MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

FEBRUARY 23-24, 2022
SUMMARY MINUTES

TABLE OF CONTENTS

MEETING PURPOSE

The United States (US) Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC) convened a meeting of the Advisory Committee on Immunization Practices (ACIP) on February 23, 2022. The meeting took place remotely via Zoom, teleconference, and live webcast. This document provides a summary of the meeting, which focused on tickborne encephalitis (TBE), cholera, influenza, hepatitis, and pneumococcal vaccines; establishment of a Measles, Mumps, Rubella (MMR) Vaccine Workgroup (WG); agency updates; and public comments.

THURSDAY: FEBRUARY 23, 2022

WELCOME AND INTRODUCTIONS

Call to Order/Roll Call

Dr. Grace Lee (ACIP Chair) called to order and presided over the February 23-24, 2022 ACIP meeting. Dr. Lee conducted a roll call, which established that a quorum was present. A list of Members, *Ex Officios*, and Liaison Representatives is included in the appendixes at the end of this summary document. The following conflict of interest (COIs) was declared:

- ❑ Dr. Chen reported that his employing institution, the University of Maryland, received a grant from Emergent BioSolutions that supported work he conducted to develop a Shigella vaccine. Given that this constituted a COI on decisions regarding the cholera vaccine recommendations and discussions during this meeting, he indicated that he would not vote on the cholera vaccine.

Announcements

Dr. Melinda Wharton (ACIP Executive Secretary, CDC) noted that copies of the slides for the day were available on the ACIP website and were made available through a ShareLink™ file for voting ACIP Voting Members, *Ex Officios*, and Liaisons. She indicated that there would be an oral public comment session prior to the vote at approximately 2:25 PM Eastern Time (ET) on February 23, 2022. Given that more individuals registered to make oral public comments than could be accommodated, selection was made randomly via a lottery. Those individuals who were not selected and other individuals wishing to make written public comments may submit them through https://www.regulations.gov using Docket Number CDC-2022-0022. Further information on the written public comment process can be found on the ACIP website.

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

Dr. Wharton announced that applications and nominations were being solicited for candidates to fill upcoming vacancies on the ACIP. Detailed instructions for submission of names of potential candidates to serve as ACIP members are available on the ACIP website. Applications for ACIP membership are due no later than July 1, 2022, for the 4-year term beginning July 2023.

TICKBORNE ENEPHALITIS (TBE) VACCINE

Session Introduction

Dr. Katherine Poehling (ACIP WG Chair) introduced this session on behalf of the TBE Vaccine Workgroup (WG). She explained that in terms of background, the Food and Drug Administration (FDA) approved the TBE vaccine **TicoVac™** manufactured by Pfizer in August 2021. Given that no TBE vaccine has been previously licensed in the United States (US), there is no existing ACIP TBE vaccine recommendation. As a reminder, the TBE Vaccine WG was formed in September 2020 to discuss the use of TBE vaccines in US persons traveling abroad and laboratory workers. The TBE Vaccine WG presented to the ACIP in October 2020 on the background of TBE disease and vaccines and a summary of Pfizer's TBE vaccine. In February 2021, the WG presented TBE epidemiology in endemic areas and TBE among US travelers and laboratory workers. In September 2021, the WG presented the immunogenicity and safety of Pfizer's TBE vaccine. In January 2022, the WG presented the Evidence to Recommendations (EtR) framework. The focus of the February 2022 session was on a brief review of TBE and TBE vaccines, review of considerations for use of TBE vaccines and proposed recommendations for laboratory workers, and review of considerations for use of TBE vaccines and proposed recommendations for persons who travel abroad.

Review of Considerations for Use of TBE Vaccine in Travelers and Laboratorians

Dr. Susan Hills (CDC/NCEZID) reminded everyone that following presentation of the Evidence to Recommendations (EtR) Frameworks for TBE vaccine during a recent ACIP meeting, the TBE Vaccine WG discussed its recommendations in light of ACIP members' feedback. In particular, the WG focused on the categories of "Recommended" and "Shared Clinical Decision-Making" in the context of travel vaccines and providing the best clarity regarding who might benefit from vaccination, given that this vaccine is more likely to be administered by general healthcare providers rather than specialist or travel medicine providers. During this session, she presented the WG's revised recommendations for ACIP members' consideration, pointing out that ACIP would be asked for separate votes on recommendations for the following: 1) Laboratory Workers; 2) Persons Who Travel Abroad (Recommended component); and 3) Persons Who Travel Abroad (Shared Clinical Decision-Making component).

After the previous meeting, members of the 2 ACIP WGs with proposed travel vaccine recommendations discussed categories with the ACIP Secretariat and received the following guidance about each component:

- Recommended:
  - Vaccine should be recommended if there is any group of people who should receive the vaccine (i.e., the benefits of receiving the vaccine clearly outweigh the risks*)

- Shared Clinical Decision-Making:
  - No group for whom the vaccine should be recommended can be identified, but some individuals might reasonably choose vaccination and some providers might reasonably wish to recommend it for some travelers OR
  - There are any groups of people where the benefits of receiving the vaccine might not outweigh the risks* or there is uncertainty

- Note on Shared Clinical Decision-Making

  - Travel vaccines often require consultation with a healthcare provider (HCP) to identify which, if any, are indicated based on the traveler's age; travel plans, including destinations, duration, and activities; and other risk factors. This is not shared clinical decision-making

*Risk-benefit consideration for vaccination should weigh factors such as the likelihood of exposure (based on location, season, time, and activities), risk of disease and its potential severity, vaccine efficacy (VE), and possibility of vaccine-associated serious adverse events (SAEs).

Before presenting the considerations that went into developing the proposed TBE vaccine recommendations, Dr. Hills provided a brief review of TBE and TBE vaccine. TBE is a flavivirus related to Powassan virus. There are 3 main subtypes of TBE virus that differ in their geographic distribution and in the severity of the disease they cause. TBE virus is primarily transmitted by infected *Ixodes* species ticks. Infections are usually acquired in wooded or surrounding areas during recreational activities (e.g., camping, hiking, fishing, or hunting) or by persons involved in outdoor occupations (e.g., forestry service, farming). TBE is focally endemic in parts of Europe and Asia. Approximately 5,000 to 10,000 TBE cases are reported annually from endemic areas. Incidence is variable from country-to-country, in areas within countries, and from year-to-year. The main risk period occurs in the warmer months from April through November when ticks are most active. Among US persons, there have been very low numbers of TBE cases, with only 20 cases diagnosed in the 20-year period from 2001-2020. Of these, 11 were among civilian travelers and 9 among military personnel. However, when neruoinvasive disease occurs, it can have potentially high fatality and sequela rates.

The TBE vaccine manufactured by Pfizer as TicoVac™ was approved by the Food and Drug Administration (FDA) in 2021 for use in persons ≥1 year of age. Although only recently licensed in the US, the current formulation of the vaccine has been available internationally for more than 20 years, and more than 75 million doses have been administered. It is currently marketed in about 30 countries, primarily in Europe. Based on the GRADE (Grading of Recommendation Assessment, Development and Evaluation) assessment conducted by the ACIP TBE Vaccine WG, immunogenicity results showed that seropositivity rates after the primary series were high at over 95% in most studies, and were also high after a booster dose. One limitation in this assessment was that the vaccine is based on a European subtype TBE virus, and there is likely but unconfirmed protection against non-European TBE virus subtypes. In terms of safety, vaccine-related SAEs were rarely reported.

In terms of key considerations for development of recommendations for laboratory workers working with TBE virus, several key factors were considered by the WG. First, TBE virus transmission has been documented in the laboratory through virus aerosolization. Transmission through accidental percutaneous or mucosal exposures is possible. More than 46 laboratory-acquired TBE virus infections have been reported globally. Fewer than 10 laboratories in the US currently work with TBE virus for diagnostic or research purposes, meaning that a limited number of staff would require vaccination. TBE vaccination will reduce laboratorians' risk of potentially very severe disease. Vaccine implementation is feasible as it likely can be implemented through existing occupational health programs. When considering all the domains of the EtR Framework for laboratory workers, the WG determined that the desirable consequences of vaccination clearly outweigh the undesirable consequences in most settings and proposed the following recommendation for ACIP consideration:

> *TBE vaccination is recommended for laboratory workers with a potential for exposure to TBE virus.*

Regarding the WG's key considerations and proposed recommendations for persons who travel abroad, the WG started by asking whether there is a group of people who should receive the vaccine, i.e., for whom the benefits of receiving the vaccine clearly outweigh the risks. Dr. Hills discussed each of the following key factors considered by the WG:

- ❑ Overall risk of disease
- ❑ Potential severity of disease
- ❑ Patterns of disease transmission
- ❑ Risk factors for disease among US travelers
- ❑ Tick-related factors
- ❑ Vaccination recommendations in endemic countries
- ❑ Vaccine-related factors

In regard to the overall risk of disease for US civilian travelers, TBE is clearly a very rare disease with only 11 cases diagnosed during the past 20 years, or about 1 TBE case diagnosed every 2 years. Based on numbers of US travelers, the risk for all US travelers to TBE-endemic countries is less than 1 TBE case per 30 million trips. To understand risk among a more select group of travelers, the WG considered just those travelers who might visit specific risk areas within endemic countries, who travel during the main transmission season, and undertake activities with risk of tick exposure. In this specific group, the risk estimate was approximately 1 TBE case per 2 million trips. Because of potential inaccuracies in assumptions required for the calculation and possible under-diagnosis of TBE or other factors, the risk range could be from 0.1-5 cases per million trips.

