opportunity to have a pentavalent vaccine because she often is giving so many vaccines in clinic that it becomes onerous to the patient. When they have to have 2 different vaccines or when she is sending them to a commercial pharmacy and they have to get 2 different vaccines, it is very complicated. The fact that she would need to separate the pentavalent by at least 6 months, usually my patients do not have 6 months to wait, and they may not return for a vaccine. This is really onerous and problematic and very messy. Vaccination for Americans needs a simpler process. Being a clinician deep in the trenches is really challenging these days and they need to provide simplicity.

Dr. Loehr asked if the ACIP voted/made a recommendation on the pentavalent vaccine during this meeting how that would affect future pentavalent vaccines in terms of whether there would be a new vote or if this vote would apply to new vaccines.

Dr. Wharton indicated that it would depend on the characteristics of future pentavalent vaccines. If the licensed indications are close to the same as this product, it probably could apply to a future vaccine. If there are meaningful differences, it would be brought back to the committee.

As a member of the Meningitis WG, he has been a strong proponent for the Q-P-B option. When this all started, he was thinking of it as an opportunity to give one less vaccine. However, he did not want to give extra antigens to people. Someone pointed out that some clinics might stock only a pentavalent vaccine, which had not occurred to him. There is no way he wants to give a pentavalent vaccine to an 11-year-old because B is not necessary at that time, which he thought was why many of the WG members voted against PICO 2. He likes the concept of not giving extra antigens and was trying to make a decision on how to vote, because that is a separate issue. The cost-effectiveness that was an issue is no longer an issue because Pfizer changed the price. He said he was disgruntled by the way Pfizer changed the price and the way they framed it, but that is the way it is and we have to accept reality as it is. Some parents ask him if he can use a different schedule for their children's vaccines. He tells them that they can, but he recommends the schedule as it is because those are the data they have. He realized that if he votes for Q-P-B, that is off-label and is not the schedule the way it was studied. That is a significant issue for him. He wanted to make sure they always have shared clinical decision-making for B. He is probably going to need to stock 3 vaccines anyway, because he is going to have some people who do not want B and he will need Q. It is just going to be complicated, so he likely would vote for the Q-P-B option, but was less starkly in favor of that than he was over the last 2 to 3 months.

Dr. Daley said he was struggling and thought that the vaccines were not well-matched. While he is grateful that there are vaccines to prevent meningococcal disease given its severity, now there is a set of vaccines and a schedule that are not well-matched with the epidemiology. In terms of Dr. Talbot's question earlier about not making a recommendation during this meeting, he is generally not in favor of "kicking the can down the road." Given that it is a licensed vaccine, the ACIP should provide some guidance. However, it is problematic that they were re-evaluating the entire schedule as they were voting and there was the added uncertainty about

the cost-effectiveness. He said he also thought that sometimes, there is a benefit of having a monovalent MenB vaccine, because that provides flexibility to time the dose when it is most effective for the circumstance. Dr. Long said it beautifully. In outbreaks, it is short-term protection. It is important for the ACIP always to think about unintended negative consequences. If there is a lot less monovalent MenB, that removes a tool from the toolbox. While he was still struggling, he said he was in favor or either not voting on a pentavalent use during this meeting, recognizing that would be problematic for the ACIP and the manufacturer who cannot plan as well, or making narrow recommendations. By “narrow” he explained that he would favor PICO 1, but with narrow recommendations because they would revisit this in the context of an overall conversation about how to best tailor the schedule for the epidemiology and resource use.

Dr. Lee said that at this point, she wanted to express the areas where she felt most strongly about this particular decision. She agreed that the benefit-risk balance in minimizing unnecessary exposure to antigens was an important one and that the reason this was complicated was due to the way the current schedule is set up. Recognizing that their colleagues had some work to do and thinking about how the post-COVID epidemiology had perhaps changed the benefit-risk balance, she also recognized the need for rigorous evaluation. She favored the Q-P-B option at this point. It’s a choice of a product people can have. Her thinking was that a pediatrician could stock QQ with shared clinical decision-making for QQ and BB as the options. But if people have a preference, or they want to have a product choice, they could decide to replace the QB combination with a pentavalent. Having said this, she realized that it sounded very confusing and challenging, especially for frontline clinicians. She would frame this not as the recommendation, but rather as a choice for people to make, and they could stick with the original schedule. As Dr. Kotton mentioned, there are situations in which transplant patients are being vaccinated who need protection for both. In those instances, she could imagine giving PP in those instances as an option for those high-risk individuals. If they assume that the current schedule remains with an option for people to choose to receive QPB as an alternative, recognizing the complexities of that, it would give the ACIP the opportunity to move toward a PP schedule in the future as they start to think about the ages. But one thing I did want to clarify and ask, actually two things. Referring to the special situations listed on Slide 2, there is some dissonance in terms of the risk-based categories for ACWY and B. She asked whether the WG could make that simple because the inconsistency makes it challenging.

With regard to the dissonance between the MenACWY and MenB recommendations, Dr. McNamara pointed out that these are longstanding recommendations that have reasons behind them. The epidemiology showed that among people with HIV infection in the US, there was a predominance of CWY disease and not B disease. Similarly, travel to hyperendemic areas is largely about the African Meningitis Belt where there is no serogroup B. They can look at this in reviewing the schedule over the next year to determine if there are opportunities to better harmonize, but probably could not make changes during this meeting.

Dr. Poehling added that the reason first year college students and military recruits are not checked on the special situations table is because the MenB column is ≥10 years of age.

Dr. McNamara noted that the recommendations for first year college students and military recruits, the recommendations are for people who did not receive MenACWY vaccines already, so they are not current for ACWY per their routine adolescence schedule. There is a shared clinical decision-making recommendation for serogroup B in the adolescent schedule, so someone who has not received those is not considered not up-to-date.

Dr. Poehling thanked everyone for wrestling with this, which was not easy and the conversation is appreciated. If the ACIP voted for the QPP, which was included in PICO 3, that has an extra ACWY dose administration. That has occurred with other combination vaccines, so she wanted to put it in the context of the current vaccine schedule.

Dr. Sanchez emphasized that meningococcal recommendations are confusing and always have been, at least to him. He understood the concern regarding minimizing antigen exposure, and they have heard about combination vaccines that result in exposure to more than 3 doses, such as Hepatitis B and with the tetanus recommendation in which one can receive acellular pertussis and diphtheria rather than just a tetanus monovalent. This is known to be safe, so he was not as concerned about this. The biggest issue to him was the that if the pentavalent vaccine was recommended for meningococcal B, that also would expose adolescents 11 to 12 years of age to antigens that are not needed until later. It seemed reasonable to offer the pentavalent vaccine if they also are recommended to receive the meningococcal B component for college entry. Many states require that as well, so it seemed like a reasonable option in certain circumstances versus universally. It certainly would reduce the number of doses of injections given. He asked what data are available on simultaneous administration of other vaccines with the pentavalent meningococcal vaccine.

Dr. Collins indicated that direct data are not available on concomitant administration of the pentavalent vaccine with other vaccines. They best they could do was to look at Nimenrix, which is the MenACWY component in the pentavalent vaccine. Information from the package insert[4] states that, "Safety and immunogenicity of Nimenrix was evaluated when sequentially administered or co-administered with a DTaP/IPV/Hib/HepB vaccine in the second year of life. The administration of Nimenrix 1 month after the DTaP/IPV/Hib/HepB vaccine resulted in lower MenA, MenC, and MenW135 Geometric Mean Titers (GMTs) as measured with a serum bactericidal assay using rabbit complement (rSBA). The clinical relevance of this observation is unknown, since at least 99.4% of subjects (N=178) had rSBA titers of ≥8 for each group (A, C, W-135, and Y)." Guidance is provided in the package insert stating that "Whenever possible, Nimenrix and a tetanus toxoid (TT) containing vaccines, such as DTaP/IPV/Hib/HepB vaccine, should be co-administered or Nimenrix should be administered at least 1 month before the TT-containing vaccine. One month after co-administration with a combined tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, there were lower GMCs observed for each of the pertussis antigens and more than 98% of subjects and antibody levels above the thresholds. Again, the clinical relevance of this observation is unknown. There are no data with the pneumococcal conjugate vaccine.

Dr. McNamara noted that the current licensed meningococcal ACWY vaccines in the US also have some similar interference with the pertussis-containing vaccines. Similarly, the clinical relevance of those observations is unknown and so there have not been recommendations to date about not providing those vaccines concomitantly.

Dr. Talbot said she greatly appreciates the need for the ACIP to review FDA-approved vaccines quickly for vaccines that are coming to market. In the cases of RSV and COVID, that was critical. However, this has diverted the ACIP away from reviewing the meningococcal guidelines first and has been a distraction. In that vein, and at the risk of having everyone on the Meningococcal WG angry with her, she asked if it would be possible to accelerate the planned review of the guidelines so that the ACIP could vote in June 2024 instead of later.

[4] https://labeling.pfizer.com/ShowLabeling.aspx?id=12217

Dr. McNamara indicated that they are still seeking a permanent replacement to serve as the Meningococcal WG lead, so she could not comment on acceleration. This has been considered extensively and there is a lot of work to do in terms of reviewing the adolescent schedule. Extended interval data for pentavalent vaccines administered ≥3 years apart is anticipated to become available over the next year, though an exact date is unknown. This information is important in terms of considering different vaccine schedule options. Speaking for herself, she would be hesitant to change the schedule in advance of having those data because she would not want to change the schedule twice.

Dr. Lee emphasized that she thought the ACIP needed to vote during this meeting, though members were free to vote not to make a recommendation.

Dr. Loehr recognized that it was nice to have an option for patients and to have a safe and effective vaccine option, and thanked the manufacturer for presenting this and making it available. He asked Dr. Wharton to inform the ACIP on Robert's Rules of Order in terms of whether it would be better to make a motion for a vote and then have someone try to table it or to make a motion to table it first.

Dr. Wharton pointed out that they could not table a vote that had not been moved. If a committee member wanted to move this toward a vote during this meeting, they should make a motion to that effect. If the motion was seconded and someone wants to amend the recommendation, they could make that motion. Then the debate would be on the amendment rather than the original motion.

Dr. Loehr made a motion in favor of the Combined Draft Proposal for Option B for the ACIP to accept the language as proposed in Dr. Collins' presentation Slide 38. Dr. Sanchez seconded the motion for the ACIP to adopt the recommendation language as proposed.

Dr. Collins read the language for the record:

> Pfizer's MenABCWY vaccine may be used when both MenACWY and MenB are indicated at the same visit. *If MenABCWY is administered in this way, a second dose of MenABCWY may be administered 6 months later to complete the series.

The footnote reads:

> *1) Healthy individuals aged 16–23 years (routine schedule) when shared clinical decision-making favors administration of MenB vaccination, 2) individuals aged 10 years and older at increased risk of meningococcal disease (e.g., due to persistent complement deficiencies, complement inhibitor use, or functional or anatomic asplenia) due for both vaccines.

Dr. Talbot made a motion to make an amendment to postpone the vote for the pentavalent meningococcal disease vaccine until after re-evaluation of the current meningococcal guidelines as there are currently adequate vaccines to cover all of these pathogens, and to reduce the complexity and the number of vaccines that need to be in a provider's office. Dr. Long seconded the motion.

Dr. Long pointed out that the ACIP has a long history of difficulty in rescinding recommendations, decreasing antigens, or decreasing vaccines. Perhaps looking at the entire schedule, they may decide that these vaccines, CWY versus B, should be separated by age group and indication. They already would change the architectural plan if they approve the combination pentavalent vaccine. Then they would have to convey to people that there is something currently licensed and recommended in an odd way, but recommended, that would be moot because most people would not receive these 2 vaccines at the same age or indication. If a bigger change is planned, the incremental change should not be made first. She also pointed out that the proposed language would not be the narrowest indication for use of the pentavalent vaccine. The narrowest indication would be to use it only when both are recommended and that would just be for the second dose of CYW.

Ms. Arthur (BIO) asked how long the delay would be before there would be a vote if the amendment were to pass. She understood that the WG is considering some data and important issues pertaining to the adolescent schedule, which could mean no vote for this product for 12 to 15 months or more.

Dr. McNamara noted that if the intent was to table the vote on this question until after the new votes on the adolescent meningococcal schedule, CDC discussed with the WG having that vote in February of 2025. Her default assumption would be that the pentavalent vote would occur at that time as well. Obviously, nothing is set in stone. However, reassessing the schedule will take a significant amount of time.

Dr. Brooks said he did not feel that the ACIP could delay the vote and spoke against the amendment. He recognized that the ACIP did not ask the manufacturer to make the vaccine as Dr. Long pointed out, but they did, and he is grateful for it as Dr. Loehr said. The WG was strongly in favor of PICO 1 and strongly against PICO 2. If there were concerns or questions, the simple thing to do would be to vote against PICO 3 and choose Option A, PICO 1 (QPB) if both are needed. That would be an incremental change that would not commit the ACIP to anything they did not want. He agreed that the ACIP has a history of making tough decisions, and this has grown tougher with every meeting.

Dr. Sanchez said he certainly understood that and wanted a revisit of the meningococcal schedule, at least in children. Knowing that will be in the distance and there is an FDA-approved vaccine is available, there are circumstances in which children will receive both vaccines, Q and B, it made sense to make it available under certain circumstances and under certain recommendations, rather than tabling it for some future change. He suggested making the recommendations without adding anything more to an already complicated schedule.

Dr. Daley pointed out that Dr. Brooks was talking about the option on the screen, but his understanding is if we are in favor of what is on the screen, ACIP would need to vote down the amendment and the first proposal both, and then someone would need to make a new motion for this.

Dr. Lee agreed with Drs. Sanchez and Brooks that the ACIP needed to make a decision, and that deferring that decision would not be helpful for frontline pediatricians and family practitioners.

Dr. Lee spoke in favor of Option A.

Vaccines for Children (VFC) Resolution

Dr. Jeanne Santoli (CDC/NCIRD) indicated that they prepared for the multiple options, which would be reflected in her presentation of the VFC Resolution. She explained that the purpose of this resolution was to update the resolution to add a new component to the VFC Resolution to reflect a newly available combination meningococcal vaccine that can be used to prevent meningococcal disease attributable to serogroups A,C,W,Y and B, and to make minor updates to the existing components of the resolution (MenACWY component and MenB component).

For the MenACWY component, there are no proposed changes to the eligible groups. For the recommended vaccination schedule and intervals, there are 3 changes. The first would be to remove Menactra, which is no longer available as an option. The second would be to remove a footnote that was used to add Menveo 1-vial to the VFC resolution when that vaccine was licensed as an alternative product to the products that already were part of the resolution. No changes were proposed for the recommended schedule, dosages, or contraindications and precautions. For the meningococcal B component, the change to the eligible groups was to reference shared clinical decision-making because it was not referenced initially, and it is referenced in the new proposed component. For consistency, that was added to the second bullet here under the eligible groups. A statement was added to the recommended vaccination schedule and intervals table that was missing from the original resolution to add a footnote making clear that MenB vaccines are not interchangeable by manufacturer. No changes would be made to the recommended dosages or contraindications and precautions.

Pertaining to the upcoming vote on the combined pentavalent serogroup A,C,W,Y, and B vaccine, Dr. Santoli reviewed the eligible groups, recommended vaccination schedules and intervals for each Option A, Option B, and Option C that mirrored what the ACIP had been discussing. For Option A, there would not be a change to the eligible groups but there is a change in the second dose for children who are not at increased risk. This clearly indicates a monovalent, which was not the case for Option B. Otherwise, Options A and B were the same in the resolution. Option C included additional changes to acknowledge the use of the combination vaccine when MenB alone is recommended. That also was reflected in the recommended vaccination schedule and intervals.

No changes were made to the standard statement indicating that when there is a published recommendation, the information is incorporated by reference. Any contraindications and precautions would be added prior to the VFC resolution being brought forward for a vote.

Discussion Points

Recognizing that the final VFC vote would depend upon the final ACIP recommendation vote, Dr. Loehr moved to accept the VFC language as presented. Dr. Daley seconded the motion.

Dr. Long said that after listening to her colleagues and understanding that there was not support for tabling the pentavalent vote, she wanted to withdraw her seconding on the motion to table the vote. With no other seconds, this amendment did not pass.

Dr. Wharton clarified that with the second withdrawn pertaining to the amendment, there now was only one motion on the table for Option B as written. The amendment does not pass and ACIP returns to the original motion put forth by Dr. Loehr, which was Option B. Is any other discussion needed at this time?

Dr. Loehr asked if any colleagues wanted to do the amendment for Option A, now would be the time to do that.

Dr. Brooks asked if we would have to vote this motion down and have that option as a second motion.

Dr. Lee said there are 2 options, Option B (the initial motion) and if anyone wanted to request an amendment to the motion, essentially going to Option A, that is acceptable. Or you could vote down this one and have another vote.For the sake of clarity, it would be easier to have all potential motions/votes on the table before moving to the voting section. She requested that Option B and Option A be displayed.

Option B and then Option A were displayed.

Dr. Lee asked if anyone wished to make an amendment to vote for Option A.

Dr. Daley made an amended motion to adopt the language for Option A as written. Dr. Brooks seconded the motion.

Dr. Lee clarified that Option A, the amendment, would be voted upon first. If that did not pass, they would move to Option B.

Dr. Talbot pointed out that many of her colleagues were concerned about postponing this vote because physicians will be asking how to use this vaccine. While that is a legitimate concern, the reality is that insurance will not cover the vaccine if the vote is postponed. It was not a question of how to use the vaccine, but whether patients would have to pay out-of-pocket. In terms of pediatricians calling with questions, there are 3 licensed vaccines that already are currently covered by insurance and the VFC. She emphasized that she did not think the ACIP should make judgments based on other people's questions or how fast a pharmaceutical company wants to push a vaccine to market and instead thought that the ACIP should make decisions based on what is the simplest and provides the best care for their patients.

As a reminder, public comment was presented prior to the votes. However, the votes were combined in this proceedings document with their respective sessions for the purpose of continuity.

Vote: Meningococcal Vaccine

Dr. Jennifer Collins (CDC/NCIRD) recapped the votes on the table for Options A and B, which were as follows:

Option A (Amended Motion)
Pfizer's MenABCWY vaccine may be used when both MenACWY and MenB are indicated at the same visit.*

Footnote
*1) Healthy individuals aged 16–23 years (routine schedule) when shared clinical decision-making favors administration of MenB vaccination, 2) individuals aged 10 years and older at increased risk of meningococcal disease (e.g., due to persistent complement deficiencies, complement inhibitor use, or functional or anatomic asplenia) due for both vaccines.

Option B (Initial Motion; only voted on if the amendment fails)

Pfizer's MenABCWY vaccine may be used when both MenACWY and MenB are indicated at the same visit. *If MenABCWY is administered in this way, a second dose of MenABCWY may be administered 6 months later to complete the series.

Footnotes
*1) Healthy individuals aged 16–23 years (routine schedule) when shared clinical decision-making favors administration of MenB vaccination, 2) individuals aged 10 years and older at increased risk of meningococcal disease (e.g., due to persistent complement deficiencies, complement inhibitor use, or functional or anatomic asplenia) due for both vaccines.

Dr. Lee reminded everyone that the second for the motion to table the vote until a future time did not pass, given that the second was rescinded and no other seconds were made. There was then a motion and a second to amend the vote on the floor to vote on Option A, which would be voted upon first. If that did not pass, they would move to Option B. If it did pass, there would not be a vote on Option B. She asked ACIP members to put their cameras on.

Motion/Vote #1: Option A Meningococcal Recommendation

Dr. Daley made an amended motion to adopt the language for Option A as written, which Dr. Brooks seconded. No COIs were declared. The motion carried with 10 affirmative votes, 4 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Vote: Meningococcal VFC Resolution

Dr. Jeanne Santoli (CDC/NCIRD) recapped the VFC vote for meningococcal vaccines, which will reflect that the ACIP voted to approve Option A that will be reflected in the VFC Resolution accordingly.

Motion/Vote #1: Meningococcal VFC Resolution

Dr. Loehr moved to accept the VFC language as presented, which Daley seconded. No COIs were declared. The motion carried with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Discussion Points

Dr. Poeling thanked everyone for the robust discussion about meningococcal vaccines. There has been tremendous benefit from the vaccines that are being administered, and there is a lot more to learn. She voted “no” to Option A because she wanted a broader recommendation, emphasizing that she respected the votes of her colleagues and expected there would be many more conversations to come about meningococcal vaccine.

Dr. Daley pointed out that one of the overarching goals of the entire program is to maximize prevention of vaccine-preventable disease, morbidity, and mortality. That is fundamental in the context of resource constraints and other constraints. Therefore, he would expect that the work of the Meningococcal WG would include evaluation of a MenB prevention strategy. The problem was that this was not the direct questions under consideration during this session, so he wanted to highlight that distinction. In fact, conflating those two made it harder to make a decision. He thought they should focus on the decision at hand, recognizing that there are compelling reasons to re-evaluate the current strategy for Men B, which is rare but severe.

Ms. McNally emphasized that while she favors MenB vaccination and fewer injections, she also was hoping for a broader recommendation.

MPOX VACCINES

Introduction

Pablo Sanchez, MD (ACIP, WG Chair) provide an introduction and overview of the Mpox session, reminding everyone that the global Mpox outbreak occurred in 2022 with the first case identified in the United Kingdom (UK) in May 2022. It primarily affected gay, bisexual, and other men who have sex with men (MSM). It was associated with person-to-person spread via close skin-to-skin contact, including sex. Deaths have occurred, primarily among persons with severe immunocompromise from advanced HIV. US case counts and deaths comprised a third of the cases and deaths, with over 30,000 cases with 54 deaths. In terms of the current global cases, during September 2023, the US has reported 30 to 99 cases. There are large numbers of cases in Southeast Asia and Indonesia during this same time.

As a reminder, the JYNNEOS vaccine is comprised of a replication-deficient vaccinia virus, which is a live virus that is replication-deficient. It is administered subcutaneously via 2 vaccine doses administered 28 days apart. Its effectiveness was assessed by comparing immunologic response to that for ACAM2000. It was licensed for prevention of both smallpox and Mpox, and it is currently recommended for persons with HIV and other immunocompromising conditions. JYNNEOS vaccine is licensed for persons ≥ 18 years of age. There is a current NIH trial underway to evaluate the safety and immunogenicity for persons 12─17 years of age.

The outbreak recommendations were previously discussed during the February and June 2023 ACIP meetings. In June 2023, the ACIP voted to recommend the 2-dose JYNNEOS vaccine series for persons ≥ 18 years of age at risk of Mpox during an Mpox outbreak. Public health authorities determine whether there is an Mpox outbreak. A single case may be considered an Mpox outbreak at the discretion of the public health authorities. The outbreak recommendations were intended for any US Mpox outbreak regardless of whether it is associated with male-to-male sexual contact. The clinical guidance, including use of the vaccine in children during

outbreaks, were discussed as well. The national Mpox vaccination strategy for pre-exposure vaccination during the current outbreak includes the following individuals:[5]

- Gay, bisexual, and other MSM, transgender or non-binary people (including adolescents who fall into the forementioned categories) who in the past 6 months have had:
  - New diagnosis of ≥1 sexually transmitted disease
  - More than one sex partner

- People with the following in the last 6 months:
  - Sex at a commercial sex venue
  - Sex in association with large public events in geographic areas where Mpox transmission is occurring
- Sexual partners of people with the above risks
- People who anticipate experiencing above risks
- People with HIV or other causes of immunosuppression who have had recent or anticipate potential Mpox exposure

The World Health Organization (WHO) is embarking on the development of an elimination program of human-to-human transmission of Mpox. Certainly, additional resources and data are needed. Immunization will be one component of the strategy for worldwide elimination of Mpox disease. Elimination is a complex issue that has not been addressed by the WG. However, a recommendation that persons at risk for Mpox during the ongoing outbreak receiving the vaccines, if they have not already, may support any upcoming strategy from the WHO with respect to future elimination of Mpox. Dr. Sanchez indicated that the interim routine recommendation to be proposed for a vote during this session would read as follows:

> ACIP recommends vaccination* with the 2-dose† JYNNEOS vaccine series for persons aged 18 years and older at risk for Mpox§
>
> *Interim recommendation that ACIP will revisit in 2-3 years
> † Dose 2 administered 28 days after dose 1
> §Persons at risk:
> - Gay, bisexual, and other men who have sex with men, transgender or nonbinary people who in the past 6 months have had one of the following:
>   - A new diagnosis of ≥ 1 sexually transmitted disease
>   - More than one sex partner
>   - Sex at a commercial sex venue
>   - Sex in association with a large public event in a geographic area where mpox transmission is occurring
> - Sexual partners of persons with the risks described in above
> - Persons who anticipate experiencing any of the above

The potential implications of an interim routine recommendation are that it would increase vaccine coverage and prevent or minimize future outbreaks, and remove some stigma and facilitate one-to-one consultation with clinicians during their appointments for vaccination. It also heralds the potential commercialization of the JYNNEOS vaccine. The product sponsor, Bavarian Nordic, has indicated that they will attempt to commercialize the vaccine if it is on a routine schedule. This would transition the vaccine from US government stockpiles, which were intended for smallpox preparedness, to the commercial sector.

[5] https://www.cdc.gov/poxvirus/monkeypox/interim-considerations/overview.htm

Regarding the tentative timeline for ACIP discussions and votes, this meeting would result in interim routine recommendations if the ACIP adopts the recommendation and clinical guidance. Publication is planned for 2 *Morbidity and Mortality Weekly Reports (MMWRs)* in 2024, including: 1) Use of the JYNNEOS vaccine during Mpox outbreaks; and 2) Use of the JYNNEOS vaccine among persons at risk during the ongoing Mpox outbreak. Potentially in 2024, the ACIP would consider the results from an ongoing NIH trial on the use of the JYNNEOS vaccine in adolescents 12–17 years of age. The epidemiology, cost-effectiveness analysis, and other data would be reviewed in 2 to 3 years to determine whether a routine recommendation should be continued.

Updates about US Mpox Epidemiology, Vaccine Safety, and Vaccine Effectiveness

Faisal Syed Minhaj, PharmD, MPH, DABAT (CDC/NCEZID) provided updates on US epidemiology, vaccine safety, and vaccine effectiveness (VE). Beginning with situational awareness and updates in terms of Mpox case counts from the beginning of the outbreak in May 2022 through September 28, 2023,[6] the peak of Mpox cases occurred during August 2022 and cases have decreased substantially in 2023. Taking a closer look at the numbers in 2023, the case counts from the beginning of the year to September 28, 2023 did not reach zero at any point. During the month of January, the 7-day average case range was generally between 5 and 7 cases per day. Cases decreased in February down to 1 to 3 cases per day. However, they rose again in the summer months up to 5 cases per day. From July through now, there is still an average of one to four cases per day. Cases have not been consistently below this level, highlighting that Mpox has not been eliminated from the US. Looking at the cases in 2023 geographically, cases are occurring across the US in different jurisdictions. Cases are spread out and many are not linked to other known cases, which suggests continued community transmission or potential underdiagnosis. During the height of the outbreak in Summer 2022 when clinician awareness was high and vaccine campaigns were occurring, the rate of undiagnosed Mpox was likely low at around 1% in the MSM population. Seeing unlinked cases currently across jurisdictions suggests additional ongoing transmission.

Cases have been seen in patients following vaccination. This has been reported since the outbreak started, including some clusters. However, it is relatively rare in comparison to the total case counts. Importantly, most patients with infection following vaccination have mild illness. Data from a recently published manuscript on infections following vaccination[7] show that the median number of lesions in these patients was 2, with an interquartile range of 1 to 5. Additionally, only 2 out of 30 patients received tecovirimat and few were hospitalized, suggesting that illness was mild following vaccination.

Reinfection of Mpox is rare and was not well-reported until the current outbreak. Potential reinfection cases have been published in the literature, but only a few with convincing evidence of true reinfection. In a recently published case series,[8] the authors found a total of 8 probable cases of reinfection. Reinfection appears to be mild with a lower lesion count and duration of rash. CDC is aware of less than 10 cases of probable reinfection, which makes up less than 0.001% of cases.

[6] https://www.cdc.gov/poxvirus/mpox/response/2022/mpx-trends.html
[7] Hazra A. Lancet Infect Dis. 2023 Sep 4:S1473-3099(23)00492-9
[8] Hazra A. Lancet Infect Dis. 2023 Sep 4:S1473-3099(23)00492-9

CDC's mpox clinical consult service was created early in the outbreak to discuss any Mpox cases and transitioned to be a resource for treatment and guidance on managing severe Mpox cases. The consultation service is the only way to access most medical countermeasures available for severe Mpox. These consultations include some new cases, but many are repeated consultations on infections that began months ago and require numerous courses of available medical countermeasures. From the beginning of the outbreak to now, 54 people have died in the US, with another 2 in September 2023. As CDC published in 2022,[9] people with severe Mpox and deaths share the same equity disparities seen between cases and vaccination. Black persons make up the majority of severe cases. Most severe cases often have advanced HIV or AIDS, are not on antiretrovirals at diagnosis, are not linked to care, many are experiencing homelessness, and importantly are not vaccinated with JYNNEOS.

In terms of demographics, the gender and age distributions of Mpox cases have not changed since the June 2023 ACIP presentation. Most cases are among cisgendered males, highlighting the population for which JYNNEOS vaccination is recommended. The race and ethnicity of reported cases also remains similar to what was reported in June. Early in the outbreak, greater than 40% of cases were detected in White persons, but during the peak of 2022, Black and Hispanic persons were most affected. Recently, there have been cases across different racial and ethnic groups, but with large proportions of cases among Black and Hispanic persons throughout the outbreak;[10] Achieving vaccine equity is needed to address this disparity. Globally, there is a different trend of cases than in North America. Between April through September 2023, there have been large increases in Southeast Asian and Western Pacific regions. Over the past month, the European region also had one of its largest relative increases from August to September. Many recent increases were from countries in East and Southeast Asia based on detections from September 4 through September 24, 2023.[11] These are not the only countries in this region experiencing an increase in cases. Earlier in the week, there were news reports of new cases detected in Vietnam and Indonesia. When examining cases globally, it is important to recognize that robust Mpox surveillance systems and vaccine implementation programs seldom exist outside of Europe, Canada, and the US.

Vaccine uptake slowed dramatically following the peak of the outbreak in July through September 2022. Since the beginning of the outbreak in May 2022, first dose vaccine coverage is 38.8% and second dose coverage is 24.3% among the estimated at-risk people who are eligible for vaccination. Those at risk for Mpox are defined as HIV-positive and pre-exposure prophylaxis (PrEP)-eligible individuals totaling an estimated 2 million persons in the US. An incredible effort was put forth into achieving over 1.3 million doses administered. However, there is room for improvement. Ninety-three percent of doses were administered in 2022, and although there was a shift from first to second doses in 2023, second dose coverage remains below 1 in 4 and 37 of 54 jurisdictions are still below these national coverage estimates, emphasizing the work needed to get at-risk people primary vaccination. Moving forward, a younger unvaccinated population also will age into those eligible for primary vaccination.

There also has been a shift in vaccine administration sites from public health clinics to medical centers. Public health providers administered 40% of all vaccines through March 2023. Medical care providers administered an increasing proportion of vaccines since the start of the outbreak, and pharmacies consistently provided 3% to 4% of all vaccines. Looking closer at the types of medical center providers giving vaccine, there were statistically significant increases in vaccines

[9] https://www.cdc.gov/mmwr/volumes/71/wr/mm7144e1.htm
[10] https://www.cdc.gov/poxvirus/mpox/response/2022/demographics.html
[11] https://worldhealthorg.shinyapps.io/mpx_global/

provided by primary care offices, Federally Qualifying Health Centers (FHQCs), and other health centers.

Now to discuss a few models[12] related to vaccination in the current outbreak and why vaccination is an important strategy to prevent ongoing cases. Based on the results from a model of Mpox transmission in Washington, DC in which the model estimated cases averted by behavioral adaptation, vaccination, or both interventions, surveys indicate that individuals reduced the number of sexual partners in response to Mpox. This scenario does not include vaccine administration. The model estimates that behavioral adaptation alone could have quickly flattened the curve, but not ended the outbreak within 1 year. Based on vaccine administration records in DC, not including behavioral adaptation, the model indicates that vaccination would have taken longer to have an effect than behavioral adaptation, but would have ended the outbreak within a year. Based on the model estimates of prevalent infections with vaccination and behavioral adaptation combined, the model estimated that combined, these 2 interventions averted 80% of potential Mpox cases in DC, with behavioral adaptations being key to averting cases early on and vaccination being key to ending the outbreak. Similar results also were found in models in other cities.

Models not only estimate that vaccination is key to ending the Mpox outbreak, but also that vaccination is key to preventing Mpox resurgence.[13] Later in the outbreak in DC, the model estimated that nearly the entire high-risk population of MSM who engages in 1-time sexual partnerships gained full or partial immunity through vaccination or through acquiring and recovering from Mpox making resurgence in DC unlikely. However, over time, population level immunity will decrease due to population turnover. Further, most US jurisdictions had a lower vaccine coverage than DC, potentially leaving them vulnerable to resurgence. For the purposes of this model, either 1- or 2-dose vaccination was used. It is known from VE data that 2 doses is greater protection. In this model, they defined a resurgent outbreak as continuous community transmission for at least 3 months, the risk of recurrence decreases linearly as population level immunity increases. While the probability of recurrence decreases linearly with population level immunity, the size of potential outbreaks has a more complex relationship with population level immunity. The model estimates that resurgent outbreaks will be very small if the population level immunity is greater than 50%. Currently, only 7 jurisdictions are above 50% with at least 1 dose of JYNNEOS coverage among the high-risk population.

In terms of the VE and safety updates. These data were presented during previous ACIP meetings. To summarizes the available VE data from 3 separate studies in the US (1 from Epic Cosmos, 1 from a multi-jurisdictional case-control, and 1 from New York State), 1-dose VE ranged from 36% to 75%. VE ranged for from 66% to 89% for 2-dose vaccination. Consistently across the studies, VE for 2-dose vaccination was higher than 1 dose, emphasizing the importance of finishing the 2-dose series.

To update VE estimates from the multi-jurisdictional case-control study that was performed in 12 US jurisdictions and initially presented during the February 2023 ACIP meeting. The population is MSM 18-49 years of age and the time period is August 19, 2022 through September 27, 2023. Cases were identified from a jurisdiction's list of Mpox cases, while controls were identified from healthcare settings providing HIV PrEP or sexually transmitted infection (STI) clinics. VE was adjusted for age, race, ethnicity, and immunocompromising conditions. It was

[12] ttps://www.medrxiv.org/content/10.1101/2023.02.10.23285772v1.full.pdf Lines and shaded regions reflect median and interquartile range from 120 simul

[13] Pollock ED. MMWR Morb Mortal Wkly Rep 2023;72:568–573

stratified by route of administration and immunocompromise status. Overall VE from partial or 1-dose vaccination was updated to 73% (59-82), with similar results for those with either administration route. This estimate is similar to the previously reported 75%, but does have a smaller confidence interval. Overall, VE from 2-dose vaccination was updated to 83% (71-90), with similar results with either administration route. These updated data suggest that the VE estimates are stable.

Looking at the updated VE estimates for self-reported immunocompromised individuals, the confidence intervals of the estimates no longer cross zero. However, it is important to note that the sample sizes are still small within this subset of individuals and have wide confidence intervals that range from 8-91 for 1 dose and 23-96 for 2 doses. The point estimates of self-reported immunocompromised status appear similar but non-significantly lower than that in self-reported immunocompetent individuals. Notably, as immunocompromised status was self-reported, it is hard to ascertain the accuracy of this measurement for those who are truly immunocompromised. For example, people living with well-controlled HIV with CD4 counts above 350 may have responded that they are immunocompromised. Overall, this data, albeit encouraging, needs to be interpreted carefully. Ultimately, more work needs to be dedicated to understanding what VE is in immunocompromised people.

CDC continues to monitor AEs after JYNNEOS using 2 surveillance systems, the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD). V-safe data collection for Mpox vaccines was available from November 2022 to March 21, 2023. Approximately 90% of the reports were submitted during the calendar year 2022. There has been a relatively small amount of additional safety data accrued during 2023, but no new safety signals have been identified and no changes have been observed since the previous ACIP presentations in February and June 2022. The AEs most commonly reported to VAERS have been injection site symptoms such as redness, swelling, pain, and itching. Myocarditis and pericarditis are adverse events of special interest (AESI) and observed rates are consistent with the expected background rates. VAERS and VSD do not suggest an increased risk for myocarditis or pericarditis following JYNNEOS vaccination, but the possibility of a small risk cannot be excluded. The frequencies of local and systemic reactions reported to V-safe after Mpox vaccine were similar to those report in clinical trials. No new or unexpected safety concerns have been identified.

In summary, Mpox cases and deaths continue to be reported domestically and globally, but no longer at the same levels observed during 2022. There was an incredible effort and robust vaccine response, but there is still room for improvement. Less than a quarter of the eligible population is fully vaccinated with 2 doses. It is important to remember that with little vaccine implementation outside the US, Canada, or Europe and with a rise in cases in Asia and other regions, the outbreak is continuing. Modeling data suggest that without vaccination, transmission of Mpox will continue with sporadic outbreaks. No new safety signals have been identified from VAERS or VSD and VE appears stable for immunocompetent people.

Discussion Points

Dr. Poehling said she very much appreciated the data using multiple studies to demonstrate that both doses of JYNNEOS are important for VE. She also highlighted that according to uptake, it appeared that about 63% of the population who start the JYNNEOS series actually finish both doses, which is very important. She asked whether there are data on the 8 cases of reinfection, which is extraordinarily low and they seem to be very mild, in terms of whether they received 1 or 2 doses.

Dr. Minhaj said that in that global case series, 1 individual was vaccinated during that time period, and there are cases following reinfection that CDC is currently investigating, some of whom were vaccinated between their first and second infection. However, the number is small and interpretation of this data can be challenging.

Ms. Bahta asked whether the cases that followed vaccination had been analyzed for method of vaccine administration.

Dr. Minhaj indicated that they are looking into this, but from VE data is that there does not seem to be a difference in VE from either administration route.

Dr. Rao added that they have looked to see if there was any pattern. For example, a cluster of cases occurred in Chicago in May that affected people who were fully vaccinated, and there does not seem to be an association with those breakthrough infections and the route of administration. There were breakthrough infections among people who received 2 doses intradermally (ID), 2 doses subcutaneously (SQ), and 1 dose SQ and 1 dose ID. Fewer received 2 doses ID that were breakthrough cases from that cluster. The national data mirrors this.

Dr. Guagliardo added that they have looked at the national case surveillance data and also assessed the route of administration amongst these breakthrough infections and have not seen any differences in severity between routes of administration. They are working on publishing that.

Ms. Bahta noted that her biggest concern was about the complexity of ID vaccination and how that might have impacted effectiveness, but it sounded like no patterns have been observed.

Dr. Kotton requested additional information about any studies underway looking at immunocompromised people and, if so, what the timeframe is for getting that information. This population was devastated by this and were among the deaths reported. Many of them were immunocompromised and from underserved and other populations.

Dr. Rao confirmed that the deaths are predominantly occurring among people who have advanced HIV or some other form of severe immunocompromise. These also are individuals who did not receive any doses of the vaccine. The VE estimates are problematic because a true VE estimate cannot be extrapolated among immunocompromised people. They also do not know VE for individuals with that degree of severe immunocompromise. They do recognize this as an absolute priority. In the multi-jurisdictional study, they are going to attempt to understand the CD4 counts and viral loads for those patients in order to determine whether they were truly immunocompromised.

Dr. McCollum added that through the multi-jurisdictional study and the case-control set up for monitoring of VE, there are opportunities for monitoring. It will be a relatively small subset of those with well-defined immunocompromise or self-reported immunocompromise. They also are actively engaged in collaborating on a longitudinal study out of the University of California Los Angeles (UCLA) to assess individuals presenting to and receiving care from HIV and sexual health clinics in the area and monitor them longer-term for self-reported and clinically defined health events and some of the defined risk factors. That also involves blood collection for serology, which will provide a nice additional laboratory component. They also have been talking to potential collaborators outside of the US to look at populations in endemic regions to ensure that they are thinking broadly about the scope of data that could be collected. This is an

ongoing story and a top priority to better understand the impact and potential necessity for vaccine use in these populations.

Dr. Kotton emphasized the importance of assessing people with advanced HIV. She also encouraged CDC to look outside of that population, given that an estimated 3% of the US population is immunocompromised.

In terms of the recommendation, Dr. Middleman (SAHM) emphasized the importance of getting this vaccine into the right people. Gender identity and sexual attraction descriptions do not necessarily translate into behaviors. In reading the recommendation and in terms of the epidemiology, her understanding was that it is the behavior that puts people at risk (e.g., receptive anal intercourse and anal intercourse in general). The first line of the recommendation is confusing and will confuse a lot of people because it is really mixing gender identity terminology with sexual attraction terminology, which does not translate into behavior. She thought it would be helpful if the recommendations actually stated the risk behavior. She did not believe a transgender male, unless they are engaging in receptive intercourse (e.g., someone assigned female at birth who is now a transgender male) would be in the risk category unless she was reading that incorrectly. While she understood why it is difficult, she also thought they should identify the behaviors that put people at risk in order to protect everyone who requires protection.

Dr. Fryhofer (AMA) said that while the safety information was very reassuring, there previously was a contraindication on giving this vaccine with COVID vaccines. She requested additional information on this and how they came to that decision.

Dr. Rao clarified that it is not a contraindication or precaution. This is co-administration guidance that is included in the CDC COVID-19 Interim Clinical Considerations and the Interim Clinical Considerations for the Mpox vaccine. They want to note that it is something people might keep in mind until there are data that can absolutely rule out even the smallest chance of myocarditis being potentiated after COVID-19 and JYNNEOS vaccines are given together. There have not been any safety signals to suggest that the JYNNEOS vaccine is associated with myopericarditis. With ACAM2000, the other orthopoxvirus vaccines, there is a definite signal for which the mechanism is not understood. Therefore, this guidance was included for JYNNEOS. While the data thus far do not support that, it is not possible to rule out the very smallest chance at this time. She noted that she would discuss this further in her last presentation of this session, and that CDC STD experts also were involved in the development of this language, so perhaps one of them could speak during the discussion session about exactly why this specific wording was chosen. It is identical to the wording that has been used throughout this particular outbreak response.

EtR Framework for the JYNNEOS Vaccine

Agam Rao, MD (CDC/NCEZID; CAPT, US Public Health Service) presented the EtR Framework for vaccination with JYNNEOS vaccine for persons at risk of Mpox. She reminded everyone that the EtR Framework is a structure to describe information considered in moving from evidence to ACIP vaccine recommendations. It provides transparency around the impact of additional factors on deliberations when considering a recommendation. For this EtR analysis, the WG's question was:

> Does ACIP recommend vaccination with the 2-dose* JYNNEOS vaccine series for persons aged 18 years and older at risk† for mpox?

*Dose 2 administered 28 days after dose 1

- Gay, bisexual, and other MSM, transgender or non-binary people who in the past 6 months have had one of the following:
  - A new diagnosis of ≥1 sexually transmitted disease
  - More than one sex partner
  - Sex at a commercial sex venue
  - Sex in association with a large public event in geographic areas where Mpox transmission is occurring
- Sexual partners of persons with the risks described above
- Persons who anticipate experiencing any of the above

The rationale for the age selection for the EtR Framework is that the JYNNEOS vaccine is currently licensed for persons 18 years and older. There is an NIH trial underway to study the safety and immunogenicity of JYNNEOS among persons 12─17 years of age. When those data are available, the WG will review them and possibly bring this back to the ACIP. The comparator is no vaccination, so when going through the EtR domains, the comparison will be the vaccination versus no vaccination. The outcomes are prevention of disease, severity of disease, SAEs, and myocarditis/pericarditis. As a reminder, the EtR domains include the public health problem, benefits and harms, values, acceptability, equity, feasibility, and resource use. Dr. Rao presented the WG's interpretation of the data for each of these domains and the response to the questions for each.

Beginning with the public health problem, Mpox cases continue to occur domestically and internationally, including in clusters, but also in cases that cannot be connected to clusters. Severe disease and deaths continue to occur as well. Over 1.25 million doses of JYNNEOS vaccine have been administered in the US, which is great. While it took a lot of effort for that to happen, national vaccine coverage remains lower than ideal. This is possibly because of the lower perceived risk of Mpox in the last 6 months. CDC modeling data suggest that larger outbreaks may occur if vaccine coverage remains less than 50% nationally for persons at risk for Mpox. Coverage is currently only about 23% to 24%, so 1 in 4 people who should be vaccinated are vaccinated at this time. To reiterate, severe disease and deaths are continuing to occur in predominantly unvaccinated people.

Moving to benefits and harms, there are 3 main sources of VE data, including the CDC Epic study, the CDC multi-jurisdictional study, and a New York State study. The methodology of these studies and the data from them were presented during the 2 previous ACIP meetings and earlier in Dr. Minhaj's presentation. To recap, 2 doses of the JYNNEOS series were found to be better than 1 dose. The estimated VE for preventing Mpox disease is 66% to 89% for the 2-dose vaccine series. The CDC multi-jurisdictional study continues to collect data. To CDC's knowledge, it is perhaps the only source of data that will be continued worldwide. CDC is attempting to estimate the VE in preventing infections among immunocompetent versus immunocompromised persons, and recognizes that this is a major gap in understanding.

The ACIP previously recommended use of the 2-dose JYNNEOS vaccine series for 2 populations, including populations at increased risk of occupational exposure to orthopoxviruses and persons at risk for Mpox during Mpox outbreaks. At that time, ACIP reviewed the GRADE data and the available VE data. Subsequent data support its effectiveness for the population impacted by the ongoing outbreak. The WG determined the desirable anticipated effects to be

large. Similarly, there have been no new safety concerns since the previous ACIP votes about the use of JYNNEOS. The AEs most commonly reported to VAERS have been injection site symptoms such as redness, swelling, pain, and itching. The WG interpreted these as being small undesirable anticipated effects. Because the desirable anticipated effects are large and the undesirable anticipated effects are small, the WG felt that the intervention of vaccination with JYNNEOS compared to no vaccination is favored.

In terms of the values domain, early in the Mpox outbreak response, multiple national surveys indicated that there was strong interest in the JYNNEOS vaccine. These data were presented in detail during the February 2022 ACIP meeting. To summarize the data, during August to November 2022, greater than 85% of respondents in the American Transformative HIV Study (AMETHST)[14] were interested in the vaccine. During August to December 2022, 50% of Porter Novelli survey responders who identified as LGBTQ+ felt the vaccination was important to protect them from Mpox.[15] During October to November 2022, greater than 70% of MSM in a San Francisco survey of persons experiencing homelessness reported that they would accept or have accepted the vaccine.[16] During October to December 2022, an American Men's Interest Survey (AMIS) showed that those who were concerned about Mpox were 3.5 times more likely to be vaccinated.[17] In addition to this information, other information also was obtained.

Early in the outbreak, not surprisingly, persons seeking vaccination were supportive of the JYNNEOS vaccine. One of those study surveys was performed during a study called the DC PET++ Study,[18] which is a CDC and DC Health collaboration to follow a cohort of persons at elevated risk of Mpox exposure in Washington DC who presented for vaccination between August 2022 through October 2022. This survey of 866 adults found that greater than 85% agreed or strongly agreed that vaccines for Mpox should be available to anyone who wants the vaccine, and 82% said that they were likely or very likely to get a third dose if it was to be recommended; however to be clear, a third dose is not recommended. Another evaluation in Washington, DC around the same time period supported the same idea.

Also early in the response, studies showed that there were some conflicting feelings among the people who are recommended to be vaccinated. A survey was performed by Curtis et al. among 320 persons,[19] primarily MSM living in Illinois and at risk for Mpox. Among the respondents, 24.1% had received 2 vaccine doses, 27.5% had received 1 dose, and 47.5% had received no doses. Persons who were vaccinated were more likely to have higher education, known someone with Mpox, expressed concern about their safety, and be less likely to report recent food insecurity. The Turpin et al. study[20] also evaluated this in qualitative interviews performed with 24 Black MSM attending HIV prevention-related activities in the greater DC area, which is a very important population. This was early in the Mpox response in May 2022. At that time, there was not as much availability of the Mpox vaccine as there is now. While there is now sufficient vaccine to vaccinate all of the people SQ who are recommended to receive the vaccine, a common concern at that time was the lack of availability of the Mpox vaccine, which implies interest in the vaccine. Vaccine hesitancy also was expressed commonly, but possibly was similar to vaccine hesitancy reported for other vaccines.

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[14] https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-21-018.html

[15] https://emoryamis.org/wp-content/uploads/2022/08/2022-Monkeypox-Survey.pdf

[16] https://www.cdc.gov/mmwr/volumes/71/wr/mm7135e1.htm

[17] Filardo TD. Vaccine. 2023 Sep 7;41(39):5673-5677

[18] Hassan, R. (in press). Sexually Transmitted Diseases

[19] https://pubmed.ncbi.nlm.nih.gov/37236817/

[20] https://pubmed.ncbi.nlm.nih.gov/37510557/

Moving to more recent data, CDC issued a "CDC's State of Vaccine Confidence Insights Report" in June 2023.[21] A month prior to issuing that report in May 2023, an Mpox cluster was identified in Chicago that predominantly affected people who received 2 doses of the JYNNEOS vaccine. This report was intended to review Mpox-related discussions on 23 news and social media outlets in the Chicago area in order to understand the sentiments of the affected population and develop communication material accordingly. Mpox vaccine hesitancy among the general public and LGBTQ-affiliated groups was noted. People questioned the effectiveness and safety of the vaccine and expressed distrust in national reporting. However, when 18 patients who were impacted by that outbreak were interviewed, 18 agreed to an interview. Among them were patients who were fully vaccinated, partially vaccinated, and unvaccinated. Most vaccinated persons felt that the vaccine was effective in reducing severity and some assumed it would prevent infection. Most stated that they would recommend the vaccine to others. Unvaccinated persons reported initial interest in the vaccine when the supply was limited and they were unable to receive it. They reported they did not seek it again because case counts decreased so they assumed diminished risk.

In June 2023, CDC performed an online focus group with 52 people to help develop CDC communication material. Participants were included if they identified as men (including transgender men and transgender women), were unvaccinated for Mpox, were never diagnosed with Mpox, were 18–45 years of age, and had sex with 2 or more men within the past 6 months. This essentially was people who were eligible for the Mpox vaccine. The participants were intentionally of diverse racial and ethnic backgrounds. They were shown various communication materials developed by the CDC. Exposure to the information about Mpox vaccine safety and effectiveness and hearing that there is a current threat of Mpox increased their interest in receiving Mpox vaccine information. Although some of the individuals participated in this focus group who were not interested in the vaccine or were ambivalent about the vaccine, that changed after seeing the materials. Many who were disinterested in the vaccine became interested and said that the current risk of Mpox and protecting their community were motivating.

To summarize the values domain data, vaccine demand was high early in the outbreak response when case counts were high. National surveys and interviews early and later in the outbreak indicated that there is overall interest in JYNNEOS vaccinations, but as with any vaccine, some people experience vaccine hesitancy. In response to whether the target population feels that the desirable effects were large relative to the undesirable effects, the WG answered "probably yes." Because interest and intent to get vaccinated varied among the affected population and a perceived lower risk of Mpox may be contributing to reduced interest in the vaccine, the WG felt that there was possibly "important uncertainty or variability" in how much people value the main outcomes.

Moving to the acceptability domain, health departments are supportive of and requested a lot of the JYNNEOS vaccine and organized vaccination campaigns. An online survey[22] early on showed that clinicians during July, August, and September 2022 were interested in getting their patients vaccinated and 69% felt that the US did not have enough Mpox vaccines to handle the outbreak at that point. A few weeks later on September 12, 2022, a survey showed that 66% had treated at least 1 Mpox patient, 76% knew where a patient could get the JYNNEOS vaccine, and 86% wanted to be able to provide the vaccine in their offices.

[21] https://www.cdc.gov/vaccines/covid-19/downloads/SoVC-MPOX-062723.pdf
[22] https://app.sermo.com/barometer/unitedstates

More recent data come from a Porter Novelli survey of pediatricians and family practice practitioners with approximately 100 people in each group performed in August 2023. The survey included 3 Mpox vaccine questions added to a survey on pediatric COVID-19 vaccine attitudes and behaviors. The responders included family practitioners (85%) and pediatricians (88%) who cared for children 12—17 years of age and family practitioners (70%) and pediatricians (60%) who cared for patients ≥18 years of age. The majority (75%) were in private practice and 14% practiced in FQHCs. About 54% were part of large practices with over 1500 patients. These data are helpful in terms of understanding themes in general. When asked whether they would prefer to provide the Mpox vaccine within their practice, family practitioners more often strongly or somewhat preferred providing the vaccine within their own practice. Pediatricians were supportive of the vaccine, but preferred to refer to an outside practice.

As Dr. Minhaj showed earlier, there has been a shift over time in vaccine administration from public health clinics to medical care centers. If the ACIP votes in favor of the proposed recommendation, vaccines would be provided in medical centers. However, that already has been happening. There has been a statistically significant increase in vaccines provided by primary care offices, FQHCs, and other health centers. This indicates that providers in these settings deem the vaccine to be acceptable.

A recent CDC online focus group was performed with HCP to further understand their thoughts, knowledge, attitudes, and practices related to Mpox. Recruitment done by an external recruiting firm resulted in a group of 41 participants who were diverse in terms of gender, race/ethnicity, practice setting, payment methods for patients, and clinical profession. Among the respondents, 61% reported spending ≥60% of their time providing sexual health services; 59% were private healthcare settings, 29% were private and publicly funded, and 10% were publicly funded; 54% were in private practice, 20% were STD/HIV/family planning clinics, 10% were FQHCs, and 25% were in ED or urgent care settings. Among the respondents, 68% had never managed an Mpox case, 34%, believe Mpox is a threat to public health, and 32% reported that Mpox is important to their patient populations. Among respondents, 51% believe that Mpox services should be integrated into standard care. It might improve access to vaccines, education and awareness about Mpox for patients, and it would ensure comprehensive STI screening and testing.

In response to the question regarding whether the intervention is acceptable to key stakeholders, the WG answer was “yes.” Health departments and clinicians are supportive of Mpox vaccines, even if pediatricians would prefer to refer patients to other clinics to receive it. Family practitioners would like to be able to actually provide the JYNNEOS vaccine in their own clinics. There has been a shift from JYNNEOS provided by public health providers to JYNNEOS provided by medical center providers, including STI and HIV clinics, where the WG thinks these vaccines will be administered if this recommendation is passed.

Moving to the resource use domain, the vaccine is currently provided through the Strategic National Stockpile (SNS) that is intended to stockpile therapeutics for bioterrorism preparedness and other similar preparedness issues. JYNNEOS has been stockpiled for smallpox preparedness, but was provided during this response since it is not commercially available. The doses would need to be replenished. There has been and will continue to be a significant use of resources (e.g., shipments, transportation, personnel monitoring) during the peak of this outbreak. A routine recommendation could be a further drain on the SNS should this vote be passed. In the future, it is possible that the vaccine will be commercialized. If so, there are

unknown costs that will be associated with that. Therefore, the WG answered that it is "uncertain" whether the intervention is a reasonable and efficient allocation of resources.

In terms of the equity domain, the WG interpreted this as trying to understand the population who was impacted by Mpox and felt that there has been a disproportionate impact of Mpox on gay, bisexual, and other MSM; Black and Hispanic persons; and persons experiencing homelessness. Any vaccine administered versus no vaccine administered may decrease the disparity between the affected population and others. The recommendation would facilitate one-to-one counseling and information sharing in the privacy of a clinic. Vaccine recommendation from a clinician is associated with increased vaccine uptake. During September 2023, $5 million were allocated to community-based organizations (CBOs) to advance Mpox prevention and vaccination efforts.[23] CBOs have played a critical role in the Mpox response so far and are essential to increasing vaccination coverage among those at risk. Thus far, 42 CBOs have been funded. If the vaccine is commercialized, there may be an impact on primary sites of vaccination in health departments. At this point, it would be conjecture to assume exactly what the impact would be. As previously mentioned, in about 2 to 3 years, it would be necessary to re-assess this interim recommendation knowing the situation at that time in terms of the epidemiology and whether the vaccine is commercialized. However, such a recommendation might facilitate product acceptance of the vaccination because everybody knows that the ACIP has a high bar for recommending a vaccine. If JYNNEOS vaccine is commercialized in the interim time period, this also would facilitate insurance companies covering the vaccine.

In response to the question regarding what the impact would be on health equity, the WG group felt that access to vaccine versus no vaccine may improve the health of persons who are at risk for impacts, and that a routine recommendation may facilitate vaccinations and that health equity would be "probably increased."

Regarding the feasibility domain, if the ACIP voted to approve the interim recommendation for JYNNEOS vaccine, the vaccine would continue to be provided through the SNS free of cost to patients and providers. While there would be a cost overall to the US Government (USG), there would not be a cost to patients and providers. Mpox provider agreements do not have a termination date.[24] They will continue as long as the vaccine is acquired via the USG program and can include new providers. In fact, CDC learned that health departments are continuing to bring on new providers. The $5 million funding that has been provided to CBOs may improve feasibility in addition to equity. These CBOs reach hard-to-reach communities and also might facilitate feasibility for those communities. If the vaccine is commercialized, it would be available through Medicare, Medicaid, and commercial plans without a co-pay. Uninsured children would be given the vaccine through the VFC. Some uninsured and underinsured adults could have difficulty, but that would be similar to the difficulty they encounter with other vaccines.

Regarding whether the intervention is feasible to implement, the WG group answered "probably yes." SQ vaccine is easy to administer, and providers know how to administer it. Standing orders are available. JYNNEOS can be stored refrigerated for 8 weeks. There has been a recent shift in vaccine providers to individual clinics, which demonstrates the continued successful integration of JYNNEOS into providers' practices (e.g., STI and HIV care settings, HIV care pharmacies, LGBTQ+ affirming primary care practices). STI, HIV, and most family medicine/internal medicine providers seem to be comfortable providing vaccines, even if some

[23] https://www.cdcfoundation.org/pr/2023/mpox-vaccination-CBO-outreach
[24] https://www.cdc.gov/poxvirus/mpox/clinicians/provider-agreement.html

pediatricians may refer patients out to other clinics. If commercialized, similar to other vaccines, the cost of vaccine might impact access to some populations.

To summarize all of the answers provided in the EtR domains, there is nothing clearly unfavorable. However, there is uncertainty pertaining to the variability and values that people have about the vaccine in general. This is possibly because they perceive that there is decreased risk, which is not the case. There is uncertainty about commercialization of the vaccine. Based on all of this, the WG determined that the desirable consequences probably outweigh the undesirable consequences in most settings. However, several WG members felt that there was enough information presented that the desirable consequences clearly outweigh the undesirable consequences despite the uncertainty. Given that more people in a straw poll supported the "probably outweigh" option, that was what was shown for the balance of consequences.

In closing, Dr. Rao posted the proposed recommendation a vote and invited input from the ACIP members and STD colleagues on the language of this vote.

Discussion Points

Dr. Poehling expressed appreciation for the team working with patients and persons who were directly impacted to co-create the educational materials. While she appreciated the question that was raised about the verbiage in the proposed interim recommendation defining persons at risk, there is overwhelming evidence that the primary sentence as stated in the proposed recommendation would be beneficial.

Dr. Poehling made a motion to approve the language as stated, "ACIP recommends vaccination with the 2-dose JYNNEOS vaccine series for persons aged 18 years and older at risk for Mpox." Ms. Bahta seconded the motion.

Ms. Bahta stressed that it is really important to understand that in terms of the launching of new vaccines as well as transitioning from the federal supply to the commercial supply that there will be decreased access. With that in mind, she emphasized the importance of establishing a Vaccines for Adults (VFA) program. Regarding the potential move to a routine recommendation, she asked for input on the current supply.

Dr. Rao indicated that there is plenty of vaccine for all of the people who are eligible for the vaccine over the next several years, including people who become eligible during that time period.

Dr. Daley indicated his support for the proposed recommendation and requested a reminder about the duration of protection from vaccination.

Dr. Rao said they are hoping to continue to evaluate duration of protection through continuing VE work. To her knowledge, the multi-jurisdictional study is the only one out of the 3 studies that will be continuing, though perhaps the New York State study also will be continuing. What is known is that the pre-licensure data indicated that an anamnestic response to the vaccine occurs for up to 2 years after the primary 2-dose series. The only reason a booster frequency of 2 years was proposed for persons at occupational risk for orthopoxviruses was that nobody had evaluated a time point later than 2 years. In the Democratic Republic of Congo (DRC), CDC has a vaccine study that is looking into this. It appears that people have mounted a robust response 5 years after the initial primary dose series, but they want to evaluate that more before

confidently expressing this. She called on Drs. McCollum and Panayampalli who led the DRC work to comment further.

Dr. Panayampalli added that participants were classified as those having never received the vaccine and those who received the vaccine during childhood. Even after several decades, people who received childhood vaccination demonstrated a robust and anamnestic response. Those individuals probably received replicating vaccine previously. JYNNEOS is a non-replicating vaccine, so they also wanted to see if JYNNEOS has a similar effect. As Dr. Rao mentioned, 5 years after people received JYNNEOS, regardless of whether any circulating antibodies were detected, a robust increase is seen in the immune response 7 days after a boost.

Dr. Cineas requested information on a timeline for a recommendation for adolescent patients who are at risk.

Dr. Rao reiterated that the reasons the proposed recommendation was for persons 18 years of age and older was because the vaccine is currently licensed in that population. There are going to be NIH data from a trial among adolescents 12—17 years of age, hopefully in 2024. She noted that she would explain the clinical guidance data further in her next presentation.

Dr. Beigel (NIH) reported that the adolescent study was fully enrolled in September 2023, which means the peak immunogenicity visits at 42 days occurred a few days before this meeting. It is designed to include a 1-year follow-up, which is in October 2024 for the full dataset. NIH can discuss with the ACIP and Bavarian Nordic about early analyses.

Dr. Zahn (NACCHO) noted that the State of California has simplified the recommendation indication that a person who is a practicing MSM who has HIV is recommended to receive the vaccine. He has been a fan of that simpler recommendation, given that persons at risk may not recognize they are at risk and/or depending upon the setting, HCP might not be comfortable going through all of the potential risks. There also is the issue of stigma because someone has practiced certain behaviors that are risk factors. While they do not have enormous uptake, he would be disappointed in not continuing to have a broad recommendation since they do continue to have sporadic disease in Southern and Northern California. Outreach to specific community settings has proven to be and will continue to be valuable. Having the continued support for their CBO partners and to public health to provide outreach over time is going to be important.

Dr. Rao agreed with the importance of continuing to support CBOs because they do very important work, particularly for this population. She noted that a lot of thought was put into whether the recommendation could be simplified, but this is an infection that occurs when there are certain behavior risk factors. To recommend the vaccine to anyone who has HIV and/or anyone who is MSM perhaps would result in giving the vaccine to people who do not need it but might be concerned about getting Mpox even though they are in a monogamous relationship and do not meet the criteria.

Dr. Quilter added that they were trying to strike a balance. She appreciated the comments about wanting to avoid stigma and to simplify the recommendation for providers, but also wanting to ensure that the vaccination being given to those who are most at risk for Mpox exposure. The version proposed was tweaked from an even more complicated version the first time around to achieve that balance.

Dr. Rao asked whether Dr. Spicknall, as a modeling expert in the Division of STD prevention, had any thoughts about just how much bigger the population would be if it was referring to all MSM or all people with HIV versus how it is described in the proposed recommendation.

Dr. Spicknall said that in terms of a larger population, it would go from roughly 2 million to 4 to 6 million people. The scope would be enlarged greatly such that folks who may not benefit from this vaccine for the reasons described would be vaccinated.

Dr. Drees (SHEA) observed that the list of people who are at risk in the proposed recommendation did not mention occupational exposures, and she wondered whether that was intentional because it would be a separate vote or if it needed to be included in this recommendation.

Dr. Rao indicated that occupational exposures intentionally were not included in this proposed recommendation because this is intended to be PrEP for the population at risk of acquiring Mpox in the current outbreak. There already are standing occupational recommendations for laboratorians and HCP on which the ACIP voted in February 2022 in terms of who needs to be vaccinated during an outbreak. Because so few healthcare-association infections have been acquired, it is not routinely recommended for clinicians who are providing care to patients who have or might have Mpox. Being in the midst of an outbreak, many laboratorians have been and can continue to be vaccinated.

Dr. Drees (SHEA) said that “wearing her other hat” as a practicing HIV provider that her state also allows anyone with HIV to be vaccinated. Clinicians have to talk about many vaccines with their populations, so she does not routinely offer Mpox vaccine to every person living with HIV because she knows many of them are not at risk.

Dr. Middleman asked about the rationale for inclusion of non-binary and transgender people. Transgender males are assigned female at birth, so it was not clear to her what the risk factors were if not just receptive anal intercourse and if there was something different about transgender males and non-binary people that put them at higher risk. She emphasized that she wanted to make sure that they were not making assumptions of behavior or increased risk based on gender identity status.

Dr. Quilter indicated that the population of persons at increased risk in the proposed recommendation was based on gender identity and sexual orientation. She did not know if there was enough information yet to specify a behavior. Based on how Mpox is transmitted through intimate or sexual contact, it could be any skin-to-skin contact with mucosal infections. It is possible through oral sex, insertive or receptive anal sex, or other mucosal exposure. The decision about persons at risk was data-driven. A CDC *MMWR* was published earlier in the year that was dedicated specifically to the epidemiology of Mpox in persons who are transgender or non-binary people. The authors found that these populations were disproportionately affected by the Mpox outbreak. Cisgender women have been minimally impacted. There has been a disproportionate impact on Mpox transgender and non-binary people. The exact wording used in the *MMWR* was reviewed and endorsed by CDC’s health equity experts so that the recommendation could be as inclusive as possible and ensure that the people who are known to be at risk are getting vaccinated.

Dr. Rao added that they know of cases of people lying very close together without clothing on and having contact with the lesions in the genital region. There have been people who said they

had penetrative sex, receptive sex, heterosexual women who seem to have acquired it from bisexual men.

Dr. Spicknall pointed out that the modeling evidence suggests that not only are personal individual-level risk factors and behavioral adaptations occurring, but also it is a group of people acting together that in effect decreases transmission.

Dr. Lee recapped that in the adolescent population, Dr. Middleman was highlighting the assumption issue. As they begin to think about the adolescent age group, they will have to question the recommendations to ensure that they are not reinforcing potential stereotypes.

Dr. Boucher (ASPR/HHS) reported that since the identification of Mpox cases in the US in May 2022, Administration for Strategic Preparedness and Response (ASPR) has shipped over 1 million vials of JYNNEOS to federal and jurisdictional partners. As Dr. Rao and others mentioned, JYNNEOS was developed by Bavarian Nordic and USG partners like the Biomedical Advanced Research and Development Authority (BARDA), and others as part of the nation's smallpox preparedness program. Given its safety profile, particularly for immunocompromised individuals, and effectiveness in reducing the frequency and severity of infections, there was a strong justification to use doses held in the SNS to support the response. In continuing to move beyond the acute phase of the response, ASPR is supportive of the transition of JYNNEOS to commercial distribution as the next correct step in ensuring continued access for those who wish to get vaccinated for Mpox. ASPR also is committed to ensuring a seamless transition if this does go to commercial distribution. There will not be gaps in the availability of JYNNEOS as ASPR "passes the baton" onto its partners at Bavarian Nordic. In January 2023, ASPR migrated jurisdictional ordering to a threshold-based system that is similar to that used for COVID vaccines and therapeutics. At that time, about 400,000 vials were put into the combined thresholds across 64 jurisdictions. To date, about 57,000 of those have been ordered. That means that there are still well over 300,000 vials available immediately to jurisdictions anytime they need to restock existing vaccination sites or supply new ones. ASPR will keep this supply reserve for the jurisdictions as they work with Bavarian Nordic and HHS partners at CDC, CMS, and several others over the coming months in order to plan and execute a smooth handoff. Regarding the question earlier about the largest supply, through ASPR's partnership with Bavarian Nordic and a lot of great efforts that they have made to expand manufacturing capacity and deliveries over the last year and a half, ASPR significantly built its JYNNEOS inventory in that period. If the JYNNEOS vaccine transitions to commercial distribution and there is a point at which demand is outpacing BN's manufacturing capacity, ASPR would still consider itself to partner with Bavarian Nordic and would be happy to work through ways that they might be able to provide support to avoid any shortages. He recognized that there were many people participating in the meeting who play viral roles in providing care to patients and reducing Mpox cases. On behalf of all of his colleagues at ASPR, he expressed gratitude for everything they do to keep people safe and healthy and thanked them for their partnership throughout the response.

Lee Ann Kimak (Bavarian Nordic) indicated that she is the US Commercial Lead at Bavarian Nordic. On behalf of Bavarian Nordic, she thanked the WG and the ACIP for their tremendous efforts and their careful deliberations on this important public health issue. Bavarian Nordic is very proud to have partnered with the USG in the successful response to meet the Mpox outbreak, including the rapid deployment of JYNNEOS. They also realize that vaccine access challenges remain. They believe that the routine preventative recommendation for at-risk populations under consideration by the ACIP is a critical step forward in addressing these inequities and access challenges. This recommendation would allow providers and retail

pharmacies to administer the vaccine where people are most comfortable seeking one, whether that is at the pharmacy, their doctor's office, or their neighborhood health clinic. If the committee votes for a routine recommendation for the at-risk population, putting Mpox vaccine on the immunization schedule, Bavarian Nordic very much looks forward to commercializing JYNNEOS in the US. They have a robust manufacturing process and ample supply to meet the need. They also have an unwavering commitment to public health and look forward to working with the agency and healthcare providers in the community to make this vaccine accessible to individuals at risk.

Dr. Sanchez asked whether Ms. Kimak could comment on the anticipated price of the JYNNEOS vaccine.

Lee Ann Kimak (Bavarian Nordic) reported that the intended list price will be in the range of $200 to $270 per dose. The list price is then negotiated down in the contracting phase, depending upon the particular reimbursement mechanism. It comes down by 25% to 30% or more, which is the range for the wholesale acquisition cost.

Review of Voting Language and Clinical Guidance

Agam Rao, MD (CDC/NCEZID; CAPT, US Public Health Service) indicated that this presentation was dedicated to guidance about whether the proposed interim recommendation should be passed and next steps. This guidance refers to vaccination before exposures to Mpox, not post-exposure prophylaxis (PEP). Much of the guidance is similar or identical to what she presented during the June 2023 ACIP meeting. All of this guidance refers to the individuals listed in the footnote included with the proposed interim recommendation who would be eligible for the vaccine and for PrEP only.

JYNNEOS is not licensed for persons <18 years of age. There are no pre pre-licensure studies in this population. However, vaccine has been administered to this population. While a good number of adolescents 12–17 years of age received a first dose of the JYNNEOS vaccine, CDC has not received any concerning safety signals in this population or VAERS reports of SAEs in this age group. For the NIH clinical trial in progress focused on safety and immunogenicity of JYNNEOS in persons aged 12–17 years of age, it sounds like data may be available by the end of 2024 and perhaps the earliest it could be presented to ACIP would be in 2025. That is why guidance is proposed saying that adolescents at risk for Mpox may receive the JYNNEOS vaccine before an exposure, which refer to adolescents with risk factors.

In terms of pregnancy or breastfeeding, available human data are insufficient to determine whether the vaccine has any risks in pregnant persons. However, animal model data are mentioned in the package insert. This includes models involving rats that have shown no evidence of harm to the developing fetus. No AEs have been reported to the US vaccine safety surveillance systems. They do not have data showing how many pregnant persons have received the vaccine during this response. However, it is reassuring that at least there have not been VAERS reports of anyone actually indicating that an AE was in a pregnant person. Similarly for breastfeeding persons, this has not been evaluated and there have been no AE reports reported in the US vaccine safety surveillance systems. JYNNEOS is not contraindicated in pregnancy or while breastfeeding, and CDC has stated such in the occupational recommendations that were published about the use of JYNNEOS in 2022. After discussing this with the American College of Obstetricians and Gynecologists (ACOG) WG member and others, the decision was made for the clinical guidance to be, “Pregnant or breastfeeding persons at risk for Mpox may receive the JYNNEOS vaccine before an exposure.”

Again, this is referring to those people with the risk factors, not all pregnant or breastfeeding persons.

Moving to HCP, healthcare-associated Mpox infections have been rare and typically associated with sharps injuries or exposure in the absence of personal protective equipment (PPE). There have been very few cases, as discussed during the June 2023 ACIP meeting, especially among people using the PPE that they should be using. HCP at risk for Mpox because of the risk factors described (e.g., MSM with more than one sexual partner) should be vaccinated. However, this recommendation is not because of occupational risk. The guidance is that JYNNEOS is not recommended as a routine vaccination for healthcare personnel unless sexual risk factors are present."

There is a known risk for myopericarditis after ACAM2000, which is the other orthopoxvirus vaccine used in the US. Given that the mechanism is unknown, a theoretical risk with JYNNEOS has not been ruled out yet. There is a known risk after COVID-19 vaccines, particularly in adolescent and young adult males. That is the reason that the CDC websites for COVID-19 and Mpox vaccines provide interim guidance for co-administration of JYNNEOS with COVID-19 vaccines. CDC's interim guidance in the clinical considerations for coadministration of JYNNEOS vaccine with COVID-19 vaccines[25] states that, "There is no required minimum interval between receiving any COVID-19 vaccine and JYNNEOS vaccine (e.g., for Mpox prevention), regardless of which vaccine is administered first. People, particularly adolescent and young adult males, who are recommended to receive both vaccines might consider waiting 4 weeks between vaccines. This is because of the observed risk for myocarditis and pericarditis after receipt of ACAM2000 orthopoxvirus vaccine and COVID-19 vaccines and the hypothetical risk for myocarditis and pericarditis after the JYNNEOS vaccine. However, if a patient's risk for Mpox or severe disease due to COVID-19 is increased, administration of JYNNEOS and COVID-19 vaccines should not be delayed."

The WG talked about the JYNNEOS vaccine and immunoglobulin products in detail, and it was presented to ACIP during the June 2023 meeting. The reason this came up is because technically, the JYNNEOS vaccine is a live virus vaccine. However, it is a non-replicating virus vaccine. The WG determined that there are no precautions necessary if JYNNEOS is administered in close temporal proximity to intravenous immunoglobulin (IVIG). With regards to vaccinia immunoglobulin intravenous (VIGIV), which is a product that basically is pooled from persons who are vaccinated with ACAM2000, it perhaps could interfere with the immune response to the JYNNEOS vaccine. Ideally, administration of JYNNEOS should be delayed if VIGIV was recently administered. The reason that VIGIV is probably administered to a patient is a severe manifestation of Mpox. At this time, those are persons for whom vaccination would not be recommended since they have acquired Mpox. Currently, the recommendation is that people who have recovered from Mpox do not need to be vaccinated. Therefore, this is not likely to come up very often if at all. If it does come up, a public health consultation should be obtained for case-specific guidance.

As far as contraindications and precautions, JYNNEOS was licensed for prevention of smallpox in addition to prevention of Mpox.[26] Because smallpox is nearly always life-threatening, there are no absolute contraindications for the use of JYNNEOS to prevent smallpox. That is why the package insert does not list an absolute contraindication. However, the considerations may be different for Mpox. Consistent with contraindications and ACIP routine schedules, the WG

[25] https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html
[26] https://www.fda.gov/media/131078/download

proposed stating that JYNNEOS is contraindicated in patients with severe allergic reaction, (e.g., anaphylaxis) after a previous dose of the vaccine or to a vaccine component. Under precautions, the WG proposed making a statement similar to what is listed for pretty much all vaccines, “Precautions: Moderate or severe acute illness, with or without fever.”

For other administration guidance, the WG wanted to stress that completion of the 2-dose series should be encouraged. If there is one message that hopefully comes from this meeting, it is that Mpox cases are still occurring, and this is not over. If people got only 1 dose or did not seek the vaccine because there was not as much availability as last year, the hope is that they will reach out now and get vaccinated as much as possible. Getting the second dose into arms would be really great for those individual patients, their friends, and others. The second dose should be administered at about 28 days after the first dose. However, the second dose can still be administered even if over a year has elapsed. Restarting the series is not required and the second dose should be administered as soon as possible.

In terms of next steps, Dr. Rao explained that the Mpox WG is not going away completely. They will publish the 2 *MMWR* ACIP recommendations about the use of JYNNEOS during outbreaks and the use of JYNNEOS among persons at risk during the ongoing Mpox outbreak in 2024 because they are complementary. Once the data are available from the NIH, perhaps the WG will reconvene toward the end of 2024 and potentially will present the data to the ACIP in early 2025. If passed, the recommendation will be revisited in 2 to 3 years when more data are available about the epidemiology to help decide whether this recommendation should be continued. The WG will revisit the EtR review, epidemiology, cost-effectiveness analyses, and other data and will present that to the ACIP to determine whether this should be continued. In the interim, this recommendation would exist if it is passed. If the vaccine becomes commercialized, there would be additional tasks that would need to be addressed.

Discussion Points

Dr. Poehling expressed appreciation for the tentative timeline and the thought of continuing to evaluate the impact to make sure the recommendations are precise and are having the desired impact. She stated that one question that we focus on for safety is myopericarditis. In the doses of JYNNEOS administered in the United States, we have not seen cases of myopericarditis in VAERS or VSD, but that does not exclude it occurring rarely, is that correct?

Dr. Duffy expressed that is the correct understanding on safety for JYNNEOS.

Dr. Loehr asked if Ms. Kimak could comment on how long the manufacturer thinks it would take to commercialize this vaccine.

Lee Ann Kimak (Bavarian Nordic) indicated that Bavarian Nordic began taking steps toward commercializing the product as soon as they learned that the ACIP would be considering a recommendation. If JYNNEOS is routinely recommended for those at risk of Mpox, this would allow Bavarian Nordic to move forward with some of the steps toward commercial insurance coverage. They anticipate that it will take a number of months to negotiate these contracts and be prepared to work through all of the necessary steps with a variety of payers in terms of setting up the distribution channels to store and administer the vaccine. As with the commercial transition of the COVID vaccines, this process can take some time. However, she would not foresee it being outside of the 6- to 9-month range.

Dr. Loehr emphasized the need for a cost-benefit analysis. The ACIP basically would be voting on and approving the interim recommendation which could be extremely costly, yet they have no sense of that. He noted that while he was in favor of the recommendation based on the current status, he wanted it to be reviewed as soon as the new data become available.

Dr. Lee pointed out that all of the ACIP's recommendations are interim and could be revisited at any moment. She suggested dropping the terminology "interim recommendation" similar to what they did for pneumococcal vaccines. The ACIP does not have "strong recommendations" or "not strong recommendations." She agreed with Dr. Loehr's point about the cost-effectiveness analysis. The unusual nature by which this vaccine is coming to market makes it somewhat complicated.

As a reminder, public comment was presented prior to the votes. However, the votes were combined in this proceedings document with their respective sessions for the purpose of continuity.

Vote: Mpox Vaccine Recommendation

Agam Rao, MD (CDC/NCEZID; CAPT, US Public Health Service) presented the proposed recommendation for a vote as follows:

> ACIP recommends vaccination* with the 2-dose† JYNNEOS vaccine series for persons aged 18 years and older at risk for Mpox§
>
> *Interim recommendation that ACIP will revisit in 2-3 years
> † Dose 2 administered 28 days after dose 1
> §Persons at risk:
> - Gay, bisexual, and other men who have sex with men, transgender or nonbinary people who in the past 6 months have had one of the following:
  - A new diagnosis of ≥ 1 sexually transmitted disease
  - More than one sex partner
  - Sex at a commercial sex venue
  - Sex in association with a large public event in a geographic area where Mpox transmission is occurring
> - Sexual partners of persons with the risks described in above
> - Persons who anticipate experiencing any of the above

Motion/Vote: Mpox Vaccine Recommendation

Dr. Poehling moved to accept the Mpox vaccine recommendation language as presented, which Ms. Bahta seconded. No COIs were declared. The motion carried with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Vote: VFC Mpox Resolution

Dr. Jeanne Santoli (CDC/NCIRD) presented the VFC Mpox Resolution for the ACIP's consideration and vote. The purpose of this resolution is to add a vaccine for the prevention of Mpox to the VFC program. The eligible groups are as follows:

- ❑ Children aged 18 years of age at increased risk of Mpox, including:
  - Persons who are gay, bisexual, and other men who have sex with men, transgender or non-binary people who in the past 6 months have had:
    - At least 1 sexually transmitted disease
    - More than 1 sex partner
    - Sex at a commercial venue
    - Sex in association with a large public event in a geographic area where Mpox transmission is occurring
  - Persons who are sexual contacts of the persons described above
  - Persons who anticipate experiencing any of the situations described above

The recommended schedule and dosage intervals are 2 doses given 28 days apart. The recommended dosages refers the reader to the product package inserts. Similarly for contraindications, there is a referral to the package insert and precautions include moderate or severe acute illness with or without fever. There will be the statement referencing future published recommendations that will be incorporated by reference.

Given the discussions, the following bullets convey vaccine availability through the VFC:

- ❑ Mpox vaccines will not be available through the VFC program immediately following the passage of this resolution because they are not yet commercially available.

- ❑ At this time, Mpox vaccines remain available under the HHS Mpox Vaccination Program.

- ❑ Following the passage of this resolution, CDC will begin the steps necessary to solicit for/award contracts for Mpox vaccines.

- ❑ The timeline for availability of Mpox vaccines commercially or through the VFC program has not yet been finalized.

Discussion Points

Dr. Talbott pointed out that this vaccine is the perfect example of why a Vaccines for Adults program is needed.

Dr. Talbot made a motion to accept this language as proposed. Dr. Poehling seconded the motion.

Motion/Vote: VFC Mpox Resolution

Dr. Talbot moved to accept the VFC Resolution for the Mpox vaccine recommendation as presented, which Dr. Poehling seconded. No COIs were declared. The motion carried with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

ADULT RESPIRATORY SYNCYTIAL VIRUS (RSV) VACCINES

Introduction

Camille Kotton, MD (Chair, Adult RSV WG) introduced the Adult RSV WG. She reminded everyone that in June 2023, the ACIP voted to recommend that adults ≥60 years of age may receive a single dose of RSV vaccine using shared clinical decision-making.[27] There are 2 FDA-approved RSV vaccines, which are as follows:

- ❑ RSVPreF3 (Arexvy, GSK) is a 1-dose adjuvanted (AS01E) recombinant prefusion F protein (preF) vaccine.
- ❑ RSVpreF (Abrysvo, Pfizer) is a 1-dose recombinant preF vaccine.

Issues under discussion since the June ACIP meeting include that the WG reviewed CDC safety surveillance plans for RSV vaccination in adults ≥60 years of age. GSK has shared with the WG results of an immune-bridging study showing non-inferior humoral immune responses to RSV vaccination in immunocompetent adults 50—59 years of age compared with immunocompetent adults ≥60 years of age in whom efficacy was demonstrated. To be clear, this is just a serology study, not an efficacy study. The WG discussed the potential role of RSV vaccination in adults younger than 60 years of age, including subpopulations who would benefit most from vaccination and equity implications. The WG reviewed CDC vaccine surveillance safety plans for RSV vaccination in adults ≥60 years of age, including V-safe that has launched for older adult RSV vaccination. Dr. Kotton encouraged everyone listening to this meeting who interacts with people who are getting the adult RSV vaccine to encourage them to sign up for V-safe so that there will be as much clinical information about this vaccine as possible.

This session did not include RSV vaccine uptake data or safety surveillance data as those data were premature early into the vaccination program. Uptake and safety results will be shared during a future ACIP meeting. This session included the following topics:

[27] https://www.cdc.gov/mmwr/volumes/72/wr/mm7229a4.htm

- ❑ RSVPreF3 safety and immunogenicity in adults 50–59 years of age, compared with adults ≥60 years of age
- ❑ Epidemiology of RSV hospitalization in adults, with a focus on adults 50–59 years of age
- ❑ WG considerations regarding RSV vaccination in adults 50–59 years of age

GSK Safety and Immunogenicity in Persons 50-59 Years of Age

Susan Gerber, MD (Medical Director, Adult RSV vaccines, GSK) presented an RSVPreF3 + $AS01_E$ (AREXVY) safety and immunogenicity update in adults 50─59 years of age. Beginning with a brief background of RSV disease in this population, there is substantial RSV burden and unmet medical need in adults 50─59 years of age. Rates of RSV-associated hospitalizations and medically-attended RSV illnesses are relatively high in this age group related to the development of immunosenescence and increased incidents of certain comorbidities. Published incidence rates likely substantially underestimate RSV burden due to lack of awareness, standardized testing, and under-detection within surveillance studies. Chronic underlying medical conditions or co-morbidities that are associated with severe RSV disease such as chronic obstructive pulmonary disease (COPD), congestive heart failure, diabetes, asthma, chronic liver disease (CLD), and chronic kidney disease (CKD) are prevalent in this age group. Additionally, observed disparities by race and ethnicity are particularly pronounced with respect to hospitalization rates among middle-aged adults 50─64 years of age.

Data from the CDC surveillance platform, RSV-NET, on unadjusted RSV-associated hospitalization rates by race and ethnicity for the last 5 seasons for persons 50─64 years of age identified consistent disparities among Hispanic, American Indian/Alaska Native (AI/AN), and Black Americans as compared with White non-Hispanic Americans.[28] Along these lines, a recent presentation at IDWeek 2023 from Dr. Angela Branche and colleagues showed that young and middle-aged adults with certain underlying co-morbid conditions are at high risk for RSV-associated hospitalization, with potentially a disproportionate risk for Black and Hispanic middle-aged adults.

Based on this unmet medical need, GSK conducted a study to evaluate their RSV vaccine in immunocompetent adults 50─59 years of age.[29] The primary objective was to demonstrate the non-inferiority of the humoral immune response after RSVPreF3 + $AS01_E$ vaccine administration in adults 50─59-years of age with and without co-morbidities well-documented to be related to RSV-associated severe disease compared to older adults ≥60 years of age. GSK previously established high vaccine efficacy against symptomatic RSV illness in adults ≥60 years of age. Primary endpoints were to evaluate the non-inferiority of RSV-A and RSV-B neutralization titers at 1 month following vaccine administration for 2 adult groups 50─59 years of age, with and without co-morbidities associated with RSV lower respiratory tract disease (RSV-LRTD), as compared to adults ≥60 years of age. Success criteria is defined as the upper limit of the 2-sided 95% confidence interval for the geometric mean titer (GMT) ratio of ≤1.5 and the seroresponse rate difference of ≤10%. Additional immunogenicity endpoints will be examined at 6 and 12 months as the study continues. Frequency of CD4+ T cells were assessed in subsets of adults 50─59 years of age and ≥60 years of age to evaluate the cell-mediated immune response. Safety endpoints also were included.

[28] Graphs independently created for GSK from original data; A/PI, Asian and Pacific Islander, AI/AN, America Indian or Alaska Native; CDC, https://www.cdc.gov/rsv/research/rsv-net/dashboard.html (accessed October 2023)
[29] ClinicalTrials.gov. NCT05590403. https://www.clinicaltrials.gov/study/NCT05590403; (accessed September 2023)

The study is a randomized, placebo-controlled, observer-blind, multi-country study. Cohorts 1a and 1b were randomized 2:1 to receive vaccine or placebo. Cohort 1a are adults 50—59 years of age with co-morbidities associated with RSV-LRTD and Cohort 1b are adults 50—59 years of age without co-morbidities associated with RSV-LRTD. Cohort 2a are adults ≥60 years of age. This standard immune-bridging, non-inferiority approach has been developed to bring vaccines faster to those at high risk for severe disease, such as COVID-19 vaccines, and was developed and agreed upon in consultation with the FDA. This presentation focused on the preliminary 1-month immunogenicity and 6-month safety results. This study included participants from 8 countries; approximately 23% were from the US. Demographic and clinical characteristics were well-balanced between the vaccine and placebo groups. Of the adults ≥60 years of age, 37.7% had at least one co-morbidity associated with RSV-LRTD similar to the proportion within the pivotal efficacy trial. In total, the most common co-morbidity was diabetes and the least common was chronic liver or renal disease.

In terms of the preliminary immunogenicity results, the first co-primary endpoint was met. The neutralizing antibody responses against both RSV-A and RSV-B were non-inferior in the groups of adults 50—59 years of age with and without co-morbidities associated with RSV-LRTD, compared with those ≥60 years of age. The GMT ratio is expressed by dividing Cohort 2 (adults ≥60 years) by Cohort 1a or 1b (those with and without co-morbidities respectively). Non-inferiority was established as the upper limit of the 2-sided confidence interval for the GMT ratio being ≤1.5. In terms of the results for the other co-primary endpoint, seroresponse rate for RSV-A and RSV-B neutralizing antibodies, with respect to the same group comparisons, the difference in seroresponse rate was established by subtracting the rate for Cohort 1a or 1b from that of Cohort 2. Non-inferiority was established as the upper limit of the 2-sided confidence interval for a seroresponse rate difference ≤10%. Non-inferiority criteria were met for both cohorts of adults 50—59 years of age, for both RSV-A and RSV-B immunologic responses. Notably, a subset of study participants across these age and risk groups had CD4+ T cells measured at 1 month after vaccination or placebo. All groups who received the vaccine had an increase in CD4+ RSVPreF3-specific T cells observed at 1 month after vaccination. Increases in the adults 50—59 years of age were consistent with those observed in the adults ≥60 years of age.

Moving now to the 6-month safety results of the solicited adverse events (AEs) reported within 4 days of vaccination. There were low frequencies of Grade 3 AEs across all study groups (adults 50—59 years of age with or without co-morbidities associated with LRTD who received vaccine or placebo, and adults ≥60 years of age who received vaccine). The most frequent overall local reported AE was pain and the most frequent overall systemic AEs were fatigue, headache, and myalgia. Duration of symptoms was brief and generally did not exceed 2 to 3 days. Regarding the results of the unsolicited AEs, SAEs, fatal SAEs and potential immune-mediated disease (pMIDs), a low frequency was reported of Grade 3 events across all groups, which were unsolicited AEs within 30 days. AEs within 30 days were comparable across all groups and there was a short median duration for most AEs. Safety data were consistent with results from the pivotal Phase 3 trial.

To summarize, the study results presented during this session met the non-inferiority success criteria in adults 50—59 years of age with and without co-morbidities associated with an increased risk of RSV-LRTD compared with adults ≥60 years of age. Although there is no established immunologic correlate of protection against RSV, the robust humoral and cellular immune-mediated response observed among adults ≥60 years of age and older after vaccination has been associated with high efficacy against symptomatic disease in this group. Thus, looking at the humoral response in adults 50—59 years of age with and without

comorbidities compared to adults ≥60 years of age, efficacy can be inferred. The safety profile for adults 50—59 years of age with and without comorbidities is consistent with those in adults ≥60 years of age.

Now to provide a safety update on AREXVY starting with an important update on reported cases of acute disseminated encephalomyelitis (ADEM) from one of GSK's earlier influenza co-administration studies[30] and information on post-authorization safety. After review of additional clinical data and re-adjudication of the diagnoses by the site investigator, the number of ADEM reports in the GSK safety database is now zero. GSK is pleased to report that over 2 million doses of AREXVY have been administered as of October 13, 2023 in retail settings in the US. This does not account for doses administered in non-retail settings and outside of the US and therefore is an under-estimate of doses administered globally to date. Reported AEs reflect the known safety profile of AREXVY, and GSK will continue to monitor the safety of this vaccine using all of the available surveillance systems.

In closing, severe RSV disease among adults 50—59 years of age with certain co-morbidities presents a significant unmet medical need. Study RSV-OA=ADJ-018 provides data to address this medical need and shows comparable immunogenicity to that in adults ≥60 years of age, suggesting efficacy will be similar. AREXVY is well-tolerated with a favorable safety profile in adults 50—59 years of age. GSK is committed to protecting individuals at risk for severe RSV disease, ensuring that all adult populations have access and improving health equity. As such and based on these results, GSK will be seeking an indication with the FDA.

Discussion Points

Dr. Talbot applauded GSK for enrolling people with co-morbid conditions and said it was a shame that that was not done to the same extent for adults ≥60 years of age. The number of co-morbid conditions among the enrolled adults ≥60 years of age was much lower than among the adults 50—59 years of age. The non-inferiority is an interesting discussion because it is a pre-specified number, which might have meaning if there was a correlate of immunity—but there is not. It appeared that compared with the participants with co-morbidity, there was a lower response in those without co-morbidities. That concerns her since there is not an immunologic correlate of protection. She also expressed frustration because there was no mention of those with immune compromise. Those would have been nice numbers to see, and it would have been more meaningful to conduct an RCT with efficacy as an endpoint because that population has such a high risk of RSV that it would be helpful know if the vaccine works in this population. These are not cheap vaccines. Methods are needed to protect people, and it is important to know if they work in the populations who are at highest risk. While she was glad GSK finally enrolled patients with co-morbid conditions, she was very disappointed that there was not an RCT. There were no immunocompromised persons enrolled. There was no data on what those co-morbid conditions were in the 1b cohort, because if it is hypertension, that does not really mean very much. She expressed her hope that in the future, there would be some RCT data with efficacy.

Dr. Gerber recapped the inclusion criteria in this trial for adults 50—59 years of age with co-morbidities, pointing out that there were criteria for chronic pulmonary diseases, chronic cardiovascular diseases, and endocrine and other diseases. They did enroll people with co-morbidities in the pivotal efficacy trial of approximately 39%. The proportion of people with co-morbidities was 37.7% in this trial, which is similar to the 39% in the pivotal efficacy trial.

[30] https://clinicaltrials.gov/study/NCT04841577

Dr. Leonard Friedland from GSK added that although they did not present the values for the GMTs for the groups of adults 50–59 years of age with and without underlying comorbidities, indeed the numerical values of the GMTs and those with the underlying co-morbidities was actually numerically higher than the group who did not have co-morbidities. While there was no formal statistical testing comparing those 2 groups, the GMTs certainly were somewhat numerically higher in those with the underlying co-morbidities. Importantly, non-inferiority was met for both groups compared to adults ≥60 years of age in whom efficacy has been demonstrated. In terms of immunocompromised patients, GSK is currently enrolling a study that is on clinicaltrials.gov in adults ≥18 years of age who have solid organ transplants (SOT) for kidney disease and lung transplants.

Dr. Talbot emphasized that it would be very helpful for the ACIP to see those data.

Dr. Kotton asked whether GSK is planning any trials, RCTs, or other studies that would show any type of clinical protection in adults with immune compromise.

Dr. Friedland said that the study he mentioned is an immunogenicity and safety study.

Referring to Slide 19, Dr. Poehling requested additional information on any potential immune mediated diseases (pIMDs) observed in this study.

Dr. Peggy Webster with GSK Vaccine Safety responded that the rates of pIMDs were extremely low in all of the groups that were evaluated. There were 8 in total, which is less than 1% across the study arms, of which only 3 were serious. There was no clustering of the specific events that were described. Among the 3 serious pIMDs, there was 1 case of pericarditis, 1 case of gouty arthritis, and 1 event of cold-type hemolytic anemia. There were no cases of Guillain-Barre syndrome (GBS) in this study.

Dr. Sanchez asked whether the 3 or 4 unconfirmed cases of ADEM were from the pivotal phase 3 RCT. Among the co-morbidity patients, he asked whether GSK has data on those patients in terms of whether they were taking immunosuppressive medications that may have affected immunogenicity.

Dr. Webster from GSK stated that those ADEM cases were from one of the original trials that was evaluating AREXVY given in co-administration with influenza vaccine. There were 2 cases of ADEM initially reported that have now been reclassified as the diagnoses were clarified as hypoglycemia plus dementia and the other as cerebrovascular accident or a stroke. In terms of data on whether the co-morbidity patients were taking immunosuppressive medications, the exclusion criteria included immunosuppressive or immunodeficient conditions and exclusion of participants who may have been obtaining chronic administration of immune modifying drugs for at least 14 consecutive days. Therefore, those particular patients would have been excluded from this immunogenicity analysis.

Dr. Kimberlin (AAP Red Book) asked whether there are any data on duration of immunologic benefit and potentially an impact of a second dose X number of years down the road. His thinking was that if there is 1 shot with 1 dose and that is it, a different conclusion might be reached about when that single dose should be administered age-wise versus if it could be re-administered every 5 years, for example.

Dr. Friedland with GSK responded that they have the data presented during the June 2023 ACIP meeting showing that 1 dose of AREXVY provides durable efficacy against RSV-LRTD for 2 full RSV seasons. That is protection against symptomatic RSV disease and also in adults with underlying co-morbidities. The plan is to continue to follow-up with patients from the pivotal efficacy study for a third season and to collect data from an additional Phase 3 study that is going to assess long-term immunogenicity and immune response following different revaccination schedules. The totality of this collection of data will then guide GSK's next actions to help inform the most optimal timing for revaccination.

Dr. Long noted that there appeared to be about 720 adults who received this vaccine in this trial, which is an extremely small number. While they are relieved that there were no neuroinflammatory events, that does not say too much. She also asked whether the FDA has continued to include these 3 inflammatory neurologic event cases that GSK thought had different explanations.

Dr. Webster with GSK Vaccine Safety responded that the 2 initially reported cases of ADEM plus the initially reported case of GBS do continue to be reflected in GSK's product information.

Dr. Long pointed out that one other thing that was very confusing to the WG and also would be to the ACIP was that the method of presentation of non-inferiority is the opposite direction than they are used to. The way that it was calculated by GSK and presented, numbers <1 would indicate on the way to superiority rather than inferiority. The WG and the ACIP are used to thinking of less good as <1, which is confusing. She also noted that one of the important comparisons is the study results was among adults 50—59 years of age versus ≥60 years of age. She asked for more information about that group.

Dr. Poehling requested a reminder of the breakdown among adults ≥60 years of age.

Referring to Slide 11, Dr. Gerber indicated that among the adults ≥60 years of age, slightly over half were 60—69 years of age, 34% were 70—79 years of age, and 12.8% were ≥80 years of age.

Dr. Poehling emphasized for everyone listening that these studies are difficult and require a lot of work. At the same time, they learned through COVID that it is possible to enroll diverse persons as GSK demonstrated with their co-morbidities. Dr. Gerber began the conversation talking about the disparities. It is really important to understand the racial and ethnic disparities, which are 3% for Black and 0.6% for AI/AN populations. She stressed the importance of paying close attention to this to ensure that the data reflect the US population.

Dr. Friedland from GSK noted that the results shown included the 8 countries in which all subjects are enrolled. GSK would be happy to follow up with the US demographics in the future. Regarding the observation about the way the non-inferiority ratios were shown, the statistical success criteria for non-inferiority that is commonly used for regulatory purposes, and happens to be the standard across GSK's analysis plans, is a 1.5-fold non-inferiority ratio for the GMTs. Mathematically, the numerator and denominator can be inverted. In that case, the success criteria would be a 0.67 lower limit non-inferiority margin. If the ratio is inverted as suggested, non-inferiority is met for the GMT ratios as it was when shown the way GSK showed it.

Regarding the safety update, Dr. Loehr recalled GSK stated that with 2.2 million doses there were no neuroinflammatory events. He requested confirmation that his recollection was correct and to ask what that was based on, given that there should be some neuroinflammatory events out of 2.2 million people.

Dr. Webster with GSK Vaccine Safety confirmed more than 2.1 million doses of AREXVY have been administered in the US. They recently had a conversation with the CDC in which they were informed of cases of neuroinflammatory-type events. GSK has very little information about these reports at this time, so she could not comment further on this.

Dr. Talbot asked what the asterisk meant beside the number of doses.

Dr. Friedland GSK added that those are doses put into arms as far as GSK knows from their data in the retail setting. As mentioned, this does not include non-retail settings or outside of the US, so that is an under-estimation of the number of people who have received the vaccine in their arm.