While TBE case numbers are low, potential severity of illness for patients with neuroinvasive disease must be considered. Most persons will require hospitalization and there are no specific antiviral treatments. Sequela have been reported in 10% to 50% of persons presenting with neurologic disease and can be severe, including permanent physical disabilities or cognitive impairment. Case fatality rates ranging from 1% to 20% have been reported.

The WG considered factors related to the patterns and distribution of disease. There is a seasonal risk, with the main risk in the warmer months from April through November when ticks are most active. Because TBE is tickborne, large outbreaks do not occur. There is some uncertainty in defining risk in specific locations within endemic areas, given that transmission

can be variable from year-to-year. Risk areas can be very focal and accurate data often are unavailable in real-time or, in some countries, at all.

The risk factors were considered for infection among US civilian travelers, although with only 11 cases there were limited data to define the epidemiology. The common factors in all cases in which itinerary information was available (8 travelers) was that they had had at least 1 opportunity for exposure to ticks and all traveled during the main TBE virus transmission season in Spring or Summer. There was no apparent association with duration of travel, with infected persons reporting travel periods from 7 days to 2 months; specific activities, with travelers reporting a variety of activities (hiking, camping, fishing, trail running); basic demographics, with cases ranging in age from a young child to a male in his 70s; or specific travel locations, with cases infected in various places throughout the risk area, including Europe, Russia, and China.

For particular tick-related factors, it was noted that humans must enter tick habitats and come in contact with ticks to have a risk of TBE because unlike mosquitoes, ticks will not search out humans. Travelers do not pose a risk for TBE virus establishment in the US and so vaccination does not have population-level benefits.

Review of national TBE vaccination recommendations in endemic countries indicates that many countries do have recommendations, but their extent varies substantially. One country has a universal TBE vaccination recommendation. Some countries have recommendations for populations living in specific highly endemic or endemic areas or only for persons at highest risk such as those in certain outdoor occupations. Some countries have no TBE vaccination policy.

Regarding vaccine-related factors, the vaccine has a very good immunogenicity and safety profile, but like any vaccine has the possibility of SAEs. For 2 of the 3 main TBE virus subtypes, there is likely but unproven effectiveness of the vaccine. These are the Siberian and Far Eastern subtypes that occur in the Eastern part of the TBE-endemic area and that cause more severe disease. TBE vaccine will cost more than $250 per dose and will be paid for out of pocket by most travelers and there might be opportunity costs if a traveler has to consider buying TBE vaccine versus purchasing travel insurance or other vaccines with available financial resources.

Noting all these factors, the WG considered whether there was any group of people who should receive the vaccine i.e., for whom the benefits of receiving the vaccine clearly would outweigh the risks. There was some variability in opinion among the WG members on this question, but the following points summarize the WG's conclusions. Firstly, even for the group of travelers to TBE-endemic areas who travel during the transmission season and undertake an outdoor activity with risk of tick exposure, the risk for TBE disease is very low with fewer than 1 TBE case diagnosed per 1 million travelers. It would be difficult to justify a TBE vaccination recommendation for all travelers in this group. However, there is likely to be a smaller group who are at higher risk. All US traveler cases reported an itinerary in which their activities would have put them at risk of tick exposure. It follows that travelers who have the most extensive exposure to ticks will have the highest likelihood of TBE virus infection. Thirdly, although TBE is a rare disease, it can be very severe, and most travelers who get neurologic disease will require hospitalization and will have a risk of sequela and death. Finally, there is a safe and effective vaccine. Based on these considerations, the TBE Vaccine WG proposed the following recommendation for ACIP consideration:

TBE vaccine is recommended for persons who are moving abroad or traveling to a TBE-endemic area and will have extensive exposure to ticks based on their planned outdoor activities and itinerary.

The WG then discussed the second component for the TBE vaccine recommendations, considering whether there is an additional group for whom a shared clinical decision-making category of recommendation would be appropriate. They discussed whether there are data suggesting that there are any groups for whom there is uncertainty in the risk-benefit considerations, or circumstances in which some individuals might reasonably choose vaccination, or some providers might recommend it for some travelers. The WG discussed several important topics including the U.S. traveler TBE cases and their extent of exposure to ticks, that there is a higher risk of a poorer medical outcome among some persons, and that there is variability in the perception and tolerance of risk among travelers.

Firstly, given the focus of the primary TBE vaccine recommendation, the WG considered whether all US traveler cases have had extensive exposure to ticks. While all US travelers reported some exposure, not all might have had what could be considered "extensive" exposure, although this was difficult to assess in all cases based on the amount of itinerary information available. Nonetheless, to protect all travelers going to TBE-endemic locations who might have tick exposure, a very large number of doses would need to be given to prevent 1 TBE case. The WG estimated that more than 1 million travelers would need to be vaccinated to prevent 1 TBE case. Secondly, in regard to higher risk of a poorer medical outcome among some persons with TBE, older persons have consistently been shown to have poorer outcomes.[1] Finally, the WG considered personal perception and tolerance of risk. For the EtR assessment, one of the surveys the WG reviewed was on decision-making on vaccination for a disease that is similar to TBE with a vaccine that is similar to TBE vaccine i.e., is safe and effective, has a similar low probability of SAEs, and costs over $250 per dose. The results indicated that 32% of respondents were somewhat or very likely to be vaccinated, 43% were somewhat or very unlikely to be vaccinated, and 25% were unsure.[2] The risk of a 1 in 1 million possibility of a severe outcome was a key factor in decision-making on whether to be vaccinated for respondents in both groups, indicating very different personal perceptions and tolerance of risk.

Considering these factors, the WG conclusions on an additional share clinical decision-making component of the TBE vaccine recommendations were that some travelers might be exposed to ticks but will not have extensive exposure, and several factors might be considered in the risk-benefit assessment for TBE vaccination. These include that there is an extremely low risk of disease overall, with heterogeneity in risk based on activities and itinerary; some persons might have risk factors for a poorer medical outcome; and there are clear differences between individuals in their perception and tolerance of risk for a severe disease like encephalitis that can cause death or disability. Given that the overall risk-benefit assessment is ill-defined for this group of travelers, but that some individuals might reasonably choose vaccination and some providers might wish to recommend it, the WG thought that a second shared clinical-decision making component for the TBE vaccination recommendations would be appropriate. Based on these considerations, the TBE Vaccine WG proposed the following recommendation for ACIP consideration:

[1] Schuler et al, Euro Surveill 2014; Lindquist, Lancet 2008

[2] Hills SL et al. Perceptions among the U.S. population of value of Japanese encephalitis (JE) vaccination for travel to JE-endemic countries; *Vaccine* 2020

TBE vaccine might be considered for persons traveling or moving to a TBE-endemic area who might engage in outdoor activities in areas ticks are likely to be found. The decision to vaccinate should be based on an assessment of their planned activities and itinerary, risk factors for a poorer medical outcome, and personal perception and tolerance of risk.

Discussion Summary

Dr. Long noted that the "might be considered" recommendation was a "proposed recommendation" and sounded like it might be applied to the group for whom the vaccine is going to be "recommended."

Dr. Hills clarified that the "proposed recommendation" heading was the second component of the overall recommendations and that this was the proposed shared clinical decision-making recommendation.

Dr. Sanchez commended the WG for this great follow-up to ACIP's previous discussions, and he agreed with the recommendation and the shared clinical decision-making recommendation.

Dr. Kimberlin (AAP Redbook) observed that typically with a universal recommendation, the vaccine should be given. In his experience with shared clinical decision-making, it is "may be considered" rather than " might be considered." He wondered whether there was any nuance between the words "may" and "might" in this proposed recommendation. Other ACIP members indicated that they had the same question.

Dr. Hills said she believed CDC has tended to use "might" rather than "may" as "might" implies possibility and "may" suggests permission. She indicated that she would confer with the Secretariat for guidance and to ensure that this was clarified before the vote.

Dr. Daley inquired as to how and where "extensive exposure" would be defined.

Dr. Hills indicated that the WG discussed this and intend to include some text with the recommendations. For shorter duration travel, it might mean frequent exposure such as daily activities in environments that might harbor infected ticks. For longer travel duration of a month or longer, it might mean regular exposure such as a few times a month.

Regarding the question of "may" or "might," Dr. Goldman expressed concern because his understanding of the Affordable Care Act (ACA) was that recommended vaccines must be covered by insurers. It was not clear to him how "might consider" and shared clinical decision-making play into that as far as the concern for equity, access, and patients being able to afford the vaccines. The comment was made earlier that this vaccine probably will be administered in general medical offices as opposed to travel clinics. While he has access to certain travel vaccines in his practice, the volume of patients presenting for these is so low that it does not allow for storing the vaccines cost-effectively. This could lead to a difficulty in access for patients to get the vaccines except at travel clinics as opposed to general medical offices. He asked whether the language could be clarified and how that might play into insurance coverage under the ACA.

Dr. Hills clarified that the ACA relates to vaccines that are on the routine vaccine schedules. Travel vaccines are not included on the routine vaccine immunization schedules.