Recalling Dr. Kimberlin's point, Dr. Kotton emphasized that there are no data showing a booster effect. She asked whether this would be a 1 and done vaccine for adults 50─59 years of age. She worries that without data supporting long-term immunogenicity, they could be doing harm by giving this vaccine earlier than when this age group might benefit from it. Perhaps they should pause and wait for some data on boosting. If there will not be boosting, she wondered what would be done about that situation. In terms of the patients for whom she cares, she was thinking about aiming this vaccine for their more vulnerable period rather than just in their 50s with co-morbidities because her hope is that they would live optimally 1, 2, 3 more decades after that, during which time they may not have RSV protection. She remains quite concerned about that. Similarly, she noted that Dr. Poehling's point was very good about knowing that people of color develop severe, hospitalized RSV much younger than Whites and Asians. It would seem that in conducting this trial, there would have been a focus on that high-risk population. Nonetheless, it looks like it was over 80% White. That is not helpful information in terms of trying to figure out who should receive this vaccine.

Dr. Friedland indicated that GSK would come back to the ACIP through the WG with the demographics breakdown and those enrolled in the US. With regard to durability of the vaccine, what is known currently is that 1 dose for AREXVY provides protection against severe RSV-LRTD and LRTD in those with underlying co-morbidities for at least 2 full RSV seasons. GSK continues to gather data through all of its clinical trials. The collection of these data will continue to inform the most optimal timing for revaccination. During this discussion, his team was able to pull up the percentage of people who were Black in the clinical study presented during this session, which was 14.8% of those enrolled in the US.

Dr. Friedland indicated that this is fairly standard for their clinical trials and fairly representative of what they have been able to enroll in their clinical trials in the US. It would seem that if this is an at-risk population, they would want more data on the at-risk population.

Dr. Lee stressed that this was a plea for addressing health equity at the clinical trial stage and especially because some of the ACIP's recommendations are focused on mitigating existing disparities. The point that the ACIP would like to make to manufacturers is that studies should be more reflective of the proportion of the US population that represents Black, Hispanic, and other race/ethnicity groups. The more that the ACIP can consider recommendations with an equity lens and provide additional augmented recommendations, the better.

Epidemiology of RSV in Adults

Dr. Monica Patton (CDC/NCIRD) provided an update on the epidemiology of RSV in adults in RSV-NET with a focus on adults 50—59 years of age. RSV-NET is a population-based hospitalization surveillance platform of RSV hospitalization in adults. RSV-NET is 1 of the 3 platforms that comprise the RESP-NET Surveillance System. COVID-NET and FluSurv-NET are the other two RESP-NET platforms. These platforms use similar surveillance methods that are used to provide comparisons between RSV-, COVID-, and influenza-associated hospitalizations. As a reminder, RSV-NET conducts active population-based surveillance of laboratory-confirmed RSV-associated hospitalizations from more than 300 acute care hospitals in 58 counties across 12 states. The RSV-NET catchment area includes about 8.6% of the US population. Hospitalizations reported to RSV-NET include all of those where a positive RSV test result was reported within 14 days prior to or during hospitalization. Testing for RSV is driven by clinical judgment and facility policies. Data on rates and basic demographic data are collected on all patients and clinical data are collected from an age and site-stratified random sample.

While the focus of this presentation was on the epidemiology of RSV-associated hospitalizations among adults age 50—59 years of age, data from other age groups was presented including persons 18—49 years of age (the youngest adult age group), 60—64 years of age (60 is the youngest age recommended for RSV vaccination based on shared clinical decision-making in the US), 65—74 years of age (65 is the common definition of older adults and is used for a number of other vaccine recommendations), and ≥75 years of age (75 is the age recommended for RSV vaccine by the UK's advisory committee).[31]

The focus of this presentation was on the epidemiology of RSV-associated hospitalizations among adults 50—59 years of age in comparison to other adult age groups, including reviewing demographics of persons hospitalized with laboratory-confirmed RSV; rates of RSV-associated hospitalizations; underlying medical conditions amongst hospitalized adults; and severe outcomes among hospitalized adults, including intensive care unit (ICU) admission, receipt of mechanical ventilation, and in-hospital death. Overall, during the 9 seasons between 2014—2015 and the most recent 2022—2023 season, there were 17,847 RSV-associated hospitalizations captured among adults ≥18 years of age. Among those hospitalizations, approximately 14% occurred among adults aged 50—59 years of age. In total, 62% occurred among White persons, 20% among Black persons, 8% among Hispanic persons, 6% among Asian or Pacific Islander persons, and 0.5% among AI/AN persons.

To review evidence related to RSV-associated risks by age, rates of RSV-associated hospitalization among US adults stratified by 5-year age groups estimated from RSV-NET during 5 RSV seasons before the COVID-19 pandemic were shared; rates were adjusted for frequency of RSV testing each season, as well as the sensitivity of the RSV diagnostic test used. RSV-associated hospitalization rates increase with increasing age and were lowest among adults 18—49 years of age and were substantially higher among adults ≥85 years of age as compared with other age groups. RSV-associated hospitalization rates ranged from 23 to 42 per 100,000 population among adults 50—54 years of age and from 26—59 per 100,000 population among adults 55—59 years of age.

[31] https://www.gov.uk/government/publications/rsv-immunisation-programme-jcvi-advice-7-june-2023/respiratory-syncytial-virus-rsv-immunisation-programme-for-infants-and-older-adults-jcvi-full-statement-11-september-202

RSV-associated hospitalizations from the most current 2022–2023 season have not been adjusted for RSV testing practices and underestimate the actual rates of RSV-associated hospitalizations, given that not all people hospitalized with respiratory illness are tested for RSV and clinician-driven testing practices may differ based on patient characteristics such as age or disease severity. In these unadjusted data, rates of RSV-associated hospitalizations also increased with increasing age.

In RSV-NET, among adults hospitalized with RSV, almost all or 94% had at least 1 underlying medical condition and more than 60% of adults had 3 or more conditions. Cardiovascular disease (CVD), obesity, diabetes, COPD, and heart failure were the most frequent underlying medical conditions among adults hospitalized with laboratory-confirmed RSV. It is important to note that these conditions occurred among patients who had clinician-directed testing and that patients with underlying medical conditions may have been more likely to be tested for RSV than those who did not have underlying conditions. However, even with this consideration, these data suggests that the proportion of patients hospitalized for RSV who have comorbid conditions is very high.

Considering the most frequent underlying medical conditions among adults hospitalized with laboratory-confirmed RSV by age group, approximately 14% of adults 18–49 years of age hospitalized with RSV had no underlying medical conditions compared to only 4% of adults ≥50 years of age. Conversely, 86% of adults 18–49 years of age with RSV-associated hospitalizations had at least 1 underlying medical condition and almost all adults ≥50 years of age had at least 1 underlying medical condition. When the number of medical conditions are further quantified, the proportion of patients with only 1 or 2 medical conditions decreases with increasing age. Among adults 18–49 years of age hospitalized with RSV, 44% percent had only 1 or 2 underlying medical conditions compared to 38% of adults 50–59 years of age and only 26% of adults ≥ 75 years of age. Conversely, the proportion of patients with 3 or more underlying medical conditions increases with increasing age. Among adults 18–49 years of age hospitalized with RSV, 42% had 3 or more medical conditions, while 58% of adults 50–59 years of age and nearly 70% of adults ≥65 years of age had 3 or more medical conditions.

Looking at the most prevalent medical conditions by age group, obesity is the most prevalent underlying medical condition for adults 18–49 and 50–59 years of age. For adults ≥60 years of age, cardiovascular disease (CVD) is the most prevalent underlying medical condition. The second most prevalent underlying conditions among adults hospitalized with RSV was asthma for adults 18–49 years of age, CVD for those 50–59 years of age, obesity for those 60–64 years of age, and heart failure for those 65–74 years of age and ≥75 years of age. The third most prevalent underlying medical condition for adults hospitalized with RSV were immunocompromising conditions for adults 18–49 years of age, diabetes for adults 50–59 years of age and 65–74 years of age, COPD for adults 60–64 years of age, and COPD and CKD for persons ≥75 years of age. These data suggests that underlying conditions that may put adults at increased risk for hospitalization for RSV differ by age, with different profiles occurring among the youngest adults 18–49 years of age and the oldest group who are ≥75 years of age.

Looking at the prevalence of certain medical conditions in the general population, as captured from the National Center for Health Statistics (NCHS), compared to the prevalence of those same conditions among patients hospitalized with laboratory-confirmed RSV, among adults 50–64 years of age and ≥65 years of age, shows that coronary artery disease, COPD, diabetes, and asthma are over-represented among hospitalized adults in RSV-NET compared to the prevalence in the general population. Those conditions are 2.7 to 5.7 times more prevalent among adults 50–64 years of age hospitalized with RSV compared to adults the same

age in the general population. These conditions are 1.6 to 3.4 times more prevalent among adults ≥65 years of age hospitalized with RSV compared to adults of the same age in the general population. Of note, obesity appears to have similar prevalence among adults hospitalized with RSV and among adults in the general population.

Based on a comparison of only adults 50–59 years of age with RSV-associated hospitalization and those who were admitted to the ICU, most underlying medical conditions were more prevalent or increased among adults admitted to the ICU compared to those hospitalized but without ICU admission. For example, CVD occurred among 43% of adults 50–59 years of age admitted to the hospital but occurred among 49% of adults 50-59 admitted to the ICU. This made it the second most common underlying medical condition among hospitalized adults 50–59 years of age but the most common underlying condition among those 50-59 admitted to the ICU. Similarly, heart failure and CKD were more prevalent among ICU patients than hospitalized patients in general. Conversely, the 5 medical conditions that demonstrated the same or decreased prevalence among adults 50–59 years of age admitted to the ICU compared to those who were hospitalized included obesity, asthma, chronic metabolic disease, blood disorders, and autoimmune disease.

Among all adults hospitalized with RSV, a large proportion are severely ill as measured by the proportion admitted to the ICU, the proportion who received mechanical ventilation, and the proportion who died in hospital. In RSV-NET data from the most recent season, about 21% of hospitalized adults 50–59 years of age were admitted to the ICU. Approximately 10% received mechanical ventilation and 3% died while in the hospital. Across all age groups, the mortality was highest in those 75 years and older at 6%. However, the proportions admitted to the ICU were similar across all age groups, ranging from 15% to 21%. Younger adults hospitalized with RSV experienced similar rates of severe outcomes as older adults.

It is possible to compare data from adults hospitalized with laboratory-confirmed RSV, influenza, and COVID-19 using data from RSV-NET, FluSurv-NET, and COVID-NET for the most recent 2022–2023 surveillance season. Active surveillance for FluSurv-NET for the most recent season occurred during a typical respiratory virus surveillance season of October through April, whereas both RSV-NET and COVID-NET surveillance occurred year-round. The proportion of adults with RSV, influenza, and COVID-19 associated hospitalizations who were admitted to the ICU by age group were equivalent across the three pathogens, indicating that RSV infection in adults may be as severe as influenza and COVID-19 infections in adults. These proportions only include ICU admissions amongst adults hospitalized with laboratory-confirmed RSV, influenza, or COVID-19 and do not take into account RSV testing practices or vaccination or treatment status of patients. More severely ill patients may be more likely to have been tested for RSV, influenza, or COVID, which may overestimate the proportion of hospitalized patients who were admitted to the ICU. Additionally, these data do not take into consideration a patient's vaccination status. Recent publications have demonstrated that patients vaccinated for influenza, or COVID-19 are less likely to require ICU admission.

Looking at comparisons of in-hospital deaths among adults hospitalized with laboratory-confirmed RSV, influenza, and COVID-19, using data from RSV-NET, FluSurv-NET, and COVID-NET for the most recent season, there are similar patterns. The proportion of adults of all ages hospitalized with laboratory-confirmed RSV, influenza, or COVID-19, who died in the hospital were similar across the 3 pathogens. Again, this indicates that RSV disease in adults is as severe as that of influenza and COVID-19 disease in adults.

Regarding the distribution of all adult RSV-associated hospitalizations by age group for the most recent season, hospitalizations among adults 50─59 years of age comprised 12% of all hospitalizations captured in RSV-NET during the most recent season. Similarly, when looking at the distribution of all adult RSV-associated ICU admissions by age group, ICU admissions among adults 50─59 years of age comprised 14% of all ICU admissions captured in RSV-NET. Adults 50─59 years of age comprise 22% of all hospitalized adults who required mechanical ventilation in the most recent season. Adults 50─59 years of age comprise 9% of all adults in hospital deaths for the most recent season.

Turning now to RSV-associated hospitalizations by race and ethnicity, the median age of White patients and Asian or Pacific Islander patients (73 years) was higher than the median age among hospitalizations among patients who are Black (62 years) or Hispanic (62 years), or American Indian or Alaska Native (64 years). The proportion of hospitalized adults whose race was reported as Hispanic or Black decreased with increasing age. Black adults accounted for 29% of hospitalized adults 18─49 years of age and 7% of those ≥75 years or older. Hispanic adults represented 18% of hospitalized adults 18─49 years of age but only 5% of those ≥75 or older. Similarly, the proportion of Black adults with RSV-associated hospitalizations who were admitted to the ICU decreased with increasing age. Black adults accounted for 39% of adults 18─49 years of age admitted to the ICU and 9% of those ≥75 years or older admitted to the ICU. This likely reflects different age distributions and life expectancy by race and ethnicity within the catchment population, as well as potentially higher risk for hospitalization among Black and Hispanic persons at younger ages resulting from racial and ethnic disparities driven by underlying medical conditions, access to medical care, and socioeconomic status.

Reviewing rate ratios of RSV-associated hospitalization rates stratified by race and ethnicity among each age group, rate ratios are calculated by dividing the hospitalization rate of one group by the hospitalization rate of a reference group in order to assess the magnitude of difference between the 2 rates. For these data, White adults serve as the reference group. Rate ratios that approach 1 have hospitalization rates that are about the same as the reference group. Rate ratios >1 indicate that the rates are that many times higher than the reference group, while rate ratios <1 indicate rates that are that many times lower than the reference group. For each group, the rate ratios data were presented as the average rate ratio across 4 pre-pandemic RSV seasons from 2016─2017 to 2019─2020. RSV hospitalization rates were adjusted for frequency of RSV testing practices each season, as well as for the sensitivity of the RSV diagnostic tests used. Across all age groups, hospitalization rate ratios for Hispanic adults were close to 1, indicating that laboratory-confirmed RSV hospitalization rates among Hispanic adults across all age groups were similar to those among White adults of similar ages. Across all age groups, hospitalization rate ratios for Asian or Pacific Islander adults were less than or close to 1, indicating that laboratory-confirmed RSV hospitalization rates among Asian or Pacific Islander adults were similar to or slightly less than hospitalization rates among White adults of the same ages.

Among Black adults 18─49 years of age, hospitalization rate ratios ranged from 1.5 to 2, indicating that laboratory-confirmed RSV hospitalization rates among Black adults 18─49 years of age were 1.5 to 2 times higher than hospitalization rates among White adults of the same age. Among Black adults age 50─59 years of age, hospitalization rate ratios ranged from 1.7 to 2.4, indicating that laboratory-confirmed RSV hospitalization rates among Black adults age 50─59 years of age were 1.7 to 2.4 times higher than those among White adults of the same age. As age increases, hospitalization rate ratios for Black persons moves closer to 1, indicating similar hospitalization rates between older Black and White adults. Similar to the patterns seen among Black adults, hospitalization rate ratios among American Indian/Alaska Native adults are

2.5 to 3.9 for adults 18–49 years of age and 1.9 to 3.3 for adults 50–59 years of age, indicating that laboratory-confirmed RSV hospitalization rates among younger American Indian/Alaska Native adults were approximately 2 to 4 times higher than hospitalization rates among White adults of the same age. As age increases, hospitalization rate ratios for American Indian/Alaska Native persons move closer to 1, indicating similar rates between older American Indian/Alaska Native and White adults.

Discussion Points

Dr. Poehling said she appreciated and recognized how hard it is to get hospitalization data on adults. She asked what percentage of the adults in RSV-NET are tested during hospitalization with respiratory illness.

Dr. Patton indicated that for the first few seasons she showed on Slide 6 were adjusted for the persons who are tested for RSV, which is done by collecting all RSV tests that were performed in those hospitals. That is the reason those data were shown only for the pre-pandemic seasons, because those are the only years they have those data to be able to adjust the rates for RSV testing practices.

Referring to Slide 23, Dr. Brooks noted that they have the hospitalization rates and that it was nice to know what 2 of the 3 were when there were no vaccines and now there are vaccines. While the tendency is to think of COVID as having a higher level of morbidity and mortality, this slide showing that RSV, influenza, and COVID are similar was very compelling. Some of it may be due to the high vaccination rate and prior infection rate of COVID. He recalled that African Americans crossed to <0 in terms of the relative rate compared with White adults with increasing age and wondered if some of that actually had to do with life expectancy. African Americans have a lower life expectancy, so there may be a lower percentage in the population who many be alive to get RSV moving into the group of adults ≥75 years of age.

Dr. Patton agreed that definitely life expectancy could have something to do with it. As age increases, the numbers become lower and could play a role in that.

Dr. Long commented that as they are thinking about how to target use of vaccine in younger people, they do not want to misunderstand any of these findings. Consideration needs to be given to whether racial characteristic are a marker of underlying conditions or a marker for how people live and their exposures and whether there is any way to tease that apart. They would not want to say that this vaccine should be targeted to Black persons if any other group who had similar underlying conditions and would have similar rates of hospitalization and severe disease. She wondered if it would be possible to separate any of these things to see if there is residual risk associated with race that still might be a marker, not for racial predisposition to severe RSV, but the likelihood that they would be exposed to small children, be crowded, or have pollution in their environment, et cetera.

Dr. Patton indicated that they do not have those data at this time. One thing they can do in RSV-NET is look at underlying medical conditions by age and by race, though she did not present that during this session. Some of the increased rates among certain populations may be due to increased numbers of medical conditions. They can put that together to share with the WG.

Dr. Loehr observed that Slide 23 had the percentages for RSV, influenza, and COVID. He asked for clarity about whether that meant that they were admitted to the ICU and they had a positive RSV test, but not influenza or COVID, or if there was a chance that they might have had 2 of the 3. That would change his perspective.

Dr. Patton clarified that there were not a lot of co-infections in any of the three platforms, although the numbers certainly could include a small number of co-infections. Importantly, this does not include vaccination status, which is likely a bigger factor impacting the relative severity of hospitalizations with the three pathogens. It may be that some patients were not admitted to the ICU because they were vaccinated against COVID-19 or influenza.

Dr. Talbot said she thought that adults 50–59 years of age in the ICU are more likely to get tested for RSV than on the wards. Patients who are stable on the wards would have less of a work-up than those who are admitted to the ICU. There may be bias of increased testing in the ICU. She still thinks RSV is an incredibly severe disease that puts many people in the ICU. Referring to Slide 8, she pointed out that the people with co-morbid conditions are not the ones enrolled in clinical trials in older adults, and emphasized that it is critically important to start mirroring the population who gets sick. Referring to Slide 18, in terms of potentially making risk-based recommendations among adults 50–59 years of age, these are the people on whom they need data. It is incredibly helpful when enrollment looks like the population for whom they want to target the vaccine. It results in much greater confidence in use and spending the money. To put it in a pediatrician's terms, it is like testing a vaccine in a 5-year-old and then using it in infants. It is critically important not only to have vaccines for adults, but also to test them in the adults for whom they are needed and indicated.

Dr. Daley asked what percentage of those with chronic medical conditions have obesity and what the WG's broader interpretation was of the ability to identify those who are at increased risk of RSV based on co-morbidity.

Dr. Patton indicated that they could remove obesity from the list of co-morbidities and provide those data to the WG if that would provide some clarification.

Dr. Daley clarified that the reason he mentioned obesity specifically was because it was the most prevalent condition.

Dr. Patton noted that one thing they talked about in the WG was that obviously these are among people who are hospitalized for RSV and not rates among all adults with specific risk conditions. RSV-NET is working on this type of analysis.

WG Interpretation and ACIP Discussion

Dr. Amadea Britton (CDC/NCIRD) reviewed the current recommendation for use of RSV vaccines in adults age ≥60 years of age; summarized the WG's interpretation of the safety and immunogenicity data GSK presented earlier on their RSVPreF3 vaccine in adults 50–59 years of age; and shared the WG's preliminary interpretation on the use of RSV vaccines in adults 50–59 years of age and upcoming policy decisions. She noted that she would not be presenting any data on initial estimates of RSV vaccine uptake or post-marketing safety surveillance data, given that limited data have been accrued this early post-recommendation. CDC recognizes the critical nature of these data and will work to publicly share updates as soon as accurate estimates are available.

Beginning with a brief overview of the current recommendation for use of RSV vaccines in adults ≥60 years of age, ACIP and CDC recommended the first 2 RSV vaccines for prevention of symptomatic LRTD in older adults, RSVPreF3 (AREXVY) made by GSK and RSV-PreF (ABRYSVO) made by Pfizer, in June 2023.[32] In making the decision to recommend RSV vaccines for adults ≥60 years of age, the WG and ACIP reviewed data from large Phase 3 clinical trials for both products. In the trials, both RSV vaccines demonstrated significant efficacy against symptomatic RSV associated LRTD among adults ≥60 years of age over at least 2 seasons. However, these trials were underpowered to show efficacy in subpopulations at the highest risk and against RSV hospitalization. From these efficacy results, acknowledging the limitations, the WG and ACIP determined that RSV vaccination has the potential to prevent considerable morbidity from RSV disease in older adults.

As part of WG and ACIP deliberations, data were reviewed on 6 cases of inflammatory neurologic events, including GBS.[33] There were 3 cases in GSK's clinical trials and 3 cases in Pfizer's clinical trials. Of note, 2 of the 3 cases in GSK's trials were reported as ADEM in participants who simultaneously received RSVPreF3 vaccine and standard dose seasonal influenza vaccine. Since FDA licensure, the site investigator who initially reported the cases has revised the diagnosis in both cases from ADEM to hypoglycemia and dementia and from ADEM to stroke. FDA's package insert for RSVPreF3 vaccine continues to list these cases as SAEs. In regard to Dr. Sanchez's question earlier, Dr. Britton noted that the 3 cases were the same 3 cases they have been talking about all along from across all clinical trials. It was only in the GSK co-administration trial that these cases were observed—not the pivotal Phase 3 efficacy trial. The Pfizer cases were observed in their pivotal Phase 3 efficacy trial. Again, these are the same 3 for Pfizer that have been discussed all along. Additionally, the WG noted there was an imbalance in the small number of atrial fibrillation events recorded within 1-month post-vaccination in each of the Phase 3 trials. Due to the small number events, it is unknown at this time whether these events occurred by chance or whether RSV vaccination increases the risk of these events.

During the June 2023 ACIP meeting,[34] the WG proposed for ACIP's consideration a universal recommendation for the use of RSV vaccines in adults ≥65 years of age with shared clinical decision-making in adults 60–64 years of age. Although this was the WG's majority opinion at the time, there was not a unanimous recommendation. During ACIP deliberations, voting members weighed the potential significant public health benefit of the vaccine, especially among those at increased risk with the existence of a potential safety signal. An amendment was proposed and accepted that all adults ages ≥60 years of age and older, including adults 60–64 years of age and those ≥65 years of age may receive a single dose of RSV vaccine using shared clinical decision-making. The shared clinical decision-making recommendation was intended to allow flexibility for providers and patients to consider individual risk for RSV disease and target vaccination to those most likely to benefit. In the supporting clinical considerations in *MMWR* for the recommendation, a number of conditions that increase risk of severe RSV disease were highlighted, including lung disease, CVD disease, and moderate or severe immune compromise. These were intended to assist providers in assessing a patients' risk of severe RSV disease.[35] Other factors associated with increased risk also were highlighted, including residence in a nursing home or other long-term care facility (LTCF), frailty, and advanced age.

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[32] https://www.cdc.gov/mmwr/volumes/72/wr/mm7229a4.htm
[33] https://www.cdc.gov/mmwr/volumes/72/wr/mm7229a4.htm
[34] ACIP Adult RSV Session. June 21, 2023. Webcast: https://www.youtube.com/watch?v=DunxtgBmRxI&list=PLvrp9iOILTQb6D9e1YZWpbUvzfptNMKx2&index=20
[35] https://www.cdc.gov/mmwr/volumes/72/wr/mm7229a4.htm

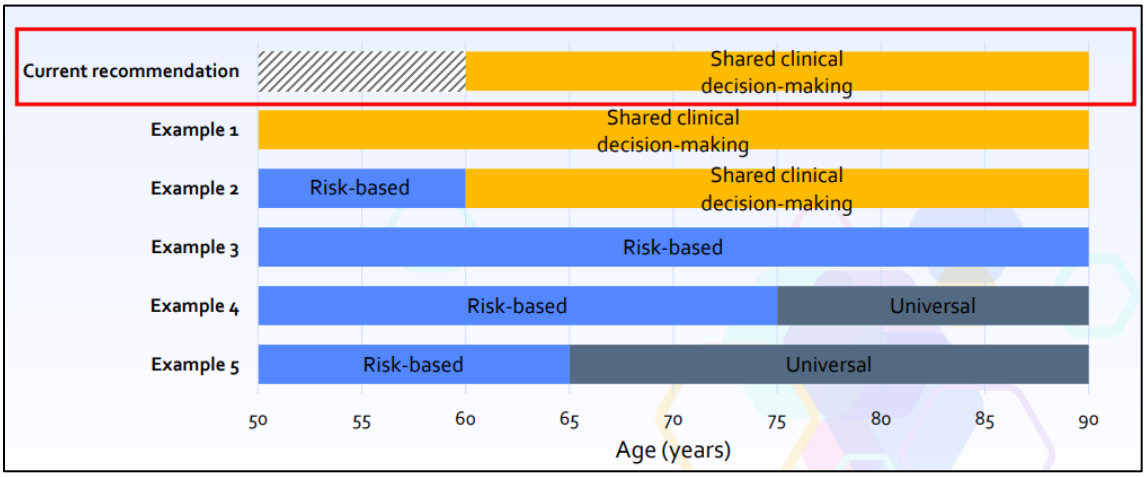
Turning to the potential use of GSK's RSVPreF3 vaccine in adults 50–59 years of age, Dr. Britton reviewed that GSK shared clinical trial data earlier today demonstrating that the humoral immune response to a single dose of RSVPreF3 in adults 50–59 years of age was non-inferior to the response in adults ≥60 years of age. Non-inferiority was demonstrated in adults 50–59 years of age with chronic stable medical conditions not associated with increased risk of RSV disease and in adults with conditions associated with increased RSV risk such as COPD and CVD disease. Cellular immune response also appeared similar across groups, but was not evaluated statistically. The safety profile among age groups also was similar. In terms of what these new data mean for future policy, the non-inferiority data suggest that RSVpreF3 vaccine efficacy in immunocompetent adults 50–59 years of age will be similar to the VE demonstrated in the clinical trials among adults ≥60 years of age. The WG notes that if FDA licensure is granted for use of RSVPreF3 in adults 50–59 years of age, the ACIP likely will need to make a policy recommendation regarding whether RSV vaccination should be recommended in this new age group and, if so, whether the recommendation should be the same for adults ≥60 years of age and older, with shared clinical decision-making or if a different type of recommendation is preferred.

The WG also expressed a number of concerns around these new data. Immunocompromised adults are known to be at increased risk of severe RSV disease, but were excluded from this and prior trials as discussed. The WG also would have preferred efficacy data in this age group, noting that there is no established immunologic correlative protection against RSV disease. The WG also expressed that those with certain risk conditions <50 years of age also are at increased risk and immune-bridging, and ideally, efficacy studies in these other age groups, would provide important information. When thinking about use in younger persons, pregnant persons also need to be considered.

In terms of preliminary considerations regarding the upcoming potential policy options, the WG noted that RSV disease is a public health problem in adults 50–59 years of age. However, the rate of RSV-associated disease in the general population of adults 50–59 years of age is less than the general population of adults ≥60 years of age. The WG also noted that while overall rates of severe RSV disease among adults 50–59 years may be lower, certain medical conditions place people at increased risk of severe RSV disease even at younger ages. According to RSV-NET, certain chronic conditions (e.g., coronary artery disease, COPD, diabetes, and asthma) are over-represented among people hospitalized for RSV compared to in the general population of adults 50–59 years of age. The WG recognizes that there is an important equity component in considering a recommendation for this age group. Black, Hispanic, and American Indian/Alaskan Native adults may develop certain chronic medical conditions at younger ages than White adults and experience disparities in other social determinants of health (SDOH), putting them at risk of severe RSV disease at younger ages. The disparity in hospitalization rates is more pronounced in adults 50–59 years of age than in adults ≥60 years of age.

Taking all this together, the WG is considering multiple policy options that incorporate the potential for licensure of RSV vaccines in adults 50–59 years of age. Members have stressed that upcoming data on the implementation of shared clinical decision-making, vaccine uptake, post-marketing safety surveillance, and effectiveness data (if available) among adults ≥60 years of age will be essential to determine the future preferred policy option among adults 50–59 years of age and adults ≥60 years of age. At this time, the WG continues to believe that a focus on those at highest risk of severe disease is warranted while awaiting post-marketing surveillance data, particularly on inflammatory neurologic events. Preliminarily, the WG broadly

agrees that the use of RSV vaccine amongst certain adults at increased risk of severe RSV aged 50–59 years of age is likely to have public health benefit. Members particularly acknowledge the equity concern of a recommendation for this age group and note that if there is no recommendation and FDA licenses RSV vaccine in adults 50–59 years of age, insurance will not cover its use, potentially furthering existing disparities. The current priority of the WG is to ensure access to vaccination among adults 50–59 years of age and those ≥60 years of age who are at substantially increased risk of severe RSV disease and likely to benefit most. The following graphic shows a range of potential policy options:



Dr. Britton emphasized that the WG is not yet recommending any of these options, but wished to share the range of potential options being discussed. The preferred option will depend upon incoming data and the full GRADE and EtR process. At the top of the figure above in the red box is the current recommendation. Expanded shared clinical decision-making along with a number of combinations of risk-based and universal recommendations are all potential options.

In terms of next steps, over the next few months, the WG will review post-marketing and observational data as they become available among adults ≥60 years of age and older. This will include vaccine uptake data stratified by demographic and risk conditions and vaccine safety surveillance data from VSD, V-safe, and other sources. The WG will be evaluating the implementation and implication of shared clinical decision-making and will then develop an updated policy question for RSV vaccination in adults through review of the updated GRADE; an updated cost-effectiveness analysis to include adults 50–59 years of age stratified by risk conditions; and an updated EtR. In the coming months, the WG also will begin reviewing safety and efficacy data of a third RSV vaccine, Moderna's mRNA-1345 for use in adults ≥60 years of age.

In closing, Dr. Britton asked the ACIP members to provide input on what additional data are needed prior to ACIP voting on updated recommendations for RSV vaccination in adults ≥50 years of age and for ACIP members to pose any questions they had as the WG plans for future policy considerations.

Discussion Points

Dr. Lee emphasized that the WG and full ACIP would continue to focus on safety and reviewing data as they become available. There are now so many seasonal vaccines, assessing the safety of concomitant vaccination continues to be an area of opportunity for the ACIP. The

importance of equity cannot be over-estimated. From the clinical trials to the recommendations, she said she was struggling with the variety of recommendations on the table because of the disparities that exist. The ACIP must grapple with whether its recommendation worsens those disparities, or keep them the same, or narrow them. Consideration must be given to the options in terms of risk-based versus broad recommendations. It is always easier to provide a universal recommendation, while a risk-based recommendation is complicated to implement and might impact access to the healthcare delivery system and the ability to identify some of the risk-based conditions in particular. The same goes for shared clinical decision-making for the same reasons. With COVID-19 vaccines, they ended up going lower in age groups with less data because they were feeling the importance of the need to address known inequities. She was very comfortable with that recommendation, even though there probably were less data than they wanted, in part because the disparities were so clear. For all respiratory diseases, it is becoming clear to her that the disparities are just baked into the way they are seeing these data. She was struggling with how to address and mitigate the disparities upfront in a way that is implementable. For whatever reason, age is the only thing that comes to mind that is easy, but she feels like they must find a better way.

As a member of the WG, Dr. Talbot indicated that when they reviewed the data on re-immunization a year later, the efficacy looked the same and not as good as the first year. That does not make physiologic sense to her because with the adjuvant, there should be a T cell response and it should be just as good. The possibility of blunting has been discussed previously, which is incredibly important. To decide on a recommendation for ≥50 years of age and over, they need third doses and fourth doses to see what is going on with this. Perhaps there should be some animal studies to figure this out, because it could have a huge impact on how the ACIP recommends these vaccines going forward.

Dr. Britton requested that their GSK colleagues share the slides for Studies 004 and 006 presented during the June 2023 ACIP meeting that included data on re-vaccination at 12 months.

Dr. Friedland (GSK) requested that the slides for Studies 004 and 006 be displayed. Looking first at Study 006, he pointed out that VE in Season 1 for LRTD was 82.6% and for severe LRTD was 90%. This slide showed efficacy against RSV-LRTD and severe RSV-LRTD as defined in the GSK protocol over the first season and then over 2 full seasons. The median time of follow-up was 18 months after the first dose of vaccine. There was high efficacy against LRTD and severe LRTD over 2 full seasons, including in those who had one or more pre-existing co-morbidities of interest. In particular, they showed VE in those who had 1 or more cardiorespiratory disorder of interest and 1 or more endocrinologic disorder of interest. This is Season 1 plus Season 2, or what happened when people were followed from Dose 1 through 2 full RSV seasons.

Dr. Britton added that to Dr. Talbot's point, VE was 55.9% in people in GSK’s trial who were revaccinated in Season 2 and 56.1% in Season 2 in people who had just gotten 1 dose and were followed 2 seasons .

Dr. Friedland (GSK) reminded everyone that what they presented during the June 2023 ACIP meeting was that when a second dose was given 12 months after the first dose, there was no additional benefit in VE. They looked at immune response as well when given at 12 months and at times past then, and as reported in the literature regarding other preF3 antigens, they saw that the humoral immune response with a dose given 12 months after the first dose does not exceed that when given just with the first dose. That was why they decided to continue to follow

patients in their clinical trials through 3 seasons and will be looking at the humoral and cellular immune response when additional doses are given more than 12 months after the first dose. They will have additional data in the future from the clinical trials.

Dr. Poehling emphasized that in terms of improving health and improving equity across the nation, having a standardized immunization platform for all adults is important. It will be difficult for people to remember whether they received a vaccine 2 years previously. She asked whether the infant platform could be expanded to include adults.

Dr. Daley said he had some discouraging feedback about the shared clinical decision-making in adults ≥60 years of age that it entails a long conversation in primary care. The public advertising is making it worse in some ways because it complicates the conversation when patients who are not at greatly increased risk are asking for this vaccine. It is difficult to develop clinical decision support that supports that kind of decision, and it is hard to have standing orders. Then there is the fundamental question about duration of immunity that has not been answered. This all would apply to decision for adults 50–59 years of age and ≥60 years of age. While he was not suggesting that they relitigate that during this meeting, all of this needs to be considered moving forward. He is appreciative that a vaccine is available for prevention and that the WG is going to continue to assess this, but it has been a challenge.

Dr. Brooks said he would want to have more comfort with correlates of protection in terms of humoral response, which they do not have. There is efficacy for adults ≥60 years of age plus what the immune response was, but no efficacy data in adults 50-59. Shared decision-making is risk-based in the sense that clinicians are talking to someone about the reason they do or do not need this vaccine, which means that generally they are at risk. Therefore, he did not endorse shared decision-making. He felt that the signal being so strong for the African American population at the younger age would be an indication in and of itself. While the statement was made about underlying conditions, there are many studies that when all SDOHs are teased out, even underlying conditions, rates are still higher. The data presented during this session were compelling regarding that. At this point, he favored either a universal or risk-based recommendation.

Dr. Loehr thought that a cost-benefit analysis would be important because his sense was that the previous recommendation was barely acceptable. For him to change from shared clinical decision-making in his practice, he would need to be much more comfortable about the neuroinflammatory risks. That is the main thing he counsels his patients on.

Dr. Whitley-Williams (NMA) expressed gratitude to the WG and presenters for the excellent job they have done. She asked whether the WG could do some modeling in terms of how many RSV-related hospitalizations, ICU admissions, and deaths there are in adults 50–64 years of age, particularly among those with comorbid conditions. This was done with pneumococcal vaccines when the age was lowered to ≥50 years of age for chronic smokers. Because of the lower life expectancy in some racial ethnic groups, it is difficult to tell the true benefit of the RSV vaccine in adults 50–64 years of age, particularly those with comorbid conditions. As Dr. Brooks just alluded to, race is a social construct. Obviously, race and ethnicity are used to try to target certain populations or understand which persons are suffering inequities, but she did not see this as being a race-based recommendation, which would not go over very well and likely would result in more resistance. The risk-based recommendation is difficult, which was why she urged the WG to assess adults 50–64 years of age so that the recommendation may not have to be risk-based unless the risk is just having a comorbid condition in that age group.

Dr. Lee emphasized while “race/ethnicity” is used, sexual orientation and gender identity (SO/GI) was brought up to be able to identify where disparities may exist. It is a different thing to make a recommendation around it and she does not feel comfortable doing that just as Dr. Whitley-Williams said. That was why she was asking for something that would allow the ACIP the ability to make a clean recommendation.

Dr. Long said she thought this was an unusual shared clinical decision-making decision, which she thought was because many of the WG members were uncomfortable with the safety without the discussion of underlying conditions for adults ≥60 years of age and ≥75 years of age. It was more than how much value there is in preventing RSV, but also the WG wanted to better understand potential AEs and that at least the vaccine would go in the arms of people who were at significant increased risk. She is 79 and on Halloween, she got her RSV vaccine and so did her husband because that was shared clinical decision-making based on the fact that they likely would be severely affected. Within a year, 2 million people will have received this vaccine, so there will be more clarity on safety. If there continue to be safety signals, then they are going to look very carefully at even younger people being recommended to receive this vaccine. How increased is the risk to receive the vaccine? Looking at the numbers, the risks of RSV-associated hospitalization and severe outcomes in adults 50─59 years of age are low.

Dr. Kotton added that when the recommendation was made for shared clinical decision-making both for adults 60─64 years of age and ≥65 years of age, she thought that the WG potentially would reconsider the recommendation once there were more data available. That is the WG’s current thinking. They do not feel comfortable making a universal recommendation for adults ≥65 years of age. That was not how they voted. Hopefully, like many other things that the ACIP does, this will evolve over time. They wanted people to have access to these 2 RSV vaccines this year so that with clinical decision-making, adults ≥60 years of age would have it covered by their insurance. Many people do not have Medicare Part D, which is highly problematic.

Dr. Sanchez commented that as the person who he believes was responsible for the shared clinical decision-making with the last vote, he still would have done the same thing. He agreed with Drs. Long and Kotton and understands the implications and time involved in shared clinical decision-making, but he also did not feel comfortable not spending that time before giving the RSV vaccine as it is currently without that shared clinical decision-making. While he was still very much in favor of that recommendation, he also agreed that it may change with time. He certainly agreed with shared clinical decision-making for adults ≥75 years of age and currently recommends that.

INFLUENZA VACCINES

Introduction

Dr. Jamie Loehr (ACIP Influenza WG Chair) introduced the influenza vaccines session, which focused on influenza vaccines in pregnancy, co-administration of influenza vaccines with other vaccines in adults, and influenza B/Yamagata surveillance. Regarding issues related to influenza vaccines in pregnancy, there is considerable experience with safe administration of influenza vaccines in pregnancy. However, there are fewer data specific to newer influenza vaccine formulations. In terms of issues related to co-administration of vaccines in adults, simultaneous administration or co-administration of all vaccines for which a recipient is due is a generally recommended practice for most combinations of vaccines. Specific data for co-administration of many combinations involving newer vaccines are limited. Data on co-

administration of 2 or more vaccines with newer adjuvants are limited. With regard to influenza B/Yamagata issues, all current US influenza vaccines are quadrivalent. They contain antigen from 4 influenza viruses, including an A(H1N1) virus, an A(H3N2) virus, and 2 influenza B viruses (one from each of two B lineages). Quadrivalent influenza vaccines initially were introduced in 2013-2014 to permit broader coverage of potentially circulating influenza B viruses. The previous trivalent vaccines contained only 1 influenza B virus from 1 lineage. There have been no confirmed detections of influenza B/Yamagata lineage viruses in global surveillance since March 2020, leading to discussion by WHO and FDA of their continued inclusion in influenza vaccines.

With all of this in mind, the 2 influenza sessions convened during this ACIP meeting and combined in this section of the minutes included the following presentations:

- ❑ Safety of Quadrivalent Recombinant Influenza Vaccine in Pregnant Women and Their Infants
- ❑ Safety of Simultaneous versus Sequential Administration of mRNA COVID-19 and Quadrivalent Inactivated Influenza (IIV4) Vaccines
- ❑ Safety of Simultaneous Vaccination with Zoster Vaccine Recombinant (RZV) and Quadrivalent Adjuvanted Inactivated Influenza Vaccine (aIIV4)
- ❑ Effectiveness of Maternal Influenza Vaccination during Pregnancy Against Influenza-Associated Hospitalizations & Emergency Department Visits in Infants <6 Months of Age
- ❑ Update on Influenza B/Yamagata Surveillance
- ❑ Post Marketing Study: Pregnancy Outcomes with ccIIV4 (Flucelvax)

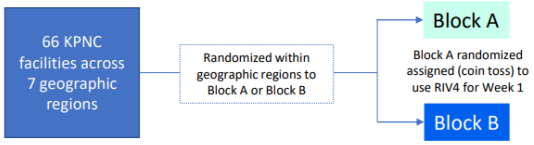
Safety of Quadrivalent Recombinant Influenza Vaccine in Pregnant Women and Their Infants

Nicola Klein, MD, PhD (Director, Kaiser Permanente Vaccine Study Center Kaiser Permanente Northern California) presented on the safety of quadrivalent recombinant influenza vaccine in pregnant women and their infants. Since 2004, the ACIP has recommended that all pregnant women receive an inactivated influenza vaccine (IIV) during any trimester pregnancy. This includes recombinant influenza vaccine (RIV), which has been available since 2013. However, there have been limited data regarding the safety of RIV during pregnancy. Therefore, Kaiser Permanente Northern California (KPNC) conducted a post-licensure observational study to assess the safety of quadrivalent recombinant influenza vaccine (RIV4) during pregnancy in the study setting of KPNC. KPNC is an integrated healthcare delivery system with an annual membership of over 4 million individuals, approximately 65% who are 18–64 years of age. Members receive nearly all their care at KPNC facilities, which includes 259 medical center clinics and 21 hospitals. KPNC has an electronic medical record (EMR) that captures all healthcare encounters, diagnoses, laboratory tests, vaccines, and medications. Within KPNC, routine influenza polymerase chain reaction (PCR) testing begins in early fall. Influenza PCR tests are ordered at each physician's discretion.

The primary objective of this study was to evaluate the safety of RIV4 compared with quadrivalent inactivated influenza vaccines (IIV4) in pregnant women and their offspring. This study included all routinely influenza vaccinated pregnant women and their live born infants at KPNC during the 2018-2019 and 2019-2020 influenza seasons. All vaccinated pregnant women were a subset of a separate cluster randomized effectiveness trial that compared the relative VE of RIV4 versus standard dose quadrivalent influenza vaccines (SD-IIV4) against influenza and influenza-related outcomes.

It is important to understand this study in the larger relative VE study context. This was a cluster randomized observational study of all KPNC adults vaccinated with either RIV4 or SDIIV4 during the 2018–2021 influenza seasons. KPNC aimed to administer 400,000 RIV4 doses and 400,000 SD-IIV4 doses to adults 18–64 years of age during each of the 3 seasons. To minimize geographic and socioeconomic imbalances between facilities and to achieve balance in covariates, facilities are cluster randomized within each of the 7 service areas to receive either RIV4 or SD-IIV4 on an alternating weekly basis. The randomization accounted for facility size and facilities within each service area. The goal was to achieve balancing covariate distribution between those who received RIV4 compared to SD-IIV4 (e.g., similar proportions of RIV4 versus SD-IIV4 who were female).

It is important to understand the design of the RIV4 and SD-IIV4 relative VE study to understand the post-licensure observational study to assess the safety of quadrivalent recombinant influenza vaccine (RIV4) during pregnancy. Overall, RIV4 vs. SD-IIV4 relative VE study included approximately 1.6 million influenza-vaccinated adults 18–64 years of age. The study ultimately included only 2 seasons, 2018–2020, due to the COVID-19 pandemic. There are 66 KPNC facilities across 7 geographic regions that were randomized within Block A or Block B, then Block A or Block B that was randomized for Week 1 to receive either RIV4 or SD-IIV4, then alternating each week so that every facility gave every vaccine on an alternating weekly basis as depicted in the following graphic:



	Week 1	Week 2	Week 3	Week 4
Facility 1	RIV4	SD-IIV4	RIV4	SD-IIV4
Facility 2	SD-IIV4	RIV4	SD-IIV4	RIV4
Facility 3	SD-IIV4	RIV4	SD-IIV4	RIV4
Facility 4	RIV4	SD-IIV4	RIV4	SD-IIV4
Facility 5	SD-IIV4	RIV4	SD-IIV4	RIV4
Facility 6	RIV4	SD-IIV4	RIV4	SD-IIV4

The current study focused on the subset of vaccinated pregnant women and their offspring from this overall relative VE study for which the pregnancy outcomes were spontaneous abortion, preterm labor, still birth/fetal death, congenital fetal anomalies detected during pregnancy, eclampsia, and placental abruption. The birth outcomes were preterm birth, low birthweight, and small for gestational age. The neonatal infant outcomes through 365 days of life included infant death, congenital anomalies, and failure to thrive.

In terms of the statistical analysis for pregnancy outcomes, the odds of a pregnancy outcome among RIV4 vaccinated pregnant women were compared to the odds of a pregnancy outcome among SD-IIV4 vaccinated pregnant women. With conditional logistic progression, which was conditioned on gestational age, the analysis was adjusted for maternal race, ethnicity, age group, BMI, presence of any chronic condition (asthma, CHD, COPD, diabetes), and trimester of influenza vaccination. For the birth and neonatal infant outcomes, the odds of birth and neonatal outcomes were compared among RIV4-vaccinated pregnant women with SD-IIV4 pregnant vaccinated women. Logistic regression was adjusted for infant sex, race, ethnicity, maternal age group, and maternal trimester of influenza vaccination.

With regard to the final study population of influenza-vaccinated pregnant women and their infants for the 2 included seasons, there were a total of 54,360 pregnant women vaccinated at KPNC. After excluding 1,628 for the RIV4 vaccinated, there were 14,981 RIV-vaccinated pregnant women and a 14,538 cohort of RIV4 infants. After excluding 3,951 of the 37,751 SD-IIV4 vaccinated pregnant women, there were 33,800 SD-IIV4 vaccinated pregnant women and

32,856 infants in the SD-IIV4 cohort. In terms of the demographics of the pregnant women, there was no difference between the trimester in which the pregnant women received their vaccines or race and ethnicity. None of the pre-defined pregnancy outcomes were statistically significant for when comparing the RIV4 with the SD-IIV4 cohorts. There also was no difference in infant demographics between the RIV4 vaccinated infants and the SD-IIV4 vaccinated infants. Importantly, there also was no difference in preterm birth for the gestational age between the 2 populations. For birth and infant outcomes up to 365 days of life, here was no difference between the RIV4 vaccinated infants and the SD-IIV4 vaccinated infants for any of the outcomes evaluated.

The strengths of the studies are that all pregnant women were a subset of a large, modified cluster randomized relative VE study of RIV4 versus SD-IIV4, which included approximately 1.6 million adults. The RIV4 recipients were very similar to the SD-IIV4 recipients with respect to risk factors for adverse outcomes and this study had fewer sources of bias than most observational studies. In terms of study limitations, there were slight imbalances in the timing of vaccination that might have been related to provider preferences. The proportion of pregnant women who received RIV4 during preconception or the first trimester was relatively higher than the SD-IIV4 group than in the RIV4 group. Historically, the OB/GYN clinics within KPNC have been accustomed to giving SD-IIV4 in pregnant women. Therefore, it is possible that providers preferred to administer SD-IIV4 once they knew an individual was pregnant. However, since demographic and covariate factors were similar between the 2 groups, such slight imbalances were unlikely to have affected the analyses.

In summary, within a large population of influenza-vaccinated pregnant women comparing RIV4 with SD-IIV4, there were no differences in pregnancy, birth, or neonatal infant outcomes. No safety concerns were identified after RIV4 use in pregnancy. The proportion of pregnancies or live births with outcomes were lower than published US rates for most other studies. The study provides reassuring safety data regarding the continued use of influenza vaccines during pregnancy.

Discussion Points

Dr. Poehling expressed gratitude for this important safety work and asked whether there also are plans to assess the effectiveness in preventing hospitalizations in this population of pregnant persons and babies after birth and whether the percentage of pregnant persons vaccinated in this population was known.

Dr. Klein indicated that all pregnant persons were included in the larger VE study for the most part, with a few minor exceptions. They were not separated out as part of the relative VE in the study. There are no plans at the moment to conduct a study of the infants, although this has been discussed. She did not have the percentage of pregnant persons who were vaccinated in this population readily available, but indicated that she would obtain that information for the committee.

Mrs. Hayes (ACNM) asked why 30% of the participants in the study had an unknown race, how long the newborns were followed and what antibodies they had in their blood for any length of time.

Dr. Klein reiterated that race is from the data that were available, which is sometimes not categorized and is sometimes difficult to assess based on medical records. She indicated that

infants were followed for outcomes through 365 days of life, but that blood was not drawn from the infants as part of the study. Therefore, antibody titers were not followed in these infants.

Dr. Amber Hsiao, Kaiser Permanente, added that race information is based on self-reported race. Unless it was recorded in the EMR, they did not have information on race.

Safety of Simultaneous versus Sequential Administration of mRNA COVID-19 and Quadrivalent Inactivated Influenza (IIV4) Vaccines: A Randomized Placebo Controlled Trial

Emmanuel "Chip" Walter MD, MPH (Duke University) discussed the safety of simultaneous versus sequential administration of the COVID-19 and IIV4 vaccines versus sequential administration of mRNA COVID-19 and IIV4 vaccines. Both influenza and COVID-19 vaccines are recommended for persons ≥6 months of age to prevent illness and complications resulting from these infections.[36] While available data support the simultaneous administration of these vaccines, there are limited data from placebo-controlled studies evaluating the safety of simultaneous administration of influenza and mRNA COVID-19 vaccines. Therefore, Duke University conducted a prospective, randomized, placebo-controlled, observer blind study to assess the simultaneous administration of these vaccines. This study included non-pregnant persons ≥5 years of age if receiving a primary 2-dose mRNA COVID-19 vaccine series or persons ≥12 years of age receiving a booster mRNA COVID-19 vaccine dose and intending to receive an influenza vaccine for that season. Persons ≥65 years of age received High-Dose IIV4 (Fluzone High-Dose Quadrivalent) and those <65 years received standard dose IIV4 (FluLaval or Fluzone Quadrivalent).

This study was conducted at 3 Clinical Immunization Safety Assessment (CISA) sites: Duke University, Cincinnati Children's Hospital Medical Center (CCHMC), and Johns Hopkins University (JHU) during the 2021-2022 and 2022-2023 influenza seasons. During Visit 1, Day 1, information was collected on baseline health, demographic, and health-related quality of life (HRQOL). Blood also was collected for COVID-19 serostatus. At Visit 1, participants received an mRNA COVID-19 vaccine, either Dose 1 of the primary series or a booster dose along with either RIV4 or a saline placebo as randomized. At Visit 2, on days 8 to 15, those who received IIV4 at Visit 1 received placebo and those who received placebo at Visit 1 received IIV4. For those ≥65 years of age and older, high-dose IIV4 was used. At Visit 3, conducted 27 to 57 days later, primary series participants received an mRNA COVID vaccine according to the recommended schedule.

The primary objective was to compare the proportion of participants with moderate or more severe fever, chills, myalgia, or arthralgia in the Simultaneous Group receiving IIV4 at the same time as mRNA COVID-19 vaccines at Vaccination Visit 1, with the Sequential Group receiving IIV4 alone 1 to 2 weeks later at Vaccination Visit 2. This was following both Vaccination Visit 1 and/or Visit 2. Reactogenicity events reported at the moderate or more severe level were included in the primary statistical reactogenicity endpoint noted. These included fever, chills, myalgia, or arthralgia as these events were considered clinically meaningful. The primary outcome was considered to be present if a participant had at least 1 of the reactogenicity symptoms on at least 1 day during Days 1 to 7 following Visit 1 and/or Visit 2. The hypothesis was that the proportion of participants with moderate or more severe fever, chills, myalgia, or

[36] https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#covid-vaccines and https://www.cdc.gov/mmwr/volumes/72/rr/rr7202a1.htm

arthralgia would be non-inferior, or not higher, in the Simultaneous Group versus the Sequential Group.

There also were a number of additional secondary and exploratory objectives. The secondary objectives were to compare the proportion of participants with the reactogenicity endpoint in the Simultaneous Group versus the Sequential Group following Vaccination Visit 1 and 2 separately; describe the proportions of participants in each group with solicited local and systemic reactogenicity events according to severity grade after vaccination visits; and describe the proportions of participants in each group experiencing at least 1 SAE and describe these events. Exploratory objectives were to further characterize and describe the proportion of participants in each group with local or systemic events of greater severity; describe the proportion of participants experiencing at least 1 unsolicited AE and 1 AESI and further characterize these events; and compare the change in HRQOL from baseline in each group following vaccination visits.

After 1:1 randomization to either the simultaneous or Sequential Group and a baseline blood draw, participants received study influenza vaccine or placebo according to assignment. Solicited reactogenicity and unsolicited AEs were assessed on Days 1 through 7 after each Visit 1, 2, or 3a. HRQOL was assessed by the EuroQol-5D-5L (EQ-5D-5L) and the EuroQol Visual Analog Scale (EQ VAS) at baseline and on Days 1 to 7 after Visit 1 only. AESIs were assessed on days 1 through 121. These included multisystem inflammatory syndrome (MIS), GBS, allergic-type reactions occurring within 7 days of a vaccination visit, myocarditis, or pericarditis. SAEs per the standard FDA definition of an SAE were assessed on Days 1 through 121.While blood draws were collected for immunogenicity at baseline and post-vaccination, those data are not yet available.

The Full Analysis Population 2 included all randomized and vaccinated participants. This population was used to describe characteristics and AE outcomes. Full Analysis Population 1 included all participants who were randomized, vaccinated, and provided at least 1 day of complete data on the symptom diary. This population was used to describe reactogenicity symptoms. In terms of statistical testing, the primary outcome was conducted at the 1-sided alpha 0.025 level using the upper bound of a stratified by site Newcombe binomial confidence interval with Cochran-Mantel-Haenszel (CMH) weighting of the difference with a noninferiority margin of 10%. Comparisons of proportions between the simultaneous and Sequential Groups used an exact Mantel-Haenszel statistic in a stratified analysis by site to control for the randomization blocks at the 2-sided alpha 0.05 level. Study site adjusted odds ratios and corresponding 95% confidence intervals for proportions also were calculated. The changes in HRQOL after Visit 1 were evaluated using Mann-Whitney U tests. For the HRQOL comparisons, a 2-sided alpha at the 0.05 level was used. Summary statistics were used to describe reactogenicity estimates, AEs, SAEs, and AESIs. The 95% confidence intervals of the difference between vaccination groups were calculated.

In total, 348 people were assessed for eligibility with 13 screen failures. A total of 335 people were then subsequently randomized, with 169 to the Simultaneous Group and 166 to the Sequential Group. One person voluntarily withdrew in the Simultaneous Group leaving 168 persons in that group, which was in the full analysis population. The population was more female than male, 70% White, 60% Hispanic, and largely 18─65 years of age. After randomization, there was some remaining imbalance in sex, with a higher percentage of males allocated to the Simultaneous Group. More participants enrolled during the 2022-2023 season than the 2021-2022 season. Just over 3% of participants received Moderna as opposed to Pfizer vaccine, with most participants receiving the Pfizer-BioNTech bivalent vaccine. Only 4

participants, all allocated to the Simultaneous Group, had not received a prior COVID vaccine. Therefore, most participants were receiving a booster dose of COVID-19 vaccine. Consequently, reactogenicity after visit 3a was not discussed. Over half of the participants had a prior COVID illness or a positive nucleocapsid antibody test at baseline.

Regarding the results, the proportion of persons reporting the reactogenicity endpoint of moderate or greater fever, chills, myalgia, or arthralgia was higher in the Sequential Group at 31% than in the Simultaneous Group at 25.6% when considering both vaccination Visits 1 and 2. The rate of moderate or more severe fever, chills, myalgia, or arthralgia in the Simultaneous Group was considered not worse or not higher than the rate in the Sequential Group. Thus, the non-inferiority criteria were met. The upper limit of the 95% confidence interval of the difference for the simultaneous minus the Sequential Group was 4% and the non-inferiority margin was designated as 10%. Therefore, the null hypothesis of inferiority was rejected. Looking at the same reactogenicity endpoint at Vaccination Visit 1 alone and the percentage reporting, the range was from approximately 24% in the Simultaneous Group to 28% in the Sequential Group. No significant difference was noted between the 2 groups. Regarding the same reactogenicity endpoint after Vaccination Visit 2 alone, the percentages reporting were overall much lower than after Visit 1, ranging from 3% to 5%. Again, no statistically significant differences were observed between the groups.

Taking a more granular look at the proportions of participants in each vaccination group reporting reactogenicity within 1 to 7 days following Vaccination Visits 1 and 2, no life-threatening or Grade 4 local or systemic reactions were reported. Most reactions were mild or moderate and occurred within a few days. In terms of local reactogenicity at Visit 1, a larger number of local reactions were reported at the COVID vaccination site compared to the influenza vaccination site, as would be suspected. At the COVID vaccination site, no differences in the occurrence of local injection site reactions were noted between the groups. However, a larger proportion of participants in the Sequential Group reported moderate to severe pain and swelling. In terms of receipt of influenza placebo, more pain and axillary swelling occurred in the Simultaneous Group who received the influenza vaccine compared to the Sequential Group who received placebo, with more in the Simultaneous Group also reporting pain at the moderate to severe level. In terms of local reactogenicity after Visit 2 at the influenza placebo site, a higher percentage in the Sequential Group receiving influenza vaccine reported pain and axillary swelling and tenderness. More in the Sequential Group also reported pain, axillary swelling, and tenderness at the moderate to severe level. Regarding systemic reactogenicity after Visit 1, no differences were noted between the groups for the reporting of any systemic reaction or a systemic reaction at the moderate to severe level. Overall, systemic reactions were less and were generally milder in nature at Visit 2 when compared to Visit 1. A higher proportion of people in the Sequential Group receiving influenza vaccine compared to the Simultaneous Group receiving placebo reported chills, fatigue, myalgia, and diarrhea. However, there were no differences between the groups for these systemic reactions at the more moderate to severe level.

There was 1 reported SAE in each group, with no statistical difference in the occurrence of SAEs. In the Sequential Group, 1 participant with a past medical history of cancer and multiple abdominal surgeries was hospitalized with an incarcerated ventral hernia and a small bowel obstruction 14 days following enrollment. This event was deemed unlikely related. In the Simultaneous Group, 1 participant had a spontaneous complete abortion at 16 weeks gestation, which was 19 weeks following enrollment. This person also reported having a COVID-19 infection 9 weeks following enrollment. This participant did not report being pregnant or having an attention of becoming pregnant at enrollment. The spontaneous abortion ultimately was

deemed unrelated to vaccination. There were 29 unsolicited AEs reported in 21 participants in the Simultaneous Group within 7 days of vaccination, and 16 events were reported in 16 participants in the Sequential Group within 7 days of vaccination. Again, there was no statistical differences between the groups in the proportions reporting an AE.

There were 28 AESIs reported during the study period, with 27 being the occurrence of a COVID-19 illness and 1 being an allergic-type reaction. There were no statistical differences in the occurrence of an AESI between the 2 groups. There were no differences between the groups in HRQOL as measured by the EQ-5D-5L index or the EQ-VAS scores during the week following Visit 1 for all participants. For those with Grade 3 reactions, the EQ-5D-5L index decreased from 0.92 pre-vaccination to about 0.8 by Day 2 and recovered to baseline by Day 3 to 4. For those with Grade 3 reactions, the EQ-VAS score decreased from about 90 pre-vaccination to about 66 by Day 2 and recovered to baseline by Day 4.

This study had several limitations. Most data came from the use of Bivalent Pfizer mRNA vaccine during 1 season, and there was very little use of the Moderna COVID-19 mRNA vaccine. Unfortunately, very few children 5—11 years of age and older adults ≥65 years of age were enrolled. The study was too small to detect rare AEs. People known to be pregnant were not included. A future CISA study will be assessing the safety of simultaneous influenza and COVID-19 vaccine during pregnancy.

In summary, simultaneous administration of influenza and mRNA COVID vaccines were well-tolerated when compared to sequential administration. The occurrence of moderate or more severe fever, chills, myalgia, or arthralgia was not higher in the Simultaneous Group versus the Sequential Group. No differences were seen between the groups in AEs occurring within 7 days, AESIs, SAEs, and HRQOL. As previously observed in other studies, injection site pain and systemic reactions were associated with the mRNA COVID-19 vaccine and influenza vaccines. Most reactions were mild or moderate. The most frequent injection site reactions after either vaccine were pain, axillary swelling, and tenderness. The most frequent systemic reactions after COVID vaccine with or without influenza vaccine were fatigue, myalgia, headache, chills, and arthralgia. Receipt of influenza vaccine alone was associated with chills, fatigue, myalgia, and diarrhea.

Discussion Points

Dr. Poehling asked what the placebo was and Ms. Bahta inquired as to what the influenza formulation was.

Dr. Walter indicated the placebo was saline and the influenza formulation was the standard-dose influenza vaccine, except for adults ≥65 years of age who received high-dose influenza vaccine.

Dr. Sanchez asked what the time interval was between the 2 doses.

Dr. Walter responded that for most people, it was 2 weeks toward the end of the study. This was modified slightly to allow a 1-week interval, but for most it was around 2 weeks. The Sequential Group received COVID and placebo and 2 weeks later received influenza. The Simultaneous Group received COVID and influenza vaccines during the first visit and subsequently, they received placebo 2 weeks later. Essentially, there was no added reactogenicity when influenza vaccine was administered with COVID vaccine.

Dr. Long asked whether the axillary swelling occurred only with COVID vaccine or if it occurred with influenza vaccine as well.

Dr. Walter replied that he was surprised by the rate of axillary swelling that occurred after influenza as well.

Safety of Simultaneous Vaccination with Zoster Vaccine Recombinant (RZV) and Quadrivalent Adjuvanted Inactivated Influenza Vaccine (aIIV4)

Kenneth Schmader, MD (Duke University) presented on the safety of simultaneous vaccination with RCV aIIV4. In terms of the rationale for this study, novel (non-aluminum) adjuvants are powerful immune stimulants employed in vaccine platforms to improve immunogenicity and efficacy. In recent years, the FDA has licensed several vaccines with novel adjuvants. Vaccines with novel adjuvants are more reactogenic than vaccines without adjuvants. Given that clinicians may opt to administer these vaccines simultaneously, data are needed on the safety of the simultaneous administration of vaccines with novel adjuvants. For older adults who want to avoid zoster and influenza, data are needed on the safety of simultaneous administration of the RZV vaccine (Shingrix) and the aIIV4 (Fluad).

The study design was a prospective, randomized, observer blinded, clinical trial. The vaccine administrator was not blinded, but did not participate in the outcome evaluations. The participants included immunocompetent, cognitively intact, community dwelling persons ≥65 years of age who had not received that season's influenza vaccine or prior RZV. Subjects were enrolled at Duke University Medical Center (Lead Site) and JHU (Contributing Site) during the 2021-2022 and 2022-2023 influenza seasons. Participants were randomized 1:1 to receive either RZV and aIIV4 or RZV and HD-IIV4. In terms of study visits, participants received RZV Dose 1 and influenza vaccine simultaneously on Day 1, with RZV in 1 arm and influenza vaccine in the other. On Day 60, participants received Dose 2 of RZV. Safety outcomes were collected through Day 103.

There was an Intention-to-Treat (ITT) Population, which was defined as all subjects who were randomized, vaccinated, and received at least 1 study vaccine. In addition, there was a Modified Intention-to-Treat (mITT) Population, which was defined as all subjects randomized, vaccinated, and provided at least 1 day of complete data on the symptom diary. A total of 285 participants were assessed for eligibility. There were 17 screen fails, leading to 268 randomized participants. There were 130 participants in the ITT and mITT Fluad groups. There were 137 Fluzone high-dose participants in the mITT group, with 1 participant missing diary entries, which resulted in 136 participants in the mITT Fluzone high-dose population. In terms of demographics, participants were about 49% female, 92% White, 1% Hispanic, and 66% ≥70 years of age. There were no meaningful differences between the 2 groups, but the study did not do a good job at enrolling under-represented populations.

The primary objective was to compare the proportion of participants with at least 1 severe (Grade 3) solicited local or systemic reactogenicity event after RZV Dose 1 in the RZV and aIIV4 Group versus RZV and HD-IIV4 Group. The hypothesis was that the proportion of participants with at least 1 severe (Grade 3) solicited reactogenicity event would be noninferior (not higher) in the RZV and aIIV4 Group compared with the RZV and HD-IIV4 Group. A non-inferiority margin of 10% was selected, which was viewed as clinically meaningful. In terms of the results for the primary outcome, the proportion of participants with at least 1 severe solicited local or systemic reactogenicity event on Days 1–8v after RZV Dose 1 in each study group, there were 15 (11.5%) Grade 3 events in the FLUAD influenza group and 17 (12.5%) in the

Fluzone-HD Group. The difference of -0.0096% had an upper bound of 0.0710%. This met the non-inferiority objective with a 10% non-inferiority margin with the upper bound of <10%. The confidence interval contained 0, so there is no claim of superiority.

The secondary objectives were to: 1) compare the proportion of participants with at least 1 severe (Grade 3) solicited local reactogenicity event after RZV Dose 1 in the RZV and aIIV4 Group vs. RZV Dose 1 and HD-IIV4 Group (non-inferiority analysis); 2) compare the proportion of participants with at least 1 severe (Grade 3) solicited systemic reactogenicity event after RZV Dose 1 in the RZV and aIIV4 Group vs. RZV Dose 1 and HD-IIV4 Group (non-inferiority analysis); and 3) compare the proportion of participants with at least 1 SAE or AESI after RZV Dose 1 in the RZV and aIIV4 Group vs. RZV Dose 1 and HD-IIV4 Group through Day 43 and describe these events (95% confidence interval comparison). In the FLUAD Group, there were 8 (6.1%) Grade 3 events and 6 (4.4%) in the Fluzone-HD. The difference was 1.7%, with the upper bound confidence interval of 7.7%, which met the non-inferior objective with a 10% noninferiority margin. The confidence interval contains 0, so there is no claim of superiority.

For the second secondary objective focusing on solicited systemic reactogenicity events on Days 1─8 after RZV Dose 1 in each study group, there were 7 (5.3%) Grade 3 events in the FLUAD Group and 13 (9.5%) Grade 3 events for a difference of minus 4.1% and an upper bound confidence interval of 2.4%. This met the non-inferiority objective of an upper bound of <10%. The confidence interval contained 0, so there is no claim of superiority. In terms of local reactions after RZV Dose 1 and influenza vaccine, because the RZV was administered in 1 arm and influenza vaccine was administered in the other arm, there are data on each of these vaccines for pain, swelling, and redness.

There were no significant differences in the proportion of moderate to severe local reactogenicity events between the aIIV4 and HD-IIV4 Groups. Looking at the combined effect of RZV and influenza vaccines together because they could not be teased out individually, there were no significant differences between the groups in terms of fever, chills, fatigue, myalgia, headache, arthralgia, nausea, vomiting, diarrhea, and abdominal pain. There were no significant differences in the proportion of moderate/severe systemic reactogenicity events between the aIIV4 and HD-IIV4 groups. In the fatigue category, 48% to 50% of individuals had no reactions despite receiving both vaccines simultaneously. In the myalgia category, 52% to 58% had no myalgia despite receiving both vaccines.

Moving to the ITT population with at least 1 SAE within 43 days after RZV Dose 1, there was 1 (0.7%) SAE in the FLUAD Group and 5 (3.6%) in the Fluzone-HD Group. The difference was 2.88 (-6.36, 0.60), with the 95% confidence interval crossing 0, which is not statistically significant. Looking at all subjects in the ITT Group with at least 1 SAE through the entire study period, there were 9 (3%) in the FLUAD Group and 5 (3.6%) in the Fluzone-HD Group. The difference was -0.57 (-4.89, 3.75), crossing 0, and not statistically significant. The following table further describes the SAEs within 43 days of RZV Dose 1 and influenza vaccination, with all participants with SAE requiring hospitalization or prolongation of hospitalization and no deaths:

Group	Age group years	Relatedness	Clinical description
aIIV4	≥70	Not related	**Pacemaker due to arrhythmia**
HD-IIV4	65-69	Not related	**Numbness, Cerebrovascular accident (CVA)**
HD-IIV4	≥70	Not related	**Acute hyperkalemia**
HD-IIV4	≥70	Not related	**Shortness of breath**
HD-IIV4	≥70	Not related	**Acute pulmonary embolism and acute deep vein thrombosis**
HD-IIV4	65-69	Possibly related	**Left partial cranial nerve III palsy**

The following table further describes the SAEs >43 days of RZV Dose 1 and influenza vaccination, with all participants with SAE requiring hospitalization or prolongation of hospitalization and no deaths:

Group	Age group years	Relatedness	Clinical description
aIIV4	≥70	Not related	**Heptocellular carcinoma**
aIIV4	≥70	Not related	**Revision of right shoulder rotator cuff surgery**
aIIV4	65-69	Not related	**Chronic obstructive pulmonary diseases (COPD) exacerbation**

In terms of the pre-specified AESIs, syncope during post-vaccination monitoring in the clinic did not occur. There also were no anaphylaxis events in the first 24 hours after immunization. There was a new-onset immune-mediated disease during 42 days after vaccination, with 1 case of partial cranial nerve III palsy, which also was considered to be an SAE. This patient was in the HD-IIV4 Group. There was a similar exploratory objective to describe and compare changes in HRQOL after RZV Dose 1 and aIIV4 with RZV Dose 1 and HD-IIV4. There were no significant differences between the groups in all participants or those who had Grade 3 events.

In terms of imitations, enrollment was limited by the COVID-19 pandemic at approximately 70% of the target. However, this did not obviate the results for the primary and secondary objectives. As mentioned earlier, the study population was mostly White, non-Hispanic, and did not have enough under-represented populations. An important point is the study was too small to detect rare AEs.

In conclusion, the proportion of participants with at least 1 severe local or systemic reaction was not higher after RZV Dose 1 and aIIV4 (11.5%) compared to RZV Dose 1 and HD-IIV4 (12.5%). The frequency of moderate-severe local and systemic reactogenicity events were similar when RZV Dose 1 was administered with aIIV4 or HD-IIV4. Few participants had SAEs during the study after RZV Dose 1 was administered with aIIV4 (3.1%) or HD-IIV4 (3.7%). The clinical conditions were those expected in a population of older adults. From a safety standpoint, this study supports simultaneous administration of RZV and aIIV4 as an acceptable option for vaccine delivery in older adults.

Discussion Points

Dr. Talbot asked whether there are any data on antibody responses, pointing out that it would be interesting to see if those who had more severe reactions had better antibody responses.

Dr. Schmader responded that they drew blood for HI, which is being analyzed now.

Dr. Daley requested a reminder about how the investigators determined that an event was not related, such as pulmonary embolism, in terms of the characteristics the investigators utilized to determine that the event was not related.

Dr. Schmader replied that the 2 they were focusing on were the neurological event of numbness and the partial cranial nerve III palsy, which was thought to be possibly related. The stroke was based on the data received from the clinicians who were seeing that patient. It also was temporal in that it occurred 26 days after vaccination. The risk window for stroke was 1 to 21 days. The pulmonary embolism also was well beyond the 21-day risk window.

Effectiveness of Maternal Influenza Vaccination during Pregnancy against Influenza-Associated Hospitalizations & Emergency Department Visits in Infants <6 Months of Age

Samantha M. Olson, MPH (NVSN Flu Lead/Epidemiologist Influenza Prevention and Control Team [IPACT], Influenza Division, NCIRD, CDC) pointed out that influenza virus infection during pregnancy is associated with severe disease and may be associated with some adverse birth outcomes. Receipt of inactivated influenza vaccine during pregnancy is safe and effective. Since 2012, WHO has recommended prioritizing vaccinating pregnant persons against influenza and vaccination also has been recommended by the CDC. Since the COVID-19 pandemic, influenza vaccination uptake during pregnancy is about 5% to 15% lower than pre-pandemic seasons. These vaccination rates have decreased despite evidence that influenza vaccination during pregnancy can protect not only the pregnant person, but also infants <6 months of age who are not yet age-eligible for vaccination and are at high risk of serious influenza-related complications.

The primary body of evidence for the protection of infants born to pregnant persons receiving influenza vaccine during pregnancy are RCTs conducted outside of the US that showed a maternal VE against laboratory-confirmed influenza in infants of 30% to 63%. However, there is a lack of real-world multi-center, multi-season, and US data on maternal VE against medically-attended influenza in infants. Data following the 2009 H1N1 pandemic are particularly limited, and data on maternal VE by timing during pregnancy are limited as well. As of the 2021-2022 influenza season, the current ACIP recommendation indicates that vaccination during July and August can be considered for pregnant persons who are in the third trimester. For pregnant persons in the first or second trimester during July and August, waiting to vaccinate until September or October is preferable unless there is concern that later vaccination might not be possible.[37]

With that in mind, the research question for this study was, “Does maternal influenza vaccination during pregnancy reduce influenza-associated hospitalizations and emergency department (ED) visits in infants <6 months of age?” For this analysis, data were used from the New Vaccine Surveillance Network (NVSN). NVSN monitors pediatric inpatient and ED visits for

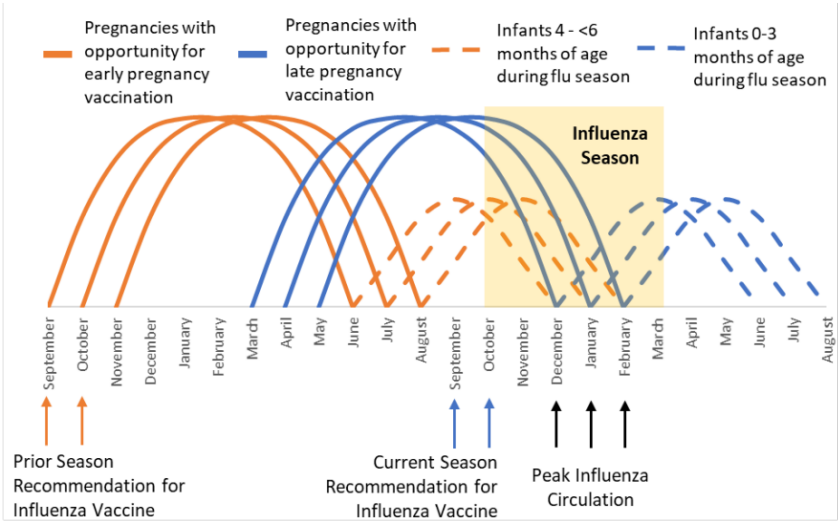
[37] https://www.cdc.gov/mmwr/volumes/71/rr/rr7101a1.htm; and https://www.cdc.gov/mmwr/volumes/70/rr/rr7005a1.htm?s_cid=rr7005a1_w

acute respiratory illness (ARI) at 7 pediatric medical institutions across the country. NVSN conducts respiratory surveillance year-round for infants and children through 17 years of age by collecting clinical testing results and conducting research testing at each of these sites.

In terms of the methods for this study, infants <6 months of age were enrolled in the study who were admitted to the hospital or ED at 7 pediatric medical centers within the NVSN during 4 influenza seasons from Fall 2016 through Spring 2020—right before the COVID-19 pandemic. Cases were defined as infants who tested positive for influenza by RT-PCR with ARI symptoms within 10 days of symptom onset. Controls were defined as infants who tested negative for influenza with the same ARI symptoms. The study had a test-negative design in which the odds of maternal influenza vaccination ≥14 days prior to delivery among case infants with influenza were compared to control infants with non-influenza respiratory illness. Vaccination status was defined as any influenza vaccine received during pregnancy using a number of sources, including documented vaccination sources such as state IISs, providers, and self-reported vaccination if timing was provided and that included either a date or if the trimester that the vaccine was received during pregnancy was self-reported. Data on maternal influenza infection during pregnancy was not collected and thus could not be assessed as a confounder in this analysis. For this statistical analysis, the equation VE= (1 – adjusted odds ratio) x 100% was used and adjustments were made for infant age, NVSN site, and calendar time.

A few other potential confounders were considered such as influenza season, sex, race, ethnicity, prematurity, underlying conditions, and mother's education. None of the other confounders were found to be significant, so the following model was used. This model depicts the complexity of maternal vaccination timing during pregnancy:

Figure. Timing of maternal influenza vaccination during pregnancy in the context of infant age and influenza seasonality



To walk through some examples of pregnancies that have an early opportunity to receive influenza vaccine, for pregnancies starting in September or October at the same time influenza vaccine is recommended to the general public, infants born to these persons also will be older during the influenza season. They would be born in the summer months and would be about 4 to 6 months of age during the influenza season and were hypothesized in this analysis to have lower VE. A second group of infants represents pregnancies with opportunity for vaccination later in pregnancy. These pregnancies would begin in the Spring in March or April and end in

the middle of influenza season around December to February. Vaccination would be received later in pregnancy and these infants would be about 0 to 3 months of age during influenza season. This group was hypothesized to have higher VE. Ultimately, considering the timing to protect both the pregnant person and baby against influenza is complex and strategies for maternal influenza vaccination will differ from vaccinations that protect against pathogens without a distinct seasonality, such as strategies for maternal vaccination that were used during the COVID-19 pandemic.

In terms of the results, there were 4,049 infants <6 months of age enrolled between the 2016-2017 through the 2019-2020 influenza seasons within NVSN. Of these, 285 were excluded (21 cases, 264 controls) because 92 infants were born to persons vaccinated <14 days prior to delivery and 193 had unknown vaccination timing. A total of 3,764 infants ultimately were included in this analysis, of whom 53% were born to vaccinated persons. A total of 223 case infants tested positive and 3,541 control infants tested negative. A total of 1,913 (54%) of control infants were born to vaccinated persons. This was similar to what other surveillance systems showed for vaccination coverage for influenza among pregnant persons during these seasons. Case infants and those born to unvaccinated persons were older than control infants and those born to vaccinated persons. Infant case status and maternal vaccination status differed by race and ethnic group. More infants born to vaccinated persons were breastfeeding on enrollment and more infants born to unvaccinated persons had underlying conditions. More infants born to unvaccinated persons were born preterm. Vaccination status differed by NVSN site and influenza season of enrollment.

Regarding the main results of the analysis of maternal VE against influenza-associated hospitalizations and ED among infants <6 six months of age, overall maternal VE against influenza hospitalizations ED visits in infants <6 months of age was 34%. Maternal VE was higher among infants <3 months of age among those born to persons vaccinated during their third trimester of pregnancy, and against hospital admission. For those younger infants, VE was 53%. For infants born to persons vaccinated during their first or second trimester of pregnancy, VE was 17%. Infants born to persons vaccinated later in pregnancy during the third trimester, VE was higher at 52%, with overlapping confidence intervals. By severity of infant illness, hospital admission VE was 39% and ED visit VE was 19%, with overlapping confidence intervals. Maternal VE was consistent with other VE estimates by influenza type and subtype for these same seasons. Similar trends were observed in terms of adult and pediatric populations. VE was 25% against influenza A, 39% against H1N1, 16% against H3N2, and 47% for influenza B.

In summary, influenza VE uptake during pregnancy is nationally consistent but suboptimal. Recent estimates show that vaccination coverage for pregnant persons for influenza has decreased since the COVID-19 pandemic. Maternal vaccination was associated with reduced odds of influenza hospitalizations and ED visits in infants <6 months of age. VE was greatest among infants <3 months of age, those born to persons vaccinated during their third trimester of pregnancy, and against influenza-associated hospitalizations. Currently, there are no anticipated changes to vaccination timing recommendations during pregnancy.

Discussion Points

Ms. Hayes (ACNM) emphasized how incredible and reassuring these data are. While uptake is low, the fact that hospitalizations can be prevented is wonderful.

Ms. McNally asked whether there is information regarding the reason for the decrease in uptake and what Tdap rates are showing during pregnancy.

Ms. Olson responded that she did not have specific information on the reasons for the decreases in uptake and that they did not assess Tdap in this study, but they will look into this and get back to the committee.

Update on Influenza B/Yamagata Surveillance

Rebecca Kondor, PhD (Interim Director, WHO Collaborating Center for Surveillance, Influenza Division, NCIRD, CDC) presented an update on influenza B/Yamagata surveillance. Beginning with an overview of global surveillance for influenza, WHO's Global Influenza Surveillance and Response System (GISRS) has been conducting influenza surveillance for over 75 years. This is a growing system of WHO National Influenza Centers (NICs), H5 Reference Laboratories, Collaborating Centers (CCs), and Essential Regulatory Laboratories (ERLs). The mission of the GISRS is to protect people from the threat of influenza by continuously functioning as a global mechanism of surveillance, preparedness, and response for seasonal, pandemic, and zoonotic influenza. It is a global platform for monitoring influenza epidemiology and disease. It is a novel global alert system for influenza viruses and other respiratory pathogens with pandemic potential.

There are over 150 GISRS NICs worldwide. NICs collect respiratory specimens through an established network of physicians, healthcare centers, and other sentinel sites and/or collect influenza-positive specimens. They are responsible for performing influenza typing and subtyping through assays developed and manufactured by the CDC and available through the International Reagent Resource (IRR) established by the CDC. Another important aspect of the NICs is that they share a subset of representative specimens and/or isolates with the WHO CCs for antigenic and genetic characterization and creation of new candidate vaccine viruses used globally. The reporting mechanism through the WHO is through RespiMart that has 2 sections, including epidemiological information through Flu Informed Decisions (FluID) and laboratory results through FluNet. The Influenza Division of NCIRD at CDC serves as a WHO CC for global surveillance, epidemiology, and control of influenza for epidemic human influenza and zoonotic influenza.

The surveillance data available in FluNet can be delineated by the type of surveillance site that a country has available. This includes sentinel surveillance systems that collect high-quality data in a timely manner, systematically and routinely, from sentinel surveillance sites representative of the population under surveillance. Case definitions for ILI, SARI, ARI and populations differ by country (e.g., only certain age groups, health-care workers, hospitalized). Data reported in the "non-sentinel" category may include outbreak investigations, universal testing strategies, or testing at point-of-care or other systems that are apart from sentinel surveillance. The "type not defined" category may include sentinel and/or non-sentinel site types. While each country performs a mixture of types of surveillance, the level of information reported to FluNet depends upon the country and the laboratory where testing occurs. Rapid tests performed in primary care or other clinic settings will determine influenza A or B. Large clinical and hospital laboratories often determine influenza A or B, with some assays also determining influenza A subtype. A

higher proportion of viruses from sentinel surveillance will include influenza A and B subtyping results.

The types of assays that are available for influenza B genotyping depend upon whether they are serology-based or molecular-based. Through serology, WHO CDC in Atlanta creates and makes available a WHO kit that uses anti-B/Victoria and anti-B/Yamagata goat antiserum that is made available through the CDC IRR. Over 52 countries have ordered this kit to use serology as their basis for B genotyping. Upon request, CDC also can make available ferret antisera again raised to specific B/Yamagata or B/Victoria viruses so the hemagglutination inhibition (HI) assay can be used to determine B lineage. Molecular-based assays are becoming more common. CDC has created an RT-PCR B lineage assay for research use only (RUO) that is available to the WHO NICs through CDC's IRR. Over 100 countries have ordered kits to perform the B lineage assay. Individual countries may have their own RT-PCR-based assays or may use sequencing, either Sanger or next-generation sequencing (NGS) to determine the B lineage.

While reports to FluNet are from the country level, the GISRS system involves the network of NICs that submit representative specimens from epidemics in their countries to WHO CC for additional characterization. All influenza B viruses received by WHO CCs also have their B lineage determined using similar methods. WHO CCs have confirmed zero circulating B/Yamagata lineage viruses collected after March 2020. Those reported as B/Yamagata were determined to be incorrect lineage reports, negative for influenza or the B/Yamagata component of LAIV among those sampled post-vaccination. Non-sentinel surveillance may use a different set of assays.

In terms of WHO GISRS influenza surveillance from September 2017 through August 2020 co-circulation of the 4 influenza viruses in the vaccine, before the COVID-19 pandemic, influenza B/Yamagata lineage viruses were the predominant B/lineage circulating during the 2017-2018 Northern Hemisphere and 2018 Southern Hemisphere seasons. In the 2018-2019 season, the Northern Hemisphere had much less B activity overall and B/Victoria lineage viruses predominated. In 2019, the Southern Hemisphere showed regional differences in B/lineage circulation with B/Yamagata mainly circulating in South America. The 2019-2020 Northern Hemisphere season began with an early B/Victoria lineage peak, followed by A(H1N1)pdm09. The COVID-19 Pandemic and its mitigation resulted in a decrease in influenza virus detection and circulation. GISRS NICs continued influenza surveillance during the COVID-19 pandemic. Between September 2020 and August 2023, influenza continued to be detected but without seasonal peaks in epidemics until late 2021. All influenza B activity was due to the B/Victoria lineage. Between February 1 – August 31, 2023, 1/3 of all viruses detected by GISRS were influenza B. Parts of the Northern Hemisphere experienced a second peak of activity due to B/Victoria and A(H1N1)pdm09 viruses. The Southern Hemisphere 2023 season experienced co-circulation of B/Victoria and A(H1N1)pdm09 viruses.[38]

In terms of countries reporting influenza B detections to FluNet from February 1- August 31, 2023, all types of global surveillance reporting influenza B and the B lineage results detected influenza B viruses. Hence, there are strong geographically diverse network reporting data. The proportion reporting B lineage depends upon the region, different surveillance networks, and types of testing reported by each country to FluNet. Several regions of NICs reported B/Victoria and B/Yamagata lineage results to FluNet. During this timeframe, there was 1 B/Yamagata report to FluNet from a non-sentinel source. No other surveillance during this time period

[38] https://app.powerbi.com/view?r=eyJrIjoiZTkyODcyOTEtZjA5YS00ZmI0LWFkZGUtODIxNGI5OTE3YjM0IiwidCI6ImY2MTBjMGI3LWJkMjQtNGIzOS04MTBiLTNkYzI4MGFmYjU5MCIsImMiOjh9

detected B/Yamamgata. The proportion that had B lineage results was low, which may be due to the types of surveillance networks in the countries reporting. Sentinel surveillance had a much higher proportion of B lineage information reported immediately to FluNet.

Looking cumulatively at the data presented from NICs from February to August 2023, almost 100,000 influenza B viruses were detected in over 139 countries. Almost 16,000 of the B lineage viruses had results from B/lineage assays reported to FluNet from all surveillance Types. The 15 initial reports to GISRS as B/Yamagata underwent confirmation by WHO CCs and the WHO Global Influenza Program staff, which confirmed that 13 of the 15 reports were negative for influenza, so their records in FluNet were updated. Of the 15 reports, 2 did not have specimens available for confirmation testing at a WHO CC and 1 was not reported to FluNet. These specimens did not yield viral isolates or sequence data. All influenza B viruses received by WHO CCs were B/Victoria lineage. Genomic surveillance of influenza B viruses found only genetic segments derived from the circulating B/Victoria lineage. These data support that B/Yamagata viruses are extremely rare and are not responsible for recent epidemics. The majority of B/Yamagata reports are due to an incorrect lineage determination to verify the report of B/Yamagata.

In terms of the WHO vaccine recommendations for the Southern Hemisphere 2024, vaccines licensed for use in the 2024 Southern Hemisphere influenza season were recommended to contain the following:[39]

Trivalent: Egg-Based Vaccines
- ❑ An A/Victoria/4897/2022 (H1N1)pdm09-like virus antigen*
- ❑ An A/Thailand/8/2022 (H3N2)-like virus antigen**
- ❑ A B/Austria/1359417/2021 (B/Victoria lineage)-like virus

Trivalent: Cell- or Recombinant-Based Vaccines
- ❑ An A/Wisconsin/67/2022 (H1N1)pdm09-like virus antigen*
- ❑ An A/Massachusetts/18/2022 (H3N2)-like virus antigen**
- ❑ A B/Austria/1359417/2021 (B/Victoria lineage)-like virus antigen

Quadrivalent: Egg- or Cell Culture- or Recombinant-Based Vaccines
- ❑ Above 3 components and
- ❑ A B/Phuket/3073/2013 (B/Yamagata lineage)-like antigen

*Different from that recommended for the 2023 southern hemisphere season but the same as the NH 2023-24 recommendation.
**Different from that recommended for the 2023 southern hemisphere season and from NH 2023-24 recommendation.

The absence of confirmed detection of naturally occurring B/Yamagata lineage viruses is indicative of very low risk of infection by B/Yamagata lineage viruses. While influenza vaccines are safe and effective, the manufacture and use of inactivated and live attenuated vaccines containing B/Yamagata lineage viruses pose a theoretical risk of reintroduction of B/Yamagata lineage virus into the population. This risk can be mitigated by the removal of B/Yamagata lineage viruses from the vaccines. It was the opinion of the WHO influenza vaccine composition advisory committee that the inclusion of a B/Yamagata antigen as a component of influenza vaccines is no longer warranted, and every effort should be made to exclude this component as soon as practically possible. The committee recognizes that national or regional authorities are responsible for approving the composition and formulation of vaccines used in each country and should consider the use and relative benefits of trivalent or quadrivalent influenza vaccines. The

[39] https://www.who.int/teams/global-influenza-programme/vaccines/who-recommendations

FDA convened a VRBPAC committee meeting in early October 2023 to discuss the Southern Hemisphere manufacturing recommendations for vaccines and agreed that the B/Yamagata lineage antigen should be excluded as a component of the vaccines as soon as possible. Vaccine manufacturers that have inactivated trivalent licenses are working closely with FDA CBER colleagues on the issue of reactivating these licenses.

In terms of ongoing influenza B surveillance, GISRS laboratories will continue to be supported by CDC for influenza testing, typing, and influenza A/B subtyping through reagents available in IRR. GISRS laboratories and WHO CCs will continue to perform B/lineage testing. Any reports of B/Yamagata viruses will be confirmed by WHO CCs. For the 2023-2024 season, US public health laboratories will continue to perform assays to determine B/lineage. All B/Yamagata detections will be sent to CDC for confirmation. All US specimens with RT-PCR results of a mix of influenza A and B also will be sent to CDC for confirmation. The majority of previous results of A/B mixtures were from individuals vaccinated with LAIV in the weeks prior to sampling.

Discussion Points

Dr. Poehling expressed gratitude for this incredible surveillance that enhances confidence in all the work that is being done.

Post Marketing Study: Pregnancy Outcomes with ccIIV4 (Flucelvax)

Gregg C. Sylvester, MD, MPH (Chief Health Officer & Vice President, Medical Affairs, CSL Seqirus) provided an update on pregnancy outcomes based on ccIIV4 results of a post-marketing prospective observational cohort study evaluating them safety of ccIIV4 among people immunized as part of their routine obstetrical care. He noted that he would be using the brand name “Flucelvax” instead of ccIIV4 for the remainder of this presentation. Flucelvax is not produced in fertilized eggs. The influenza viruses are propagated in mammalian cell cultures that are an exact immunogenic match to the original viruses recommended. The data presented during this session was added to the US package insert in February. This influenza season is the first time these data appear in the Flucelvax label.

The purpose of this study was to fulfill a post-marketing commitment with the FDA as part of the licensure process. The main objective was to study the safety of Flucelvax with regard to specific pregnancy and infant outcomes. The study was designed as a prospective pregnancy exposure registry in line with the FDA guidance. An expert panel of independent medical professionals was assembled to oversee this study. The committee was comprised of experts in the fields of obstetrics, maternal-fetal medicine, pediatrics, clinical research, infectious disease, epidemiology, genetics, and teratology. A teratologist, blinded to exposure timing, reviewed and classified reported congenital malformations using the Metropolitan Atlanta Congenital Defects Program (MACDP) criteria. MACDP is a birth defects surveillance system established by the CDC in 1967 that is considered to be a gold standard in birth defects surveillance systems. The pre-negotiated outcomes of interest with the FDA are in this table:

Pregnancy Outcomes

- **Live birth**
- **Stillbirth:**
  - Fetal death occurring ≥20 weeks' gestation, or if gestational age was unknown, a fetus that weighed 500 gm or more
- **Spontaneous abortion:**
  - Fetal death <20 weeks' gestation, including missed abortion, incomplete abortion, and inevitable abortion
- **Elective termination**
  - Voluntary interruption of pregnancy, including pregnancy termination that occurred electively, to preserve maternal health, or due to fetal abnormalities

Events of Interest

- **Preterm birth**:
  - A live-born infant born at gestational age <37 weeks
- **Low birth weight**:
  - A live-born infant whose birth weight is <2500 gm
- **Major Congenital Malformation:**
  - Any major structural or chromosomal defect or combination of three or more conditional defects in live- or stillborn infants, or fetal losses of any gestational age, including outcomes prior to 20 weeks' gestation or weighing <500 gm

In terms of the inclusion/ineligibility criteria, participants were enrolled prospectively by obstetric healthcare professionals who had committed to enrolling all eligible persons in their clinics who consented to the study. Participants from whom sufficient data were available to confirm receipt of the vaccine, pregnancy outcomes, and evaluate whether an event of interest had occurred in the fetus or infant at the time of the pregnancy outcome were enrolled in this study. HCP's contact information was collected to allow for follow-up. Subjects may have self-enrolled or may have been enrolled by a participating OB/GYN clinic after providing informed consent. A passive and active system were used. Retrospective cases were ineligible for enrollment as were persons who had prior knowledge of an adverse pregnancy outcome, such as a major malformation suggested by prenatal testing. These cases would be reported to Seqirus's pharmacovigilance system.

This study was conducted over 3 influenza seasons using a passive enrollment process, meaning that enrollment was solicited via the internet. Eligibility requirements were posted on clinicaltrials.gov, the Seqirus website, and on the Society of Maternal-Fetal Medicine (SMFM) website. When this was not successful, enrollment was changed to active participation for the remainder of the study. There were 5 study sites in 4 states (Georgia, North Carolina, New York, and Idaho). Total enrollment was 693 pregnancies over the 3 years. Of these, 27 participants were lost to follow-up and 1 individual was deemed ineligible because they enrolled retrospectively. Therefore, the primary analysis population included 665 individuals. Of note, the demographic characteristics of those lost to follow-up were similar to those who completed the study. A sample size of at least 600 would provide adequate power to detect a 2-fold increase in major congenital malformations, which was the lowest rate of detection among the study outcomes.

The demographics of the participants in this study were fairly typical. There was about 28% missing data in terms of ethnicity, given that 1 of the 5 enrollment sites did not report ethnicity in their medical records. Race was approximately 60% White, 29% African American, and 4.4% Asian. In terms of baseline characteristics, the mean and median of the pre-pregnancy body mass index (BMI) were both in the high 20s with a wide range of 15 to 65. The number of previous pregnancies were fairly equally distributed. The history of a congenital malformation was reported in a small percentage of offspring, but larger percentages among maternal, paternal, and any family history. There was a high percentage of concomitant medication use, which included prenatal vitamins and Tdap vaccination. In terms of gestational age when

Flucelvax was administered as part of routine obstetrical care, 28% of vaccinations occurred in the first trimester, 41% in the second trimester, and 30% in the third trimester. Approximately 1/3 of patients were enrolled before 20 weeks of gestation.

Regarding the results for pregnancy outcomes, 99.1% of births were live, there were no stillbirths, and no maternal deaths were reported in the study. Spontaneous abortions were analyzed. Only 1 one elective abortion occurred, which was before 20 weeks, and there were 4 (2.7%) spontaneous abortions. There was 1 ectopic pregnancy, which was not part of the pre-specified outcomes. With regard to events of interest in the fetus or infant, US background rates were determined by the National Center for Health Statistics (NCHS) for premature birth, which reported that 10.2% of live births are premature compared to the study finding of 9.2%. For low birth weight, the prevalence rate was used from the National Vital Statistics System (NVSS), which reported that 8.3% of live births are low birth weight compared to the study's 5.8%. The MACDP's major congenital malformation rate of 2.8% of live births, still births, or any fetal loss in any gestational age was used for major congenital malformation compared to the study's 1.9%. While diverse malformations were identified and classified, no clustering was observed of any single type of birth defect or groups of defects. The expert committee reviewed individual reports and aggregated data and found no pattern among the reported events, and was unable to assess temporality.

As with every study, there are strengths and limitations in this study. The strengths of the study are that over 660 subjects were enrolled across 3 influenza seasons. A diverse population was enrolled, which included a variety of racial and ethnic groups and a broad range of maternal ages. Enrollment occurred in 5 study sites in 4 states. However, there also were limitations. The effect of potential confounders (e.g., previous pregnancy outcomes, pregnancy complications, et cetera) cannot be ruled out. There was a potential for missing data or a limited level of detail collected as part of routine care. In addition, the MACDP counts major congenital malformations detected up to the age of 6 years.

In conclusion, these findings are consistent with published data from various databases and surveillance systems that monitor the safety of influenza vaccines during pregnancy. The committee of independent experts concluded that there was no evidence of a safety concern from the data in this study. These data support the use of Flucelvax during pregnancy for immunization against influenza in this population.

UPDATE ON COVID-19 AND INFLUENZA VACCINE SAFETY

Introduction

Tom T. Shimabukuro, MD, MPH, MBA (CDC/NCEZID) provided an update on COVID-19 and influenza vaccine safety. By way of background, a statistical signal for ischemic stroke after the Pfizer-BioNTech bivalent mRNA COVID-19 vaccine was detected in CDC's Vaccine Safety Datalink (VSD) in person ≥65 years of age during the fall of 2022. This information has been presented during prior ACIP meetings and efforts have been underway to evaluate the signal.[40] During this session, Dr. Shimabukuro summarized the results of some of the post-signal analyses. Based on these post-signal analyses, it can be concluded that the available data do not provide clear and consistent evidence of a safety problem for ischemic stroke with bivalent mRNA COVID-19 vaccines when given alone or given simultaneously with influenza vaccines,

[40] https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-02/slides-02-24/COVID-02-Shimabukuro-508.pdf; and https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-04-19/03-COVID-Shimabukuro-508.pdf

or when influenza vaccine is given alone. For the purpose of this presentation, influenza vaccine given alone means not with a COVID-19 vaccine, but possibly with other vaccines. Variable and inconsistent results were obtained in some analyses of the risk of ischemic stroke following bivalent mRNA COVID-19 vaccination, simultaneous bivalent mRNA COVID-19 and influenza vaccination, and influenza vaccination alone. Most study results have not shown an association between vaccination and ischemic stroke, and no clear pattern demonstrating increased risk has emerged. It is important to keep in mind that any real or theoretical risks of vaccine adverse events need to be placed in the context of the known benefits of COVID-19 and influenza vaccination in preventing diseases and their potentially serious complications, including stroke. Vaccine safety monitoring systems are designed to be sensitive, and the detection and assessment of potential safety signals and communication of safety information to the public is an example of the vaccine safety monitoring process working.

Dr. Shimabukuro provided a summary of 7 analyses of ischemic stroke and bivalent mRNA COVID-19 vaccination and influenza vaccination, described some additional data on ischemic stroke, and presented an interpretation of the data on ischemic stroke and bivalent mRNA COVID-19 and influenza vaccination and then wrap up with interpretation and next steps.

Dr. Shimabukuro showed a slide listing the 7 selected analyses of ischemic stroke and bivalent COVID-19 and influenza vaccination. These analyses were presented in slides corresponding to the analysis number 1-7 and described below. Note the term bivalent vaccine as used below refers to bivalent mRNA COVID-19 vaccine.