Vote #1: TBE Vaccine for Laboratory Workers

Dr. Susan Hills (CDC/NCEZID) presented proposed recommendation #1 for TBE vaccine as follows:

> *TBE vaccination is recommended for laboratory workers with a potential for exposure to TBE virus.*

Motion/Vote #1: TBE Vaccine for Laboratory Workers

Dr. Talbot made a motion for ACIP to adopt the recommendation stating that, "TBE vaccination is recommended for laboratory workers with a potential for exposure to TBE virus." Ms. Bahta seconded the motion. No COIs were declared. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Vote #2: TBE Vaccine for Persons Moving Abroad or Traveling to a TBE-Endemic Area

Dr. Susan Hills (CDC/NCEZID) presented proposed recommendation #2 for TBE vaccine as follows:

> *TBE vaccine is recommended for persons who are moving abroad or traveling to a TBE-endemic area and will have extensive exposure to ticks based on their planned outdoor activities and itinerary.*

Discussion Summary

Dr Long pointed out that "moving abroad" is a large place across an ocean and proposed deleting the word "abroad" and instead state, "people who are moving or traveling to an endemic area." She also suggested that the asterisk be included in the recommendation about other considerations such as activities and outbreaks.

Dr. Hills shared the additional information that would be included in the Clinical Consideration, on the CDC website, and in a box to draw people's attention to the information. If CDC becomes aware of a particular concern regarding an outbreak, the Division of Global Migration and Quarantine (DGMQ) would likely be responsible for posting a notice to alert travelers.

Dr. Poehling reported that the WG engaged in extensive conversations about this in terms of figuring out how best to word the recommendation. Their assessment was they preferred the wording to focus on the planned activities and itinerary and highlight the main components, while providing the details in the Clinical Considerations and they liked the box to draw people's attention to relevant information.

Dr. Lee expressed appreciation for Dr. Long's editorial eye. She reminded everyone that ACIP tries in general to keep recommendations succinct and allow for the details to be provided in the Clinical Considerations as long as it does not change the intent of the recommendation.

Dr. Long said she was comfortable with the wording as stated, with the intent of the Clinical Considerations capturing the detailed information, considering Dr. Poehling's additional comments, and the fact that no hands were raised by practitioners in the meeting.

With no objections to the clarification, Dr. Lee indicated that the motion would stand but with the suggestion to amend the wording slightly for clarity by removing the word "abroad."

Motion/Vote #2: TBE Vaccine for Persons Moving Abroad or Traveling to a TBE-Endemic Area

Dr. Sanchez made a motion for ACIP to adopt the recommendation with the proposed amendment stating that, "TBE vaccine is recommended for persons who are moving or traveling to a TBE-endemic area and will have extensive exposure to ticks based on their planned outdoor activities and itinerary." Dr. Ault seconded the motion. No COIs were declared. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Vote #3: TBE Vaccine for Persons without Extensive Tick Exposure Moving or Traveling to a TBE-Endemic Area Based on an Assessment of Additional Risk Factors

Dr. Susan Hills (CDC/NCEZID) presented proposed recommendation #3 for TBE vaccine as follows, with the amendment to change "might" to "may":

> *TBE vaccine may be considered for persons traveling or moving to a TBE-endemic area who might engage in outdoor activities in areas ticks are likely to be found. The decision to vaccinate should be based on an assessment of their planned activities and itinerary, risk factors for a poorer medical outcome, and personal perception and tolerance of risk.*

Motion/Vote #3: TBE Vaccine for Persons without Extensive Tick Exposure Moving or Traveling to a TBE-Endemic Area Based on an Assessment of Additional Risk Factors

Ms. Bahta made a motion for ACIP to adopt the recommendation stating that, "TBE vaccine may be considered for persons traveling or moving to a TBE-endemic area who might engage in outdoor activities in areas ticks are likely to be found. The decision to vaccinate should be based on an assessment of their planned activities and itinerary, risk factors for a poorer medical outcome, and personal perception and tolerance of risk." Dr. Daley seconded the motion. No COIs were declared. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Discussion Summary

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

Dr. Kotton commented that as someone who has practiced travel medicine for over 20 years, she was very happy about this overall recommendation, the thoughtfulness that went into it, and the flexibility it would provide for clinicians practicing travel medicine.

Dr. Lee commended Drs. Poehling and Hills for their leadership of this WG and recognized the effort of the WG that went into considering and addressing the complicated issues involved, and the importance of this recommendation.

Dr. Chen noted that he had the pleasure of serving on the TBE Vaccine WG for more than a year during their many discussions. He congratulated and thanked Dr. Poehling for Chairing the WG, Dr. Hills for guiding the discussions, and her team for all of their hard work in helping to pull all of this together. He commented that even though the burden of TBE is not perceived to be large and it might be difficult to implement this vaccine due to the complexity of assessing where tick habitats are, tick and mosquito habitats continue to expand and flavivirus circulation continues to increase with the trends of global warning. This is a reminder that because flaviviruses, such as West Nile Virus (WNV) and Yellow Fever (YF), continue to scourge the world, these types of vaccines will become increasingly important.

CHOLERA VACCINE

Session Introduction

Dr. Pablo Sanchez (ACIP WG Chair) introduced this session on behalf of the Cholera Vaccine WG, indicating that the policy topic under consideration by the WG for which there would be a vote was, "Should ACIP recommend CVD103-HgR for children and adolescents aged 2-17 years traveling to an area with active cholera transmission?" In June 2016, ACIP recommended cholera vaccine for adult travelers 18-64 years of age traveling from the United States to an area with active choleric transmission. In December 2020, FDA extended the approved usage to include children and adolescents 2-17 years of age. In February 2021, the WG presented background information and the manufacturer presented pediatric clinical trial data. In January 2022, the WG presented the EtR Framework and the manufacturer presented data on pediatric dose development. This session focused on the presentation of evidence, recommendation summary, considerations for use, and proposed policy options for the cholera vaccine among children and adolescents 2-17 years of age.

Clinical Considerations for Use of Cholera Vaccine in Children and Adolescents 2–17 Years of Age

Dr. Jennifer Collins (CDC/NCEZID) pointed out that the PICO (population, intervention, comparison, outcomes) components related to the policy question include the population of children and adolescents aged 2-17 years traveling to an area with active cholera transmission; an intervention of lyophilized CVD 103-HgR single-dose, oral, live-attenuated bacterial vaccine; a comparison of no cholera vaccine; and the outcomes of moderate or severe cholera diarrhea, any severity of cholera diarrhea, SAEs, and/or non-SAEs. To summarize the EtR Framework presented on January 12, 2022, the WG felt that cholera is probably a public health problem among children and adolescents aged 2-17 years traveling to an area with active cholera of transmission. The WG determined that desirable anticipated effects were moderate, the undesirable anticipated effects were small, and that the balance of benefits and harms favors CVD 103-HgR with low overall certainty for the critical outcomes. The WG determined that CVD 103-HgR is acceptable to key stakeholders, that the effect on equity varies, and that it is probably feasible to implement among children and adolescents aged 2-17 years traveling to an area with active cholera transmission. The WG determinations for values and resource use were "do not know." The WG consensus was that desirable consequences probably outweigh undesirable consequences in most settings, given that there were only indirect data upon which to assess the desirable consequences. The WG consensus was to recommend the intervention CVD 103-HgR for children and adolescents aged 2-17 years traveling to an area with active cholera transmission.

In terms of considerations for prevention of cholera and use of CVD 103-HgR, CDC's Travelers Health Branch updates the list of countries with active cholera transmission on a monthly basis.[3] The destination pages specify whether cholera transmission is localized to certain areas or widespread.[4] As of January 2022, the following 15 countries were considered to have active cholera transmission:

[3] https://wwwnc.cdc.gov/travel/diseases/cholera
[4] https://wwwnc.cdc.gov/travel/destinations/list

- **Africa:** Benin, Cameroon, Democratic Republic of the Congo, Ethiopia, Kenya, Mozambique, Niger, Nigeria, Somalia, Uganda
- **Asia:** Afghanistan, Bangladesh, India, Nepal, Yemen
- **Americas:** None
- **Pacific**: None

Regardless of cholera vaccination status, travelers to cholera-affected areas should use personal protective measures. That is, they should consume safe food and water, wash hands often with soap and safe water, and follow recommended sanitation practices (e.g., using latrines or burying stool). More detailed prevention information is available on two CDC websites.[5] shown on the slide.

CVD 103-HgR is the only cholera vaccine licensed for use in the US. It is a single-dose, live, attenuated, oral vaccine derived from *Vibrio cholerae* O1. Production has been temporarily discontinued during the COVID-19 pandemic, but the manufacturer has specified that it will be available again beginning May 1, 2022. Regarding Dr. Brooks' question in January about the number of doses administered, the manufacturer provided data indicating that 62,179 doses of CVD 103-HgR were sold in the US during 2016-2019. The WG did not have data on how many of those doses were administered. Although production began in 2016, ACIP approval for adults did not occur until June 2016. The initial authorization also required that the vaccine be stored frozen. Regarding administration setting, the WG feels the CVD 103-HgR may be optimally administered in a travel clinic, given the relatively complicated dose preparation and administration. However, as ACIP members noted previously, many travel clinics have closed during the pandemic and whether they will reopen is uncertain. The WG agreed that administration in non-travel clinics is permissible. Regardless of setting, CVD 103-HgR should be prepared and consumed in a medical office to minimize potential dosing errors. Providers should carefully follow instructions in the package insert.