1. **VSD Rapid Cycle Analysis (RCA) of Ischemic Stroke after Pfizer-BioNTech Bivalent Booster Dose (Centers for Disease Control and Prevention)[41]**

   The data source for this analysis is the VSD data contributing sites. The primary methodology was a vaccinated concurrent comparator assessing bivalent vaccinated people compared to other bivalent vaccinated people using a 21-day risk interval and a 22- to 42-day comparison interval. The supplemental analysis was of bivalent vaccinated versus bivalent unvaccinated, but eligible for bivalent vaccine in a 1- to 21-day risk interval. The age groups included 18–64 and ≥65 years of age. The main findings were a statistical signal for ischemic stroke detected in the primary analysis after Pfizer-BioNTech in the age group ≥65 years using a 1- to 21-day risk interval. This signal attenuated over time as more data were accumulated. A post-signal assessment detected an elevated risk in the age group ≥65 years receiving same-day Pfizer-BioNTech and a high-dose inactivated influenza (HD-IIV4) or an adjuvanted influenza vaccine (aIIV4), this finding also attenuated over time as more data accumulated. No elevated risk was detected for ischemic stroke in the supplemental analysis using secondary comparators. Additional supplemental analyses suggested the comparison interval rates of ischemic stroke were lower than expected.

2. **Ischemic Stroke after Bivalent COVID-19 Vaccination: A Self-Controlled Case Series Study (Kaiser Permanente Southern California)[42]**

   This self-controlled case series study was conducted by Kaiser Permanente Southern California through an NIH grant. This is separate from the VSD, although Southern California is a VSD site. This was a separate analysis conducted independently by Southern California and it used their electronic health record (EHR) data. It was a modified self-

[41] https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-04-19/03-COVID-Shimabukuro-508.pdf)
[42] https://www.medrxiv.org/content/10.1101/2023.10.12.23296968v1)

controlled case series using age groups ≥12 years, 12—64 years, and ≥65 years. The main findings were that no elevated risks were detected for either the Pfizer-BioNTech or Moderna vaccines in any age groups in the automated data with a 21-day risk interval. There were no elevated risks detected for either Pfizer-BioNTech or Moderna vaccines in the age group ≥65 years in the automated data with a 42-day risk interval. There were several analyses with statistically significant elevated risks in the age group 12—64 years in the automated data with a 42-day risk interval. For Pfizer-BioNTech with simultaneous influenza vaccination, overall and in those with the history of SARS-CoV-2 infection and in Modernain those with a history of SARS-CoV-2 infection. Those were the strata in which the statistically significant findings were observed. After limiting the signaling analyses to chart-verified cases, the findings were no longer statistically significant.

3. **Evaluation of Stroke Risk Following COVID-19 mRNA Bivalent Vaccines among US Adults Aged ≥65 Years in CMS data (US Food and Drug Administration)[43]**

   This is an FDA-sponsored study for which the data source was Medicare claims data. The populations were community-dwelling Medicare beneficiaries ≥65 years of age. The primary population were recipients of bivalent COVID-19 vaccines. The secondary population were recipients of a HD-IIV4 or aIIV4 influenza vaccine. The methodology was a modified self-controlled case series with Farrington adjustment. In terms of the main findings, the primary population analyses did not show any consistent stroke risk after mRNA COVID-19 vaccination. An increased risk was observed with concomitant or same-day administration of influenza vaccination. These findings were for non-hemorrhagic stroke after Pfizer-BioNTech and HD-IIV4 or aIIV4 vaccine with a 22- to 42-day risk interval and transient ischemic attack after Moderna and HD-IIV4 or aIIV4 vaccine with 1-to 21-day risk interval. The secondary population analyses showed a small increased risk of non-hemorrhagic stroke after HD-IIV4 or aIIV4 influenza vaccines, with a 22- to 40-day risk interval. The risk remained for people without concomitant bivalent mRNA COVID-19 vaccination.

4. **Ischemic Stroke after mRNA COVID-19 Bivalent Vaccine Administration in Patients aged ≥65 Years: Analysis of Nation-Wide Patient Electronic Health Records (Case Western Reserve University School of Medicine)[44]**

   The data source for this analysis was the TriNetX system, which is a cloud-based analytics platform that includes EHR data on over 90 million unique patients in the US. In terms of the methodology, this was a retrospective cohort study among people ≥65 years of age. The main findings were that patients who received bivalent Pfizer-BioNTech vaccination had a similar hazard for ischemic stroke encounters compared to those who received bivalent Moderna vaccination, but had a lower hazard ratio than those who received the monovalent Pfizer-BioNTech or Moderna booster vaccines 1—-21 or 22—42 days post-vaccination.

5. **Stroke, Myocardial Infarction, and Pulmonary Embolism after Bivalent Pfizer-BioNTech COVID-19 Vaccination (EPI-PHARE Scientific Interest Group, France)[45]**

   The data source for this study was the French National Health Data System (SNDS) linked to the national coronavirus disease 2019 (Covid-19 vaccination database. It was a matched cohort study matching 1:5 in people ≥50 years of age. A recipient of a monovalent vaccine was matched to recipients of bivalent mRNA COVID-19 vaccines. These individuals were

[43] https://www.medrxiv.org/content/10.1101/2023.10.10.23296624v1)
[44] https://www.medrxiv.org/content/10.1101/2023.02.11.23285801v1)
[45] https://www.nejm.org/doi/full/10.1056/NEJMc2302134)

followed for 21 days after vaccination. The main findings were that compared to monovalent Pfizer-BioNTech vaccination, bivalent Pfizer-BioNTech vaccination was not associated with an increased risk of ischemic stroke, hemorrhagic stroke, myocardial infarction, or pulmonary embolism in people ≥50 years of age. The authors previously found no increased risk in the incidence of stroke, acute myocardial infarction, pulmonary embolism, or pulmonary embolism after administration of the monovalent Pfizer-BioNTech vaccine.

6. **BA.1 Bivalent COVID-19 Vaccine Use and Stroke in England (UK Health Security Agency and the London School of Hygiene and Tropical Medicine)[46]**

   The data source for this analysis was the National Health Service (NHS) hospital admissions in England linked to the National Immunisation Management System (NIMS). In terms of the methodology, this was a self-controlled case series in people ≥50 years of age and ≥65 years of age using a 1- to 21-day risk window, with further analysis in people ≥65 years of age given simultaneous bivalent mRNA COVID-19 vaccine and influenza vaccination. Regarding the main findings, there was no increased risk of stroke in the 21 days after vaccination with either the Pfizer-BioNTech or Moderna bivalent mRNA vaccines. Similar results were obtained for ischemic and hemorrhagic stroke for the subset of people ≥65 years of age given influenza vaccine on the same day as the bivalent mRNA COVID-19 vaccines.

7. **Safety of Monovalent and Bivalent BNT162b2 mRNA COVID-19 Vaccine Boosters in At-Risk Populations (Israel)[47]**

   This was a large-scale retrospective self-controlled case series study. The data source was the Clalit Health Services (CHS) medical records. This is the largest healthcare organization in Israel with over 3.5 million enrollees, 1.2 million of whom are ≥60 years of age. It was a self-controlled case series. The main findings were that no safety signals were detected for ischemic stroke after either monovalent or bivalent Pfizer-BioNTech COVID-19 vaccines used in Israel in the overall analysis or in people ≥65 years of age.

In terms of additional data on ischemic stroke, there were no unusual or unexpected reporting patterns observed and no evidence of a safety concern detected for ischemic stroke with either of the bivalent mRNA COVID-19 vaccines in VAERS monitoring. FDA monitoring in the CMS data and in the VA monitoring system did not detect any safety signals for ischemic stroke following bivalent mRNA COVID-19 vaccination using historical comparator designs. A separate ad hoc CDC analysis during the bivalent Pfizer-BioNTech ischemic stroke signal assessment did not detect an elevated risk for ischemic stroke after influenza vaccination alone. Surveillance conducted by international regulatory and public health partners did not detect a safety concern for ischemic stroke following bivalent mRNA COVID-19 vaccination. No evidence of a safety signal for ischemic stroke was detected in the manufacturers' global monitoring of bivalent mRNA COVID-19 vaccination. No safety signals were detected for ischemic stroke for primary series or monovalent boosters for Pfizer-BioNTech or Moderna vaccines in US and global monitoring. Data suggest that COVID-19 and influenza disease are associated with an increased risk of stroke, which was previously presented during an ACIP meeting.[48]

[46] https://jamanetwork.com/journals/jama/fullarticle/2806456)
[47] https://www.sciencedirect.com/science/article/pii/S1473309923002074?via%3Dihub)
[48] https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-02/slides-02-24/covid-05-twentyman-508.pdf

Data on disease are important in the context of these findings. Looking at some of the data from the FDA study, monthly incidence rates of non-hemorrhagic stroke (NHS) in Medicare claims data suggests seasonality. There are other data showing this pattern of seasonality. Incidence tends to be higher in the Winter months, dips down in the Summer months, and then starts creeping back up in the Fall. This offers some indirect evidence of possible correlation with circulating viral respiratory pathogens. Looking at data of outpatient visits for respiratory illness in the US from ILINet and focusing on the 2022-2023 season, there was what seems to potentially be a relatively severe influenza-like illness (ILI) season with a fairly sharp peak compared to some of the other seasons and it peaked early. There is some evidence that infection is associated with stroke, particularly with COVID-19 and influenza. It is important to also consider respiratory and viral illnesses when looking at these vaccine safety data.

Regarding the interpretation of the analyses of ischemic stroke and bivalent COVID-19 and influenza vaccination, variable and inconsistent results were obtained in some analyses of the risk of ischemic stroke following bivalent COVID-19 vaccination, simultaneous bivalent COVID-19 and influenza vaccination, and influenza vaccination alone. There is a lack of consistency in findings from different data systems, when using different methods, across age groups, and across sub-group analyses. The most common findings across the studies are findings of no association. Multiple comparisons were conducted in studies without adjusting for multiplicity, and few of these reached statistical significance. The studies were not designed to account for the potential protective effect of vaccination on stroke in later post-vaccination periods. Adjusting for seasonality and restricting analyses to chart-verified cases frequently resulted in attenuated findings or findings that were no longer statistically significant. The remaining statistically significant findings tended to be relatively small in magnitude (i.e., RRs<2). Ischemic stroke cases in the analyses are predominantly occurring in older people and in people in the upper ranges of the age groups studied (e.g., upper range of a 12–64-year-old age group), meaning that there are relatively few cases in younger people.

The available data do not provide clear and consistent evidence of a safety problem for ischemic stroke with bivalent mRNA COVID-19 vaccines when given alone or given simultaneously with influenza vaccines, or when influenza vaccine is given alone. Most study results have not shown an association between vaccination and ischemic stroke, and no clear pattern demonstrating increased risk has emerged. Seasonality of stroke risks and an unusual respiratory illness pattern in 2022 and 2023 could be impacting the results of some of these analyses. Unrecognized SARS-CoV-2 infection also could play a role in occurrence of stroke after vaccination. It is important to recognize that any real or theoretical risk needs to be placed in the context of the known benefits of COVID-19 and influenza vaccination in preventing COVID-19 and influenza disease and their potentially serious complications, including stroke. Simultaneous vaccination provides substantial benefits in keeping patients up-to-date with recommended vaccines and protected from vaccine-preventable diseases. Vaccine safety monitoring systems are designed to be sensitive, and the detection and assessment of the ischemic stroke signal and communication to the public is an example of the vaccine safety monitoring process working.

The next steps are to conduct additional analyses on the possible relationship between ischemic stroke and bivalent mRNA COVID-19 vaccination, simultaneous administration of bivalent mRNA COVID-19 and influenza vaccines, and influenza vaccine alone. Vigilant safety monitoring will continue of the 2023-2024 COVID-19 and influenza vaccines, including for ischemic stroke. CDC will be happy to brief the ACIP when additional safety data become available.

Discussion Points

Dr. Loehr noted that the Influenza WG heard about the FDA study referred to on Slide 7 a couple of weeks before this ACIP meeting, which had some concerning findings. A couple of days before the meeting, the presenter provided the WG with more details about this. The WG asked for context and a presentation during this meeting. Hence, this all came together from Dr. Shimabukuro in 48 hours. Dr. Loehr expressed appreciation for the details and a perspective of all of the studies, not just the one study that came out 2 weeks previously. The context of the vast number of studies which are suggesting that there is not a consistent pattern of concern.

Dr. Daley noted a similar observation to Dr. Loehr's and expanded on that further. Vaccination programs and vaccine safety monitoring has taught everyone to be quite humble. By that he meant that there have been circumstances in which he heard something at first that seemed fairly implausible: intussusception following an oral or virus vaccination the first time he heard of it. The first time he heard about myocarditis, he thought that seemed unlikely. He thought Slide 16 reflected one of the best examples of integrating multiple data sources, multiple platforms, multiple study designs, and then helping the ACIP interpret this for themselves and the public. As Dr. Shimabukuro concluded, the vaccine safety monitoring system is working and working well, even though everyone recognizes that this is complex and they need to be humble, by that he meant expect the unexpected. The system was designed to be sensitive in order to cast a wide net, realizing that this is difficult to explain to the public. Casting a wide net, may mean that there are things that turn out to be what is called a "false positive signal." That is a contradistinction and in distinction to what was found for myocarditis, which is a rare adverse event . It was consistent across multiple systems in timing, vaccine types, and dose. That was very different from what they were seeing with this presentation. He expressed appreciation for the ability to bring this to the full ACIP for full transparency and to help understand it.

Dr. Shimabukuro emphasized that there are multiple complementary systems that work in different ways and use different methods within CDC and across the federal government with partners such as the FDA, Department of Veterans Affairs (VA), and Department of Defense (DoD). As Dr. Daley noted, these systems are designed to be sensitive to be able to rapidly detect and assess potential safety problems. CDC strives to be timely and transparent in its communication of safety information. He agreed that consistency of findings across different systems using different methods is important and tells something about a potential adverse event . The myocarditis signal is a great example in which the evidence from multiple systems inside and outside the US all pointed to a common finding that is a much different situation than myocarditis.

Dr. Lee expressed appreciation to Dr. Shimabukuro for adding clarity when often times it feels like there is a lot of uncertainty. She also emphasized that they spent the last half of this day focused on vaccine safety as a topic of great interest. The ACIP is committed to continuing to review the benefit-risk balance in real-time and always revisit decisions, recognizing that as things change, the ACIP's decisions also must change. Given the totality of the data Dr. Shimabukuro presented, she felt comfortable with the current recommendations rolling forward. Moving into the respiratory season, she was grateful to have the opportunity to have vaccines to prevent much of this illness. She thought it would begin to look very different in the next year or two, the more they are able to tackle disease. As Dr. Shimabukuro brought up, the ACIP typically focuses on vaccine-preventable illnesses, but COVID-19 has taught them that there are longer-term effects of some of these infections and that preventing infections not only may prevent the acute illness, but perhaps provides longer-term protection more than they realize. Akin to the comment that respiratory viral infections have a seasonality, many of the serious

illnesses (e.g., stroke, myocardial infarction, and other outcomes) also have some seasonality and can be associated with or triggered by an initial respiratory illness. She thinks vaccines and the impact they have on the health of the individual are undervalued. She encouraged continued pursuit of rigorous safety from a broad-scale perspective, and looking for opportunities to better understand the longer-term impact of these vaccines on the health of populations, given that this longer-term impact seems far greater than they think.

PUBLIC COMMENTS

Overview

The floor was opened for public comment on October 25, 2023 at 12:50 PM ET. Given that many more individuals registered to make oral public comments than could be accommodated during this meeting, selection was made randomly via a lottery. Dr. Lee provided a gentle reminder that the ACIP appreciates diverse viewpoints that are respectful in nature and issue-focused rather than comments directed at individuals. The comments made during the meeting are included in this document. Members of the public also were invited to submit written public comments to ACIP through the Federal eRulemaking Portal under Docket Number ID CDC-2023-0079. Visit http://www.regulations.gov for access to the docket or to submit comments or read background documents and comments received.

Public Comments

Mr. Edward Nirenberg
Vaccine Advocate

I just wanted to say good afternoon first and thank the ACIP, CDC, and the FDA for their continued tireless efforts in keeping the American public safe through their guidance and the transparency with which they've conducted themselves. I find that to be truly commendable. I do want to highlight several concerns. The first of these I think is the urgent need for a Vaccines for Adults Program. Vaccines for Children is a critical tool in our arsenal for protecting kids, and I would second calls for simplification of the vaccine schedule and echo concerns on voting on the meningococcal vaccination today before those recommendations have been revised. I think that we may be putting the "cart before the horse" there. I would also like to ask that in the future there be closer communication with manufacturers regarding what is feasible for implementation to allow for better scale-up as new products are rolled out. I'm really thrilled that nirsevimab exists. It's a tremendous triumph of our science and medicine to have this passive immunization as an option, but right now demand far outpaces supply in large part because the breadth of the recommendation by CDC covered far more individuals than the manufacturer was prepared for. I don't think that the recommendation was a mistake. I wish to be clear about that. But in creating such a large demand for the monoclonal antibody, many parents are now finding it impossible to obtain and consequently, children are forced to rely solely on maternal antibodies for protection. I would also like to finally underscore the devastating effects that mis- and dis-information continue to have on public health. I implore that regulators and CDC respond to it actively. Recently, the Surgeon General of Florida, who in the past has tampered with investigations of vaccine safety to fabricate findings of a mortality signal that is not present, released a Provider Alert enumerating numerous canards about the safety of vaccines regarding mRNA vaccines and urged that they not be given to those under 65. There might be room to debate the value and necessity of a COVID-19 booster in those who are at apparently low risk, although I would note that this group does not begin and end with people who are

under 65. That debate fundamentally needs to be based on accurate premises. In “poisoning the well” with lies, the Surgeon General is obstructing the provision of informed consent. It is, furthermore, deeply disappointing to see at this very moment an extremely poorly done pre-print alleging DNA content in the mRNA vaccines beyond regulatory limits is gaining substantial traction on social media, going as far as claiming the existence of SV40 promoter sequence in the plasmid that is used to help select for [unclear] and pairing the plasmid during the production represents a hazard to vaccines. I think it would be helpful if materials were available enumerating the manufacturing process in greater detail from sources like the CDC to help provide perspective on the matter. Thank you so much.

Ms. Elizabeth Ditz
Vaccinate California

Good morning. It’s still morning here in California. I'm Liz Ditz from Vaccinate California. Thank you, committee members, again for your dedication to public health—not just today and tomorrow, but all the work that leads up to these meetings. I'm over 65 and I have 10 grandchildren under the age of 15. I look at vaccine policy through those 2 lenses—vaccines for seniors and pediatric vaccines. A committee member whose name I did not catch said earlier this morning during the Mpox vaccine discussion, "We really need a Vaccines for Adults Program." Yes, we do. The cost of vaccines is prohibitive for many. I know this committee rightly has a well-defined role. It only recommends vaccines and schedules, but I want to take a minute to tell you what I'm seeing as a person who advocates for vaccines, both in person in my community and on social media. As Peter Hotez has been saying for years now, “The rise of anti-science is deadly.” We need a vaccine advocacy program as well-funded and well-connected as the forces that spread fear and distrust of vaccines. This can't be a government program. It must fall to non-government advocacy organizations such as Vaccinate Your Family, grassroots organizations such as Voices for Vaccines, single disease organizations such as Family Fighting Flu, and the many state-level immunization coalitions such as the California Immunization Coalition. *Rolling Stone* recently published an article detailing the amount of funds flowing to the forces, the organizations, that are engaged in grassroots marketing of fear, uncertainty, and doubt about vaccines. There's no such flow of funds, none really, to non-governmental vaccine advocacy organizations. As the recent rollout of vaccines for seniors, the Beyfortus™ vaccine, as my friend and colleague Edward Nirenberg mentioned, has been disastrous. Anything that increases the difficulty of getting a vaccine a person wants reduces the trust in vaccines. I urge the committee to consider those factors going forward as they recommend future vaccines. Thank you, committee. I really appreciate your work. That's the end of my comments.

Joanna Colbourne, CAE
Deputy Executive Director
National Foundation for Infectious Diseases

Good afternoon. Thank you for the opportunity to comment on behalf of the National Foundation for Infectious Diseases, or NFID. For 50 years, NFID has been educating and engaging the public, communities, and healthcare professionals about infectious diseases across the lifespan. We thank ACIP for its important work in guiding US immunization policy and protecting public health. Although the work of NFID covers all infectious diseases, my comments today will address 5 vaccine-preventable diseases in particular: meningococcal disease, Mpox, flu, RSV, and COVID-19. Meningococcal disease is a serious illness. Even with treatment, approximately 1 out of every 10 people who get meningococcal disease will die. Of those who survive, up to 20% suffer serious and permanent complications. Despite the availability of safe and effective

vaccines, many US adolescents are not fully vaccinated. By making clear and easy-to-understand recommendations, ACIP can help raise awareness about the importance of vaccination to help protect young people from multiple strains of meningococcal disease. Mpox is a rare but potentially serious disease. Thousands of cases have been reported in the US, including more than 50 deaths during the 2022-2023 outbreak. Vaccination of those at high risk is crucial to prevent further cases, yet vaccination rates remain low, especially among Black and Hispanic populations who are disproportionately affected. Strategies are necessary to help increase Mpox vaccination rates among vulnerable populations. Flu, COVID-19, and RSV can each be serious, causing mild to severe symptoms and potentially life-threatening complications. For the first time this season, there are vaccines available to help protect against all 3 diseases, but a recent NFID survey of US adults found that many underestimate the severity of these diseases and do not plan to get vaccinated during the 2023-2024 season. Fewer than 1 in 4 US adults are concerned about themselves or someone in their family getting infected with flu, COVID-19, RSV, or pneumonia. Forty-three percent of US adults do not plan to or are unsure if they will get vaccinated against flu this season, and about 1 in 4 US adults who are at higher risk for flu related complications said that they were not planning to get vaccinated. Only 40% of US adults plan to get an updated COVID-19 vaccine. Among adults aged 60 years and older, only 40% plan to get an RSV vaccine. For each of these diseases, among those who do not plan to get vaccinated, the top reasons cited included concerns about potential side effects or general distrust of vaccines. These findings underscore the urgent need for greater education and awareness. Additional information about the NFID survey and other resources are available at www.nfid.org. NFID stands ready to work with the 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.

Mrs. Alicia Stillman, MBA, MPH
Director, Emily Stillman Foundation
Co-Founder, Meningitis B Action Project

Hi. Thank you very much for giving me the opportunity to speak and I also want to thank you for everything that you do. My name is Alicia Stillman. I am the Director of the Emily Stillman Foundation and also the Co-Founder of the Meningitis B Action Project. In February of 2013, I lost my 19-year-old daughter Emily to meningitis B just 36 hours after her first symptoms. This summer, my husband and I had the blessing of being able to walk our other 2 children down the aisle to marriage and I would've given anything to have Emily there with us. She was funny, witty, and warm and I know she would've made that day even more special. But I'm not here today to tell you again my sad story. Most of you know it. I'm here as a concerned citizen and a public health advocate committed to making sure that this doesn't happen again to other mothers, in other families, and to other children. I understand the importance of considering the cost-effectiveness of the vaccine when determining how best to recommend it. What I don't understand, though, is why cost-effectiveness should be considered more strongly than other factors, primarily, the actual feasibility of implementing such a recommendation successfully. I've long looked forward to the day when meningitis vaccination would become simpler. I thought when a pentavalent vaccine would become available, I would be out of a job. There would no longer be a need to advocate and educate, but I am afraid that the recommendation you are considering most strongly would further complicate an already complicated issue. PICO 1 would require providers to stock and discuss 3 different types of meningitis vaccines—something you all know they are unlikely to do. The MenB dose would also remain a shared clinical decision-making recommendation, even though we already know that shared clinical decision-making for the MenB vaccine has not worked out since it was first implemented. PICO 1 would only worsen the already low vaccination rates for the meningitis B and deepen the

equity gap for adolescent vaccination. I urge you to look beyond the cost-effectiveness data, consider the real-life consequences of your recommendation, and make a routine recommendation for all meningitis vaccines so protection can be within reach for all who need it. If not, we'll continue to see lives lost. It's your duty and your responsibility to mothers and fathers just like me and just like you. Again, thank you for your consideration and for all that you do.

Mrs. Patti Wukovits, BSN, RN, AMB-BC
Executive Director, Kimberly Coffey Foundation
Co-Founder, Meningitis B Action Project

My name is Patti Wukovitz. I want to thank you very much for giving me the opportunity to share my thoughts today. I very much respect the work that you do. I'm a Registered Nurse. I'm the Executive Director of the Kimberly Coffee Foundation and Co-Founder of the Meningitis B Action Project. Meningococcal meningitis vaccination is a topic that's very, very close to my heart. In 2012, I lost my daughter Kimberly Coffee to meningitis B at the age of 17, just 3 days before her high school graduation and only a few months before starting college to become a Pediatric Nurse. Within hours of Kim's first symptoms, her heart and kidneys were failing. Shortly after, she was declared brain dead and I had to make the unbearable decision to remove my beautiful daughter from life support. Kimberly didn't have the opportunity to be vaccinated against meningitis B. While she had received the MenACWY vaccine, at the time, the MenB vaccine was not yet available to protect her. It is today and that's why I'm here. Since Kim died, I've shared her story and educated at hundreds of schools, universities, and medical facilities across the country. I've worked really hard over the last 10 years, but I'm not sure how much of a difference my hard work has made. Why do I say this? Because the current shared clinical decision-making recommendation for the MenB vaccine simply doesn't work in clinical practice because it's perceived as less important than routine vaccinations, and there's data to back that up. According to a recent study, as many as 49% of pediatricians have not discussed the MenB vaccine with their adolescent patients and more than 80% of parents have not heard of the MenB vaccine. So how can parents act on what they don't know? But today is the day I have been waiting for since I said goodbye to my daughter. Today is a major turning point. We now have a vaccine that can help protect adolescents against all 5 serogroups in 1 vaccine. The availability of the pentavalent vaccine has the potential to completely change the landscape of meningitis vaccinations, but only if the pentavalent vaccine receives a recommendation that is representative of how vaccines are actually used in clinical practice. Quite simply, shared clinical decision-making recommendations don't work for Men B vaccination. The low uptake rates of MenB vaccines speak for themselves. Only 3 out of 10 17-year-olds have received 1 dose of the MenB vaccine. As a nurse who administers vaccines, as a public health advocate, and most importantly, as Kimberly's mom, I urge you to consider the public health consequences of how your recommendations are perceived by healthcare providers, by school and college administrators, and by parents and adolescents. I urge you to please issue clear and simple recommendations to end the confusion by giving a routine recommendation for all available meningococcal vaccines. My daughter didn't have the choice to get fully vaccinated, and I owe it to her to make sure that other kids do. Thank you so much.

Michelle Fiscus, MD
Chief Medical Officer
Association of Immunization Managers

Thank you for the opportunity to provide remarks on behalf of the Association of Immunization Managers. I'm Dr. Michelle Fiscus, AIM's Chief Medical Officer. AIM is the non-profit organization that supports the 64 CDC-funded Immunization Program Managers across the 50 states, 8 US territories and affiliated states, and 6 major cities, including Washington, DC. As a pediatrician and a mom, I would like to thank the 2 mothers who just shared their stories and I'm very sorry for the loss of your daughters. This has been yet another remarkable year for immunizations. We can protect more children than ever before from serious infection from respiratory syncytial virus. We can also protect pregnant people and older adults from that disease, and now we have the opportunity to bring Mpox and updated meningococcal vaccines into the VFC Program. We thank the members of the ACIP for working so diligently to vet the evidence and we're excited about additions to the VFC Program, which ensures vaccines are available to all children regardless of their family's ability to pay for them. Access to vaccines through the VFC Program has been estimated to have saved over a million lives, prevented more than 472 million illnesses among children, and has saved over $2.2 trillion in societal costs. This is an extraordinary return on the investment and should rank among the most successful governmental programs in American history. We need to continue to share the success of this program because support for the VFC Program is more important now than ever. Immunization Program Managers continue to be challenged to maintain program operations, enroll new VFC providers such as birthing hospitals, incorporate new products, deal with delays and shortages, chase and mitigate outbreaks of vaccine-preventable diseases, and modify Immunization Information Systems (IISs) to include functionality that meets the nuanced needs of new products and improved data quality. Yet just last week, the CDC sent a report to Congress documenting that the current funding level of the Section 317 immunization program is nearly $1 billion below the estimated national needs. There are only 64 Immunization Program Managers in the United States in its territories. Two-thirds of them are new to their roles since the pandemic and are only just now learning how to manage a program outside of a pandemic emergency response. We all hoped there would be a return to normal operations once COVID-19 vaccines were available, but then it was Mpox and now it's nirsevimab and RSV vaccines, and we need to navigate even greater barriers to equitable access that we have faced than ever before. We would like to thank the ACIP, HHS, FDA, and our ever-growing list of partners that work alongside AIM and Immunization Program Managers every day to prevent suffering and death. We're equally appreciative of the dedicated team at CDC who has worked tirelessly to partner with jurisdictions through these challenging times. Thank you.

Ms. Francesca Testa, MPH
Quinnipiac University

Good afternoon and thank you for the opportunity to speak. My name is Francesca Testa and I testify before you today as a survivor of meningococcal disease. Children, adolescents, and young adults should not be suffering or dying from a vaccine-preventable disease when we have vaccines available to protect against it. I urge you all today to vote to provide the broadest access available to our children from meningococcal disease for MenACWY and B. At 17 years old, my life was changed forever when in April of 2006, I came down with what seemed like the flu and the next morning, within hours, my mother tried to wake me and I was unresponsive, being airlifted to Yale New Haven Hospital, where I slipped into a coma and was put on a respirator to stabilize my breathing. Within hours, I went from being an athletic and energetic teenager to having less than a 20% chance of survival. Over the next week, although my

condition stabilized, my recovery was daunting, having to learn to walk again from damage caused by the septic shock and battling severe neurological symptoms. Although I survived, the long-term complications and disabilities will remain with me for the rest of my life. At 17 years old, it's a very difficult thing to come to terms with. I had not been vaccinated against meningococcal disease, and what concerns me today is that the recommendation being considered most strongly by the ACIP for the pentavalent vaccines will not make the meningitis prevention process more straightforward, but rather further complicate already difficult-to-navigate clinical guidelines for meningococcal vaccination. We cannot put a price tag on our children's lives. Shared clinical decision-making does not provide physicians and families with a clear and unambiguous recommendation. Shared decision-making only works if physicians do it. We know there is great inequity of information across this country because physicians are confused by the recommendation and it is not uniformly adopted. The low uptake rates of the MenB vaccine speak for themselves when only 3 out of 10 17-year-olds have received even just 1 dose of the MenB vaccine. Vaccine protection should not be left up to chance. Even though I'm recovered, I will never be the same. I will battle hearing loss, vision loss, chronic migraines, and long-term cognitive impairments for the rest of my life. In addition to cost-effectiveness data, I urge you to consider prioritizing the real-life consequences of this disease and the feasibility of implementing your recommendations in a clinical setting to make a routine recommendation for all meningitis vaccines. I would also encourage you to consider that the reason we've seen such low levels of disease is because we have the current recommendations in place. But given the devastating nature of meningococcal disease, we need stronger, more routine recommendations versus complex weak ones that can only create barriers to uptake. Thank you so much for your time and consideration today.

THURSDAY: OCTOBER 26, 2023

AGENCY UPDATES

Centers for Disease Control and Prevention

Demetre Daskalakis, MD, MPH began with an update on CDC's primary focus at this time of year, respiratory virus season, for which the ACIP's partnership is so important in terms of protecting people against respiratory diseases. This Fall and Winter are not only a top priority for the agency, but also for the nation. It is important to protect the population and healthcare so that the nation has the capacity of HCP who do not have respiratory diseases to treat and care for people. The good news is that thankfully, they are in the strongest position ever for fighting the respiratory conditions of COVID-19, RSV, and influenza. With such an erudite group, it is important to note that there are more than these 3 conditions with which they work during this and other seasons because there are many exciting interventions to address them. These 3 conditions tend to be the ones that are detectably causing the largest strain on healthcare and burden of disease. While COVID-19 activity currently continues to decline in most parts of the country, in the context of the overall story it remains the principal cause at this time of year of respiratory virus-associated hospitalizations and deaths. Influenza activity also remains relatively low, but not for long as activity is starting to increase in the country. Some areas are seeing a significant increase in influenza, particularly Alaska and the Mariana Islands. This also is officially RSV season, with the 3% threshold having been reached. The normal progression of RSV is being observed in the country starting in the South and slowly making its way North, with the expectation that RSV will occur throughout the country in 1 to 2 months.

To highlight a couple of important efforts, CDC published the "Healthcare Provider Toolkit: Preparing Your Patients for the Fall and Winter Virus Season"[49] that provides talking points for clinical and other partners for influenza, COVID-19, and RSV and interventions, including vaccines and treatments. There also is a focus on co-administration and some print materials that can be provided to patients. Dr. Daskalakis touted the importance of vaccines, emphasizing that vaccines remain the safest protection to avoid hospitalization, long-term health impacts, and death. Vaccines are especially important for people who are at higher risk of developing serious complications, including older adults and those who have weakened immune systems. Though it is a campaign that focuses on influenza, so much of this falls into the "wild to mild" category that these vaccines are taming these infections, this is an effective way of communicating the role of these vaccines in people's health and in public health. The bottom line is that this encourages everyone to stay up-to-date on their vaccinations.

Another important activity this season is a significant change in the way COVID-19 vaccines are distributed in the US. They have had the experience of the largest USG-implemented vaccination program in US history, with 700 million doses of COVID-19 vaccination administered to over 270 million people. That is amazing. On September 15th, a shift was made from USG distribution of COVID-19 vaccine to distribution through commercial networks. That has been really instructive in terms of the important observation that strategies for public health distribution of vaccine tend to be different than strategies for commercial distribution of vaccine. Despite a year plus of planning, some very important lessons learned have been learned about how public health potentially can better influence how commercial vaccine moves in the country. The US does not have a Vaccines for Adult Program. As COVID-19 vaccine shifted to the commercial market, it became clear that there is a need to ensure that uninsured or underinsured people in the US are able to access vaccination regardless of their insurance status. Thus, CDC launched the COVID-19 Vaccine Bridge Access Program in mid-September, an accelerated and very large program that created the possibility of access for 25 to 30 million Americans who are uninsured or underinsured. The Bridge Access Program leverages unique public-private partnerships with pharmacies and vaccine manufacturers to create a 2-channel system. This public health channel focuses on vaccine partners who work in health departments and providers who administer vaccines to their jurisdiction. There also are great partnerships with the important retail pharmacy channel, with 3 partners that are participating in providing access to vaccines.

The Bridge Access Program that provides COVID-19 vaccination is temporary and provides only COVID-19 vaccination. Therefore, a Vaccines for Adults (VFA) Program is an important strategy. The VFC program has been a "game changer" for children. Having worked with various infectious disease spaces in his career, Dr. Daskalakis said he thinks of 2 efforts that have had enormously high impact in terms of public health interventions, the Ryan White HIV/AIDS Program and the VFC Program. These programs have been so important in the world in terms of providing people with prevention and services that they need to stay healthy. His hope is that a bridge to somewhere is a bridge to a VFA Program. It is important to think about strategies to create a program in the US that is not a 2-legged stool that is wobbly, but a 3-legged stool that includes the 317 Program VFC and a VFA Program. The VFC is an amazing federally-funded, mandatory entitlement program that provides vaccines at no cost to children who might not otherwise get them. Imagine what could be done with both VFC and VFA programs. The VFC has a 30-year history during which it has prevented 472 million illnesses, over 1 million deaths, and nearly 2.2 trillion in societal costs. Every dollar spent saves $10 to $11 in projected health care costs. Since 1994, the VFC Program has been critical in increasing

[49] https://www.cdc.gov/respiratory-viruses/tools-resources/health-care-providers.html

rates of vaccine uptake in US children, reducing vaccine-preventable diseases, and serving as an equity intervention that reaches the most vulnerable people who otherwise may not be able to get vaccine. The primary purpose of the VFC is to buy vaccine, with 90% of that program funding coming from that. In terms of the difference between VFC, VFA, and 317, about 3% of the 317 budget goes to purchasing vaccine. It is an emergency safety valve that provides infrastructure to support the VFC Program and could support a VFA Program. These 3 legs on the stool are critical to be able to achieve the goal.

Something to be aware of that the ACIP is tracking closely is nirsevimab, which is a very important long-acting preventative antibody to prevent RSV illness in newborns. There have been some supply constraints and a limited supply. CDC issued a Health Alert Network (HAN) alert on October 23rd that advises HCP to prioritize the antibody to those who need it most—young infants from birth through 5 months of age and infants with high-risk conditions. It also is critical to have nirsevimab reach American Indian and Alaska Native infants, given the burden of disease in that population—especially if they are in remote settings. Additionally, the HAN reminded people of alternatives for some babies and newborns between 8 to 19 months of age with certain medical conditions specifically palivizumab in order to spare some of the 100 milligram doses, which is where most of the issues are occurring with nirsevimab. This highlights that there is another way to protect newborns from RSV, which is vaccination of pregnant persons. CDC continues to be in close contact with Sanofi to make sure that there is a plan moving forward for the season, remembering that commercial distribution and supply are different from public health or USG distribution of supplies. To uplift an important point for RSV prevention, there are the 3 options of nirsevimab, palivizumab, and vaccination in pregnant persons at 32 to 36 weeks of pregnancy. It is critically important to get vaccines to people from the manufacturing and distribution side, as well as the access and coverage side. While they are in a place of strength, there also are some important areas to continue to address in order to maintain that strength and do so in an equitable way.

Centers for Medicare and Medicaid Services

Mary Beth Hance provided CMS updates, noting that they were consistent with what they just heard from CDC. She highlighted that the Inflation Reduction Act (IRA) provision that requires traditional Medicaid to cover all ACIP-recommended vaccines without cost-sharing went into effect on October 1st. This is for adults who are enrolled in traditional Medicaid, which is the pre-expansion Medicaid. Previously, vaccines were optional for states and there could be cost-sharing. All states covered some vaccines, but most did not cover all ACIP-recommended vaccines. This is very exciting from the Medicaid perspective and vaccines for adults. Obviously, there is still a lot of work to do in this space, but this is an important step forward. CMS issued guidance to states in the form of a Fact Sheet at the end of June. In terms of recent vaccinations and importantly coordination with CDC, a lot has happened in the Fall and CMS has worked closely with CDC on all of them. The commercialization of COVID-19 vaccines was a very important transition. CMS worked hard to amplify messaging to get information out that was consistent with what CDC was sharing. She expressed appreciation for CDC colleagues speaking to Medicaid agencies about the Bridge Access Program. CMS also has worked closely with CDC in terms of the new products that are available for RSV and amplifying important information about them being available, including the supply issues that that they just heard about and making sure everyone knows about everything that is available in this space. It is also important not to lose sight of routine immunizations with everything else that is happening in this space. Therefore, CMS continues to amplify the importance of routine immunizations and has reiterated that message many times to states.

Food and Drug Administration

David Kaslow, MD reported that since the last ACIP agency report in June 2023, FDA has approved or authorized 10 vaccine products, issued an updated guidance to industry, and convened a Vaccines and Related Biologics Products Advisory Committee (VRBPAC) meeting. On June 30th, FDA's Center for Biologics Evaluation and Research (CBER) approved a change to the prescribing information of DENGVAXIA, the Dengue Tetravalent Vaccine, Live to include safety and efficacy data that support the use of DENGVAXIA in individuals 6─16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas. On July 20th CBER approved CYFENDUS Anthrax Vaccine Adsorbed, Adjuvanted indicated for post-exposure prophylaxis (PEP) of disease following suspected or confirmed exposure to *Bacillus anthracis* in persons 18─65 years of age when administered in conjunction with recommended antibacterial drugs. On July 27th, CBER approved a change to the prescribing information of ERVEBO, the Ebola Zaire Vaccine Live Vaccine to extend the indication for use in individuals ≥12 months of age. On August 21st, CBER approved ABRYSVO, the RSV vaccine indicated for active immunization of pregnant individuals at 32 to 36 weeks gestational age for the prevention of LRTD and severe LRTD caused by RSV in infants from birth─6 months of age. On September 11th, CBER approved COMIRNATY and SPIKEVAX 2023-2024 formula COVID-19 mRNA vaccines for use in individuals ≥12 years of age and amended the Emergency Use Authorizations (EUAs) of Moderna COVID-19 vaccine and Pfizer-BioNTech COVID-19 vaccines to include the 2023-2024 formula for use in individuals 6 months─11 years of age to prevent COVID-19. On October 3rd, CBER amended the EUA of the Novavax COVID-19 vaccine adjuvanted to include the 2023-2024 formula for use in individuals ≥12 years of age and older to prevent COVID-19. On October 20th, CBER approved PENBRAYA meningococcal groups A, B, C, W and Y vaccine indicated for active immunization to prevent invasive disease caused by Neisseria meningitidis serogroups A, B, C, W, and Y approved for use in individuals 10─25 years of age. On October 19th, CBRE issued "Development and Licensure of Vaccines to Prevent COVID-19: Guidance for Industry" to assist sponsors in the clinical development and licensure of vaccines for the prevention of COVID-19. On October 5th, VRBPAC convened an open session to discuss the strain selection for influenza virus vaccines for the 2024 Southern Hemisphere influenza season. The committee unanimously recommended excluding the B/Yamagata lineage component from quadrivalent influenza vaccines as soon as possible, as well as recommended the composition for egg-based trivalent and quadrivalent 2024 Southern Hemisphere formulations of influenza vaccines. Dr. Kaslow personally thanked the review teams, supervisors, and the management at CBER who worked diligently to thoroughly review these 10 regulatory actions since the June 2023 ACIP meeting, as well as the CDC staff for their many contributions and their alacrity in these efforts.

Health Resources and Services Administration

CDR Reed Grimes, MD, MPH provided the Health Resources and Services Administration (HRSA) update for its injury compensation programs. The National Vaccine Injury Compensation Program (VICP) continues to process a high volume of claims in fiscal year 2023. Petitioners have filed 1129 claims with the VICP and nearly $174 million have been awarded, including awards to petitioners and their attorney's fees and costs. In addition, the VICP had a backlog of 657 claims alleging vaccine injury that were awaiting review. Previously, there had been nearly a 12-month wait time between when a petition was found to have adequate medical records to review by the time a HRSA provider was able to review it. As of October 1, 2023, those wait times had been reduced significantly to below a 6-month wait time, so they are working through the backlog in the VICP program. More data about the VICP can be

obtained at the VICPs website.[50] For the Countermeasures Injury Compensation Program (CICP), in the decade prior to COVID-19, only 500 claims had been filed with the CICP. CICP received its first direct appropriation in fiscal year 2022 and the program has used those funds to increase its capacity to conduct medical reviews by hiring and training new review staff and contractors, pay compensable claims, and improve information technology and other communication with requesters. The CICP recently made improvements to foster enhanced communication with requesters, allowing the requesters the capability of checking their claim status in real-time on the website[51] and launching a chat function on its website to assist requesters with frequently asked questions (FAQs). As of October 1, 2023, there have been 12,233 claims alleging injuries or death from COVID-19 countermeasures that have been filed with the CICP, including 9221 claims alleging injuries from COVID-19 vaccines. CICP has rendered 1267 decisions on COVID-19 claims.

Indian Health Services

Matthew Clark, MD, FAAP, FACP provided an update for the IHS, emphasizing that the IHS continues to prioritize vaccination as its principal clinical and public health prevention priority. As part of the IHS E3 Vaccine Strategy, the IHS seeks to ensure that every patient at every encounter is offered every recommended vaccine when appropriate. In partnership with staff at Federal Tribal and Urban Indian Organization (UIO) facilities, the IHS has collected and shared best practices and lessons learned from dozens of E3 Champion Pilot Sites across the country for cross-pollination of the IHS system of care. The IHS is actively engaged in its Fall respiratory viral season vaccine campaign, with the goal to mitigate morbidity and mortality from vaccine-preventable illness in its vulnerable service population. Following approval of the 2023-2024 monovalent COVID-19 vaccine and RSV vaccines for elders and pregnant women, the IHS distributed guidance to clinicians, public health staff, tribal leaders, and tribal communities about the importance of these countermeasures. Similarly, coinciding with the ACIP recommendations, the IHS took quick action to add nirsevimab to the IHS National Core Formulary to further promote access to this immunization for infants and young children. They also have reached out to federal, tribal, and urban Indian organization partners to provide guidance about the recommendation that all infants under 8 months of age in their first RSV season and all American Indian and Alaskan Native children 8–19 months of age in their second RSV season to receive nirsevimab. Currently, all ACIP-recommended vaccines and long-acting monoclonal antibodies are listed on the IHS National Core Formulary. In addition, IHS continues as a long-term partner with the VFC Program and remains committed to providing support to facilities interested in the CDC's Bridge Access Program for COVID vaccines for eligible persons. Moving forward, in collaboration with partners and tribal communities, the IHS will continue to promote access, quality, value, and equity related to immunizations in Indian Country.

National Institutes of Health

John Beigel, MD reported that for COVID-19 several months ago, the National Institute of Allergy and Infectious Diseases (NIAID) and BARDA announced project NextGen. This is a coordinated effort in which the federal government works with the private sector to advance a pipeline of new and innovative vaccines and therapeutics for COVID-19. NextGen vaccines include those with an enhanced breadth, improved durability, and ability to block transmission or infection, including mucosal vaccines. They are looking for ways to improve upon the currently

[50] https://www.hrsa.gov/vaccine-compensation
[51] https://www.hrsa.gov/cicp

approved vaccines and have plans to leverage existing infrastructure and networks to implement these studies. Evaluating multiple next generation COVID-19 links to the program will be in the written updates.[52] For Mpox, the immunogenicity trial with JYNNEOS Mpox vaccine discussed the previous day includes an evaluation of a lower intradermal dose and a non-inferiority adolescent safety and immunogenicity trial for which both stages have completed enrollment. The data for the initial results for the intradermal stage are expected in early 2024, with the adolescent data coming later. For meningitis, researchers from the NIAID-funded Infectious Diseases Clinical Research Consortium (IDCRC) provided an interim report on the pentavalent meningococcal serogroup, A, C, Y, W, X conjugate vaccine in comparison to the A, C, W, W, Y conjugate vaccine to the WHO Strategic Advisory Group of Experts (SAGE). This is different from the pentavalent vaccine discussed the previous day, including serogroup X that is seen in many African countries. The study results showed that the pentavalent vaccine is safe and highly immunogenic. The pentavalent vaccine already had been shown to be immunogenic and was approved for people 1─85 years of age. This was the pivotal study that extended that down into the infant age group so that vaccine can be used as part of the routine immunization schedule in low- and middle-income countries. For HIV, NIAID continues to support multiple programs in pursuit of an HIV vaccine. To highlight the first human trial for HIV vaccine development by NIAID's Vaccine Research Center (VRC), which includes an engineered outer domain germline targeting 60-mer nanoparticle designed to prime VRC01-class HIV-specific B cells. The result of this early-phase clinical study was published earlier in *Science Translational Medicine*.[53] In response to the persistent health challenges of herpes simplex virus (HSV), the NIH released a "Strategic Plan for Research on Herpes Simplex Virus 1 and 2." This includes a framework with 4 strategic priorities, including improving fundamental knowledge of HSV biology, pathogenesis, and epidemiology; improving HSV diagnostics; improving strategies to treat HSV while seeking a curative therapeutic; and advancing preventative measures including HSV vaccines. Hopefully, this will help stimulate and lead to effective HSV vaccines. For leadership updates, Dr. Tabak, the Acting Director of the NIH, named Dr. Jeanne Marrazzo as the Director of NIAID, who is internationally recognized for her research and education efforts in the field of sexually transmitted infections (STIs), especially as they affect women's health. NIH is excited to have Dr. Marrazzo leading NIAID as they continue efforts for new and better vaccines.

Office of Infectious Disease and HIV/AIDS Policy

Susan Farrall, MPH reported that federal agencies comprising the e Federal Interagency Vaccine Work Group (IVWG), provided feedback to inform the "Vaccines Federal Implementation Progress Report" expected in December 2023. The progress report will give an overview of progress from 2021 to 2023 toward achieving the goals of the Vaccines National Strategic Plan (VNSP), which provides a roadmap for the coordination of vaccine development and use in the US. The Office of the Assistant Secretary for Planning and Evaluation (ASPE) and the Office of Infectious Disease and HIV/AIDS Policy (OIDP) jointly released an environmental scan report titled, "Environmental Scan of Best Practices for COVID Vaccination and Testing for Underserved Populations."[54] This document provides a comprehensive literature review and describes initiatives and interventions to improve COVID vaccination for people who are medically or socially at disproportionate risk of COVID-19. The forthcoming National Vaccine Advisory Committee (NVAC) meeting is scheduled for February 22-23, 2024.

[52] https://www.niaid.nih.gov/diseases-conditions/next-generation-covid-19-vaccines
[53] https://www.science.org/doi/10.1126/scitranslmed.adf3309
[54] https://aspe.hhs.gov/sites/default/files/documents/cf956deab718c4c439631f284fec6095/environmental-scan-covid-19.pdf

Sanofi Statement

Julian Ritchey, MBA (Head of Public Affairs and Patient Advocacy for Sanofi Vaccines) expressed appreciation on behalf of Sanofi Vaccines and their alliance partner AstraZeneca for the opportunity to provide a comment on the current market situation for Beyfortus® or nirsevimab. As Dr. Daskalakis shared, they are experiencing unprecedented demand for Beyfortus® in response to the unmet need that has existed in RSV prevention. Despite an aggressive supply plan built with the goal of outperforming past pediatric immunization launches and built to anticipate the demand of this season, the demand that has materialized has been much higher than forecasted across both the 50 milligram and 100 milligram presentations. Both product dose presentations continue to ship to fulfill existing orders. However, for the 100-milligram presentation they have stopped accepting new orders as demand has consumed the supply currently available for the season. They will continue shipping doses of 100 milligram to fulfill orders already on hand over the coming weeks, and orders are still being accepted for the 50-milligram presentation. They are working closely in collaboration with the CDC to ensure equitable distribution of available doses through the VFC Program. The approach to fulfilling existing orders and taking new orders for the 50-milligram product across the private marketplace also will be done in a similar manner with equity in mind. Sanofi Vaccine appreciates the clinical guidance provided by CDC earlier in the week via the HAN that was mentioned before. Additionally, they are working with the FDA together with AstraZeneca, Sanofi's partner in charge of the manufacturing and supply, to deliver all of the doses planned for this season. They appreciate the challenge that these supply constraints present for providers, parents, CDC, FDA, AAP and others as they introduce Beyfortus® and are thankful for everyone's patience and collaboration. They are already working to ensure that there will be sufficient supply available for next season and continue to focus on making this season's doses available as rapidly as possible. In addition, they will continue to update the ACIP and providers on the status of orders and remaining shipments. For questions about the status of Beyfortus® orders currently placed, providers can reach out to their local Sanofi representative or call 1-855-239-3678 (1-855-BEYFORTUS) regarding private sector doses. For public sector doses, providers can reach out to their state and local VFC Programs.