The buffer component and active component packets should be stored refrigerated at 36°F to 46°F (2°C to 8°C). Packets should not be out of refrigeration for more than 12 hours before reconstitution, and they should not be exposed to temperatures exceeding 80°F. They also should be protected from light and moisture. In accordance with the package insert,[6] recipients should avoid consuming food or drinks for 60 minutes before and after vaccine administration and only cold or room temperature, purified bottled or spring water should be used to reconstitute the buffer. Tap water contains chlorine that can affect the viability of orally ingested live attenuated bacterial vaccines. Detailed preparation and reconstitution instructions are available in the package insert. First, the buffer is mixed with 100 milliliters of cold or room temperature purified bottled or spring water. According to Step 5 in the insert, the buffer solution should be mixed with a disposable stirrer until it completely dissolves. For children aged less than 6 years, half of the reconstituted buffer solution should be discarded after the buffer sachet is mixed with water. The active component packet is then added and stirred until it disperses to form a slightly cloudy suspension that may contain light particles. If the packets are reconstituted in the improper order, the vaccine must be discarded. The prepared vaccine must be consumed within 15 minutes.

[5] https://www.cdc.gov/cholera/preventionsteps.html; https://wwwnc.cdc.gov/travel/diseases/cholera#areas
[6] https://www.fda.gov/media/128415/download

Administration of CVD 103-HgR with sweeteners is not currently covered in the package insert. As noted on January 12, 2022, the manufacturer anticipates a supplemental filing with FDA early in 2022. Unpublished data presented by the manufacturer in January 2020 demonstrates CVD 103-HgR is not compatible when mixed with medicine flavorings that contain propylene glycol or when mixed with food and drinks (e.g., rice cereal, applesauce, juice, or milk). Data presented support that the vaccine is compatible when mixed with 1-4 grams of sucrose or table sugar or 1 gram of stevia sweetener. Of the vaccine recipients 2-17 years of age, 93% in the clinical trial consumed the vaccine with PureVia Stevia. Providers also should advise recipients about the most common side effects within 7 days of CVD 103-HgR, including fatigue, headache, abdominal pain, nausea or vomiting, lack of appetite, and/or diarrhea. These adverse reactions were most commonly rated as mild in the clinical trials. No clinical trials have evaluated the safety or efficacy of booster doses of CVD 103-HgR in preventing cholera. The duration of protection beyond the 3-month period evaluated in adults 18-45 years of age is unknown. The serum vibriocidal antibody assay used in the pediatric clinical trials is likely a surrogate for protection mediated by intestinal mucosa.

In terms of co-administration with other medicines or vaccines, antibiotics might have activity against the vaccine strain. Therefore, CVD 103-HgR should be administered at least 14 days after completion of either oral or intravenous (IV) antibiotics. A shorter duration may be acceptable if travel cannot be avoided but may diminish the effectiveness of the vaccine. The optimal duration between completion of CVD 103-HgR and starting antibiotics is unknown. In certain circumstances, antibiotics may be clinically necessary after the vaccine, such as to treat an unrelated infection. Nearly all (93%) of vaccine recipients in the clinical trials had seroconversion by 10 days, suggesting that administration of antibiotics after this may not affect protection. Chloroquine may diminish the immune response to CVD 103-HgR. Therefore, CVD 103-HgR should be administered at least 10 days before starting chloroquine, such as for malaria prophylaxis. No data are available on concomitant administration with other vaccines. Enteric-coated, live-attenuated typhoid vaccine, Ty21a,[7] is another common oral travel vaccine. Experts suggest taking the first dose of Ty21a at least 8 hours after CVD 103-HgR. This might decrease potential interference of the buffer of CVD 103-HgR with the Ty21a vaccine.

Moving to contraindications and precautions, CVD 103-HgR is not licensed for children less than 2 years of age or adults ≥65 years. No data exist about the safety and effectiveness of the vaccine in these populations. CVD 103-HgR should not be administered to persons with a history of severe allergic reaction, such as anaphylaxis, to any component of this vaccine or to a prior dose of any cholera vaccine. No data are available regarding the current formulation of CVD 103-HgR during pregnancy or breastfeeding. Pregnant women are at increased risk for poor outcomes from cholera infection. Pregnant women and their clinicians should consider the risks associated with traveling to areas with active cholera transmission. The vaccine is not absorbed systemically. Therefore, maternal exposure to the vaccine is not expected to result in exposure to the fetus or breastfed infant. However, the vaccine strain might be shed in stool for at least 7 days after vaccination, and theoretically, the vaccine strain could be transmitted to an infant during vaginal delivery.

No data are available regarding the current formulation of CVD 103-HgR in persons with altered immunocompetence. Persons with altered immunocompetence and their clinicians should consider the risks associated with traveling to areas with active cholera transmission. Consultation with a specialist in infectious diseases or immunology should be considered if travel to an area with active cholera transmission is necessary. ACIP generally advises against

[7] Trade Name: Vivotif

administering live vaccines to persons with most forms of altered immunocompetence.[8] CVD 103-HgR may be shed in the stool of recipients for at least 7 days. Patients should be counseled that the vaccine strain can potentially be transmitted to non-vaccinated close contacts such as household contacts, and to wash their hands thoroughly after using the bathroom and before preparing or handling food for at least 14 days after vaccination.

Given all of these considerations, the WG proposed the following draft recommendation for ACIP consideration:

> *Lyophilized CVD 103-HgR is recommended for children and adolescents aged 2-17 years traveling from the United States to an area with active cholera transmission.*

Discussion Summary

Dr Poehling noted that for many oral vaccines, consideration is given to withholding the vaccine if there are persons with serious immunocompromising conditions in the family. With that in mind, she asked whether this would be a consideration for the cholera vaccine.

Dr. Collins indicated that the package insert notes that providers should consider whether to administer the vaccine if the recipient has an immunocompromised household or other close contact. The WG discussed this and felt that that language was somewhat strong. In a small study of the preliminary formulation of CVD 103-HgR, there was no household transmission. This study included 66 healthy adults who were randomized 5:1 to vaccine or placebo. Stool shedding occurred in 11% of vaccine recipients. The study also enrolled 24 household contacts of vaccine recipients. None had the vaccine strain isolated from stool on a Day 7 specimen, and none had virucidal seroconversion on a Day 28 specimen. This may depend on the individual and providers may want to counsel people who they do not think have access to adequate hygiene and sanitation measures. Most people in the US do have adequate access. With adequate hand washing and sanitation, the WG did not feel like the risk posed to household contacts acquiring it was substantial enough to recommend withholding vaccine. The WG also noted that the vaccine has been attenuated.

While mention was made that the duration of protection is unknown, Dr. Loehr pointed out that the background information provided to ACIP members in preparation for this meeting included a study of long-term immunogenicity that was published in 2021 that showed that 65% of people have seroprotection at 2 years. He asked Dr. Collins to comment on that, whether they should trust the seroprotection data, and if she was just saying that there are no randomized controlled trial (RCT) data with actual disease.

Dr. Collins indicated that essentially, there are no long-term efficacy data in which an oral challenge study has been conducted. That would be the gold standard to determine whether the vaccine is still effective that far out. The data to which Dr. Loehr referred were data the manufacturer shared during the February 2021 presentation. Based on those data, seroconversion rates and geometric mean titer (GMT) levels remain somewhat high up to 2 years out. The issue is that it is unknown how good of a marker of long-term protection serum vibriocidal antibody antibodies are. Her understanding is they may not be the best marker of long-term protection. This is the best available and best accepted measure to use in clinical trials in which efficacy is not being directly assessed. While serum vibriocidal antibody

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

antibodies are the best immunologic parameter available, they are mostly a surrogate and are not likely mechanistic. Instead, they are a marker of complement-mediated bactericidal activity that does not really account for why they would explain the protection that is thought to be mediated by an immune response at the intestinal mucosa. While these data are encouraging in some ways, the experts in the field would not necessarily trust them to say that the vaccine is protective that far out without an oral challenge study.

Dr. Long observed that the statement to "wash hands thoroughly after using the bathroom and before preparing or handling food for at least 14 days after vaccination" suggested that hand washing was not recommended any other time after these activities. She suggested stating that hand washing is always recommended after using the toilet and adding after diaper changes since some 2-year-olds are still in diapers. It should state that hand washing always should be done in these cases, but should be done with special attentiveness during the period of shedding vaccine bacteria.

Regarding pregnancy and the potential for exposure of the infant during vaginal delivery, Dr. Kimberlin (AAP Redbook) asked whether there was any consideration by the WG of interfacing with the American College of Obstetricians and Gynecologists (ACOG) to determine whether a limitation should be made during which the vaccine should not be administered to pregnancy women, such as after 36 or 38 weeks to minimize vaginal transmission.

Dr. Collins indicated that the WG did not directly discuss that. The WG was focused primarily on children and adolescents 2-17 years of age. Of course, adolescents can become pregnant. This language came from the previous adult *Morbidity and Mortality Weekly Report* (*MMWR*), but ACOG's input would be welcomed.

Dr. Ault recalled that this was discussed previously when the focus was on adults. The best advice would be not to go to the area with cholera. This issue arose when CDC workers were going to Haiti a few years ago. He did not have any problems with the way the recommendation was worded and pointed out that experience with these vaccines would be gained as they get used more often, including during pregnancy.

Dr. Sanchez indicated that the WG did not specifically comment about not giving the vaccine in the 14 days before planned delivery. It would be important to ascertain the risks versus benefits. It may be better for a woman who may be exposed during that time to receive the vaccine. Consideration also should be given to the fact that it is an attenuated strain.