Discussion Points

Dr. Kotton asked Dr. Daskalakis to address RSV vaccine availability for pregnant people and how that is going.

Dr. Daskalakis responded that they will have a better view of what is happening in terms of coverage as they go further in this season. But in general, because this is a commercially distributed vaccine, CDC has been in close contact with manufacturers and distributors to have a sense of what is happening on the ground. CDC also has had close discussions with stakeholders around the country, including professional organizations, et cetera. There does not appear to be a bottleneck in production of the vaccine. From the perspective of what they have heard from manufacturers and distributors, vaccine is flowing. What they are hearing is that there are some barriers related to concerns around coverage. CDC is actively engaging across stakeholders that deal with coverage (e.g., governmental, CMS, and others) to make sure the message is clear in terms of the importance of this vaccine product for pregnant people and their newborns. Additionally, many engagements have happened and more are planned to be able to sort of tout the importance of the vaccine and do some myth-busting around what is available and what is forecasted in terms of coverage scenarios. There will be some coverage issues because there are some limits to the speed at which a private insurer needs to cover

this, but CDC is engaging with them as well to highlight the importance of a public health view in terms of strategies that tend to be more on the commercial side.

Dr. Long asked Dr. Ritchey from Sanofi whether they should be winding down on the need for the 100 milligram vials as they catch people who are a little older at the beginning of the season. The 50 milligram vials will be needed for coverage through March for those who are the most vulnerable. She asked what level of uptake they planned for this and what they anticipate as far as potential shortages of the 50 milligram vials.

Mr. Ritchey replied that he did not have the specific numbers to share in terms of volume, but they are watching this closely. At this point, they are trying to understand the early levels of ordering in terms of the stocking, ordering, and utilization that will go forward. CDC can speak to the specifics of the VFC Program details.

Dr. Sanchez asked whether administering 2 doses of the 50-milligram presentation would be giving too much of whatever else is contained in the product.

Dr. Ritchey noted that use of 2 vials of 50 milligrams is outside of the indication and consistent with the HAN is not recommended. At this point, consuming 2 doses that would be used in otherwise young individuals, and considering that there are other options presumably for the individuals for whom the 100-milligram formulation would be recommended. He called on Dr. Rizzo to comment as well.

Christopher Rizzo, MD, FAAP responded that the excipients include arginine, histidine, polysorbate, and sucrose. He agreed that the HAN does not recommend administering 2 doses. In addition, because of the ability of giving 2 of the 50 milligram vials to 2 babies who are younger, rather than 1 baby who's older and older babies who are at very high risk.

COMBINED IMMUNIZATION SCHEDULE

Introduction

Sybil Cineas, MD, FAAP, FACP (ACIP Combined Immunization WG Chair) reminded everyone that the Combined Immunization Schedule WG updates the Child and Adolescent and Adult Immunization Schedules[55] annually. The Child and Adolescent Immunization Schedule summarizes ACIP's vaccination recommendations for persons ≤18 years of age and the Adult Immunization Schedule summarizes ACIP's vaccination recommendations for persons ≥19 years of age. Both immunization schedules represent current approved ACIP policy and are designed to be a guide for HCP to ensure that individuals receive all of their vaccines when they need them. The goal of the Combined Immunization Schedule WG is to better harmonize the child/adolescent and adult schedules. No new policy is established by the schedules, which instead reflect a summary of ACIP recommendations. The WG presents the schedules for a vote every Fall because ACIP's approval is necessary prior to publication of the schedules by CDC. In addition, ACIP's approval is necessary before CDC's partners from the following professional organizations approve the schedules:

[55] https://www.cdc.gov/vaccines/schedules/index.html

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)

The traditional timeline that has been used to publish the immunization schedules is that ACIP votes to approve the immunization schedules in October, professional organizations approve the schedules between November and December, the accompanying *MMWR* reports for both schedules are drafted and cleared between December and January of the next year, and the *Annals of Internal Medicine* report is drafted during that same timeframe for the adult schedule only. All publications occur on the same day in early February each year. The traditional timeline and process of updating the schedules has resulted in a few significant challenges in the implementation of routine vaccinations. This includes insurance reimbursements to HCP; the ability of certain HCP, such as pharmacists, to administer vaccines in some jurisdictions; and delays in updating HCP knowledge and practices related to new vaccine recommendations. To mitigate some of these challenges, the WG is proposing publishing the 2024 immunization schedules via web, app, and pdf versions in November. The *MMWR* article summarizing the updates to the 2024 schedule would then be published a few months later, but earlier than the current February dates.

As a reminder, presentations and updates to both schedules may include the use of vaccine trade names. This is for identification purposes only and does not imply endorsement by CDC. The proposed edits presented during this session were subject to change based on ACIP's discussion and vote. The presentations for this session focused on harmonization between the child/adolescent and adult schedules, edits to all tables, content changes of the notes, content changes to the appendix listing contraindications and precautions, discussion, and a vote.

2024 Child and Adolescent Schedule Revisions

Patricia Wodi, MD (CDC/NCIRD) presented the 2024 updates to the Child and Adolescent Schedule, including the proposed changes for the following sections and a new addendum:

Proposed Updates to the 2024 Child/Adolescent Immunization Schedule

Changes to Tables	Changes to Vaccination Notes	Changes to Appendix	Addendum (new)
▪ Cover Page ▪ Table 1 ▪ Table 2 ▪ Table 3	▪ COVID-19 ▪ DTaP ▪ HPV ▪ Influenza ▪ MMR ▪ Meningococcal ▪ Mpox ▪ Pneumococcal ▪ Polio ▪ RSV monoclonal antibody ▪ RSV vaccine	▪ COVID-19 ▪ DT ▪ Hib ▪ Meningococcal ▪ Mpox ▪ RSV monoclonal antibody ▪ RSV vaccine	

Dr. Wodi noted that she would present only the substantive updates to the schedule, but minor grammatical formatting edits to improve clarity would not be presented.

Beginning with the cover page, in the box for "How to use the child and adolescent immunization schedule," a sixth step was added for providers to review the Addendum for ACIP recommendations that occur after the schedule is published. The title for the table listing the names and abbreviation was changed to "Vaccines and Other Immunizing Agents . . ." because nirsevimab was added to the table. Nirsevimab was added in a separate section at the top to indicate that it is a monoclonal antibody and not a vaccine. In the table listing the vaccine names and abbreviations, Abrysvo was listed for the RSV vaccine because this is the only brand approved for use in pregnancy. In the pneumococcal conjugate vaccine row, PCV13 and PCV20 were added to be consistent with the current guidelines. New rows were added for the JYNNEOS Mpox vaccine and the pentavalent meningococcal vaccine. Some vaccines were deleted from the cover page that are no longer distributed or recommended for use in the US, including bivalent mRNA vaccine, diphtheria/tetanus, and Menactra.

Moving to Table 1 that outlines the immunization schedule by age, the column header was changed to "Vaccine and Other Immunizing Agents" to account for adding nirsevimab to the table. A new row was added for nirsevimab. Ages from birth–6 months were shaded in yellow indicating the age for routine immunization, with an overlay in text state "1 dose depending on maternal RSV vaccination status." Ages 8–19 months were shaded in purple to indicate children at increased risk of severe RSV disease and a "See Notes" to direct HCP to the notes section for more information for these 2 age groups. RSV vaccine was added to Table 1 with 11–18 years of age shaded in purple and inclusion of overlaying text stating, "Seasonal administration during pregnancy, See Notes." In the pneumococcal conjugate row, PCV13 was removed and PCV 20 was added. The pneumococcal polysaccharide row was deleted because that vaccine is no longer recommended for all children who are at increased risk for IPD. In the meningococcal row, Menactra was removed. In the COVID-19 row, the overlaying text for mRNA bivalent was changed to indicate use of the 2023/24 formula of the vaccines. A new row was added for Mpox vaccine and purple shading was added to indicate that it should be used based on risk factors.

Regarding Table 2 that outlines the catch-up schedule for children and adolescents who are beginning their immunization later on more than 1 month behind, there were 2 minor edits. In the DTaP row for Dose 4 to Dose 6, the interval was clarified with the addition of a noted stating that the 5th dose is not necessary if the 4th dose was administered at ≥4 years of age and at least six months after Dose 3. Menactra was removed from the Meningococcal ACWY row.

Table 3 that lists the immunization schedule by medical indication was revised extensively to align it more closely with the instructions to be used to assess additional vaccines that will be needed based on medical condition or indications. This was done because of the feedback received from many HCP that the legend definitions were unclear and were used inconsistently across the row. When the color definitions were changed and Table 3 was harmonized with the child schedule, it applied to all of the rows. Table 3 looks much different in the 2024 schedule to include the new legend color definitions to clarify that yellow represents "Recommended for all age eligible children who lack documentation of a complete vaccination series." Purple was revised to state that purple means "Not recommended for all children, but some children can receive the vaccine based on their increased risk for all severe outcomes from disease." The definition for brown did not change and still indicates that additional doses are needed, but the color of the text was changed so that the overlaying text would be more visible. Gray was

changed to, “No Guidance/Not Applicable.” The table header was revised for clarity to state, “Always use this table in conjunction with Table 1 and the Notes that follow. Medical conditions are often not mutually exclusive. If multiple conditions are present, refer to guidance in all relevant columns. See Notes for medical conditions not listed.” Similar to Table 1, the first column in the table header was changed to “Vaccine and Other Immunizing Agents.”

The DTaP and Tdap rows were combined into one row and the pregnancy column indicates that 1 dose of Tdap is recommended for each pregnancy. The pneumococcal rows were merged into a single row with an indication in color that additional doses are needed for those with medical conditions. A new row was added for nirsevimab, with brown highlighting for children and adolescents who are immunocompromised or have chronic lung disease to indicate that additional doses are needed. Overlaying text was added to say “2nd RSV Season (See Notes).” For RSV vaccine, the pregnancy column is in yellow indicating that it is recommended for all pregnant women. The overlaying text added reads, “Seasonal administration, See Notes). All other medical conditions have purple because any pregnant person who has any of these medical conditions also can receive the RSV vaccine. Finally, a new row was added for Mpox vaccine, with all of the medical conditions shaded in purple, indicating that anyone who has this medical condition and has the sexual risk factors should be vaccinated.

Moving now to the edits to the notes, in the “Additional Information Section” in the bullet for the National Vaccine Injury Compensation Program (VICP), RSV was added as one of the vaccines that is not covered by VICP. The COVID-19 vaccination notes were extensively revised to align with the current recommendation. The “Routine Vaccination” section lists the recommendations for persons who are not moderately or severely immunocompromised, and outlined the recommendations by age group and the number of previous COVID-19 doses received. The “Special Situations” section outlines the recommendations for persons who are moderately or severely immunocompromised, and the recommendations are outlined by age group and number of previous doses received. At the end of the COVID-19 notes, some information is included that should be helpful for healthcare providers, including that there is no preferential recommendation when more than 1 recommended age-appropriate vaccine is available. Links were included to the age transition information the interim guidance EUA. The definition for “previously vaccinated” was added. Lastly, a note was added for additional doses in persons who are moderately or severely immunocompromised.

Some minor edits were made to human papillomavirus (HPV). The bullet on an interrupted HPV schedule was removed because this information is on the cover page, and it applies to all vaccines. For situations where no additional doses are recommended, the language was clarified to indicate that persons who have completed their HPV series with any HPV vaccine do not need additional doses. This was done by adding “of any valency” to the relevant sentence. For influenza vaccination, out bullets were removed for persons who have a history of egg allergy, and included a note at the end of the section saying that “Persons with an egg allergy can receive any influenza vaccine (egg-based and non-egg-based) appropriate for age and health status.” A link was included to the current recommendation for the 2023-2024 season. In the MMR vaccination notes, the bullet for the minimum interval between MMR doses was moved to the end of the section and an asterisk was added to indicate that it applies to routine, catch-up, and special situations. Previously, it was in the “Catch-Up Vaccinations” section and some HCP found that confusing.

For MenACWY, Menactra was deleted from all sections and the pentavalent meningococcal vaccine was added. At the end of that section, information was added for the newly recommended pentavalent vaccine. A note was added stating that, “Children age 10 years or

older may receive a single dose of Penbraya™ as an alternative to separate administration of MenACWY and MenB when both vaccines will be given on the same clinic day, and a single injection with Penbraya™ is preferred." In the MenB note, a link was added to the shared clinical decision-making resource. At the end of the notes, information was added for the use of the pentavalent meningococcal vaccine reading, "Children age 10 years or older may receive a dose of Penbraya™ as an alternative to separate administration of MenACWY and MenB when both vaccines will be given on the same clinic day, and a single injection with Penbraya™ is preferred. For age-eligible children who are not at increased risk, if Penbraya™ is used for dose 1 MenB, Trumenba should be administered for dose 2 MenB. For age-eligible children who are at increased risk of meningococcal disease, Penbraya™ may be used for additional MenACWY and MenB doses (including booster doses) if both vaccines would be given on the same clinic day **and** at least 6 months has elapsed since the most recent Penbraya™ dose. Children age 10 years and older recommended to receive booster doses of MenACWY and MenB less than 6 months after a dose of Penbraya™ should receive MenACWY and Trumenba separately."

A new section has been added for Mpox vaccination that lists the recommendations for persons age 18 years and at risk for Mpox, with risk factors listed. There is a bullet for pregnancy stating that, "There is currently no ACIP recommendation for JYNNEOS use in pregnancy due to lack of safety data in pregnant persons. Pregnant persons with any risk factor described above may receive JYNNEOS." For pneumococcal vaccination, PCV13 was removed and PCV 20 was added. A note was added stating that, "Either PCV15 or PCV20 can be used when PCV is indicated. PCV20 is not indicated for children who have received 4 doses of PCV13 or PCV15 or another age-appropriate complete PCV series." In the list of medical conditions that increase the risk for IPD, chronic kidney disease excluding maintenance dialysis and nephrotic syndrome, because these are listed in immunocompromising section. Chronic liver disease was added back. For chronic lung disease, language was added to specify that this includes moderate persistent or severe persistent asthma. The recommendations were outlined by each group based on their previous pneumococcal vaccination history.

For poliovirus vaccination, language was added in the catch-up section based on the new recommendation for those who are age 18 years who are known or suspected to be unvaccinated or incompletely vaccinated. The language also was clarified to convey that. "Unless there are specific reasons to believe they were not vaccinated, most persons aged 18 years or older and born and raised in the United States can assume they were vaccinated against polio as children." The "Special Situations" section was revised to include the recommendation for those who completed their primary series but were at increased risk of exposure to poliovirus. A note at the bottom defines what a "complete primary series" means.

For RSV immunization with nirsevimab, a new note section was added and in the "Routine Immunization" includes 2 bullets. One outlines the recommendations for infants from October through March in most of the continental US and the other outlines the recommendations for infants born April through September. Each of these bullets outlines the recommendation based on maternal RSV vaccination history. In the "Special Situation" the recommendations are outlined for children ages 8─19 months who are at increased risk for severe RSV disease. In that section. A bullet also was included for age-eligible children who are undergoing cardiac surgery with cardiopulmonary bypass who need an additional dose of nirsevimab, along with a link to more information. At the end of this section, information was added on the timing of nirsevimab administration based on local RSV seasonality and information on the use of nirsevimab in children who are eligible to receive palivizumab. A link was added to the nirsevimab Frequently Asked Question (FAQ) webpage. For RSV vaccine, the routine recommendation was outlined for pregnant women at 32─36 week's gestation from September

through January most of the United States. There also is a noted indicating that either maternal RSV vaccination or infant immunization with nirsevimab is recommended to prevent RSV disease in the infant. Just like in the nirsevimab section, information was included on the timing of RSV vaccine based on local RSV seasonality. In the notes for Tdap, some edits were primarily to clarify that Tdap dose for children 11─12 years of age is the adolescent booster.

Moving to the appendix, which lists the contraindications and precautions for each vaccine in the schedule, a link was added to the header to the Contraindications and Precautions for COVID-19 vaccine, the most recent influenza recommendations for 2023-2024, and JYNNEOS vaccination. The header for the first column was changed to "Vaccines and Other Immunizing Agents." This year, the contraindications and precautions for COVID-19 vaccines have been incorporated into the table. There is one row for mRNA COVID-19 vaccines and a separate row for the protein subunit vaccine. Nirsevimab and RSV vaccine were added to the table and a link to the package insert for nirsevimab was included in the footnotes. The pentavalent meningococcal vaccine and JYNNEOS Mpox vaccine were added to the table listing the contraindications and precautions. Lastly, some information was deleted from this table in the DTaP to remove the diphtheria-tetanus vaccine that is no longer distributed in the United States. In the Haemophilus influenzae row, the bullet was removed for severe allergy to latex because that is no longer included in the package insert. In the meningococcal row, information for Menactra was removed. The addendum is currently blank. After this schedule is published, the intent is to list any ACIP vote or recommendation in the addendum.

Discussion Points

Dr. Poehling expressed gratitude to the entire team for the enormous amount of data and modifications that were put into this in a very coherent and understandable way. In terms of polio, she asked whether the recommendation was included for those ≥18 years of age who are unvaccinated.

Dr. Wodi indicated that a bullet was included in the catch-up vaccination section for those who are suspected to be unvaccinated or incompletely vaccinated.

Regarding the wording for pentavalent meningococcal vaccine, Dr. Poehling expressed concern that the end it sounded like a preferential recommendation was made though it was not. She was concerned that this would be misinterpreted.

Dr. Wodi said they went back and forth about this, but were not sure how to communicate that if the patient or the provider had a preference.

Dr. Poehling thought it would be okay to say that they "may receive a single dose of Penbraya™ an alternative to separate administration of MenACWY and MenB when both vaccines would be given on the same clinic day." Deleting "and a single injection with Penbraya™ is preferred" could be removed. That would clearly communicate that both are equally reasonable options.

Regarding PCV15 and 20, Dr. Poehling was concerned that people would look at the routine recommendation and not realize that the recommendations were changed for "Special Situations" unless someone had a condition listed there. She suggested adding something to tell people to look at the next page.

Ms. Bahta raised a concern that seemed to be bubbling up related to giving HPV and a more routine recommendation starting at 9 years of age when it can be given as early as 9. Growing data show that there is better completion of HPV when the series is started at age 9 years of age. It removes some of the sexual implications and is easier to talk about cancer prevention. The data are conflicting to some degree, but she expressed her hope that the WG could look at that more closely.

Dr. Wharton indicated that while there is interest in reconvening the HPV WG to address this issue as well as some others, given the large number of WGs the ACIP currently has to support, they have been delayed on getting that started. Hopefully, they will able to reconvene that WG soon.

Referring to the RSV line on Table 3, Dr. Kotton noted that while the column for pregnancy was marked in yellow, the bar is purple for all of the other indications. It made it seem like it was only for pregnant people with those indications. Someone with chronic heart, lung, et cetera could consider getting this vaccine even if they are not pregnant. She suggested not keeping the line purple because it suggested that RSV vaccine should be given to a lot of people for whom it is definitely not approved. The purple bar seemed erroneous.

Dr. Wodi indicated that this has been a recurring issue with Table 3 in terms of whether to limit the information for each column to only the vaccine that is recommended, or if it also should communicate that people with those conditions should receive other vaccines based on routine recommendation or their risk factors. To try to address that problem, the WG leaned toward communicating to providers that people who have this medical condition also should get their routine vaccines. When they revised the color legend, they wanted to leave yellow for those vaccines that are routinely recommended for everyone who has that condition. Purple was intended to be recommended based on their increased risk for infection or severe outcomes. The WG struggled with maternal RSV vaccine because it does not really fit into any of the colors, because it is not given to the mother to prevent RSV disease. It is for the benefit of infants, but none of the other colors fit.

Dr. Kotton advocated for turning the purple to gray because there is no guidance or it is not applicable and to keep the yellow for pregnant people, because this has not been a risk based-vaccine for pregnant people. For all of the other groups, she advocated for flipping the purple to gray to make it obvious to everybody that this is not recommended outside of pregnant children and adolescents.

Dr. Kimberlin (AAP Red Book) asked whether a new recommendation after the schedule was approved would appear on the addendum page and also would result in a change in the table, or if it would appear only on the addendum page and the schedule would go through the standard process. It seemed like it would be challenging to constantly be trying to redo everything. As long as it was listed on the addendum page, that should be enough in his judgment.

Dr. Wodi indicated that a new recommendation that comes out after the schedule is published would be listed on the addendum page. They are currently working on transitioning to a more responsive schedule and hope to have that plan finalized in the next few months. Meanwhile, the plan is to publish new recommendations after the schedule is approved on the addendum page and not change the other tables until the new process for having a responsive schedule is finalized.

Dr. DeShon (NAPNAP) asked whether any thought had been given to adding page numbers. She has dropped the pages before, and it is cumbersome to put them back in order. She also asked whether any thought had been given to alphabetizing the vaccines on the tables and the catch-up schedules like is done in the notes and the appendix for ease of use.

Dr. Wodi indicated that they could see if page numbers could be added. In terms of listing the schedule in alphabetical order, the vaccines are listed according to when they will be given in Table 1. For instance, HepB is listed first because it is given at birth.

Dr. Daley proposed having a modest research agenda. This is a tremendous amount of information that they are trying to convey, and it is becoming increasingly more detailed. There is going to come a time when the schedule will not fit on one page. Because he is color-challenged, he uses the schedule less than he did 20 years ago. He also pointed out that practitioners are often operating in a circumstance in which there is an EHR. Some vaccines are amenable to EHR record prompts and some are not, such as a special situation. He often is looking up a specific vaccine because he needs some details. This requires going from a table to the notes to get the additional information versus some other strategy that would allow for finding vaccine recommendations very quickly, such as app-based. That should be factored in whether one is operating in an EHR environment. That suggested to him that perhaps research is needed on how best to convey this information to frontline providers.

Referring to Table 3 by medical indication, Dr. Long recognized that they were not making policy and that there was not currently an active Varicella WG. However, the MMR and varicella rows were in red and yellow with an asterisk indicating that these are contraindicated during pregnancy but to vaccinate after pregnancy. She recently saw 2 children from immigrant families in the first month of life with mild varicella and she asked where they had been. One mother was from South America and the other was from Central America. The one from South America did not have varicella as a child, so undoubtedly the baby had no antibody. The mother got the vaccine in the postpartum period the day she delivered, went home, got a few lesions, the baby got skin disseminated varicella, and neither was severely ill. However, that led to spinal tap treatment with Acyclovir thinking it was herpes. Happily, she was there because no other people in the place had seen varicella to know what it looked like. While it is a public health measure, she did not think vaccinating people postpartum was a good time for this vaccine because it is skin transmissible if the mother gets lesions. Perhaps the mother from South America who never had varicella was more likely to get lesions than those who are given the vaccine in the US. She thought they were reaching the point where babies were being born with only maternal vaccine protection. Because it states “after pregnancy” she suspected that people were translating this to “postpartum.” Another public health measure is that when people come to the border, they are given many vaccines. There was a child presented at IDWeek who received MMRV at 15 to 16 months of age and 10 days later was diagnosed with severe malignancy. This child ended up with an enormously complicated course with terrible varicella, vaccine virus pneumonia, and then measles. While she did not know what to do about that and still thought it was a good idea to vaccinate, maybe it was just about education. In terms of a specific recommendation, she suggested including a note following “after pregnancy” clarifying that it should not be given in the first few days postpartum. She did not think this schedule should be changed, but she did not want to see the same question next year without some modeling not immunizing all of these people compared to immunizing the mom on the first postpartum day.

Dr. Lee requested that they table this question and ask the subject matter experts (SMEs) for varicella to work offline with Dr. Long to make sure that they are not changing the recommendation, but ensure that it is consistent.

CDR Grimes (HRSA) noted that with the inclusion of Mpox in the Child and Adolescent Immunization Schedule, JYNNEOS vaccine is covered under the CICP Program, so this section needs to be edited to recognize that.

Dr. Poehling suggested that one option regarding Dr. Long's question would be to remove the asterisk from the red part of the bar, which might make clear that it is just a consideration for the WG that is going to discuss it. Second, she noted that under the pentavalent vaccine, there were 2 paragraphs side-by-side that included preferred working that should be removed on both.

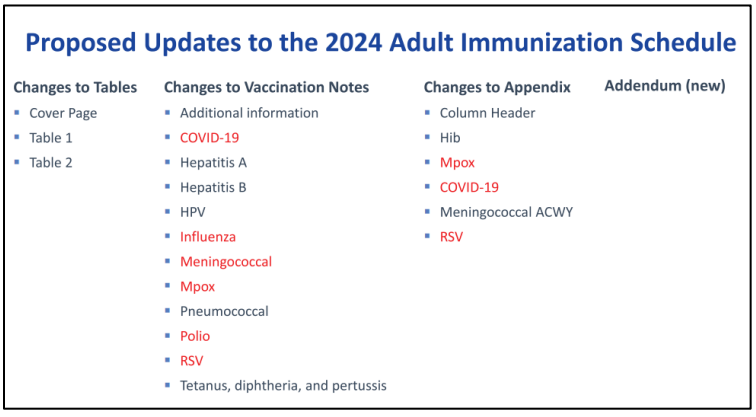
Regarding Dr. Long's observations, Ms. Hayes (ACNM) pointed out that the vast majority of women who have not been vaccinated are immigrants and they are covered by Medicaid during their hospitalization for the birth. Once they leave the hospital, they are uninsured and often are lost to follow-up and care. For as long as she has been a midwife, that has been the reason they have been recommended to be vaccinated immediately postpartum.

Looking at the RSV nirsevimab line, Dr. Lee noted that the second RSV season had heart disease or chronic lung disease, and the question will come up about whether heart disease should be included for the second season. In her opinion, as they move toward a respiratory viral prevention platform, perhaps consideration should be given to harmonizing across influenza, COVID, and RSV. She did not think that there were unusual circumstances like CSF leaks with pneumococcal vaccine, but this schedule highlighted some of the minor differences that could be significant to patients. She thought they should harmonize some of the conditions, as evidence allowed and was reasonable from an implementation standpoint, for providers given the complexity of the schedule.

Regarding the suggestion to remove the asterisk, Dr. Wodi reminded everyone that it was added because they wanted to encourage providers to vaccinate pregnant women after the pregnancy for vaccines that are contraindicated during pregnancy.

2024 Adult Schedule Revisions

Patricia Wodi, MD (CDC/NCIRD) presented the 2024 updates to the Adult Immunization Schedule, including the proposed changes for the following sections and a new addendum:



Similar to the Child and Adolescent Immunization Schedule, the 2024 Adult Immunization Schedule includes changes to the cover page, tables, vaccination notes, and appendix, and includes the new addendum.

On the cover page under “How to use the adult immunization schedule,” a fifth step was added instructing providers to review the addendum where recommendations that occur after the schedule is published will be listed. In the table listing the names and abbreviations, the pentavalent meningococcal vaccine, Mpox, and RSV vaccines were listed. There are 2 brands listed for the RSV vaccine. The bivalent mRNA COVID-19 vaccines and Menactra were removed from the table on the cover page.

Table 1 lists the recommended adult vaccines by age. For COVID-19, the overlaying text was changed to specify that the 2023-2024 formula should be used. For RSV, adults 19–49 years of age, the purple part of the bar indicates that it is recommended for some adults not all adults. There is overlaying text stating “Seasonal administration during pregnancy. See Notes.” For adults ≥60 years of age, there is a blue bar indicating that this is a shared clinical decision-making recommendation. For the pneumococcal row, the overlaying text was removed that stated “Either use PCV15 plus PPSV23 or PCV20” because the recommendations are outdated and there is a lot more nuances than what was there. Mpox was added, with all ages shaded in purple indicating that those who have risk factors should be vaccinated.

Table 2 lists the recommendations by medical indications and is similar to Table 3 in the child/adolescent schedule. The same thing was done to align the table more closely with the instructions on the cover page about how to use the schedule. The second box states “Assess need for additional recommended vaccinations by medical condition or other indication (Table 2).” The color legends for this table were revised and harmonized with the child/adolescent schedule. Yellow now reads, “Recommended for all adults who lack documentation of vaccination OR lack evidence of past infection.” Purple now states, “Not recommended for all adults, but it is recommended for some adults based on either age **OR** increased risk for or severe outcomes from disease.” Brown is new to the table to indicate that for some of these medical conditions, additional doses of vaccines will be needed. This was to harmonize with the child/adolescent schedule. The indicates that there is “No Guidance/Not Applicable.” The same header was added as was done in Table 3 in the child/adolescent schedule letting providers know to use this table with Table 1 and that there are some medical conditions that are not listed on the table, to see the notes section, and that individuals could have made multiple medical conditions. For the Hepatitis B row for diabetes, there is an indication in the diabetes column that for adults ≥60 years of age, the recommendation is shared clinical decision-making. For RSV, there is a yellow indicator for pregnancy with overlaying text stating “Seasonal administration. See Notes.” The rest of the bar is blue for the other medical conditions, with overlay testing of “See Notes” because of the shared clinical decision-making recommendation for older adults. Looking at this and based on the previous conversations, Dr. Murthy recognized that perhaps the bar should be changed to gray. In the Mpox row, the entire row is purple across all of the medical conditions because anyone with medical conditions can have the sexual risk factors recommended for vaccination. “See Notes” was added for pregnancy, MSM, and HCP.

Moving to the notes section, an addition was made in the “Additional Information” section to harmonize with the child/adolescent schedule. In the bullet for the VICP, RSV was added. In Mpox will be added as well. COVID-19 vaccination was extensively revised to align with the new recommendation for routine vaccination. This is for people who are not moderately or severely

immunocompromised. The “Special Situations” section lists the recommendations for people who are moderately or severely immunocompromised based on their previous COVID-19 vaccination history. As was done with the child/adolescent schedule, links were added to the schedule and the EUA to help professionals. The definition for “previously vaccinated” and some information was added for additional doses and those who are moderately or severely immunocompromised. For Hepatitis A routine vaccination, the description was revised to clarify that people who are not fully vaccinated who do not have a risk factor can receive the vaccine if they request it. The bullet reads, “Any person who is not fully vaccinated and requests vaccination (identification of risk factor not required) . . .” For those who are at risk, the wording was changed to match what is included in the “Routine Vaccination” section. For Hepatitis B, a new bullet was added stating that “Any adult age 60 years of age or older who request HepB vaccination should receive a HepB vaccine series.” For those living with diabetes who are ≥60 years of age, a notation was added to state that this is a shared clinical decision-making recommendation.

For HPV vaccination, the bullet on an interrupted schedule was revamped to clarify that if someone completed the HPV vaccination series with any of the HPV vaccines, additional doses would not be needed. For influenza vaccination, the bullet was removed for persons with a history of egg allergy and a note was added that they can now receive any influenza vaccine appropriate for their age and health status. A link was added to the 2023-2024 recommendation. The bullet was removed for people with a history of GBS within 6 weeks of influenza vaccine because that is already in the appendix. For meningococcal vaccination, information was added for the shared clinical decision-making resource and the pentavalent meningococcal vaccine was added. At the end, the preferred will be removed from this section as well.

For Mpox vaccine, there is a “Special Situation” for those with the listed risk factors. A bullet was added for pregnancy reading, “There is currently no ACIP recommendation for JYNNEOS use in pregnancy due to lack of safety data in pregnant persons. Pregnant persons with any risk factor described above may receive JYNNEOS.” In addition, a bullet was included for HCP stating that “Except in rare circumstances (e.g., no available personnel protective equipment), healthcare personnel who do not have any of the sexual risk factors described above should not receive JYNNEOS.” This was added because there have been questions about whether HCP providing clinical care for patients with Mpox should be vaccinated. The meningococcal section was extensively revised primarily to clarify the minimum intervals based on which product is used. Based on the new recommendation for polio vaccination, there is now routine vaccination wording stating that “Adults known or suspected to be unvaccinated or incompletely vaccinated: administer remaining doses (1, 2, or 3 IPV doses)to complete a 3-dose primary series. In the “Special Situations” section there is a statement that “Adults who are at increased risk of exposure to poliovirus who have completed the series: may receive one lifetime IPV booster.” A definition is included to explain the meaning of a “complete primary series.”

For RSV vaccination, the routine section addresses the recommendations for pregnant persons stating, “Pregnant at 32-36 weeks gestation from September through January in most of the United States . . .” Language also was included on timing and based on local RSV seasonality. It also was important to refer to nirsevimab in this section. Language was included indicating that either maternal RSV or infant immunization with nirsevimab is recommended. A reference is made to the child/adolescent schedule for nirsevimab recommendations in infants. The “Special Situations” section for RSV addresses shared decision-making for those ≥60 years of age. The 2 vaccine brands that can be used are listed here. Information is provided for persons who are considered to be at increased risk for severe RSV disease. For the Tdap notes, a note

was added to clarify that “Tdap administered at 10 years may be counted as the adolescent dose recommended at age 11─12 years.”

Moving to the appendix, which contains the contraindications and precautions, the header was revised to include the links to the contraindications for JYNNEOS and COVID-19 vaccine. The link was updated to the current recommendation for influenza vaccine. COVID-19 vaccines were incorporated into the table. There is now a different row for mRNA COVID-19 vaccines and for the protein subunit vaccine. RSV vaccine was added to the contraindications and precautions to the table. The pentavalent meningococcal vaccine and Mpox were added to the table. Similar to the child/adolescent schedule, the bullet was deleted for severe allergic reaction. Menactra was deleted from the meningococcal vaccine row. As with the child/adolescent schedule, the addendum is currently blank. After this schedule is published, the intent is to list any ACIP vote or recommendation in the addendum.

Discussion Points

Referring to Table 1 and the orange color, Dr. Long pointed out that “lack of evidence of past infection” did not apply to most of the vaccines and that there was nothing in the notes that helped with that.

Dr. Wodi agreed that it did not apply to all of the vaccines, but it did apply to measles and varicella. She noted that the WG struggled with that.

Dr. Long said it applied to varicella and it should be placed there rather than applying it to all of the oranges.

Dr. Kotton said it applied to Hepatitis A, Hepatitis B, measles, and others that are used all of the time in the adult world.

Dr. Wodi pointed out that the General Recommendations allow for serologic evidence for past infections and is consistent with some of the Policy Notes for some infections (e.g., measles, mumps, rubella, varicella, Hepatitis A).

Dr. Long suggested putting that in the notes on the few vaccines for which it would apply, going down the line of vaccines.

Dr. Wodi said the WG was open to suggestions on how to handle the support tables because it applies to some and not others.

Referring to the RSV line on Table 2, Dr. Kotton agreed that the blue was great for shared clinical decision-making, but suggested that “≥60 years of age” replace “See Notes” because “See Notes” meant to click again. Anytime a clinician has to click again, it enhances burnout, frustration, and fatigue. The CDC had a very nice release the previous day about mental health in clinicians and she wanted to link that advocacy to the “See Notes” text. She realized that they may be considering adults 50─59 years of age, so there may need to be a change. However, she advocated for the text overlay to be “≥60 years of age” as was done in the HepB row. When things are similar, it is a lot easier.

Referring to the Cover Page and the Table, Dr. Goode (APhA) noted that inactivated and recombinant influenza vaccine were listed cell culture-based was not. In addition, she noted that polio was listed everywhere, but not in the table; and that perhaps the pneumococcal row should include “See Notes.”

Dr. Grohskopf said that essentially, the cell culture-based vaccine is considered to be one of the inactivated influenza vaccines. It is different in that it is cell culture-based as opposed to egg-based like the other vaccines, but they are essentially interchangeable and would not be treated differently from a policy perspective.

Dr. Cineas noted that pentavalent meningitis was not listed on Table 2, but it would be indicated for patients with asplenia who potentially would need both MenB and MenACWY at the same visit if they were under 25 years of age.

Dr. Whitley-Williams (NMA) noted that while LAIV on Table 1 made sense, have LAIV4 on the third line after IIV4 or RIV4 on the second line made it look like a separate vaccine from the other 2 vaccines, which was confusing. The message was not clear because the “or” had disappeared. This made it look like 2 separate standalone vaccines, but one would not get 2 vaccines (e.g., IIV and LAIV). She also noted that the row was purple under 1 dose for MSM, but she was not aware that this was an indication for LAIV.

CDR Grimes (HRSA) noted that the Cover Page for the adult schedule needed to be adjusted in terms of the language pertaining to injury claims for Mpox.

Dr. Wodi indicated that the pentavalent was not added to Tables 1 and 2 because it did not change the recommendation. When the WG discussed this with the SMEs, the decision was made to include the information in the notes because the recommendation was the same. For Table 2, they could add the “or” for clarity between IIV4 and RIV4 “or” LAIV.

Regarding the comments on LAIV, Dr. Grohskopf indicated that LAIV was called out for MSM 19–49 years of age. The same was called out for HCP 19–49 years of age. They wanted to call out that there was a maximum age for which LAIV could be used.

Dr. Poehling made a motion to approve the language as presented for the Child and Adolescent Immunization Schedule and the Adult Immunization Schedule, with the incorporation of the suggestions where relevant. Dr. Loeher seconded the motion.

As a reminder, public comment was presented prior to the vote. However, the vote was combined in this proceedings document with its respective session for the purpose of continuity.

Vote: Immunization Schedules

Patricia Wodi, MD (CDC/NCIRD) presented the proposed recommendation for a vote as follows:

> ACIP approves the recommended Child and Adolescent Immunization Schedule United States, 2024 and the recommended Adult Immunization Schedule United States, 2024.

Motion/Vote: Immunization Schedules Recommendation

Dr. Poehling moved to accept the Child and Adolescent Immunization Schedule and the Adult Immunization Schedule language as presented, which Dr. Loehr seconded. No COIs were declared. The motion carried with 13 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

CHIKUNGUNYA VACCINE

Introduction

Beth Bell, MD, MPH (Chair, ACIP Chikungunya Vaccines WG) provided an introduction to the chikungunya vaccines session. In terms of background, she reminded everyone that the expected licensure date for Valneva's Chikungunya vaccine was revised from August 2023 to November 2023. No chikungunya vaccine has ever been licensed in the US or globally, so there are no existing ACIP chikungunya vaccine recommendations. The Chikungunya Vaccines WG is developing policy options for ACIP's consideration for use of chikungunya vaccine among US persons at risk of chikungunya, including travelers, laboratory workers, and residents of US territories and states with, or at risk of, transmission.

To recap previous presentations to ACIP, the WG presented an overview of chikungunya virus disease and vaccines and they heard about the immunogenicity and safety of Valneva's chikungunya vaccine during the October 2022 ACIP meeting. During the February 2023 ACIP meeting, the WG discussed the global epidemiology of chikungunya, chikungunya among US travelers, and the issue of persistent arthralgia following chikungunya disease. During the June 2023 meeting, data were presented that reported on the value of a vaccine to US travelers, chikungunya virus infection among laboratory workers, and observations on a large chikungunya outbreak occurring in Paraguay.

This session included EtR Framework presentations for chikungunya vaccine use among US travelers and among laboratory workers to prepare for an anticipated vote during the February 2024 ACIP meeting if the vaccine is licensed in the interim.

EtR and Proposed Policy Options for Chikungunya Vaccine Use Among US Adults Traveling Abroad

Susan Hills, MBBS, MTH (CDC/NCEZID) explained that chikungunya is caused by chikungunya virus, which is an alphavirus that is transmitted primarily by *Aedes (Stegomyia)* species mosquitoes, primarily *Aedes aegypti* and *Aedes albopictus*. In addition to mosquito-borne transmission, other uncommon modes of chikungunya virus transmission include laboratory exposure, intrauterine and intrapartum transmission, and bloodborne transmission through needlestick injury. Chikungunya virus occurs in tropical and subtropical regions and has caused large outbreaks throughout most parts of the world. Attack rates in outbreaks are often high, with one-third to three-quarters of the population affected. Clinical illness is characterized by the acute onset of fever and polyarthralgia, which is often severe and can be debilitating. Although serious complications can occur (e.g., neurologic illness, myocarditis, or hepatic or renal disease), they are rare and mortality is less than 1%. In the absence of specific antiviral treatment, the approach to management typically involves rest, fluids, and use of analgesics and antipyretics. Risk factors for more severe disease include age >65 years or <1 year, underlying medical conditions (e.g., diabetes, cardiac disease, or hypertension), infection following intrapartum transmission). Intrapartum infections can result in neonatal complications including neurologic or myocardial disease or dermatologic or hemorrhagic symptoms and signs.The chikungunya vaccine is a live-attenuated vaccine that is manufactured by Valneva. It has a single dose primary schedule, with initial licensure to be for adults ≥18 years of age. The vaccine is currently under consideration by FDA and is not yet licensed anywhere in the world. There are currently no existing vaccine recommendations from ACIP or other vaccine advisory groups around the world.

To discuss the EtR Framework for adults who travel abroad to areas with risk for chikungunya virus transmission, it is important to keep in mind that with licensure still pending, any new information at the time of licensure that modifies any of the data or information presented during this session might require the EtR to be updated. The policy question is, “Should chikungunya vaccine be recommended for use in persons aged ≥18 years traveling to areas with risk of chikungunya virus transmission?

To answer the first domain of the EtR regarding whether chikungunya is of public health importance, the WG considered 4 key factors. Chikungunya is of public health importance globally, with hundreds of thousands of cases reported annually. There is particular concern when outbreaks occur because they can have substantial consequences related to morbidity and also impact health services. However, for US persons traveling to areas with transmission, the risk and therefore public health importance is variable as transmission varies substantially from location-to-location and from year-to-year. Although there is likely substantial under-diagnosis, about 100 to 200 chikungunya cases are reported annually among US travelers. The greatest risk for travelers is when outbreaks occur. In terms of the disease, infection with chikungunya virus can cause an acute illness with arthralgia that can be severe and debilitating, and there is no specific antiviral treatment available. In addition, arthralgia can sometimes persist for months or even years. However, overall mortality is less than 1% and in general, serious outcomes of illness are a more important consideration for some higher risk travelers, such as older persons, particularly those with underlying comorbidities. The WG’s conclusion was that public health importance varies for the US traveling population based on the level of transmission at the destination and individual factors, such as the traveler's age and underlying medical conditions.

The WG next considered the benefits and harms of chikungunya vaccine with the result based on the GRADE assessment. The first question regarded how substantial the desirable anticipated effects are. The outcomes assessed were short- and long-term protection from disease. Of note, there were no efficacy data and this approach for vaccine licensure would have been logistically challenging because outbreaks are unpredictable, and their duration can be relatively short. In the absence of efficacy data, the WG reviewed immunogenicity data. However, there is no correlate of protection. In considering the data, the WG noted that the approach being used for licensure of the vaccine is through the accelerated approval pathway. With this approach, demonstration of effectiveness is based on clinical trials showing the vaccine has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. There is a post-licensure requirement for VE studies to confirm the clinical benefit. In the clinical trials, the marker of protection used was based on a neutralizing antibody titer estimated from a validated non-human primate (NHP) model. There were 2 studies providing evidence for short-term protection from disease after vaccination, 1 RCT and 1 lot-to-lot consistency study that did not include a placebo group. There were 622 subjects total in the 2 studies and seroresponse at 28 days after vaccination was at least 98% in both studies. None of the 96 subjects in the placebo arm of the RCT had a seroresponse. The evidence used to evaluate long-term protection after vaccination was from 1 study that included 360 subjects. At 12 months after a single dose of vaccine, seroresponse was detected in 99% of subjects. Based on these data, the WG considered the desirable anticipated effects to be large.

The next question for this domain regarded how substantial the undesirable anticipated effects are. For this question, the WG considered that the critical outcomes were SAEs, arthralgia, and arthritis. In regard to SAEs, in 2 clinical trials, 51 (1.5%) of 3,490 vaccinated subjects reported SAEs. In the 1 RCT, 8 (0.8%) placebo recipients reported SAEs, which was not a statistically significant different percentage from the 1.5% of subjects in the vaccinated group with SAEs. Among all the SAEs, 2 were considered probably vaccine-related by study investigators. They included severe myalgia beginning 1 day after vaccination in a 58-year-old woman with a history of fibromyalgia. She was admitted to the hospital for pain management and diagnostic procedures. The second was a hospitalization of a 66-year-old man for a SAE beginning 3 days after vaccination of myalgia, high fever, syndrome of inappropriate anti-diuretic hormone excretion (SIADH), and atrial fibrillation.

The second outcome of interest was arthralgia and arthritis. Given that arthralgia is a key feature of clinical illness with chikungunya virus infection and the vaccine is live-attenuated, the WG closely investigated outcomes of arthralgia or arthritis after vaccination. While the manufacturer provided data from 2 studies, Dr. Hills presented the results of the randomized placebo-controlled trial for simplicity. The second study was a lot-to-lot consistency study with 408 vaccinated subjects, but without a placebo group. The percentages of each AE were similar in vaccinated subjects in both studies. Overall, 17% of subjects reported any arthralgia as a solicited AE within 10 days of vaccination. This percentage was significantly higher than the rate of 5% reported in the placebo arm. Severe arthralgia, which was defined in the studies as an event that prevented daily activity, occurred in 0.3% of vaccinated subjects and no subjects in the placebo arm. This difference was not significantly different. Persistent arthralgia, defined as arthralgia commencing with 10 days of vaccination and with duration longer than 15 days, was present in 0.3% of subjects. This was not significantly different from the percentage with this outcome in the placebo group. Arthritis and osteoarthritis were collected as unsolicited AEs and were reported at rates of 0.2% and 0.4% in the vaccinated group, respectively. Neither rate was significantly different in the control group.

Overall, for these 5 outcomes, the only event for which an arthralgia or arthritis outcome was reported at a significantly higher rate in the vaccinated group compared with the placebo group was any arthralgia within 10 days of vaccination. However, in assessing these outcomes, the WG noted that the number of subjects included in the studies was too low to adequately assess potentially rare events like severe or persistent arthralgia, arthritis, or new onset or worsening osteoarthritis. Based on the results of the SAEs of arthralgia and arthritis, the WG considered the undesirable anticipated effects of vaccination to be small.

The WG then considered whether the desirable effects outweigh the undesirable effects. The WG noted that there were high seroresponse rates through at least 1 year after vaccination, and no serious safety concerns were identified in the clinical trials performed to date that included approximately 3,500 vaccinated individuals. In addition, vaccination can prevent a disease that can result in severe arthralgia during acute illness, rare serious complications, and sometimes long-term arthralgia. However, the WG noted that healthcare providers should discuss the desirable and undesirable effects with individual travelers in the context of the disease risk at their destination, activities, and personal factors (e.g., age and underlying medical conditions). As with any vaccine, rare SAEs can occur and for some travelers, even a low probability of an SAE might be higher than their disease risk. Therefore, vaccination should be targeted to travelers at higher risk for disease. Overall, the WG determined that the risk-benefit assessment will vary substantially and inversely with transmission intensity and other factors and is favorable if the vaccine is used in line with the WG's proposed recommendations.
Finally for this domain, the WG considered the GRADE assessment results to determine the overall certainty of the evidence for the critical outcomes. The overall certainty of evidence for short-term and long-term protection after vaccination was low. Certainty was downgraded based on very serious indirectness because the likelihood of protection from disease was based on immunogenicity data in the absence of VE data. There is no established correlate of protection and demonstration of effectiveness for vaccine licensure was based on a surrogate endpoint that was reasonably likely to predict clinical benefit. The results will require post-licensure VE studies to confirm the results. The overall certainty of the evidence for the SAEs of arthralgia and arthritis was low. Certainty was downgraded for individual safety outcomes because of various serious imprecisions related to the small sample size, because the confidence interval around the effect estimates indicated the potential for possible benefit or harm from vaccination, or because of indirectness related to a suboptimal method for collection of specific outcome information. Although the WG assumes results will be similar when the vaccine is used in larger populations, real-world data would be important to confirm the safety profile available from the clinical trials.

For values domain, 2 studies informed the WG's response on the extent to which the target population feels the desirable effects of vaccination are large relative to undesirable effects and whether there is an important variability in how much people value the main outcomes. The first study was an online study conducted in 2022 with questions prepared by CDC staff and that considered perceptions of a chikungunya vaccine among US adults. Participants were provided with information on risk for disease with travel during outbreak or non-outbreak periods, rates of chronic arthralgia after chikungunya disease, and a hypothetical vaccine cost. Results showed that during an outbreak period defined as a traveler having a 1 in 150 risk of disease, the likelihood respondents would receive the vaccine was 42% very or somewhat likely, 32% very or somewhat unlikely, and 26% unsure. During a non-outbreak period defined as a risk of disease of 1 in 15,000, the likelihood respondents would receive the vaccine was 27% very or somewhat likely, 49% very or somewhat unlikely, and 24% unsure. There was variability in responses, with a lower likelihood of vaccination among persons 18–29 years of age compared with adults in older age groups and among those with lower education and household income

levels. People of Black race were less likely to be interested in being vaccinated than those in other race or ethnicity groups. Consistent with results for the high and low risk scenarios, the most important factor considered by respondents in making a decision on vaccination was the risk of disease. Also important for many respondents were the risk of vaccine side effects, the chance to avoid possible long-term joint pain through being vaccinated, and vaccine cost.

The second study was an online survey funded by the vaccine manufacturer and conducted in 2021 among approximately 2,000 US residents ≥18 years of age who had traveled internationally during the last 3 years or planned to do so within the next 3 years. Limited information was provided about participants, but anyone who self-identified as anti-vaccination was excluded. After being provided basic information on chikungunya and its sequelae, 72% were very or somewhat likely to ask a healthcare provider about a vaccine and 80% were very or somewhat likely to be vaccinated if the vaccine was recommended by a healthcare provider.

Although there were substantial limitations of both of these studies, overall the WG determined that it is likely US travelers will have variable opinions about whether the desirable effects of vaccination are large relative to the undesirable effects, and that there likely will be important variability in how much people value the vaccine, with level of disease risk being a key factor in determining likelihood of vaccination. The WG noted that clinicians should allow for discussion of individual values and preferences in their discussions on vaccination against chikungunya.

The next domain focused on the acceptability of chikungunya vaccine. In considering acceptability, the WG thought that key stakeholders would be US travel medicine and other healthcare providers and travelers. In regard to travel medicine and other healthcare providers, an online survey in 2021 funded by the vaccine manufacturer and conducted among 158 US healthcare providers who routinely provide travel health services found that 80% were very or somewhat likely to recommend the vaccine if it was recommended by ACIP. For travelers, vaccine recommendations are expected to be acceptable because vaccine availability gives an option in addition to mosquito bite prevention measures for protection from a disease that can cause severe arthralgia and potentially long-term joint pain. Therefore, the WG thought that the intervention would be acceptable to key stakeholders.

For the resource use domain, the WG considered whether chikungunya vaccination is a reasonable and efficient allocation of resources. A cost-effectiveness analysis for chikungunya vaccination of travelers has not been conducted. Most travel vaccines are not cost-effective, and chikungunya vaccine for travelers is not likely to be cost-effective because the number of US travelers needed to be vaccinated to prevent 1 case is high. However, the WG noted that cost-effectiveness considerations are less relevant for a travel vaccine because the decision on vaccination is for an individual traveler and is not being made for the population, broad resource allocation decisions are not being made, and the vaccine is typically paid for by the traveler themselves and is often not covered by insurance. The WG also noted that vaccine recommendations targeted to higher risk groups are probably an efficient use of resources as the financial implications of vaccine purchase will be borne by travelers most at risk of a disease or severe outcomes who will receive the most benefit. Therefore, the WG determined that chikungunya vaccination is probably a reasonable and efficient allocation of resources, if chikungunya vaccine recommendations are targeted to higher risk groups.

For the equity domain, the WG considered the impact on health equity. Chikungunya vaccine probably will have to be paid for out-of-pocket by most travelers. Some travelers will have resources to pay for vaccine and others will not. In addition, travel medicine providers are likely to have a better awareness of chikungunya disease and vaccine availability than non-specialist

providers, but people with fewer resources are less likely to attend a specialist travel medicine provider. These issues might cause health disparities, but the WG noted that the chikungunya vaccine recommendations cannot address these issues. The WG's conclusion was that health equity probably would be reduced by chikungunya vaccine availability, but the issue cannot be addressed within the context of the vaccine recommendations.

For the final domain, the WG considered the feasibility of implementation of chikungunya vaccination. The WG noted the vaccine has a single dose primary series, which should allow for easy administration during a pre-travel consultation. One topic the WG discussed was that disease risk is highest during outbreaks and vaccination will be of most benefit for travelers during an outbreak. However, a challenge might be a delay in awareness of an outbreak with travelers potentially exposed during high-risk periods in the early stages of an outbreak. To address this as best as possible, CDC will post information on outbreaks on the CDC website as soon as the agency becomes aware of outbreaks. Although this was discussed as a challenge, most of the WG members did not think it would be appropriate to address the issue by recommending vaccination to every traveler traveling to any destination with risk of chikungunya, because there likely would be an adverse risk-benefit assessment given the variable and often very low risk for travelers, and because of the substantial differential between risk during outbreaks and at other times. The decision overall was that vaccination is probably feasible to implement.

Overall, when considering all of the domains of the EtR Framework, the WG determined that the desirable consequences probably outweigh the undesirable consequences in most settings. With all of this in mind, Dr. Hills presented the following draft recommendations prepared by the WG for ACIP's consideration:

- ❑ Chikungunya vaccine is recommended for persons aged ≥18 years traveling to a country or territory where there is a chikungunya outbreak

- ❑ In addition, chikungunya vaccine may be considered for the following persons traveling to a country or territory without an outbreak but with evidence of chikungunya virus transmission among humans within the last 5 years:
  - Older persons (e.g., >65 years), particularly those with underlying medical conditions, who are likely to have at least moderate exposure to mosquitoes
  - Persons staying for a cumulative period of 6 months or more during a 2-year period

To provide data to support the WG's primary recommendation for vaccination for persons traveling to a location where there is a chikungunya outbreak, Dr. Hills provided an example from US traveler chikungunya data from 2023. There was a large outbreak of chikungunya in Paraguay during 2023[56]. Among all US travelers to destinations with risk of chikungunya, fewer than 1% traveled to Paraguay. However, among all US traveler chikungunya cases reported to date during 2023, 26% of them or 18 of 69 cases have been among persons who traveled to Paraguay. These data clearly demonstrate the substantially higher risk for travelers during an outbreak. To clarify what is meant by an outbreak in the language of the recommendations, an outbreak will be defined as occurring when CDC posts information on an outbreak on the CDC website. As noted earlier, a notice will be posted as soon as CDC becomes aware of an outbreak. A similar process is used for cholera and in relation to the cholera vaccine recommendations, with information posted when a cholera outbreak occurs.

[56] Preliminary ArboNET data, 2023

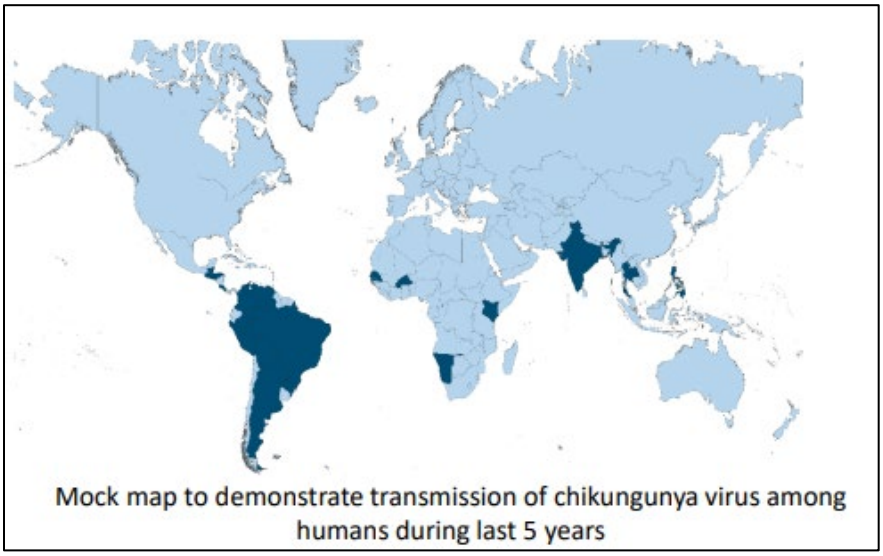
For some additional explanation about the second part of the WG's recommendations, the shared clinical decision-making component, chikungunya vaccine may be considered for the following persons traveling to a country or territory without an outbreak, but with evidence of chikungunya virus transmission among humans within the last 5 years. This includes older persons (e.g., >65 years of age), particularly those with underlying medical conditions who are likely to have at least moderate exposure to mosquitoes and persons staying for a cumulative period of 6 months or more during a 2-year period. For these groups, there is definitely more uncertainty in the risk-benefit assessment. However, there are likely to be circumstances when some individuals might reasonably choose vaccination or some providers might wish to recommend it. Dr. Hills further explained the WG's deliberations noting that older persons, particularly those with underlying medical conditions, should be considered for vaccination and provided some data supporting the inclusion of this group. Among adults, the key risk factors for severe chikungunya disease are older age and underlying medical conditions. Similarly for chronic arthralgia, risk factors include older age and the presence of pre-existing joint problems, which is more likely in older persons. The risk for higher morbidity and mortality in older persons is supported by data from the recent outbreak in Paraguay.[57] Although overall risk for hospitalization and death from chikungunya is low, there is a markedly higher risk for older persons. Looking at data by age group, the data clearly point to the high risk for hospitalization and death in those >65 years of age. The WG discussed a broader recommendation for vaccination for any adult with a medical condition. However, with more than 50% of the US adult population having an important medical condition such as hypertension, diabetes, or heart disease, that would be a very large population for a recommendation. In relation to that, the WG discussed the importance of having additional data from post-marketing surveillance to confirm the vaccine safety profile. Therefore, most WG members thought the best approach was to restrict the recommendation in a non-outbreak setting when risk is often low to those >65 years of age, particularly those with underlying medical conditions.

The second group, noted as a group for consideration of vaccination based on shared clinical decision-making, is travelers who have a cumulative period of travel of 6 months or more during a 2-year period. The key risk factor for chikungunya virus infection among travelers is the intensity of transmission far more so than the duration of travel. However, if there is equivalent transmission in different areas, the cumulative duration of exposure becomes important. Additionally, even though a destination might be a low-risk environment overall, transmission patterns can be unpredictable over the longer term and over a 6-month period and there is likely to be some seasonal variation in mosquito activity that might impact risk. Therefore, the WG considered that a shared clinical decision-making recommendation for this group also was appropriate. The 2-year period is based on immunogenicity data showing a high seroresponse rate of 99% of 1 year after vaccination, which suggests there should be good protection from vaccination at least through the second year. However, the WG did not have any longer-term data at the current time.

To explain why the recommendation refers to evidence of chikungunya virus transmission among humans within the last 5 years, the rationale for the timeframe is that given the challenges and deficiencies in surveillance, a 5-year timeframe provides an interval that allows reasonable confidence that there is transmission in a certain location or conversely that there is insufficient transmission for there to be a concern for travelers. The tool to provide this information will be a map which shows countries with reported chikungunya virus transmission

[57] Torales M, et al. Notes from the Field: Chikungunya Outbreak - Paraguay, 2022-2023. MMWR Morb Mortal Wkly Rep 2023; 72:636-638

among humans during the last 5 years, posted on the CDC website. A mock-up example is provided below:



Mock map to demonstrate transmission of chikungunya virus among humans during last 5 years

To describe one final point, the recommendation refers to moderate exposure. Text will be provided within the recommendations that indicates the following:

> Moderate exposure could include travelers who might have at least 2 weeks (cumulative) of exposure to mosquitoes in indoor and/or outdoor settings. It does not include travelers who might have limited exposure to mosquitoes (e.g., those traveling for business and likely to be mainly in mosquito-protected indoor settings).

In conjunction with the recommendations, there also will be General Considerations language noting the following:

- ❑ All persons who travel to areas with possible chikungunya virus transmission should be advised to take precautions to avoid mosquito bites

- ❑ The risk for chikungunya for most US travelers to countries or territories with evidence of transmission is low. However, some travelers are at increased risk for infection or more severe disease. In the discussion between the healthcare provider and traveler on the need for vaccination, consideration should be given to:
  1) Whether there is a recognized outbreak or ongoing disease activity
  2) The duration of travel or residence, including likelihood of future travel to an area with chikungunya virus transmission
  3) The likelihood of exposure to Aedes mosquitoes
  4) Older age (e.g., >65 years)
  5) Underlying medical conditions that increase the risk for severe disease (e.g., diabetes, cardiac disease, hypertension)
  6) Underlying conditions that increase the risk for chronic arthralgia after infection (e.g., existing joint disease)
  7) An individual's personal perception and tolerance of risk

Discussion Points

Dr. Poehling thanked the WG, emphasizing that this vaccine has never been reviewed, this is enormous amounts of work, and people who get chikungunya get very sick. She also recognized the importance of this vaccine and appreciated the explanation of the morbidity and mortality with this illness with age. She requested a reminder of the age groups included in the clinical trials.

Dr. Hills indicated that for the RCT, the age groups included persons ≥18 years to ≥65 years. The oldest was 91 years of age. In the immunogenicity subset, there were 59 subjects ≥65 years of age in the RCT. The lot-to-lot consistency study was among persons 18─45 years of age.

Dr. Kotton requested confirmation that because this is a live-attenuated vaccine and replicating virus, similar to measles, yellow fever, varicella that immunocompromised will be a contraindication to vaccination. Along those lines, she would have safety concerns about recommending the vaccine for older persons ≥65 years of age about a replicating virus and the ability to clear replicating virus. Perhaps the WG should review the safety data on the 59 people ≥65 years of age before making a recommendation. While it looked like there were no significant safety concerns, she had concerns. Certainly, they learned a lot during the COVID-19 pandemic. She learned a lot about immunocompromised people in their 70s and 80s and that the immune system wanes with age.

Referring to Slide 83, Dr. Hills agreed that this is an important question and stressed that the WG considered it very closely. While the rate and severity of arthralgia after vaccination did not increase with age, this is an important point and the WG will be interested with the FDA assessment when the vaccine is licensed as well as ongoing safety monitoring of the vaccine.

Dr. Daley asked what is known about clearance of the natural infection, clearance in vaccination, and persistence of infection related to arthralgia.

Dr. Hills responded that it is cleared fairly rapidly in relation to arthralgia. There have been situations in which RNA has been detected in the synovial fluid longer-term. Though not definitively determined, it is believed to be more of an immunological issue than persistent virus.

In terms of the draft recommendations, Dr. Daley suggested placing an “or” between the second bullet meaning “age over 65 years OR 6 months.”

Ms. McNally asked what the treatment is for chikungunya and whether the WG has any information about cost for this vaccine.

Dr. Hills responded that there is no specific antiviral treatment for chikungunya. It is typically managed with fluids, rest, and use of medications for fever and for pain. The WG does not have any information on the cost of the vaccine at this time.

Given that this vaccine likely will be administered as part of a visit to a travel medicine clinic, Dr. Cineas asked whether the WG has any data or information on co-administration with other travel vaccines.

Dr. Hills indicated that there have been no studies conducted that focus on co-administration with other vaccines. Therefore, the recommendations will indicate that there are no data at this time.

Dr. Kotton suggested that in the first bullet in the recommendation about older persons with underlying medical conditions, some phrasing should be included about making sure they are not immunocompromised to make that obvious. She sees live-virus vaccines being given to people she wishes had not received them.

Dr. Long asked whether there would be any immunogenicity data in persons ≥65 years of age with underlying conditions to understand whether the vaccine is as immunogenic in that group.

Dr. Hills indicated that the immunogenicity data gathered to date include subjects up to about 90 years of age. There are approximately 60 subjects for whom immunogenicity data have been collected. People typically were healthy for inclusion in the clinical trial or did not have any serious underlying medical conditions.

Dr. Bell indicated that someone may be on the line from Valneva who may be able to comment on the potential cost of the vaccine and the last question about additional data in older adults.

Dr. Ellen Shannon from Valneva reported that the expected price of the vaccine will be in line with the other travel vaccines on the market.

Dr. Katrin Dubischar from Valneva indicated that Valneva has generated some additional immunogenicity data in older adults in which the sample goes up to roughly above 100. They continue to see very high seroresponse rates that do not differ from younger adults. In terms of the population that was studied, she supported the answer that Dr. Hills gave that the study population was a generally healthy adult population, but it did include participants with underlying diseases that were stable and controlled.

Dr. Poehling emphasized that for people attending this meeting who do not give travel vaccines on a routine basis, it would be helpful if Valneva would be willing to share a price range.

Dr. Shannon from Valneva reported that in line with a previous presentation by Dr. Hills during the June 2023 ACIP meeting, the cost would be in the vicinity of $350 or slightly less.

EtR and Proposed Policy Options for Chikungunya Vaccine use Among Laboratory Workers

Susan Hills, MBBS, MTH (CDC/NCEZID) next presented the EtR Framework and proposed policy options for chikungunya vaccine use among laboratory workers beginning with a brief reminder of general considerations for laboratory transmission of chikungunya virus. At least 44 cases of chikungunya virus infection among laboratory workers have been reported worldwide during the last 50 years. Of these, 43 cases were overt disease, 1 was an asymptomatic infection, and there were no deaths. In regard to US laboratorians, 4 disease cases have been reported in the 8-year period since chikungunya became a nationally notifiable disease in the US in 2015. However, the identified cases likely under-represent all infections in laboratory workers, as there is no formal laboratory surveillance system for reporting these events.[58]

[58] The Subcommittee on Arbovirus Laboratory Safety of the American Committee on Arthropod-Borne Viruses. Am J Trop Med Hyg 1980; and Rusnak JM, et al. J Occup Environ Med 2004; 3. US national arboviral disease surveillance system, 2015–2022.

Documented routes of transmission of chikungunya virus in the laboratory have been through the aerosol route and the percutaneous routes. Among cases of percutaneous transmission with more detailed information available, 2 researchers experienced a needlestick injury while they were working with and injecting mice. For the third case, a researcher experienced a forceps prick while dissecting mosquitoes infected with chikungunya virus. Transmission through accidental mucosal exposure is also possible.

The policy question the WG considered was, "Should chikungunya vaccine be recommended for laboratory staff at risk for chikungunya virus infection?" Of note, the same GRADE assessment for outcomes of vaccination was used for laboratory workers as was used for travelers. Therefore, Dr. Hills did not present the GRADE results again. However, when discussing laboratory worker recommendations, the WG specifically discussed the topic of cross-protection provided by vaccination against the 3 genotypes of chikungunya virus, given that laboratory workers might be exposed to high titers of a specific genotype. The WG noted there are very limited data from laboratory studies to confirm cross-protection. However, they also noted that although there are multiple genotypes of chikungunya virus, they are generally considered to constitute a single serotype and the differences in antigenicity are relatively limited. There also is no evidence of reinfection in humans with different genotypes.

For the first domain of the EtR, the WG determined that chikungunya cannot be considered of public health importance overall, as there are only occasional cases reported among US laboratory workers. However, for laboratorians working with the virus, there is the potential for acute infection with severe polyarthralgia and the possibility of chronic arthralgia. For values, the WG considered that scientists are likely to consider the desirable effects of vaccination to be large relative to the undesirable effects, and that there is unlikely to be important variability because they likely will understand the risks of disease and risks and benefits of vaccination, and most scientists value vaccination. Chikungunya vaccine is likely to be acceptable to key stakeholders, including occupational health directors, laboratory managers, and laboratorians as its availability will improve laboratory safety. For resource use, the WG felt that chikungunya vaccination was a reasonable allocation of resources because vaccination recommendations will be for a limited number of staff undertaking research or specific diagnostic work and that paying for vaccination is a small cost for administrators to pay to avoid the substantial impact and costs of a worker becoming infected. The WG thought that equity probably would be increased because if employers offer chikungunya vaccination to laboratory staff, it will improve safety for workers and address an occupational health issue. The WG thought the vaccination was feasible to implement as it will likely be incorporated into existing occupational health programs for laboratory workers. When considering all of the EtR Framework domains overall, the WG determined that for chikungunya vaccination for laboratory workers, the desirable consequences probably outweigh the undesirable consequences in most settings. The WG's draft recommendation for ACIP members' consideration:

- ❑ Chikungunya vaccination is recommended for laboratory workers with a potential for exposure to chikungunya virus.

The recommendations would be presented with additional texts to provide clear information for implementation, including noting the following:

- ❑ Local institutional biosafety committees should undertake a risk assessment of the potential for exposure to chikungunya virus for each laboratory worker working with the virus, considering the type of work to be performed and the biosafety level at which work will be conducted.

- ❑ Vaccination is not necessary for workers handling routine clinical samples, who should routinely use standard practices for handling patient samples.

Discussion Points

Dr. Stanley Grogg indicated that he has a travel medicine certificate from the International Society of Travel Medicine (ISTM), and they take mission teams to different areas of the world. The 6-month time period seemed somewhat unusual to him. It takes only one mosquito bite to give someone chikungunya and he has seen chikungunya in a lot of areas, such as Haiti and Nicaragua. He thought that rather than the 6-month time period, the recommendation should be expressed in terms of geography. Someone in the countryside for any particular short time period easily could be exposed to chikungunya.

Dr. Hills agreed that it takes just one mosquito bite, but it needs to be an infected mosquito. There are millions of travelers to areas with the risk for chikungunya virus transmission each year, but only 100 to 200 cases are reported annually. There had been about 70 cases of chikungunya virus transmission at the time the WG had these discussions, so they were trying to weigh the benefits of vaccination in terms of protection from disease with a risk-benefit assessment in terms of the risks and need for vaccination. The WG wanted to provide a time period to provide fairly clear advice for healthcare providers. Unlike Dr. Grogg who has a certificate from the ISTM, many healthcare providers are not familiar with chikungunya virus. In fact, in a survey that the manufacturer conducted, they identified that only 50% of travel medicine providers would describe themselves as familiar with chikungunya. The WG was trying to weigh that and did not want to specify the location because the *Aedes aegypti* mosquito is a very domestic mosquito, so it can be found around homes. It breeds in containers like flower vases, the base of flowerpots, and in trash lying around. Therefore, it can be of very high-intensity in urban areas unlike some other diseases such as Japanese encephalitis for which there is more risk in rural areas.

Dr. Poehling agreed that having this option for laboratorians who work with this virus makes sense. A clarification that would help her understand the feasibility and equity would be when a vaccine is recommended for occupational health, whether people exposed in the workplace would be covered by the employee or if the employer has to cover the expense of this vaccine.

Dr. Hills said that as she understood it, in many if not most cases, it is covered by the employer. For example, CDC pays for the vaccine. A member of the WG works in a research facility that works with the virus and pays for employees to receive the vaccine. While she could not comment definitively on every institution, she believes that most employers will pay for it.

Dr. Kotton asked whether it would be appropriate to put “non-immunocompromised” in front of “laboratory workers” or if it would appear only in the fine print. She emphasized that an estimated 3% of the US population is immunocompromised and that they would not want someone to accidentally get chikungunya vaccine.

Dr. Hills indicated that she would note this. There will be a clear section in the *MMWR* that includes contraindications. They are waiting for the FDA;s licensure of the vaccine to confirm what the contraindications are, but certainly it is an important point with a live-attenuated vaccine.

Dr. Talbot expressed her hope for clarification about coverage because she recalled having an extensive discussion about rabies and technicians working in veterinary offices whose rabies vaccines were not covered. It was not clear to her that chikungunya vaccine would be different. She is worried that it should, but may not be, covered by employers.

Dr. Lee responded that the ACIP does not direct coverage by employers, but invited Dr. Hills to provide any addition information she could that would be helpful.

Dr. Hills indicated that while she did not have any additional information on payment coverage, it will be clearly indicated that the vaccine is recommended for people who are at risk for potential exposure.

Dr. Kotton agreed with Dr. Talbot's comment, emphasizing that laboratory workers, especially microbiology workers, work in an area that has been decimated from the pandemic. Staffing issues are quite significant, so she wanted to lend support for advocacy in protecting them with vaccines that hopefully could be covered by their workplace or other modalities—something along the lines of a vaccination program for laboratory workers. Many patients are impacted by the staffing shortage as well, so they would be better protected by better protection of American healthcare personnel.

Dr. Lee asked whether there is a way to follow up on payment coverage, such as through a survey to understand current practice.

Dr. Hills said they could look further into this to determine whether any information is available that could shed light on this issue.

DENGUE VACCINE

Wilbert Chen, MD (ACIP, WG Chair) presented an update on dengue vaccine, reminding everyone that dengue presents a significant public health problem to areas that suffer from the burden of endemic dengue. While dengue has frequent/continuous transmission (endemic) in six US territories or freely associated states (Puerto Rico, the US Virgin Islands, American Samoa, the Federated States of Micronesia, the Republic of the Marshall Islands, and the Republic of Palau), it is not endemic in US states. Dengvaxia™, which is manufactured by Sanofi Pasteur, was the first dengue vaccine licensed by the FDA. It was approved on May 1, 2019. The ACIP developed the following recommendation for Dengvaxia™ in June 2021:

> Three doses of Dengvaxia are indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3, and 4 in people 9–16 years old with:
>
> laboratory confirmation of previous dengue virus infection
>
> AND
>
> living in endemic areas.

Takeda's dengue vaccine candidate, TAK-003, is the second dengue vaccine that has been under review by the Dengue WG since August 2022. The Dengue WG presented to the ACIP on 3 different occasions, including October 2022 and February and June 2023. In October 2022, the WG reviewed dengue epidemiology and the Sanofi Dengue vaccine and the ACIP made a recommendation that was approved. In February 2023, Takeda presented their data on the

safety and efficacy of the vaccine and the WG provided a summary and interpretation of the data that was presented. In June 2023, the policy questions, economic and cost-effectiveness analysis, and a partial EtR Framework were presented. For the October 2023 meeting, the original intent was to present the draft recommendations and a full EtR Framework.

As a reminder, there was a pivotal Phase efficacy trial that was designed for the primary endpoint of virologically confirmed dengue (VCD) among seropositives. Protection was documented for all 4 serotypes of dengue for VCD and the more severe endpoint of hospitalization. Among seronegatives, protection was demonstrated against serotypes 1 and 2. However, no efficacy was documented for the seronegatives against serotypes 3 and 4. The data were insufficient to rule out increased risk of VCD for DENV-3 among vaccines because of the very low numbers of events. In terms of evaluating hospitalizations as an outcome, the more severe measure among seronegatives, there were low numbers of events. Efficacy was not demonstrated for serotype 3 and there was only a single hospitalization event for dengue serotype 4. Therefore, efficacy remains unknown.

The European Medicines Agency (EMA), in cooperation with the WHO, provides reviews for markets outside of the European Union (EU) through a procedure known as the EU-Medicines for All (EU-M4all). On October 14, 2022, the Committee for Medicinal Products for Human Use (CHMP) of the EMA provided a positive opinion for TAK-003 and recommended the approval of TAK-003 for the prevention of dengue disease caused by any serotype in individuals ≥4 years of age in Europe and in dengue endemic countries participating in that EU-M4all procedure year. On December 8, 2022, the European Commission granted marketing authorization for TAK-003 under the tradename QDENGA®. Since then, TAK-003 has been approved in the EU, UK, Brazil, Argentina, Indonesia, and Thailand.

On July 11, 2023, Takeda announced that they voluntarily withdrew the Biologics License Application (BLA) from the FDA.[59] Their reason was that the FDA had requested additional data that were not collected in the pivotal Phase 3 efficacy study. Meanwhile in September, the WHO SAGE recommended that TAK-003 be considered for introduction in settings with high dengue disease burden and high transmission intensity to maximize the public health impact and minimize any potential risk to seronegative persons. SAGE also recommended that the vaccine be introduced to children 6─16 years of age and that within this age range, the vaccine should be introduced 1 to 2 years prior to the age-specific peak incidence of dengue-related hospitalizations. The vaccine was recommended to be administered in a 2-dose schedule with a 3-month interval between the 2 doses. SAGE recommended that vaccine introduction be accompanied with a well-designed communication strategy and community engagement, which is important for all dengue vaccines to be launched. They also recommended that post-authorization studies should be conducted to further study VE and safety against serotypes 3 and 4.

While the potential for future use of TAK-003 in the US will be further evaluated by Takeda, the ACIP Dengue Vaccine WG will be paused until the BLA for TAK-003 is resubmitted to the FDA or a new dengue vaccine is submitted to the FDA review for the WG to consider.

[59] https://www.takeda.com/newsroom/statements/2023/takeda-announces-voluntary-withdrawal-of-US-biologics-license-application-for-dengue-vaccine-candidate-TAK-003/

Discussion Points

Dr. Long requested information about uptake of the previously recommended vaccine for children 9 years of age in Puerto Rico who are seropositive in terms of whether that had increased from what was woefully infrequent.

Dr. Paz-Bailey indicated that implementation of Dengvaxia™ has been complicated first because it started during the COVID-19 vaccination campaign and second because they had to set up the laboratory procedures for pre-vaccination screening and the 2-test algorithm that is required. Implementation is still slow, with only 100 doses of the vaccine administered thus far.

Dr. Kotton asked if this vaccine will be available in other places, what the recommendation will be for patients who are going to live somewhere where the vaccine is available but is not an approved vaccine in the US.

Dr. Chen said the simple answer is that they will not be able to obtain it because it is not FDA-approved. Those who plan to travel internationally could seek it internationally, but it requires a lot of effort. Therefore, those who will be traveling internationally should seek a vaccine site as early as possible.

COVID-19 VACCINES

Introduction

Matthew F. Daley, MD (ACIP, WG Chair) reported that on September 11, 2023, the FDA authorized the updated mRNA COVID-19 vaccines for use in persons 6 months─11 years of age under EUAs. On that same date, the FDA approved the updated mRNA COVID-19 vaccines in persons ≥12 years of age under a supplemental Biologics License (sBLA). The next day, the ACIP convened and ACIP voted to recommend vaccination with updated 2023-2024 formula COVID-19 vaccines as authorized under the EUA or approved under the BLA in persons ≥6 months of age. On October 3, 2023, the FDA authorized the updated 2023-2024 formula of Novavax COVID-19 vaccine for use in persons ≥12 years of age under EUA.

Since the September 12, 2023 ACIP meeting, the ACIP COVID-19 Vaccines WG met several times during which they reviewed and discussed COVID-19 vaccine safety, including the data that Dr. Shimabukuro presented the previous day. The WG also discussed a number of important COVID-19 vaccine implementation issues. During this session, the ACIP would hear a review of a number of aspects of COVID-19 vaccine implementation and COVID-19 policy updates.

Implementation Update on 2023–2024 COVID-19 Vaccines

Shannon Stokley, DrPH (CDC/NCIRD) provided an update on the implementation of the 2023-2024 COVID-19 vaccines. Beginning with some of the changes with the transition from the US government (USG) COVID-19 Vaccination Program to distribution through the commercial market, the USG COVID-19 Vaccination Program was discontinued on September 12, 2023 as it applied to the bivalent Moderna and Pfizer-BioNTech vaccines and October 3, 2023 as it applied to the ancestral (Original) Novavax COVID-19 vaccine. All current COVID vaccines are available on the commercial market. Although the USG COVID-19 Vaccination Program has ended, providers are encouraged to continue administering COVID-19 vaccines at their

locations and also to participate in vaccines.gov where they can list vaccine availability at their locations. With the end of the federal program, there have been changes to provider agreements and to data reporting. Vaccine data reporting has transitioned to routine reporting processes for jurisdictions. This applies to immunization information systems and relying on state policy for reporting to the vaccine registry and to CDC.

Although COVID-19 vaccine has been commercialized, updated vaccines are available to most people living in the US at no cost through their private health insurance or through Medicare and Medicaid plans. Private health insurance plans that are ACA-compliant are required to cover COVID-19 vaccines from an in-network provider at no-cost sharing. The vaccines also are covered under Medicare Part B without cost-sharing, through the Inflation Reduction Act (IRA) that eliminated cost-sharing for all ACIP-recommended vaccines under Medicaid and Medicare Part D. The Vaccines for Children (VFC) program also provides vaccine at no cost to children through 18 years of age who are Medicaid-eligible, uninsured American Indian or Alaska Native, or underinsured. The Bridge Access Program provides vaccines at no cost to adults ≥18 years of age who are underinsured or uninsured.

Overall, there is an increasing supply of vaccine to meet demand. All 3 2023-2024 COVID vaccines are available (Moderna, Pfizer-BioNTech, and Novavax). With the transition of the vaccine to the commercial marketplace, there have been some reports of initial delays in distribution and questions about adequate supply. Transitioning from the federal vaccination program to commercial distribution involves very different systems. Under emergency conditions within the federal distribution system, millions of doses were distributed within a very short amount of time. With the transition to the commercial market, distribution of COVID vaccines is now similar to that of routine vaccines. Therefore, supply is distributed over time to meet demand rather than all at once. The supply is not going to look the same as it did under the Public Health Emergency (PHE). Also, there were reports of delays in distribution early on and shipments taking longer than expected, but this has improved significantly. CDC continues to work with jurisdictional partners to optimize supply and distribution, and also continues to have conversations with manufacturers and distributors to ensure timely distribution.

As mentioned earlier, the Bridge Access Program provides no-cost COVID-19 vaccines to adults who do not have health insurance and adults whose insurance does not fully cover all COVID-19 vaccination costs. All CDC-recommended COVID-19 vaccines are included in this program, which will end by December 31, 2024. The Vaccines for Adults (VFA) program that has been proposed in multiple Presidential Budgets, would be a long-term solution to ensure that all adults have access to recommended vaccines, including COVID-19 vaccine at no cost. Because this program does not exist at this point, the Bridge Access Program is critical to fill the gap for uninsured or underinsured adults. Adults ≥18 years of age who are uninsured can find free vaccination at any of the participating Bridge Access Program sites. Adults with health insurance that does not cover all COVID-19 vaccine costs can find free vaccination at any of the participating Bridge Access Program sites that are in-network for their health insurances. Patients will need to understand within their insurance plan where the in-network providers are and seek vaccination at those locations. This may involve seeking vaccination within a specific health system, within a specific state, a specific set of retail pharmacies, or a certain type of provider. It is important to note that patients do risk receiving bills for vaccination if they accidentally misrepresent their insurance coverage when seeking vaccination through a Bridge Access Program site.

The Bridge Access Program is leveraging existing public health infrastructure through jurisdictions, immunization awardees, local health departments, and HRSA-supported health centers to provide no-cost vaccination to adults without health insurance. Adults without health insurance can get vaccines at HRSA-supported health centers enrolled in their local health department's 317 Program and also participating in the Bridge Access Program. Members of federally-recognized tribes also can get no-cost vaccines at IHS Tribal or Urban Indian Health Program (UIHP) facilities regardless of their provider's enrollment status with the Bridge Access Program. Contracts were renewed with CVS, Walgreens, and eTrueNorth to provide no-cost vaccination at these retail pharmacies to adults without insurance and adults whose insurance does not fully cover the cost of vaccination. Of note, eTrueNorth is a pharmacy aggregator that enrolls smaller and independent pharmacies into the Bridge Access Program. There also may be community events or pop-up sites with these groups as the season continues. Those seeking vaccines are encouraged to visit vaccines.gov to find a provider near them who is offering vaccine. It is a requirement that all of the participating sites list their vaccine availability on vaccines.gov.

Doses for the Bridge Access Program are monitored through pharmacy and immunization program partners. Contracted pharmacies are required to provide CDC with the number of sites that are operating and how many doses have been administered on a daily basis. For public health partners who receive COVID vaccine doses through CDC, the agency is able to track the orders, including where they go, the number of providers ordering vaccine, and the number of doses ordered. Currently, there are over 24,000 contracted pharmacy locations and over 380,000 doses have been administered by these sites. There are over 4,400 public health safety net providers that have placed more than 6,100 orders for over 287,000 doses of COVID-19 vaccine using their 317 funds. Nationally, 81% of people without insurance are estimated to live within a 5-mile driving distance to a Bridge Access Program provider.

For a snapshot of various data sources, CDC continues to receive data from Immunization Information Systems (IISs), the National Immunization Survey (NIS), claims data and other surveillance systems. To provide some preliminary data about vaccination coverage, the NIS has an adult COVID module and a child COVID module that are administered every week. For those not familiar with the NIS, this is a random digital dial (RDD) telephone survey of cell phone numbers and vaccination status that is self-reported by the respondent. An important caution is that sometimes, there may be a potential for overestimation since the information is self-reported. Looking at the data for the week of October 8-14, 2023 for adults ≥18 years of age, an estimated 7% are reported to have received a 2023-2024 COVID-19 vaccine. CDC also assesses vaccine intentions among individuals who have not received a vaccine. About 25% of adults say they will definitely get vaccinated and about 38% say they probably or definitely will not get vaccinated. Data also are collected on sociodemographic variables. COVID-19 vaccine was more frequently reported among adults who were older, insured, and with higher incomes. In terms of data reported by parents on children through 17 years of age for the week of October 8-14, 2023, about 2% of children were reported to have received a COVID vaccine. A little over a quarter of children have a parent who have said they definitely will get their child vaccinated, while about 38% have a parent that said they definitely will not get vaccinated.

Discussion Points

Ms. Bahta asked whether there was a status on vaccine supply. Some pediatricians are experiencing difficulty in getting the Moderna product. They have heard reports from some of their community members that they have gone to a pharmacy through the Bridge Access Program and were charged for the vaccine.

Dr. Stokley said her understanding was that vaccine supply is available for ordering, even for Moderna vaccine. She said she would speak with Ms. Bahta offline specifically for her location.

Dr. Kimberlin (AAP Red Book) observed that 2% of children have received the current version of the vaccine and 40% of parents say they are not going to get their children vaccinated, while 7% of adults have received the current vaccine and 40% or so say they are not going to get vaccinated. He said he did not have words for this. While he appreciates everything the AAP, ACIP, and CDC are doing to make recommendations, the recommendations are not being heard. He suggested that during a future ACIP meeting, additional detail be provided on communication strategies, not additional adjustments to the current recommendations, but what is being done to make sure that they are doing better as a country to get those recommendations to the people who need to hear them in a way that they want to hear them and to which they are receptive. Unless they address this issue, it will not make any difference how many recommendations they make because they will "fall on deaf ears."

To follow-up on Ms. Bahta's comment, Dr. Poehling indicated that providers in North Carolina are reporting trouble with both Moderna and Pfizer vaccines for young children. This is an important issue that needs to be investigated to support people. She expressed gratitude to the CDC for the Bridge Access Program, which is a very important program. She also appreciated the comment about having to figure out which location is in the network. This is an important communication message in terms of helping people with access.

Dr. Meyer commented that with regard to the points made about pediatric vaccination, from what they are hearing, it is not necessarily a supply issue or distribution issue. While there have been some issues that have had to be worked out through the transition to commercialization, in the rollout, there was a delay in getting the Moderna supply. However, that has improved and now they are more about how difficult it is for pediatricians to be able to carry these products in terms of storing, stocking, and implementation issues around providing this vaccine. She noted that Dr. Wallace would be talking about some of the new guidance that makes the vaccine better implementable in the pediatric office setting. In terms of the VFC, they have continued to increase allocations so that states can order more VFC doses. An addendum has been provided to the VFC Operations Guide that provides additional flexibility around borrowing to help further smooth some of the implementation challenges that pediatric providers are facing.

Dr. Talbot agreed that the Bridge Access Program is amazing, but the population using the Bridge Program does not have the time, energy, or bandwidth to find the pharmacy or the person who can deliver the vaccine. These are the folks who are working 2 jobs and do not have insurance. She applauded the amazing amount of work, but it further reiterates the need for standard funding for adult vaccines.

Dr. Lee highlighted that while acceptability is a component of the low uptake, the access issues are real. It is not only supply, but also the whole financial model for vaccination. As these vaccines are getting more expensive, they have to recognize they are asking pediatricians, family practice offices, and now adult practices to bear the cost of vaccines that may not get reimbursed at cost and they also might lose doses. Given that uptake is unpredictable right now, it makes it a challenge to understand how many doses a practice should stock. It is somewhat of a "chicken and egg" dilemma right now. The VFC, Bridge Access Program, and VFA programs are unbelievable, and it is unclear where they would be without them. She appreciates all of the efforts that go into funding vaccines because it does make it at least feasible, but the model of payment is being changed such that the upfront cost is borne by

providers, which makes it very challenging to continue to scale up along with all of the other implementation considerations.

Dr. O'Leary (AAP) emphasized that primary care is stretched incredibly thin right now with staffing shortages and financial issues. A lot of the practices are essentially small businesses with very thin margins. With the recommendations for COVID vaccine in particular, similar to recommendations for influenza vaccine, trying to vaccinate one's entire patient cohort from 6 months of age with influenza vaccines is one thing since the vaccine products are not that expensive. However, a product that costs $120 to $130 for an entire patient population makes it challenging for clinicians to purchase the product. The way the US delivers vaccines is fragmented and broken. The difference between 2% uptake and what parents are willing to do is close to 60% or 70%. That difference is delivery. If the product is available in every pediatric and family medicine office and clinicians give a strong recommendation, they will get much closer to 50% to 60% that they achieve with influenza vaccine, which pediatricians and family doctors have been working for years to build up to. He does not know how the pricing was determined for these products, but to ask clinicians to purchase these very expensive products for their entire cohort when they do not even know if they will be reimbursed is a lot to ask.

Dr. DeShon (NAPNAP) said that after 25 years as a pediatric nurse practitioner in a primary care office, she was disappointed that there was not the single dose option for young children as well, which would be a great option. Their facility is going to have the COVID-19 vaccine, but only in certain locations mainly because of the price. They also have experienced issues with availability. There is going to have to be cohesiveness of all pediatric and family providers with the recommendation because there are a lot of opinions, but families do listen to their providers. Availability of funding for mobile vaccines in vans would be amazing as well.

Ms. Hayes (ACNM) said she has a friend who is a Kaiser patient in Georgia who was unable to get the vaccine because Kaiser could not figure out what the billing code was for it. She had a similar experience in trying to get the vaccine herself when she went to a local pharmacy. They had access to order the vaccine, but they could not figure out how to enter it into their system. These large computer systems could not get the right ICD-10 codes. The computer glitches may be contributing to low uptake.

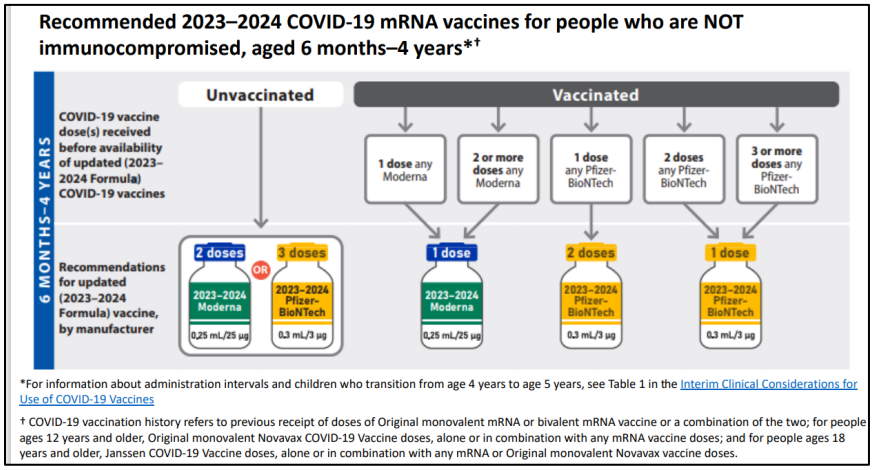
COVID-19 Vaccine Policy and Next Steps

Megan Wallace, DrPH, MPH (CDC/NCIRD) began with a brief update on current COVID-19 epidemiology. The trends in the weighted variant proportion and Nowcast estimates in the US by 2-week increments and a more detailed breakdown of the Nowcast estimates for the first 2 weeks in October, there are quite a few SARS-CoV-2 lineages currently circulating as has been the case for the past few months. The vast majority of these are still XBB sub-lineage variants.[60] Looking at the weekly population-based rates of COVID-19 associated hospitalizations by season from COVID-NET, a season is defined as October through September so that each season covers a full 12 months. As discussed during the September ACIP meeting, hospitalization rates tended to be lower this past year than in previous years. However, COVID-19 hospitalization rates typically begin to increase in November or December. Therefore, it was still too early to predict how COVID-19 hospitalization rates would compare in the upcoming respiratory season to past seasons.[61] Still looking at the weekly population-based rates of COVID-19 hospitalizations, but now stratified by age group over the past year, the highest

[60] https://covid.cdc.gov/covid-data-tracker/#variant-proportions
[61] Coronavirus Disease 2019 (COVID-19) Hospitalization Surveillance Network (COVID-NET); https://www.cdc.gov/coronavirus/2019-ncov/covidnetdashboard/de/powerbi/dashboard.html. Accessed October 16, 2023

hospitalization rates continue to be in adults ≥65 years of age.[62] This is the group in which the recent increase in hospitalization rates is most apparent.[63] In terms of the number of weekly COVID-19 new hospitalization admissions over time from the NHSN, despite hospitalizations being relatively lower than seen at previous points, currently there were over 18,000 new hospitalizations a week. Regarding the number of weekly COVID-19 deaths, though nothing like seen in the past, there were over 1,200 deaths a week.[64]

Moving to current COVID-19 vaccine policy. ACIP met on September 12, 2023 to review the available evidence for updated COVID-19 vaccines that have a monovalent XBB.1.5 component. ACIP recommended updated COVID-19 vaccines as authorized under the EUA or approved by BLA in persons ≥6 months of age. This includes Moderna COVID-19 vaccine in persons ≥6 months of age, Pfizer-BioNTech COVID-19 vaccine in persons ≥6 months of age, and Novavax COVID-19 vaccine in persons ≥12 years of age. All anticipated updated vaccines are now authorized or approved. To go through the recommendations in more detail, children in the youngest age group 6 months–4 years of age without immunocompromise are recommended to receive an initial series of mRNA vaccine with at least 1 dose of 2023-2024 vaccine, and these doses should be homologous. Infographics of the vaccine recommendations are available on the Interim Clinical Consideration website, such as the one below:



Children 6 months–4 years of age who are unvaccinated should receive 2 doses of the updated Moderna vaccine or 3 doses of the updated Pfizer vaccine as depicted on the leftmost part of the graphic. Those who are vaccinated, shown on the right side of the graphic, with 1, 2, or 3 or more doses also should receive at least 1 or 2 updated doses of mRNA vaccine depending upon which manufacturer they received initially.

With regard to interchangeability of COVID-19 vaccines, which is an important consideration in this age group, there previously was language in the Interim Clinical Considerations detailing the exceptional circumstances in which a different age-appropriate COVID-19 vaccine may be administered. However, this language was leading to implementation barriers among providers:[65]

[62] https://www.cdc.gov/coronavirus/2019-ncov/covidnetdashboard/de/powerbi/dashboard.html. Accessed October 16, 2023
[63] COVID-19–associated hospitalization data reported to CDC's National Healthcare Safety Network (NHSN). https://covid.cdc.gov/covid-data-tracker/#trends_weeklyhospitaladmissions_select_00
[64] Provisional Deaths from the CDC's National Center for Health Statistics (NCHS) National Vital Statistics System (NVSS). https://covid.cdc.gov/covid-data-tracker/#trends_weeklydeaths_weeklydeathrateaa_00
[65] https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#Interchangeability

- **Exceptional situations:** In the following exceptional situations, a different age-appropriate COVID-19 vaccine may be administered:
  - Same vaccine not available
  - Previous dose unknown
  - Person would otherwise not complete the vaccination series
  - Person starts but unable to complete a vaccination series with the same COVID-19 vaccine due to a contraindication

- A Vaccine Adverse Event Reporting System (VAERS) report is not indicated for these **exceptional situations**.

In response, the language around interchangeability has been updated in the Interim Clinical Considerations to clarify the circumstances under which it is acceptable to administer COVID-19 vaccine doses from different manufacturers. The bolded text represents the changes:

- COVID-19 vaccine doses from the same manufacturer should be administered whenever recommended. In the following **circumstances**, an age-appropriate COVID-19 vaccine from a different manufacturer may be administered:
  - Same vaccine not available **at the vaccination site at the time of the clinic visit**
  - Previous dose unknown
  - Person would otherwise not **receive a recommended vaccine dose**
  - Person starts but unable to complete a vaccination series with the same COVID-19 vaccine due to a contraindication

- A Vaccine Adverse Event Reporting System (VAERS) report is not indicated **in these circumstances**.

Notably, they moved away from the “exceptional circumstances” language and now simply refer to these as “circumstances.” Additional descriptions are provided for what these circumstances can be. A VAERS report is not indicated in these circumstances. Additionally, in an effort to simplify pediatric vaccine recommendations, guidance was updated for children who transition during the initial COVID-19 vaccination series from 4 to 5 years of age and children who are moderately or severely immunocompromised and transition from 11 years of age to age 12 years of age to receive the age-appropriate dosage based on their age on the day of vaccination.

All people ≥5 years of age without immunocompromise recommended to receive 1 dose of updated 2023-2024 vaccine. mRNA COVID-19 vaccines are authorized or approved for ≥6 months of age and Novavax COVID-19 vaccine is authorized for ≥12 years of age. One important caveat to the single-dose recommendation is that unvaccinated persons receiving Novavax COVID-19 vaccine should complete a 2-dose initial series. For children 5─11 years of age, the dose may be either Moderna or Pfizer-BioNTech regardless of vaccination history. Moderna’s dose is the same for the younger age group. In the recommendations for those ≥12 years and older, Novavax is also an option. For Novavax, those who are previously unvaccinated are recommended for 2 initial series doses while those who have any previous vaccinations are recommended for a single updated dose. For the mRNA vaccines, it is a single dose regardless of past vaccination history.

For all age groups, persons who are moderately or severely immunocompromised are recommended to receive an initial series of COVID-19 vaccine and then at least 1 updated 2023-2024 COVID-19 vaccine dose. They also may receive 1 or more additional updated COVID-19 vaccine doses informed by the clinical judgment of their healthcare provider and patient personal preference and circumstances. Anyone who is 6 months—4 years of age who is unvaccinated is recommended to receive 3 doses. Doses are determined for those who have been vaccinated based on how many doses they received by manufacturer. These are the same recommendations for vaccines for those who are 5—11 years of age who are moderately or severely immunocompromised. The recommendations are the same as those for 6 months—4 years of age with one exception. Once the initial series vaccination is complete, for any additional doses, this age group can receive either mRNA vaccine. For those ≥12 years of age who are moderately or severely immunocompromised, Novavax also is an option. It is important to note that Novavax does not have an initial series specific to those who are moderately or severely immunocompromised. They have the same 2-dose initial series recommendation as for those who are not immunocompromised, but like the mRNA vaccines, they do have the flexibility to receive additional doses.

In terms of the WG's upcoming policy discussions, first on the horizon is consideration of additional COVID-19 vaccine doses in older adults. This discussion is anticipated during the February 2024 ACIP meeting. If the WG aims to bring that before ACIP during that meeting, the policy discussion will occur prior to individuals reaching 6 months since their last dose. Then they will pivot to preparations for future COVID-19 vaccine formula updates, with those discussions beginning during the June 2024 ACIP meeting. As always, there will be continuously monitoring of VE, vaccine safety, and COVID-19 epidemiology. COVID-19 vaccine recommendations can be updated if needed.

Discussion Points

Dr. Sanchez stressed that this remains very complicated. He wondered what the protocol would be for children 6 months—4 years of age who received 1 dose, but did not know which and were not up-to-date.

Dr. Wallace indicated that there is a full appendix that lists all the iterations of scenarios that could occur based on the number of doses people think they received in the past. This is an area in which interchangeability is allowed. At the very least, they receive 1 updated dose of whatever was available in their doctor's office at the time.

Dr. Sanchez pointed out that if someone had not been vaccinated previously, they would require 2 doses of Moderna or 3 doses of the Pfizer. If it was unknown which one someone received or it was not available, he asked whether the old recommendation to give 3 doses would still be applicable.

Dr. Wallace said that if someone received at least one dose in the past, it would have to do with age and they would receive at least 2 updated doses, but 3 doses would not be recommended.