Dr. Collins pointed out that the ACOG statement discusses travel in general during pregnancy. Their statement says most commercial airlines allow pregnant women to fly up to 36 weeks of gestation, some restrict pregnant women from international travel or from international flights earlier in gestation, and some require documentation of gestational age.

Dr. Long said she was expecting to see the vaccine recommended for children with no contraindicating underlying immune deficiencies versus recommending it for all children.

Dr. Collins indicated that the WG discussed that there is a lack of data in immunocompromised children and adolescents upon which to make a decision. The WG members shared Dr. Long's concern about providing the vaccine to children who are immunocompromised, particularly with severe immunocompromising conditions. Some of the rationale behind the proposed language was for clarity to harmonize it with the language for adults. The recommendation for adults 18-64 years of age is straightforward, with the stipulation about persons with immunocompromising

conditions included in the guidance. She stressed that the WG certainly would welcome further discussion about whether that is the correct approach.

Dr. Sanchez indicated that the WG did discuss this and were of the opinion that it immunocompromising conditions should be taken up in clinical considerations in terms of potential precautions against the use of the vaccine in such children and adolescents.

Dr. Wharton added that for many vaccines, contraindications and precautions are not necessarily included in the recommendation statement. Those are typically included as additional clinical information that accompanies the recommendation statement.

Dr. Poehling made a minor editorial suggestion to remove "from the United States" because it did not add anything and some people may be traveling through the US on a circuitous route to an active cholera transmission area, with which other ACIP members agreed.

Vote: Cholera Vaccine Recommendation

Dr. Jennifer Collins (CDC/NCEZID) presented the proposed recommendation, including the revised language based on the editorial suggestion to remove "from the United States," as follows:

> *Lyophilized CVD 103-HgR is recommended for children and adolescents aged 2-17 years traveling to an area with active cholera transmission.*

Motion/Vote: Cholera Vaccine

Dr. Poehling made a motion for ACIP to adopt the recommendation stating that, "Lyophilized CVD 103-HgR is recommended for children and adolescents aged 2-17 years traveling to an area with active cholera transmission." Dr. Daley seconded the motion. Dr. Chen declared that his employing institution, University of Maryland, received a grant from Emergent BioSolutions that supported the work he conducted to develop a Shigella vaccine, which constitutes a conflict and resulted in his abstention from this vote. The motion carried with 14 affirmative votes, 0 negative votes, and 1 abstention. The disposition of the vote was as follows:

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

Discussion Summary

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

Dr. Chen emphasized that while having a cholera vaccine is terrific, there are many other diarrheal disease agents throughout the world that afflict and create major inequities in vulnerable populations such as very young children; low- and middle-income countries; and countries that do not have intact clean water, sanitation, and hygiene. His career focuses on

trying to develop other diarrheal vaccines and he aspires to seeing that these types of vaccines are available in the countries in which these diseases are endemic.

INFLUENZA VACCINE

Session Introduction

Dr. Keipp Talbott (ACIP, WG Chair) introduced this session, indicating the presentations would include a review of vaccines for older adults in terms of literature retrieved, meta-analysis results, GRADE, and the discussion of a modeling assessment that was done to determine the potential impacts of preferential recommendations for influenza vaccines in this population. Influenza vaccines have been recommended for adults over 65 years of age and those at high risk for many years now. That recommendation preceded the ACIP and was issued by the Surgeon General. Influenza is unique in that while there is a new vaccine every year with 4 virus strains, it tends to be thought of as one vaccine. This variation coincides with the variation in the vaccine strains and the circulating virus strains. The data reviewed for older adults has included RCTs, which are typically considered to be the gold standard. Unfortunately, 1 or 2 years of data in an influenza year is equal to 1 or 2 years of data in influenza. It is extremely important for the WG and WG leads to review all of the observational data associated with enhanced vaccines and older adults. These data are incredibly relevant because they will span seasons and provide more information about head-to-head vaccines. She emphasized that the data to be presented represented an incredible amount of work for which the WG could not thank their CDC colleagues enough. As they reviewed all of these data in a very condensed and dense format, she expressed her hope that the rest of the ACIP voting members would ask questions.

Influenza Activity Update

Dr. Lisa Grohskopf (CDC/NCIRD) provided a brief update on domestic influenza activity. The percent of assessments that were positive peaked in December 2021 at about 6% and subsequently declined to about 2% by mid-January 2022. However, 3% of specimens submitted to the clinical laboratories were positive for the most recent reporting week of February 12, 2022 (Week 6). Most positive specimens were influenza A, with most subtyped specimens being H3N2. These viruses thus far have been genetically closely related to the vaccine virus, but there are some antigenic differences that have developed as H3 viruses have continued to evolve. Influenza like illness (ILI) activity peaked in mid- to late-December and declined to below the epidemic threshold since then. Sporadic influenza activity continues throughout the country and is increasing in some parts of the country. This season, cumulative hospitalizations are tracking higher than the 2021 season, but are still substantially lower than the previous four seasons 2016-2017 through 2019-2020. The cumulative hospitalization rate thus far this season is 4.7/100,000. For the current week, 22.6% of deaths were attributed to pneumonia, influenza, or COVID-19. Only 1 pediatric death was reported for the 2020-2021 season, while a total of 5 pediatrics deaths have been reported thus far for the 2021-2022 season.

In terms of preliminary interim VE for influenza vaccines, the US Flu VE Network is comprised of 7 sites and provides estimates of laboratory-confirmed medically-attended influenza illness each season. The US Flu VE Network enrolled outpatients ≥6 months of age with acute respiratory illness (ARI) and cough of less than or equal to 7 days duration. Through January 22nd, 2,758 persons have been enrolled at the 7 sites. Of these, 147 (5%) were positive for influenza, which is fairly low. For the influenza A viruses isolated, all subtyped viruses have been H3N2 and all sequenced viruses of H3N2 belong to a single genetic group 3C.2a1b,

Subclade 2a.2. To summarize early preliminary interim VE against influenza A and H3N2 among patients ≥6 months of age thus far this season, for influenza A for all ages, adjusted VE was 8% with a 95% confidence interval of -31% to 36%. VE for H3N2 was 14% with a 95% confidence interval of -28% to 43%.

To note some limitations that are important to consider when thinking through these data, this is the lowest influenza positivity rate (5%) observed over the past 10 seasons among US Flu VE network participants with respiratory illness. Numbers of influenza-positive participants were insufficient to estimate age groups specific VE or to compare effectiveness of different influenza vaccine products against the predominant A(H3N2) virus. Moreover, healthcare seeking behavior has changed during the COVID-19 pandemic in ways that might affect influenza VE. VE estimates are limited to mild illness and evaluation of VE against influenza hospitalizations is ongoing this season. Again, it is important to note that these are preliminary interim data that are expected to change over time.

Discussion Summary

Dr. Brooks requested clarity about which VE estimate mentioned for A(H3N2), 33% versus 14%, was more indicative of the true VE.

Dr. Grohskopf clarified that because these are observational data and adjustment for confounders would be important, it would be the adjusted estimate of 14% for all A(H3N2).

Dr. Long emphasized that it was becoming trickier to talk about percent positive specimens. The problem is when dealing with percent positives in the middle of a pandemic, and especially with the Omicron surge, numbers for influenza in the middle of December would have been about this 6%. But if the aberration of the pandemic and all of the specimens that were COVID-19 specimens, it seems that about 25% to 30% would have been influenza positive. It seemed misleading to her, especially for the public, to be talking about percent when the denominator was unknown and it is unclear what percent were related to a surge of COVID-19. She expressed her hope that they could find a better way to describe the activity of a virus rather than percent of positive specimens.

Dr. Fry responded that CDC focused on symptomatic people, not asymptomatic people. That is where a lot of the confusion with Coronavirus occurs. In this particular case in the CDC surveillance systems, these estimates were among people who presented for testing with an ARI who tested positive for influenza. There also is a percent who tested positive for COVID-19, which is the differential diagnosis. COVID-19 makes things very complicated in terms of who is being tested, local circulation, et cetera. This makes it difficult sometimes to tease everything out completely.

Recommending Enhanced Seasonal Influenza Vaccines in Adults ≥65 Years of Age: Potential Impacts on Influenza Burden

Dr. Sinead Morris (CDC/NCIRD) reported that the primary goal for this effort was to use mathematical modeling to explore how a new preferential recommendation for enhanced vaccines (e.g., high-dose, adjuvanted, recombinant) over standard vaccines (SVs) in adults ≥65 years of age could impact influenza burden over the course of the season. The approach to the model included 2 elements, which were to: 1) create a baseline model to capture influenza dynamics under current guidelines when there is no preferential recommendation in place; and

2) model what might happen following a preferential recommendation for enhanced vaccines (EVs).

The baseline model was created in order to have something with which to compare everything else. Because influenza burden can differ from season-to-season, consideration was given to a high severity season and a low severity season. While this does not represent any particular season, it can be thought of as the high severity season representing a season dominated by H3N2 and the low severity season being more similar to a season dominated by H1N1. The model used was an age-structured Susceptible Exposed Infectious Removed (SEIR) model in which individuals were stratified based on age and disease status. People start out susceptible and then upon infection, they progress through a series of states where they are first exposed but not yet infectious. Then they become infectious and potentially symptomatic. Finally, they recover and are assumed to be immune for the remainder of the season. Vaccination also was incorporated into the model, with adults under 65 years of age receiving SV and adults ≥65 years of age receiving either SV or EV that offers greater protection. The model is first calibrated by using published parameter estimates from the literature and verifying that it can capture the dynamics that would be expected in typical high and low severity seasons.

One example is the efficacy produced by the model for the number of symptomatic cases per 100,000 people. The model was recalibrated so that the high severity season had a higher and an earlier peak than the low severity season, as is often the case for H3 versus H1 dominated seasons. The peak for seasons over the last 10 years was used to verify that the timing of the peak produced by the model agreed with what was seen in product data quality (PDQ). Other calibration checks were performed as well. Once the modelers were satisfied that the model was producing reasonable dynamics, they moved on to the second step.

The second step of the model explores what might happen following a preferential recommendation for EVs. First, it was assumed that there would be benefits to new recommendations. For example, if given the choice, more people would choose an EV over an SV standard vaccine, meaning that the percentage of adults ≥65 years of age getting an EV would increase. But the model also explored the potential tradeoffs that could occur. For example, there could be a delay in people receiving those additional EVs if there was higher demand or it took longer to find a provider who offers that vaccine. There also could also be a reduction in overall coverage in the ≥65 years of age group if individuals only offered SVs did not take them. Monetary or individual costs like safety were not considered in the model. Instead, the model focused on the opportunity costs from a society perspective.

To model the impact of a new recommendation, values had to be assigned to the benefits and opportunity costs. For the benefits, the percentage of vaccinated adults ≥65 years of age to receive an EV can increase by up to 20% compared with the baseline value with no recommendation. For example, if the percentage receiving an EV at baseline is 75% and an increase of 10% is assumed, 85% would receive an EV with the new recommendation. For opportunity costs, 3 levels of possible delays and reduction in overall coverage were considered. The best case was when delays and reduction in overall coverage were 0, or all the benefits without any additional cost. For the intermediate values, a 3-week delay and a 10% reduction in overall coverage were used. For the worst-case options, a 6-week delay and a 20% reduction in coverage were used. It is important to note that no assumptions were made about how likely any of these different opportunity costs were to occur. They were just used to explore a range of possible outcomes.

In addition, 2 other important parameters were varied in this analysis. First, it was assumed that EVs were between 5% and 50% more effective than SVs, which translates to an effectiveness of 26% to 60% in absolute terms. This wide range reflects the large variation and uncertainty in estimates from the literature, one of which was a 2014 paper used to calibrate this frame.[9] Second, it was assumed that at baseline with no recommendation in place, between 60% and 80% of vaccinees ≥65 years of age received EV and the remaining fraction received SV. This range was based on a number of recent studies with some additional uncertainty included.[10] To incorporate all of these components into the model, the benefits and those 2 important EV parameters were varied between the ranges outlined earlier (parameters varied 1000 times, benefits increased EV uptake by 0%-20%, EV effectiveness of 5%-50% greater than SV, and EV uptake at baseline of 60%-80% of vaccinees 65+). Uncertainty was directly incorporated in these values in the analysis. For each combination of the opportunity cost parameters, the model was simulated with and without a preferential recommendation in place. The change in hospitalizations and deaths that occurred also were calculated.

In terms of the number of hospitalizations that were averted with a new recommendation in place, the delay in receiving additional EV was increased from 0 to 3 to 6 weeks. The reduction in overall coverage was increased across the columns from 0 to 10% to 20%. The first important takeaway is that, as might be expected, when both parameters were at their best-case values of 0, a positive change was always seen or was better with the recommendation in place. That makes sense because this assumes all of the benefits without any of the opportunity costs. Increasing the delay while keeping a 0% reduction in overall coverage introduced some potential for negative impacts in the high severity season, while the impact remained mainly positive in the low severity season, so the benefits could still outweigh the opportunity costs. However, if instead the reduction in overall coverage was increased to 10, there was always a negative impact that increased as the reduction increased to 20%. For the parameter values explored here, the opportunity costs also could outweigh the benefits quite substantially. Importantly, the magnitude of this effect was more sensitive to the reduction in overall vaccine coverage.

To note some of the limitations to the approach and important points to keep in mind when interpreting these results, first, it was assumed that vaccines only protect against symptoms (i.e., no additional effect on infection or onward transmission). Thus, the results focus on the direct effects of vaccination without consideration for how indirect effects may change these results. Second, high and low severity seasons were used to explore a range of possible outcomes that could be expected. They do not represent any one particular season and are not exact predictions. Third, EVs were not stratified by type (high-dose, adjuvanted, recombinant). However, a wide range of parameter values were explored that should account for variations in uptake and effectiveness between the different vaccine types. Fourth, the tradeoff scenarios made necessary assumptions about how individual vaccine-seeking behavior might change. These were used to provide examples of the range of possible outcomes, but the model did not assess how likely they are to occur.

To summarize the main findings, in the best-case scenario with no delays or reductions in overall coverage, a new recommendation always has a positive impact. However, switching to the intermediate- or worst-case values can introduce negative impacts that can range from relatively small to more substantial. Overall, the outcomes are more sensitive to the reduction in overall vaccine coverage. In terms of what could be done to maximize the chance of having a

[9] Diaz Granados et al. (2014) NEJM
[10] Izurieta et al. (2019, 2020, 2020) JID, CID

positive impact, the results so that it is necessary to get as close to the best-case scenario as possible and to avoid delays in vaccine uptake. For instance, this can be achieved by ensuring timely access to EVs and minimizing reductions in overall coverage by stressing the importance of still getting SV if EV is not available.

Discussion Summary

Based on current distribution numbers, Dr. Lee inquired about the likelihood of an adult ≥65 years of age going to a vaccination site that did not have an EV available, whether there is regional or local variability in availability that could impact some communities more adversely than others, and if there has been an assessment of potential gaps that need to be closed from an implementation standpoint.

Dr. Talbot indicated that approximately 80% of adults currently get an EV. One of the reasons the WG greatly appreciated this presentation was that if ACIP recommends only 1 vaccine as EV and only 1 vaccine as preferential and there was a delay in that vaccine, there may be an issue in the timing of immunization of older adults. If more than 1 vaccine is recommended, this would provide more options and reduce the likelihood of a manufacturing or contamination issue, which would then lead to a delay in immunization in older adults.

Dr. Drees (SHEA) asked when a decision about a preferential recommendation would be made. While ACIP was not going to vote on this during this meeting, everyone is ordering their influenza vaccines now for the next season. If a vote is planned for June or October, that would be problematic in terms of most places not having ordered a sufficient supply for an increase in demand and would impact uptake as well.

Dr. Talbot noted that this is always an issue with influenza vaccine, given that there is a new vaccine every year. One issue is that the full data analyses and information from GRADE took slightly longer than anticipated because of the 2-year pandemic in which everyone has been participating and continues to participate. The GRADE assessment was finally completed and the WG reviewed it and was excited to share it with the rest of the ACIP voting members later in this session. The next step would be the EtR framework, after which a vote could be taken, which may conflict with influenza purchasing times.

Dr. Daley asked whether vaccine supply posed any major issues, what is known about the 20% of older adults who received SV, whether that was because EV was not available, and/or if logistics played a role.

Dr. Talbot responded that there are not currently any supply issues. There have been issues in the past, the most memorable of which occurred in 2005. Among the 20% of older adults who do get vaccinated each year but not with EV, it is likely due to the location to which they have presented no having EV. Although currently there is not a preferential recommendation, many but not all hospitals and healthcare systems purchase EV for adults over 65 years of age. The question of who over 65 years of age is not getting vaccinated is one that needs further exploration and improvement.

In terms of the best-case scenarios that were highlighted, Dr. Bell wondered whether there is a way to look at the Y axis to explain in more detail exactly how much incremental benefit the preferential recommendation might provide.

Dr. Morris replied that this would be possible. While she did not have the exact numbers, the mean is about 1,000 and the bar probably goes up to about 3,000. It is important to remember that the seasons are modeled on what would be expected in a typical influenza and are not fit to any one season in particular. Therefore, these are not exact predictions of what would happen.

Influenza Vaccines for Older Adults

Dr. Lisa Grohskopf (CDC/NCIRD) reminded everyone that as described in previous meetings, older adults are defined as adults ≥65 years of age. This group is at high risk for influenza-associated morbidity and mortality, but also is a group for whom influenza vaccines are often less effective than is the case for younger persons. Influenza vaccines licensed for this population include high-dose influenza vaccine (HD-IV), adjuvanted influenza vaccine (aIIV), and recombinant influenza vaccine (RIV) licensed for adults ≥18 years of age and have been studied against standard dose IIV (SD-IIV), unadjuvanted, and inactivated influenza vaccines in this population. For this presentation, these 3 vaccines were referred to collectively as EIVs. This review sought to answer the following question. "Do the relative benefits and harms of HD-IIV, aIIV, and RIV (referred to collectively as enhanced influenza vaccines or EIVs) as compared with one another and with standard-dose unadjuvanted influenza vaccines (SD-IIV) favor the use of any one or more of these vaccines over other age-appropriate influenza vaccines for persons ≥65 years of age?"