Dr. Poehling expressed appreciation for the clarification, which illustrated that the feedback provided clearly informed the modification of the recommendations and considerations. In terms of vaccine coverage in young children, there is a misperception that children do not get very sick with COVID-19, so she wondered whether there was any updated information on the hospitalization rate among children.

Referring to her first back-up slide, Dr. Wallace indicated that hospitalization rates among children are lower than hospitalization among older adults, but there still is a substantial amount of morbidity among children, particularly among those in the youngest age groups. The rates are beginning to rise moving into the Fall respiratory season. She called on Dr. Havers from COVID-NET to provide any information she would like to add.

Dr. Havers added that the data shown was from last year. As Dr. Wallace pointed out, the highest rates of hospitalization are in very young infants, particularly among those <6 months of age. School-aged children have lower hospitalization rates than very young infants. Hospitalization rates by age group have been going up, but have started to decline recently. It is not clear what to expect over the next year.

Dr. Kotton emphasized that rates of revaccination and vaccination are abysmal. Her patients seem very confused, with many telling her that they are up-to-date even though their last vaccine was in 2021. Many are amenable to vaccination when she brings it up, but they are not necessarily knowledgeable. Given the confusing information circulating, it seems like a better job could be done in terms of general education of the public. It did not seem clear whose responsibility that is, but from a public health perspective, she wondered if the CDC has a plan for rolling out updates.

Dr. Wallace indicated that this season, they have been trying to focus on how to simplify and streamline all of the information that is being shared with the public and providers because it is not only new COVID and influenza information, but also RSV that is new to everyone and timing and populations of interest. CDC is trying to take a more integrated and comprehensive approach that also includes the COVID-19 information. They have been working on a number of materials for the public and providers, including putting out the provider toolkit that has additional clinical education resources. Many of the communication efforts geared toward the public have been continued and there are some additional initiatives as well. For instance, there is a communication campaign geared toward educating the population about the Bridge Access Program to let everyone know that it exists and how to access it. They have been trying to work through that this season, taking an integrated approach to the 3 vaccines that protect against respiratory viruses. They have learned through surveys and other work that the agency is doing that there is a lot of vaccine fatigue among the public. Among the provider community, there is concern that patients do not want this vaccine and that if they bring it up, it could harm their ability to talk to patients about other vaccines. CDC is trying to approach it not only from an education standpoint and supporting the public, but also in terms of supporting providers in having those conversations and answering their questions.

Dr. Kotton expressed gratitude for all the agency is going. She encouraged members of the press who were listening to convey appropriate information about vaccine, given that many people get their information from outside of standard medical channels or CDC channels. While many people who signed up to be journalists did not necessarily do so to save lives, but as learned during the pandemic, the role of members of the press is important. It takes a multi-pronged approach, and she expressed appreciation for the thoughtfulness on behalf of the CDC.

Dr. Daley noted that taking a big picture view, the 1,200 deaths a week from COVID are largely vaccine-preventable. People who have not gotten a vaccine this Fall are not adequately protected, which the message he thinks they are all trying to convey. Referring to Slide 38, he agreed with Dr. Poehling that this is important because vaccination is transitioning to the medical home by and large in addition to other settings that are probably going to carry just 1 of

the 2 COVID vaccines for the practical reasons that Dr. O'Leary highlighted. It is expensive, challenging, and patients who typically would present to their medical home essentially were being turned away because their medical home was not carrying the mRNA product specifically that they received previously and that was creating barriers. He thanked everyone at the CDC who has worked hard to change this language to make it broader, as well as their colleagues at the FDA. Realizing that this is both scientific and regulatory, this is an example of federal agencies and public health agencies working together to help remove barriers so that when somebody shows up, they can be vaccinated.

Dr. Goode (APhA) said she loved the infographics and wondered if it would be possible to add the dosing intervals there to keep people from having to look elsewhere for that information.

Dr. Lee observed that there seems to be less hesitancy this year and asked whether vaccination uptake among healthcare workers is being tracked, and if there is a difference between influenza and COVID vaccine uptake among HCP in order to protect the patients they care for. This is particularly important because many HCP are caring for medically fragile patients, so it is important to protect HCP and patients. With a reduction in masking, there certainly is more respiratory viral transmission occurring in healthcare delivery settings.

Dr. Wallace indicated that CDC monitors influenza vaccine among HCP annually through various sources. There is an annual survey among HCP to assess their vaccination status that asks about COVID. There is monitoring of long-term care facility (LTCF) staff, which is updated on the COVID-NET site. They can get back to the group on this with more details.

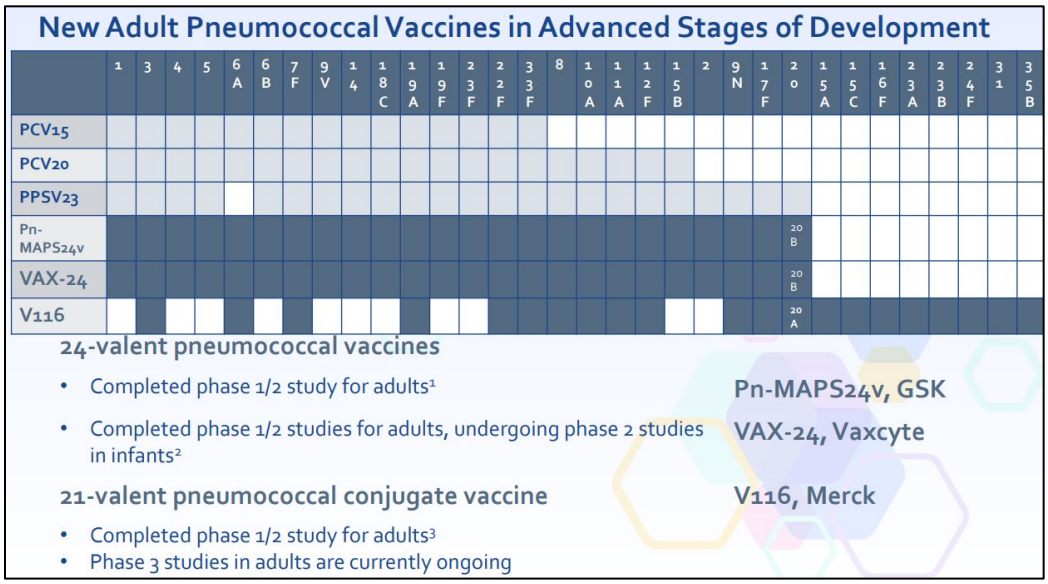
PNEUMOCOCCAL VACCINES

Miwako Kobayashi, MD, MPH (CDC/NCIRD) presented a brief summary of pneumococcal disease epidemiology and pneumococcal vaccines in development for adults. As a reminder, the Pneumococcal Vaccines WG reviews current data on pneumococcal disease burden and the efficacy, effectiveness, immunogenicity, and cost-effectiveness of pneumococcal vaccines and assesses the strength of evidence; reviews current pneumococcal vaccine recommendations, considering up-to-date evidence; and develops revised or updated policy options for pneumococcal vaccines as needed.

There are currently 2 types of pneumococcal vaccines recommended in the US, a pneumococcal polysaccharide vaccine (PPSV23) that has been recommended since the1980s, and pneumococcal conjugate vaccines (PCVs). The first pneumococcal conjugate vaccine, PCV7, containing 7 pneumococcal serotypes was recommended for children in 2000. PCV7 was replaced in 2010 by PCV13 containing 6 additional serotypes not included in PCV7. PCV13 was the first conjugate vaccine that was recommended for adults in 2012. In 2021, 2 new pneumococcal conjugate vaccines, PCV15 and PCV20, were recommended for adults. These vaccines contain additional serotypes not included in PCV13 and initially were recommended for adults who had not received a pneumococcal conjugate vaccine or whose vaccination history is unknown. Later, the recommendation for PCV20 was expanded to include adults who previously received PCV13. PCV15 and PCV20 are now recommended for children. Adult pneumococcal vaccine recommendations have been updated multiple times since 2012.

To briefly summarize pneumococcal disease burden among US adults,[66] among adults of all age groups, there were an estimated 100,000 non-invasive pneumococcal pneumonia hospitalizations and 30,000 invasive pneumococcal disease (IPD) cases, with 3,000 IPD deaths every year prior to the COVID-19 pandemic. Preliminary data show an increase in the number of IPD cases in late 2022 after reductions in IPD incidence across all age groups early in the COVID-19 pandemic.[67] This increase was seen with other invasive bacterial infections, especially among children.[68]

IPD incidence among adults aged ≥65 years reached a historically low level early in the COVID-19 pandemic. However, IPD incidence increased in 2022. Among adults ≥65 years of age in 2018-2019 and 2020-2021, approximately 40% of IPD cases were caused by pneumococcal serotypes not contained in any of the existing vaccines. There are new pneumococcal vaccines in advanced stages of development that are expected to provide broader serotype coverage compared with existing vaccines. In the following graphic,[69] the currently recommended vaccines (PCV15, PCV20, and PPSV23) and the serotype coverage are shown on the top. There are 2 24-valent pneumococcal vaccines in advanced stages of development for adults. These vaccines provide comparable serotype coverage compared with PPSV23. The 21-valent vaccine does not include some of the serotypes contained in existing vaccines, but does include 8 additional serotypes not contained in the existing vaccines. Phase 3 trials in adults are currently ongoing.



[66] Kobayashi M. October 20, 2021 ACIP Meeting Presentation. Considerations for Age-Based and Risk-Based Use of PCV15 and PCV20 among U.S. Adults and Proposed Policy Options.
[67] CDC Active Bacterial Core surveillance unpublished data
[68] Notes from the Field: Update on Pediatric Intracranial Infections — 19 States and the District of Columbia, January 2016–March 2023 | MMWR (cdc.gov); Notes from the Field: Increase in Pediatric Invasive Group A Streptococcus Infections — Colorado and Minnesota, October–December 2022 | MMWR (cdc.gov)
[69] 1. Chichili et al. Vaccine 2022; 2.ClinicalTrials.gov ID: NCT05266456, NCT05297578, and NCT05844423; 3. Platt et al. Lancet ID 2022.

After a brief break in the summer, the Pneumococcal Vaccines WG will be reviewing evidence on use of the 21-valent pneumococcal conjugate vaccine V116 for adults. Submission of a BLA for V116 to the FDA is anticipated in Quarter 4 of 2023, with possible FDA approval in the first half of 2024. The WG plans to review evidence to support the EtR domains, including epidemiology of pneumococcal disease among US adults, assessment of pneumococcal disease caused by serotypes not included in V116 but included in existing vaccines, Phase 2 and 3 clinical trial data on V116 among adults, feasibility and resource use involved in V116 used among adults, and health equity considerations. The aim is to have an ACIP vote on policy options shortly after FDA approval of V116.

Discussion Points

Dr. Talbot emphasized that there had been discussion over the last 2 days about vaccine recommendations that have been stuck. The polysaccharide vaccine has been in use since the 1980s. She asked whether the WG will have the opportunity to review the polysaccharide vaccine to determine whether that is still the best vaccine to keep on the adult schedule.

Dr. Kobayashi responded that the WG definitely would be revisiting the current recommendations as they start the discussions. She understands that there is a lot of interest in simplifying vaccine recommendations in general, so that will continue to be the priority.

Dr. Talbot pointed out that it is not just a matter of simplification, although she would be a big fan of simplifying the pneumococcal guidelines. The polysaccharide vaccine is a sugar vaccine and older adults do not create a T cell response and get blunting of the B cell response with use of the polysaccharide vaccine. As a person who wants to save all of her older colleagues, friends, neighbors, Americans, she is not sure that this is the best vaccine for them. However, it has continued to be used even though newer conjugate vaccines that provide a better immune response are available.

Dr. Loehr said he wanted to use this opportunity to get back on his “soapbox” to point out that there are still insurance companies that have not approved PCV15 for infants, let alone PCV20. He is faced with giving infants PCV13, which is not recommended by the ACIP at this time. Some insurance companies already have approved nirsevimab, including some that have not approved PCV15 or the PCV20. It is very frustrating and very hard to be a practitioner and not know what vaccine to give because he does not know what the insurance is going to cover. He plead with all insurers to cover ACIP recommendations as soon as possible. He knows that is possible because he has one that covers vaccines as soon as they are published in the *MMWR* or approved by the CDC Director.

Dr. Jessica Grubb (AHIP) said that while she could not make a statement at this time, the AHIP will take this back to their team as a trade organization.

Dr. Sanchez added to Dr. Talbot’s comments that the 23-valent is not just for adults. It is used in pediatrics and children who have some immunocompromising condition. Among his patients, it is about those with cochlear implants secondary to congenital cytomegalovirus (CMV)-related hearing loss who received the pneumococcal 23-valent polysaccharide vaccine and whether they subsequently should receive PCV20. That also should be reconsidered.

Dr. Poehling thanked Drs. Talbot and Sanchez for their comments and said she wanted to publicly state that she is hearing from a lot of allergy and immunology folks that like PPSV23 for helping them evaluate the immune system. Therefore, they wanted her to state that there is still a use for this product, though maybe for a different function.

Dr. Talbot said she thought they could stockpile some PPSV23 for the allergist and immunologist, but feels that it is a horrible idea to blunt immune responses in older adults in the setting of immunosenescence.

Dr. Lee said that in terms of Dr. Loehr's comment, she did not know whether there was a reasonable expectation with Affordable Care Act (ACA) coverage that applies to timing of availability. It is anchored to ACIP recommendations and people define that differently. Perhaps having clarity around that would be helpful so that there is consistency. She also wondered from a transparency perspective if people could publish what their policies are as it relates to preventive healthcare and the timing of availability because it seems like there is a ton of variability that frontline clinicians are being asked to manage. Not everyone is a part of a large health system. There are some small practices as well. She said she wanted to advocate for those who are just trying to deliver preventive care and are actually carrying the cost of this for people to make it easier.

Dr. Loehr said that his research into the legalities of this revealed that ACA requires coverage. The clock starts either when a recommendation is published or when it is approved by the CDC Director. Insurance companies are required to implement the recommendation with the following plan year. For instance, if the ACIP recommends PCV15 in September 2022, the 1-year mark would pass in September 2023. The next plan year would not be until January 2024, which would be when the insurance companies would be required to cover it.

Dr. Sanchez noted that there is a publication of the children's PCV20 recommendation already that could be provided to the insurance companies, which Dr. Loehr stressed starts the clock.

PUBLIC COMMENTS

Overview

The floor was opened for public comment on October 26, 2023 at 10:10 AM ET. Given that many more individuals registered to make oral public comments than could be accommodated during this meeting, selection was made randomly via a lottery. Dr. Lee provided a gentle reminder that the ACIP appreciates diverse viewpoints that are respectful in nature and issue-focused rather than comments directed at individuals. The comments made during the meeting are included in this document. Members of the public also were invited to submit written public comments to ACIP through the Federal eRulemaking Portal under Docket Number ID CDC-2023-0079. Visit http://www.regulations.gov for access to the docket or to submit comments or read background documents and comments received.

Public Comments

Mrs. Erica DeWald
President & Founder
Coffeehouse Communications

Good morning. I'm Erica DeWald, President and Founder of Coffeehouse Communications. Thank you so much for the opportunity to comment today. We hear a lot during these meetings about the need to make sure the schedule can be easily understood by providers. And while this is of course important, I think we rarely consider how easy the schedule may be for patients. As many of you know, children who are uninsured are 6 times less likely to be vaccinated than insured children. We also see lower rates of vaccination among children who live in rural areas. While the Vaccines for Children program covers the cost of vaccines, it's clearly not enough to solve all of the access barriers children face. Families living in rural areas and at or below the poverty line have limited opportunities to vaccinate their children. Obviously, in an ideal world, we would have more locations for vaccinations, such as mobile vans or extended clinic hours and time off work for parents to get their children vaccinated. And while we should continue to work toward those goals, in the meantime, there's something that we can control and that's a streamlined vaccination schedule, particularly for adolescents. The pentavalent meningococcal vaccines are a prime example of the opportunity before you. We can increase vaccination rates against a devastating, unpredictable disease by protecting our adolescents against all strains with a combination vaccine. It doesn't perfectly align with prior recommendations for individual ACYW and B vaccines, but that's why the work group did incredible work to rethink how we protect our children against meningococcal strains. I would respectfully request that all the working groups consider equitable access to vaccines as they form their recommendations. It might also be time to reexamine the schedules in totality to determine if there are ways to streamline recommendations moving forward, particularly, as we know, more lifesaving vaccines and mAbs are going to become available soon. If families can't get to all their vaccine appointments, then it really doesn't matter how well providers understand the schedule. So, thank you for all of your hard work and for taking my comments into consideration.

Brian Koffman, MD, CM
Co-Founder, Chief Medical Officer, & Executive Vice President
CLL Society, Inc.

Thank you to ACIP for this time to talk. I'm Dr. Brian Koffman, a CLL patient myself, a retired family doctor, and the Co-Founder, Chief Medical Officer, and Executive Vice President of the non-profit CLL Society dedicated to the unmet needs of those with chronic lymphocytic leukemia. I will be speaking as a physician and a patient advocating for the immunocompromised. As the committee well knows, CLL is a cancer of the B lymphocytes. Its associated immune deficiencies often results in no response or clinically relevant reduction in response to vaccines. This problem is amplified by commonly used therapies, including B-cell depleting monoclonal antibodies. I use CLL as my example as I understand it best, but know that the committee recognizes that CLL is one of many conditions where the disease themselves or their treatment render patients immunocompromised or immunosuppressed. These include, but are not limited to, other B-cell malignancies regardless of their treatment status, advanced HIV, congenital immune deficiencies, patients on immunosuppressive drugs to prevent transplant rejections or to treat their cancers, rheumatoid neurological, or other autoimmune disorders. Some examples specific to CLL patients in vaccines—there is well-documented diminished serological and T-cell response and much more importantly, diminished protection from hospitalization, ICU admissions, and death with the different COVID-19

vaccines. Responses are known also to be diminished to herpes zoster and hepatitis B vaccines. I respectfully ask ACIP to continue to study the protection provided by all appropriate vaccines in vulnerable communities and, where needed, develop different vaccine protocols as it was done with COVID-19. This logically leads to a bigger ask. I ask respectively to ACIP to expand its area of review under its remit, which is to develop recommendations for US immunization. Immunization, as we know, is not synonymous with vaccination, but rather a broader term meaning to make one resistant to an illness. Please consider advising on pre-exposure prophylaxis, PrEP, with long-acting antibodies such as those for RSV and COVID-19. These passive immunity approaches are critical to communities like ours, whose members are not reliably able to mount a robust response to the more commonly active immune measures such as vaccinations. We believe having ACIP advise on all methods of immunization for the most vulnerable could only benefit the immunocompromised community. Thank you for your attention to this important matter for my vulnerable and often invisibly disabled community.

Reiss Dorit, PhD, LLB
Professor of Law
UC Law San Francisco

Hello. My name is Dorit Reiss. I'm a Professor of Law at UC Law San Francisco. Thank you again for the chance to comment and for all your work, especially at the time when public health is under pressure and people working to protect others from disease are subject to attack and targeting. I want to say 3 things. First, thank you for the extensive work you're putting into revising and clarifying the schedule. Dr. Cineas opened with this, but I want to re-emphasize, not for the committee but for others, that the October meeting about the schedule is not to change the schedule, but to update it with that year's recommendations and work on making the schedule more readable before they're published in February. This is not when you add vaccines. I'm saying this because, as you know, this was a point of misinformation a couple of years ago. And thank you for the effort that goes into making the tables easier to read. And I hope the committee in its annual work, given the complexity, continues to put a premium on simple and clear recommendations going forward. Second, in the name of increasing transparency and because of past misinformation, I would suggest the CDC include a short explanation about this in your “Who Sets Immunization Schedule” page. It currently addresses ACIP's role and the role of experts, but not the technical process. Add a couple of paragraphs that say CDC updates the immunization schedule once a year. ACIP discusses revision in October, and the updated schedules are published in February, and the October discussion is not where schedules are changed just when the tables are updated. Using for example, the nice graphic image that Dr. Wodi’s excellent presentation included, will not be much work and can help people understand the process better, especially if others try to represent it going forward. Finally, like several others, I'm very excited to have a pentavalent vaccine against meningococcal disease. I know you will be discussing updating the meningococcal vaccine schedules in coming meetings, and I hope you'll consider, in addition to protecting our teens and young people and people at risk for this very frightening disease, how to make that schedule easy to understand and accessible. And I have to admit, I have some concerns that yesterday's decision might cause confusion or cause scarcity for practices. For example, I worry that many practices will not carry the new vaccine because of confusion. Thank you for your time.

Judy Klein
President
Unity Consortium

Good morning. I'm Judy Klein, President of Unity Consortium. Thank you for this opportunity to provide comments and for your ongoing commitment to including perspectives of a wide array of stakeholders. Unity is a nonprofit that unites diverse groups around a common passion—the imperative to protect equitably all adolescents and young adults against vaccine-preventable diseases to support lifelong health. Our vision is for at least 9 in 10 adolescents and young adults to be fully vaccinated on time with recommended vaccines. My comments will reinforce aspects of yesterday's discussions on the use of a new pentavalent meningococcal vaccine and are relevant to ACIP's plans to revisit the adolescent immunization schedule for mening vaccines. Yesterday, there were observations about the low uptake of Men-B vaccines and the challenges healthcare providers face in implementing shared clinical decision-making recommendations, and I'd also add the persistent gaps in coverage among adolescents for other recommended vaccines like HPV, flu, and COVID-19. Unity listens to the perspectives of parents on vaccinating their adolescents so we can better understand their experiences, concerns, and questions. And we conduct routine research with parents and have an established Mom's Advisory Council. Last month, our mom advisors talked with us about meningococcal vaccines and the possibility of changes to recommendations and vaccine options for their younger and older teens. The group raised numerous concerns about potential confusion to changes in age recommendations, and that such changes may translate into reduced trust or signal mixed messages about recommendations from CDC. The moms wondered that if we have been successful at preventing meningitis disease, why should we change something that is working? Our research indicates, and our mom advisors share, that they trust their adolescent’s healthcare provider when it comes to making vaccine decisions for their children. They value provider recommendations that are confident and concise, and this translates into vaccination. ACIP recommendations influence the confidence in decision-making process for parents and the vaccines discussions they have with their providers. Providers, as we know, have limited time during patient visits and may be unable to spend the extra time discussing confusing recommendations. I urge you to approve clear vaccination recommendations that are straightforward to implement and support providers to make confident, concise vaccination recommendations to parents. Unity remains dedicated to working with stakeholders in all sectors to address the challenges of implementing sound and practical recommendations to ensure our adolescents and young adults are protected against vaccine-preventable diseases. And we thank you for your tireless efforts to develop these recommendations that guide our providers, families, and individuals. Thank you.

Mr. Noah Louis-Ferdinand
Communications Coordinator
Voices for Vaccines

Hi, my name is Noah Louis-Ferdinand. I'm the Communications Coordinator at Voices for Vaccines. Thanks so much for giving me the time to speak today. I just wanted to comment on the way in which information gets shared at these meetings. I've noticed that there is a lot of public discussion and scrutiny as to what gets said here. Almost always after these meetings, we do a lot of work kind of trying to understand what questions people have about public health recommendations, vaccine recommendations, and I'll see like screenshots from the slideshows or even little video clips of people speaking here posted online on social media and whatnot. A lot of public discussion of what is very dense scientific information sometimes understood and

interpreted correctly, sometimes not. But even for myself as somebody who tries to follow along so that I can hopefully explain to other people why recommendations made the way that it was, I find I maybe lose some of the key details over the course of say a 100 plus slide presentation. It's just very dense information and it's science—it has to be. So that's kind of a course, but something that I think would be helpful for me and I hope for other people, is just a little bit more of an eye towards how communicable are these recommendations? How intuitive are these recommendations? What would somebody who's not necessarily familiar with this process think about the information presented here? And again, I understand that this is a scientific discussion, but even like a slide or 2 maybe anticipating key questions that somebody might have and responding to those or trying to state in plain language and takeaways that you would want the public to have. I think that would go a long way, things like that towards not only making this information more accessible, but also making it easier to communicate because at least in my work, I will get questions that are very curious and thoughtful, not just about the vaccines, but the public health process behind the recommendation. I mean these people sometimes want to know why something was recommended the way that it was. A good example of this has to do with like the updated vaccine. I think that a lot of people kind of intuitively understand why somebody who was 65 with a health condition would want to get that. But then they'll ask specifically about their age or like I have a 14-year-old daughter and that stuff is in these presentations. That information is discussed, but it's not always practical or easy to go back and kind of dig that stuff out every time somebody asks kind of questions like that. So, anything that can be done to have a little bit more of an eye towards anticipating people's questions, people's concerns, what people are saying already about these meetings that people are paying a lot attention to I think would just go a long way towards helping people understand the scientific discussion and maybe getting more out of it. So, I very much appreciate what you do here. I don't mean to imply it's opaque, but just maybe something on the side of communication could help a little bit more. So that's all I had to say. Thanks so much for the time and I will yield the rest of it.

CERTIFICATION

Upon reviewing the foregoing version of the October 25-26, 2023 ACIP meeting minutes, Dr. Grace Lee, ACIP Chair, certified that to the best of her knowledge, they are accurate and complete. Her original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

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ACRONYMS USED IN THIS DOCUMENT

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ABCs	Active Bacterial Core Surveillance System
ACA	Affordable Care Act
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
ADEM	Acute Disseminated Encephalomyelitis
AE	Adverse Event
AESI	Adverse Event of Special Interest
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
AMIS	American Men's Internet Survey
AOA	American Osteopathic Association
APhA	American Pharmacists Association
AR	Adverse Reaction
AREXVY	RSVPreF3 + AS01E
ARI	Acute Respiratory Illness
ASPE	Office of the Assistant Secretary for Planning and Evaluation
ASPR	Administration for Strategic Preparedness and Response
ASTHO	Association of State and Territorial Health Officers
AUC	Area Under the Curve
BARDA	Biomedical Advanced Research and Development Authority
BEST System	Biologics Effectiveness and Safety System
BLA	Biologics License Application
CAP	Community-Acquired Pneumonia
CBER	Center for Biologics Evaluation and Research
CBO	Community-Based Organization
CC	Collaborating Center
CCHMC	Cincinnati Children's Hospital Medical Center
ccIIV4	Cell-Culture Based Vaccine
CDC	Centers for Disease Control and Prevention
CFR	Case Fatality Rate
CHD	Chronic Heart Disease
CHIKV	Chikungunya Virus
CICP	Countermeasures Injury Compensation Program
CISA	Clinical Immunization Safety Assessment Project
CKD	Chronic Kidney Disease
CLD	Chronic Liver Disease
CLI	COVID-Like Illness

CMC	Chronic Medical Conditions
CMH	Cochran-Mantel-Haenszel
CHMP	Committee for Medicinal Products for Human Use
CMS	Center for Medicare and Medicaid Services
CMV	Cytomegalovirus
COI	Conflict of Interest
CONUS	Continental United States
COPD	Chronic Obstructive Pulmonary Disease
COVID-NET	Coronavirus Disease 2019 (COVID-19) Hospitalization Surveillance Network
CSF	Cerebrospinal Fluid
CSTE	Council of State and Territorial Epidemiologists
CVD	Cardiovascular Disease
DCAC	Dengue Case Adjudication Committee
DENV	Dengue Virus
DFO	Designated Federal Official
DM	Diabetes Mellitus
DoD	Department of Defense
DRC	Democratic Republic of Congo
DSMB	Data Safety Monitoring Board
DVA	Department of Veterans Affairs
eCRF	Electronic Case Report Form
ED	Emergency Department
EMA	European Medicines Agency
EMDS	Enhanced Meningococcal Disease Surveillance
EMR	Electronic Medical Record
EQ-5D-5L	EuroQol-5D-5L
EQ VAS	EuroQol Visual Analog Scale
ERL	Essential Regulatory Laboratory
ET	Eastern Time
EtR	Evidence to Recommendation
EU	European Union
EUA	Emergency Use Authorization
EU-M4all	EU-Medicines for All
FAS	Freely Associated States
FDA	Food and Drug Administration
fIPV	Fractional Doses of IPV
FQHC	Federally Qualified Health Centers
FluID	Flu Informed Decisions
FluSurv-NET	Influenza Hospitalization Surveillance Network
FRN	Federal Register Notice
FRPP	Federal Retail Pharmacy Program
GACVS	Global Advisory Committee on Vaccine Safety
GBS	Guillain-Barré Syndrome
GISAID	Global Initiative on Sharing All Influenza Data
GISRS	Global Influenza Surveillance and Response System
GMC	Geometric Mean Concentrations
GMT	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
HCP	Healthcare Personnel / Providers

HD-IV	High-Dose Influenza Vaccine
HHS	(Department of) Health and Human Services
HI	Hemagglutination Inhibition
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HRQOL	Health-Related Quality of Life
HRSA	Health Resources and Services Administration
HZ	Herpes Zoster
IC	Immunocompromising Conditions
ICER	Incremental Cost Effectiveness Ratio
ICU	Intensive Care Unit
IDCRC	Infectious Diseases Clinical Research Consortium
IDSA	Infectious Disease Society of America
IHR	International Health Regulations
IHS	Indian Health Service
IIS	Immunization Information System
IIV	Inactivated Influenza Vaccine
ILINet	Influenza-like Illness Surveillance Network
IM	Intramuscular
IMD	Invasive Meningococcal Disease
IPD	Invasive Pneumococcal Disease
IRA	Inflation Reduction Act of 2022
IRR	International Reagent Resource
ISD	Immunization Services Division
ITT	Intention-to-Treat
IV	Intravenous
IVIG	Intravenous Immune Globulin
IVWG	Federal Interagency Vaccine Work Group
JHU	Johns Hopkins University
LAIV	Live-Attenuated Influenza Vaccine
LGBTQ+	Lesbian, Gay, Bisexual, Transgender, Queer or Questioning, or Other
LRTD	Lower Respiratory Tract Disease
LRTI	Lower Respiratory Tract Illness
LTCF	Long-Term Care Facilities
MAAEs	Medically Attended Adverse Events
MACDP	Metropolitan Atlanta Congenital Defects Program
MIS	Multisystem Inflammatory Syndrome
mITT	Modified Intention to Treat
MMWR	*Morbidity and Mortality Weekly Report*
MSM	Men Who Have Sex with Men
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
NGS	Next-Generation Sequencing

NHANES	National Health and Nutrition Examination Survey
NHP	Non-Human Primate
NHSN	National Healthcare Safety Network
NIAID	National Institute of Allergy and Infectious Diseases
NIC	National Influenza Center
NICU	Neonatal Intensive Care Unit
NIH	National Institutes of Health
NIS	National Immunization Survey
NMA	National Medical Association
NNDSS	National Notifiable Diseases Surveillance System
NP	Nasopharyngeal
NREVSS	National Respiratory and Enteric Virus Surveillance System
NSSP	National Syndromic Surveillance Program
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
OIDP	Office of Infectious Disease and HIV/AIDS Policy
PCP	Primary Care Provider/Practitioner
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccines
PEP	Post-Exposure Prophylaxis
PHAC	Public Health Agency Canada
PHE	Public Health Emergency
PICO	Population, Intervention, Comparison, Outcomes
PIDS	Pediatric Infectious Disease Society
pIMD	Potential Immune-Mediated Disease
PK	Pharmacokinetics
PPE	Personal Protective Equipment
PPSV23	Pneumococcal Polysaccharide Vaccine
PPV	Positive Predictive Value
preF	Prefusion F Protein
PrEP	Pre-Exposure Prophylaxis
QALY	Quality-Adjusted Life Year
QIV	Quadrivalent Inactivated Influenza
QOL	Quality of Life
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RDD	Random Digital Dial
RIV	Recombinant Influenza Vaccine
RESP-NET	Respiratory Virus Hospitalization Surveillance Network
ROU	Research Use Only
RSV	Respiratory Syncytial Virus
RSV-LRTD	RSV Lower Respiratory Tract Disease
RSV-NET	Respiratory Syncytial Virus Hospitalization Surveillance Network
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
SES	Socioeconomic Status
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
SNS	Strategic National Stockpile
SO/GI	Sexual Orientation and Gender Identity
SOT	Solid Organ Transplants
STIs	Sexually Transmitted Infections
UIHP	Urban Indian Health Program
UK	United Kingdom
UKHSA	UK Health Security Agency
US	United States
USG	United States Government
VAERS	Vaccine Adverse Event Reporting System
VCD	Virologically Confirmed Dengue
VFA	Vaccines for Adults
VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VFA	Vaccines for Adults
VFC	Vaccines For Children
VICP	National Vaccine Injury Compensation Program
VIGIV	Vaccinia Immunoglobulin Intravenous
VNSP	Vaccines National Strategic Plan
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VRC	Vaccine Research Center
VSD	Vaccine Safety Datalink
WG	Work Group
VRC	Vaccine Research Center
WGS	Whole Genome Sequencing
WHO	World Health Organization

WRITTEN AGENCY UPDATES SUBMITTED

CDC Agency Updates

Respiratory Virus Season Overview:

- Protecting people against respiratory diseases this fall and winter remains a top priority for CDC, its partners across federal and state governments, and for America's healthcare system.
- Thankfully, we're in our strongest position yet to fight flu, COVID-19, and respiratory syncytial virus, or RSV, which we expect to circulate simultaneously in the coming months.
- Currently:
    - COVID-19 activity continues to decline in many areas of the country, but remains the cause of most new respiratory virus hospitalizations and deaths.
    - Influenza activity remains low in most areas of the country, but small increases have been reported in some areas, particularly Alaska and the Northern Mariana Islands
    - RSV transmission has increased to seasonal epidemic levels in the Southern regions of the United States and is expected to continue to increase in the rest of the country within the next 1–2 months.
- On October 23, CDC published a "Healthcare Provider Toolkit: Preparing Your Patients for the Fall and Winter Virus Season". The Toolkit provides clinical and other partners talking points on "How to talk to your patients about flu, COVID-19, and RSV vaccines" and co-administration of vaccines, as well as print materials for providers and patients.
- Vaccination remains the safest protection to avoid hospitalizations, long-term health impacts, and death. It is especially important for people who are at higher risk of developing serious complications, such as older adults or those with a weakened immune system.
- We encourage all Americans to stay up to date on their vaccinations, particularly the new immunizations available to fight this fall/winter virus season.

Transition to Commercial

- Over the last two years, the United States Government and partners effectively implemented the largest adult vaccination program in U.S. history, with nearly 700 million doses of COVID-19 vaccines given to 270 million Americans.
- On September 15th, COVID-19 vaccines transitioned to the commercial market. Healthcare providers, pharmacies, and community vaccine partners are ordering and receiving most vaccine doses directly from manufacturers.
- While fighting COVID-19 remains a key public health priority, ensuring that all Americans have continued, easy access to routine immunizations regardless of insurance status, is an essential public health priority.

Bridge

- CDC launched the COVID-19 vaccine Bridge Access Program in mid-September to provide access for COVID-19 vaccines to the roughly 25-30 million Americans without health insurance and many more whose insurance does not provide coverage to COVID-19 vaccines at no cost.
- The Bridge program leverages a unique public-private partnership to help maintain uninsured individuals' access to COVID-19 care at their local pharmacies, through existing public health infrastructure, and at their local health centers.

- CDC has shipped all vaccines in our depots to jurisdictions who have ordered COVID-19 vaccines through the Vaccines for Children (VFC) and Bridge Access programs. The first doses under the Bridge Access Program were administered on September 13th.

VFA

- I want to stress that the COVID-19 Bridge Access program is a **temporary fix** to longstanding barriers to adult vaccination, including lack of accessibility, availability, and confidence, and is ***solely limited to COVID-19 Vaccines***.
- A longer-term solution is the Vaccines for Adults (VFA) program, which would to create permanent public health infrastructure modeled after the successful Vaccines for Children (VFC) program. As proposed by the administration, VFA would cover all recommended vaccinations at no cost for uninsured adults.
- A VFA program is essential to increasing vaccine equity, by providing broader access to vaccines. This core public health infrastructure would help prevent these seasonal infectious disease threats and may be leveraged in the event of a public health emergency.

Importance of VFC

- The Vaccines for Children program (VFC) is a federally-funded, mandatory entitlement program that provides vaccines at no cost to children who might not otherwise be vaccinated because of their inability to pay.
- In it's 30 year history, VFC has **prevented 472 million illnesses, help avoided 1,052,000 deaths, and saved nearly $2.2 trillion in societal costs.**
  - Every dollar spent on childhood vaccination saves $10.90 in projected healthcare costs.
- Since its implementation in 1994, the VFC program has been credited with increasing rates of vaccine uptake among US children, decreasing vaccine-preventable disease incidence, and reducing racial and socioeconomic disparities in vaccine uptake.
- **More than 90% of VFC program funding is used to purchase vaccines**. Remaining funds are used for operational activities including recruitment and enrollment of private providers, vaccine ordering and accountability efforts, vaccine distribution to public clinics and private vaccination providers, and program evaluation.
- **VFC helps ensure that all children have a better chance of getting their recommended vaccines.** The VFC program supplies >50% of vaccines for children in the US, or 40 million vaccinations to uninsured children across the United States annually.

Nirsevimab and transition to Sanofi

- CDC is aware that there is limited supply of nirsevimab, a long-acting preventive antibody recommended to protect infants from severe RSV illness. On October 23rd, CDC issued a Health Alert Network (HAN) Health Advisory advising healthcare providers to prioritize this preventive antibody for those who need it the most: young infants (birth through age 5 months), infants with high-risk conditions, and American Indian or Alaska Native infants and toddlers in remote settings or communities with known high rates of severe RSV disease in young children.
- For babies between 8-19 months with certain medical conditions, healthcare providers may use palivizumab instead, which is another preventive antibody that has a long track record of protecting babies at highest risk for severe RSV.
- CDC recommends that all infants should be protected against RSV through either vaccination during pregnancy or receiving nirsevimab after birth.
- CDC continues to discuss these supply and demand issues with the manufacturer, Sanofi, to chart a path forward for this RSV season.

- While nirsevimab may be limited, there are other ways to protect infants, their families, and our communities from RSV:
    - Providers should encourage pregnant people to get the recommended maternal RSV vaccine (Abrysvo) during weeks 32-36 of pregnancy. Most babies born to a mother who was vaccinated against RSV during pregnancy are already protected and do not need nirsevimab.
    - As always, families should use everyday preventive measures, including handwashing, covering coughs and sneezes, cleaning frequently touched surfaces, and keeping their baby away from people who are sick.
    - Anyone who is sick should stay home to limit the spread of RSV, or other illnesses.
- Vaccines save lives. As a reminder, it's time to get your updated COVID shot and annual flu shot. Consult with your healthcare provider if RSV immunizations are right for you.

CMS Update

- Inflation Reduction Act (IRA) – beginning on 10/1/23, coverage of ACIP recommended vaccines is mandatory for adults enrolled in Medicaid without cost-sharing. CMS issued guidance to states on 6/27/23 (SHO, fact sheet).
- Continue to work very closely with CDC, as well as with states and other partners, on many vaccine issues including:
    - commercialization of the COVID vaccine. CDC has shared information on Bridge Access program with state Medicaid agencies
    - new RSV products
- Continue to emphasize that we can't lose sight of the importance of routine immunizations

IHS Report
ACIP Meeting October 2023

The Indian Health Service continues to prioritize vaccination as our principle clinical and public health prevention priority. As part of our IHS National E3 Vaccine Strategy, we seek to ensure that every patient at every encounter is offered every recommended vaccine, when appropriate. In partnership with staff at our federal, tribal, and Urban Indian Organization facilities, we have collected and shared best practices and lessons learned from dozens of E3 Champions pilot sites across the country for cross-pollination of our IHS system of care.

We are actively engaged in our Fall respiratory viral season vaccine campaign with the goal to mitigate morbidity and mortality from vaccine preventable illness in our vulnerable service population.

Following approval of the 2023-2024 monovalent COVID-19 vaccine and RSV vaccines for elders and pregnant women, the IHS distributed guidance to clinicians, public health staff, tribal leaders, and tribal communities about the importance of these countermeasures.

Similarly, coincident with the ACIP recommendations, the Indian Health Service took quick action to add nirsevimab to the IHS National Core Formulary to further promote access to this immunization for infants and young children. We have also reached out to our federal, tribal, and Urban Indian Organization partners to provide guidance about the recommendation that all infants under 8 months of age in their first RSV season and all AI/AN children 8-19 months of age in their second RSV season receive nirsevimab.

Currently, all ACIP-recommended vaccines and long-acting monoclonal antibodies are listed on the IHS National Core Formulary.

Moving forward in collaboration with our partners in tribal communities, we will continue to promote access, quality, value, and equity related to immunizations in Indian Country.

National Vaccine Program

Office of Infectious Disease and HIV/AIDS Policy (OIDP)
Update to the Advisory Committee on Immunization Practices (ACIP)
October 24, 2023

- Federal agencies comprising the Interagency Vaccine Working Group have provided feedback to inform the Vaccines Federal Implementation Progress Report, expected in December 2023. The Progress report will give an overview of progress from 2021- 2023 toward achieving the goals of the Vaccines National Strategic Plan, which provides a roadmap for the coordination of vaccine development and use in the United States

- The Office of the Assistant Secretary for Planning and Evaluation (ASPE) and the Office of Infectious Disease and HIV/AIDS (OIDP) have jointly released an environmental scan report entitled, "Environmental Scan of Best Practices for COVID Vaccination and Testing for Underserved Populations." The document provides a comprehensive literature review and describes initiatives and interventions to improve COVID-19 vaccination and testing services for people who are medically or socially at disproportionate risk of COVID-19.

- The forthcoming National Vaccine Advisory Committee (NVAC) meeting is scheduled for February 22 and 23, 2024.

National Institutes of Health Update

ACIP: October 2023

COVID-19

- **Next Generation COVID-19 Vaccines:** The National Institute of Allergy and Infectious Diseases (NIAID) and the Biomedical Advanced Research and Development Authority (BARDA) announced Project NextGen - a coordinated effort where the federal government works with the private sector to advance the pipeline of new, innovative vaccines and therapeutics for COVID-19. NIAID plans to leverage existing infrastructure and network sites to implement a structured program evaluating approximately 10 next generation COVID-19 vaccines in Phase 1 and Phase 2 clinical trials. Next generation vaccines include those with enhanced breadth of protection to variants, improved durability, and those with an enhanced ability to block infection/transmission including mucosal vaccines, relative to currently approved vaccines. **NIAID news release, July 13, 2023:** https://www.niaid.nih.gov/diseases-conditions/next-generation-covid-19-vaccines . NIAID Project NextGen website: https://www.niaid.nih.gov/diseases-conditions/project-nextgen
- **COVID-19 Vaccination and Boosting During Pregnancy**: Receiving a COVID-19 mRNA vaccine or booster during pregnancy enhances maternal binding and neutralizing antibody responses and transplacental antibody transfer to the newborn, according to results from the Multisite Observational Maternal and Infant Study for COVID-19 (MOMI-VAX), which was funded by NIAID. **NIAID news release, August 11, 2023:** https://www.niaid.nih.gov/news-events/covid-19-vaccination-and-boosting-during-pregnancy-benefits-pregnant-people-and
- **Risk of COVID-19 after natural infection or vaccination**
  While prior trials have established the efficacy of COVID-19 vaccines for preventing disease, phase 3 efficacy studies have generally not comprehensively evaluated protection provided by previous infection or hybrid immunity (previous infection plus vaccination). Individual patient data from US government-supported harmonized vaccine trials provide an unprecedented sample population to address this issue. Previous infection, any hybrid immunity, and two-dose vaccination all provided substantial protection against symptomatic and severe COVID-19. Too few infections were observed to draw statistical inferences comparing hybrid immunity to vaccine alone. Considering the risks of infection, vaccination remains the safest approach to protection against COVID-19. **Rick *et.al***. Risk of COVID-19 after natural infection or vaccination, ***eBioMedicine* 2023; 96: 104799 DOI:** https://doi.org/10.1016/j.ebiom.2023.104799

Mpox Therapeutic and Vaccine Trials:

- NIAID's **immunogenicity trial of the JYNNEOS** mpox vaccine, including both evaluation of lower intradermal doses and an adolescent safety and immunogenicity trial, has completed enrollment and is expected to report initial results in 2024. https://classic.clinicaltrials.gov/ct2/show/NCT05512949
- NIAID continues to support the **STOMP** trial, a Phase 3 clinical trial evaluating the antiviral tecovirimat, also known as TPOXX. The trial aims to enroll more than 500 adults and children of all races and sexes, people with HIV, and pregnant and lactating people across 60 sites in the United States and Mexico, with an option for remote enrollment from other U.S. locations. The STOMP trial is sponsored by NIAID and led by the NIAID-funded AIDS Clinical Trials Group. https://www.stomptpoxx.org/main

- NIAID is co-sponsoring the **PALM007 trial** of tecovirimat as treatment for clade 1 mpox in the Democratic Republic of the Congo (DRC) with the DRC's National Institute of Biomedical Research. PALM007 is actively enrolling. https://clinicaltrials.gov/study/NCT05559099

Meningitis

Meningococcal Pentavalent Vaccine Recommendation: Researchers from the NIAID-funded Infectious Diseases Clinical Research Consortium (IDCRC) provided an interim report of the meningococcal serogroup ACYWX conjugate vaccine in comparison with MenACWY-TT Conjugate Vaccine in infants to the WHO Strategic Advisory Group of Experts (SAGE) on Immunization. The study results show that the pentavalent (NmCV-5 or MenFive®) vaccine is safe and highly immunogenic at 28 days post-vaccine. NmCV-5 had already been found safe and immunogenic for people ages 1 to 85 years and is approved by WHO for this age group. This is the pivotal study for the extension of WHO prequalification of this vaccine in the infant age group, so that the vaccine can be used in the routine immunization schedule of low- and middle-income countries. **IDCRC news release, October 3, 2023:** https://idcrc.org/about/news-archive/pentavalent.html

HIV

- **Clinical Trial of HIV Vaccine Begins in United States and South Africa:** A trial of a preventive HIV vaccine candidate has begun enrollment in the United States and South Africa. The Phase 1 trial will evaluate a novel vaccine known as VIR-1388 for its safety and ability to induce an HIV-specific immune response. **NIAID news release, September 20, 2023:** https://www.niaid.nih.gov/news-events/clinical-trial-hiv-vaccine-begins-united-states-and-south-africa
- **Encouraging First-in-Human Results for a Promising HIV Vaccine:** the recent first-in-human trial of an HIV vaccine made in the lab from a unique germline targeting protein nanoparticle. The engineered outer domain germline targeting 60-mer nanoparticle was designed to prime VRC01-class HIV-specific B cells that would need to be matured, through additional heterologous immunizations, into B cells that are able to produce broadly neutralizing antibodies. The results of this early phase clinical study published recently in *Science Translational Medicine* and earlier in *Science*, showed that the experimental HIV nanoparticle vaccine is safe in people. This vaccine alone will not offer HIV protection and is intended to be part of an eventual broader, multistep vaccination regimen**. Science Translational Medicine. May 2023**. https://pubmed.ncbi.nlm.nih.gov/37224227/

Influenza

- **NIH Clinical Trial of Universal Flu Vaccine Candidate Begins; Nanoparticle Vaccine Targets Six Flu Strains**
  Enrollment in a Phase 1 trial of a new investigational universal influenza vaccine candidate has begun at the NIH Clinical Center in Bethesda, Maryland. The new clinical trial is expected to enroll 24 healthy volunteers, aged 18-50 years, who will receive two intramuscular injections of the FluMos-v2 vaccine candidate designed by researchers at NIAID's Vaccine Research Center (VRC). **NIAID news release, September 15, 2023:** https://www.niaid.nih.gov/news-events/nih-clinical-trial-universal-flu-vaccine-candidate-begins

Sexually Transmitted Infections

- **NIH Releases Strategic Plan for Research on Herpes Simplex Virus 1 and 2**
  In response to the persistent health challenges of herpes simplex virus (HSV), the NIH released the Strategic Plan for HSV Research. The plan outlines a research framework with four strategic priorities: improving fundamental knowledge of HSV biology, pathogenesis, and epidemiology; improving HSV diagnostics; improving strategies to treat HSV while seeking a curative therapeutic; and advancing preventative measures including HSV vaccines. **NIAID news release, September 19, 2023:** https://www.niaid.nih.gov/news-events/nih-releases-strategic-plan-research-herpes-simplex-virus-1-and-2

Kyasanur Forest Disease Virus

- **Promising Experimental Vaccine for Tick-borne Kyasanur Forest Disease (KFD) Virus**
  Kyasanur Forest disease (KFD) or Alkhurma hemorrhagic fever (AHF) are flaviviruses, part of the same family as Yellow Fever and Dengue. Both viruses are hemorrhagic fever viruses, meaning they can cause internal and external bleeding, organ failure, brain inflammation and death. A vaccine exists in India for KFD, but it requires multiple doses, elicits a short duration of protection, and its effectiveness is in question. In a new study, researchers from NIAID's Rocky Mountain Laboratories describe the use of vesicular stomatitis virus (VSV) as a potential single-dose KFD vaccine, and demonstrated safety and efficacy in mice and pigtail macaques. They also showed that the vaccine generated cross-neutralizing immune responses against AHF.
  NIAID Now Blog post: https://www.niaid.nih.gov/news-events/vsv-vaccine-kfd

Maternal Health

- **NIH establishes Maternal Health Research Centers of Excellence:** NIH has awarded $24 million in first-year funding to establish Maternal Health Research Centers of Excellence. Part of NIH's Implementing a Maternal health and PRegnancy Outcomes Vision for Everyone (IMPROVE) initiative, the centers will develop and evaluate innovative approaches to reduce pregnancy-related complications and deaths and promote maternal health equity. **NICHD news release, August 17, 2023:** https://www.nichd.nih.gov/newsroom/news/081723-Maternal-Health-Research-Centers

Leadership Updates

- **NIH Selects Dr. Jeanne Marrazzo as Director of NIAID**: Lawrence A. Tabak, D.D.S., Ph.D., acting director for NIH, named Jeanne M. Marrazzo, M.D., as director of NIAID. Dr. Marrazzo is internationally recognized for her research and education efforts in the field of sexually transmitted infections, especially as they affect women's health. **NIAID news release, August 2, 2023**: https://www.niaid.nih.gov/news-events/nih-selects-dr-jeanne-marrazzo-director-national-institute-allergy-and-infectious