In terms of the PICO, the population of interest is adults ≥65 years of age. Interventions of interest included EIVs (HD-IIV, aIIV, and RIV)—quadrivalent and trivalent formulations. EIVs were compared with SD-IIVs, as well as with one another. Critical benefits include influenza illness, influenza-associated outpatient/ED visits, influenza-associated hospitalizations, and influenza-associated deaths. Important harms outcomes included occurrence of any SAE and any solicited injection site reactions Grade 3 or higher. Critical harms included occurrence of any solicited adverse reaction Grade 3 or higher and Guillain-Barré Syndrome (GBS). There were 6 total of vaccine comparisons as shown in this table:

EIVs vs SD-IIVs	EIVs vs One Another
HD-IIV vs SD-IIV	HD-IIV vs aIIV
aIIV vs SD-IIV	HD-IIV vs RIV
RIV vs SD-IIV	aIIV vs RIV

The analyses considered influenza seasons separately where possible because the VE of these vaccines and relative VE of vaccines to one another vary from season-to-season. Comparisons of trivalent and quadrivalent vaccines are combined, given data indicating that quadrivalent formulations have been roughly equivalent in terms of safety and immunogenicity to their trivalent counterparts. In cases where a study recorded separate estimates for different IIV comparator vaccines, the SD-IV was generally selected and was specified as egg- or cell-based. The egg-based comparator was included since that is probably the most likely scenario given the currently availability of vaccines. Estimates for composite outcomes (e.g., combined inpatient/outpatient visits; hospitalizations/ER visits) were not included in the main analyses or GRADE and were described separately.

For Comparison 1 (HD-IIV vs SD-IIV), there was a high certainty of evidence (Level 1) for the outcome of influenza illnesses favoring HD-IIV3 over SD-IIV. This is based on a single large RCT that included roughly 32,000 persons ≥65 years of age covering 2 influenza seasons and that used a laboratory-confirmed influenza outcome. There was moderate quality evidence favoring HD-IIV for influenza-associated outpatient and ER visits from retrospective cohort

studies. This result was downgraded because of risk of bias given the cohort design of the study and use of the non-laboratory confirmed influenza outcomes. For hospitalizations, there was not an RCT that directly evaluated influenza-specific hospitalizations as a primary outcome. However, 2 RCTs examined hospitalizations and other severe events as a secondary post-hoc analysis, and 1 case review of diagnostic codes associated with SAEs that occurred in a previous trial and in the other 2 chart reviews. Neither of these outcome definitions involved influenza testing performed within the context of the study. There was no significant difference with moderate certainty evidence (Level 2). However, for hospitalization, there also was moderate certainty evidence (Level 2) favoring HD-IIV3 against pneumonia and influenza-coded hospitalizations from a cluster randomized trial, as well as from a number of observational studies primarily of a retrospective cohort design. These were downgraded to moderate certainty (Level 2) on the basis of using diagnostic code-defined outcomes rather than laboratory-confirmed outcomes. Finally, there was moderate certainty (Level 2) evidence favoring HD-IIV3 against influenza-associated death, which was downgraded primarily because of potential risk of bias from using a code-based definition for the outcomes.

Moving on to harms, there was high certainty (Level 1) evidence favoring HD-IIVs for SAEs. In the 2 pathogenicity outcomes, the point estimate for solicited injection site reactions Grade 3 or greater was approximately 4.9 (0.85, 28.36). However, it did not meet statistical significance due to a wide confidence interval. There was overall low-quality (Level 3) evidence for a similar risk of Grade 3 or higher local or systemic reactogenicity events and it was downgraded due to imprecision. It is not easy to study GBS in an RCT. However, 1 RCT reported on GBS as an adverse event of special interest (AESI) as specified in the protocol. No cases were recorded in either group in that paper.

For Comparison 2 (aIIV vs SD-IIV), there were no RCTs examining laboratory-confirmed influenza outcomes. The 1 RCT was primarily an immunogenicity and safety study that examined clinical effectiveness against ILI using a symptomatic definition as an exploratory outcome with no laboratory confirmation. It was not powered to attest to efficacy. No compatible studies of other types were found that could be pooled with these data. The study noted no significant difference in ILI, and it was downgraded due to risk of bias concerns given the non-laboratory-confirmed outcomes. However, there was some mixed evidence with regard to influenza-associated outpatient visits from a mix of study types. These results could not be pooled into one result because of differences in the statistical analyses and denominator techniques, so there were 2 separate estimates—one showing a significant difference favoring adjuvanted vaccines and the other showing no significant difference. Overall quality for this group of studies was moderate (Level 2) and was downgraded because most of the data came from studies using code-based rather than laboratory-confirmed outcomes. There was somewhat stronger and more uniform evidence for influenza-associated hospitalizations. This was somewhat more consistent across study designs, similar to what was see in the last comparison of HD-IIV3 versus SD-IIV. The pooled estimates favored IIV versus SD-IIV, with moderate certainty (Level 2).

With regard to harm, there was no significant difference for safety outcomes in the pooled estimate for any SAE with moderate certainty (Level 2) due to imprecision. There was low certainty evidence (Level 3) favoring SD-IIV for injection site reactogenicity events. This was downgraded for imprecision of the confidence interval. This result was driven largely from 1 study which noted that there were no severe pain events in either vaccine group. There was no significant difference in systemic reactogenicity events, with downgrading for uncertainty due to imprecision. One of the general themes here is that for many of the safety outcomes, the main source of downgrading is the precision of the confidence interval. For the last outcome of GBS,

there was 1 RCT of adjuvanted versus standard dose that noted 1 instance of GBS in the SD-IIV3 group. There also was 1 retrospective cohort study of 3 seasons from Italy that noted zero cases of Definite, Probable, or Possible GBS in either arm during a 42-day window.

Regarding Comparison 3 (RIV vs SD-IIV), 2 RCTs were retrieved that addressed influenza illnesses with a pooled estimate showing no significant differences and moderate certainty (Level 2) due to imprecision. For influenza-associated hospitalizations, there was 1 retrospective cohort study of CMS data. This estimate favored RIV with moderate certainty (Level 2). In terms of harms, with any SAE and both reactogenicity outcomes, the pooled estimates also were RCTs that indicated no significant differences. For all cases, outcomes were low (Level 3) largely due to imprecision. For GBS, there was one retrospective cohort study of trivalent recombinant versus inactivated standard dose vaccine that had this as an outcome. There were 4 cases that all occurred among SD-IIV3 recipients and none among RIV recipients that occurred within a 41-day post-vaccination window. Certainty was very low (Level 4) because of the diagnostic code-based outcomes and imprecision.

Turning to Comparison 4 (HD-IIV3 vs aIIV3), there was one small RCT for the illness outcome (used for all 3 EIV versus aIIV3 outcomes). This RCT included a total of about 90 people and all 3 intervention vaccines (HD-IIV3, aIIV3, and RIV4). It was primarily an immunogenicity and safety study that included polymerase chain reaction (PCR)-confirmed ILI only as an exploratory outcome. This study was not powered for efficacy. No additional data were found with which to pool these data. It was included here for completeness. For the first outcome, there was no significant difference between the HD-IIV and aIIV groups. They were downgraded for risk of bias as this is an open label study and has imprecision. For influenza-associated outpatient ER visits, there were 3 retrospective cohort studies with no significant difference in the pooled estimates. Certainty was downgraded due to the use of non-laboratory confirmed outcomes and inconsistency of the estimates that were observed in this study. For influenza hospitalizations, there were 4 retrospective cohort studies. There was no significant difference between group estimates. Certainty was downgraded due to the use again of non-laboratory confirmed outcomes and imprecision. In terms of harms, there was low certainty (Level 3) evidence of a similar risk of SAE Grade 3 or higher for injection site or systemic reactogenicity events, which were roughly equivalent between the 2 groups. For GBS, there was 1 RCT that included GBS as an AESI for this comparison. No cases were reported in the paper for either group.

For Comparison 5 (HD-IIV3 vs RIV4), the data became sparser because there is not as much literature on RIV as on the other vaccines. For influenza illnesses, there was the same small RCT mentioned in the last comparison that examined PCR-confirmed ILI and exploratory outcomes, with no significant difference in ILI between groups. This was downgraded again because of the imprecision due to the small sample size and being an open label study. For hospitalizations, there was one retrospective cohort study, which was a fairly large CMS study. However, it was for one season and had an effect estimate favoring RIV4. Certainty was downgraded because of the use of diagnosis code-based outcome data rather than laboratory-confirmed data and for imprecision in the study. For safety outcomes for this comparison, there were 2 RCTs that each addressed the any SAE and both reactogenicity outcomes. There were no significant differences between the vaccine groups for any outcomes. Certainty was downgraded for imprecision.

With regard to Comparison 6 (aIIV3 vs RIV4), there was the same small RCT mentioned earlier. There were no significant differences between the 2 conditions. This was downgraded for imprecision and having been an open label study. For hospitalizations, there was 1 retrospective cohort study with an effect estimate favoring RIV4. Certainty was downgraded to moderate (Level 2) because of the use of diagnostic code-based outcome definitions rather than laboratory confirmation. With regard to harms and safety outcomes for this comparison, there was 1 RCT that addressed each of the SAEs in both reactogenicity outcomes. This study observed no significant differences between the 2 vaccines groups for any outcomes and certainty was downgraded for imprecision. The following 2 tables assemble all of the evidence across outcomes:

Evidence Summary: EIVs vs SD-IIVs

Outcome	Importance	HD-IIV3 vs SD-IIV	aIIV3 vs SD-IIV	RIV vs SD-IIV
Benefits				
Influenza illnesses	Critical	Level 1 (High) Favors HD-IIV3	Level 2 (Moderate)	Level 2 (Moderate)
Influenza outpatient/ER visits	Critical	Level 2 (Moderate) Favors HD-IIV3	Level 2 (Moderate)	
Influenza hospitalizations	Critical	Level 2 (Moderate) Favors HD-IIV3	Level 2 (Moderate) Favors aIIV3	Level 2 (Moderate) Favors RIV4
Influenza deaths	Critical	Level 2 (Moderate) Favors HD-IIV3		
Harms				
Any Serious Adverse Event (SAE)	Important	Level 1 (High) Favors HD-IIV3	Level 2 (Moderate)	Level 3 (Low)
Solicited injection site adverse events Grade ≥3	Important	Level 3 (Low)	Level 3 (Low) Favors SD-IIV	Level 3 (Low)
Solicited systemic adverse events Grade ≥3	Critical	Level 3 (Low)	Level 3 (Low)	Level 3 (Low)
Guillain-Barré syndrome	Critical	Level 3 (Low)	Level 3 (Low)	Level 4 (Very low)
OVERALL CERTAINTY		**Level 3 (Low)**	**Level 3 (Low)**	**Level 4 (Very low)**

Evidence Summary: EIVs vs One Another

Outcome	Importance	HD-IIV3 vs aIIV3	HD-IIV3 vs RIV	aIIV3 vs RIV
Benefits				
Influenza illnesses	Critical	Level 4 (Very low)	Level 4 (Very low)	Level 4 (Very low)
Influenza outpatient/ER visits	Critical	Level 2 (Low)		
Influenza hospitalizations	Critical	Level 3 (Low)	Level 2 (Moderate) Favors RIV4 (1 retro cohort study)	Level 2 (Moderate) Favors RIV4 (1 retro cohort study)
Influenza deaths	Critical			
Harms				
Any Serious Adverse Event (SAE)	Important	Level 3 (Low)	Level 3 (Low)	Level 3 (Low)
Solicited injection site adverse events Grade ≥3	Important	Level 4 (Low)	Level 3 (Low)	Level 3 (Low)
Solicited systemic adverse events Grade ≥3	Critical	Level 3 (Low)	Level 3 (Low)	Level 3 (Low)
Guillain-Barré syndrome	Critical	Level 3 (Low)		
OVERALL CERTAINTY		**Level 4 (Very low)**	**Level 4 (Very low)**	**Level 4 (Very low)**

For HD-IIV3 and SD-IIV, there was high certainty evidence favoring HD-IIV3 for influenza illnesses and moderate certainty evidence for outpatient visits, hospitalizations, and deaths. For safety outcomes, there was high certainty evidence favoring HD-IIV3 for SAEs, with the remaining safety outcomes favoring neither vaccine and having low certainty, mainly due to imprecision of estimates. For adjuvanted influenza vaccines, there was moderate certainty evidence favoring neither vaccine for illnesses and outpatient visits, but there was moderate certainty evidence favoring aIIV for hospitalizations. For safety outcomes, there was moderate certainty evidence of similar risk of SAEs and low certainty evidence favoring SD-IIV for local reactogenicity. For RIV, there was moderate certainty evidence favoring neither vaccine for illnesses and moderate certainty evidence favoring RIV4 for hospitalizations. For SAEs and

reactogenicity outcomes, there was low certainty evidence of similar risks of these events. Overall, there was relatively little data on GBS, with low to very low-quality evidence across the 3 comparisons.

For comparisons of EIVs versus one another, there were no significant differences except moderate certainty evidence favoring RIV4 over both HD-IIV3 and aIIV3 for hospitalization among the 4 efficacy outcomes. This was on the basis of 1 observational study conducted over 1 season. This was a study of a retrospective cohort of CMS data totaling roughly 13 million people. For safety outcomes, the evidence review was overall low mainly due to imprecision of estimates, and there were no significant differences for any outcomes.

In conclusion for EIVs vs SD-IIVs, there was limited RCT data. There were mainly 2 studies that examined laboratory-confirmed influence outcomes, 1 for high-dose and 1 for recombinant. These represent relatively few influenza seasons overall. With influenza, examining seasons is important because of the variability of both VE and relative VE. There was high quality evidence favoring HD-IIV3 over SD-IIV3 from 1 RCT specifically for the illness outcome. Evidence for the other outcomes fell more into moderate certainty evidence. From observational data, there was overall moderate certainty evidence favoring each EIV over SD-IIV against influenza-related hospitalization, which is an important outcome in this population. The limitations of these data include that they were mostly from large retrospective cohort studies for which outcomes were defined by diagnostic codes rather than laboratory-confirmed influenza. However, they did have a very large sample size and in some cases were conducted over multiple seasons. Moreover, many of them used relatively specific influenza codes rather than pneumonia and influenza codes. Although there were some of the latter as well. The largest quantity of data were available overall for HD-IIV3, somewhat less for aIIV3, and the least with regard to RIV. Overall, there were a few differences in safety outcomes and none for critical outcomes.

With regard to EIVs versus one another, there were more limited data. In general, there was only very low certainty RCT data from 1 study that was not intended to examine efficacy as a primary outcome. From observational data, there was moderate quality evidence favoring RIV over both HD-IIV3 and aIIV3 against hospitalization. However, this was from 1 retrospective cohort study conducted over a single season. No safety differences were observed among the three EIV comparisons, and overall evidence providing direct comparisons of EIVs with one another did not seem to indicate superiority of any 1 of these 3 vaccines over the others. Overall, there was evidence of benefits favoring HD-IIV over SD-IIVs. The most evidence was available for high-dose vaccine. There were fewer studies and no RCTs including laboratory-confirmed influenza for adjuvanted vaccines. There were the fewest studies for RIV overall. There was no strong evidence favoring one EIV over others among studies providing direct comparisons of these vaccines to one another. Limitations include overall few RCT data representing few influenza seasons, and no data reflecting the currently available formulations of HD-IIV and aIIV. All of the data reviewed regarding those 2 vaccines by this measurement reflect the trivalent formulation of the vaccine. Both of those vaccines are now available in quadrivalent formulations only. However, pre-licensure studies generally have indicated similar immunogenicity and safety of quadrivalent vaccines and their trivalent counterparts.

Discussion Summary

Dr. Loehr called everyone's attention to the amount of work that went into this GRADE review over the last 2 years in terms of the approximately 3,500 full text reports assessed and the number of studies that actually were included in the analysis of 49. With no disrespect to other WGs, in a later study they would hear that the full text assessed were 60 to 100 and 7 were

included in the analysis. The amount of work by Dr. Grohskopf over the last several weeks to develop it into a presentable fashion for the ACIP has been outstanding.

Dr. Lee agreed and added that if they all were in a room together, they would give Dr. Grohskopf a round of applause.

HEPATITIS VACCINE

Session Introduction

Dr. Kevin Ault (ACIP, WG Chair) introduced the hepatitis vaccine session, reminding everyone that universal adult hepatitis B (HepB) vaccination was approved in 2021; FDA approved PreHevbrio, a 3-antigen HepB vaccine, in 2021;[11] and ACIP heard a presentation by the manufacturer on the safety and immunogenicity of PreHevbrio on January 12, 2022. The focus of this session was PreHevbrio for adults, including EtR and GRADE. Subsequent WG terms of reference will include exploration of preferential use of HepB vaccines among specific risk groups.

PreHevbrio for Adult HepB Vaccination: EtR and GRADE

LCDR Mark K. Weng, MD MSc (CDC/NCHHSTP) discussed PreHevbrio for adult HepB vaccination and presented the WG's modified EtR and GRADE. The policy question was, "Should PreHevbrio be recommended as an option for adults recommended for hepatitis B (HepB) vaccination?" In terms of the PICO, the population is adults ≥18 years of age. The intervention is 3 doses of PreHevbrio over 6 months. The comparison is existing HepB vaccines licensed for adults in the US (TWINRIX, Engerix-B, Recombivax-HB, HEPLISAV-B).[12] The outcomes considered included HepB virus infection (Critical), SAEs (Critical), and mild AEs (Important but not critical). Persons on hemodialysis, pregnant persons, or persons who were breastfeeding were not discussed in this EtR Framework. The safety and effectiveness of PreHevbrio have not been established in adults on hemodialysis. In addition, there are no adequate and well-controlled studies of PreHevbrio in pregnant women. Available human data on PreHevbrio administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy. Data are not available to assess the effects of PreHevbrio on the breastfed infant or on milk production or excretion.

In terms of background, PreHevbrio is a mammalian cell-derived, alum adjuvanted, 3-dose HepB vaccine. The previously approved Engerix-B and Recombivax-HB are 3-dose vaccines as well. Heplisav-B approved in 2018 is adjuvanted with CpG 1018 and is a 2-dose single antigen vaccine. In 2021, ACIP approved universal HepB vaccine recommendations for adults 19-59 years of age as reflected in the 2022 Adult Immunization Schedule published the previous Friday, February 18, 2022. An additional HepB vaccine that is safe and non-inferior to existing ACIP-approved HepB vaccines could be a beneficial adjunct in achieving the HHS goals of eliminating HepB as a public health threat in the US by 2030.

The literature search identified 4,148 initial records of which 1,660 were duplicates. After title and abstract review, 64 records remained for full text review. Of these, 57 records were excluded due to a variety of reasons (e.g., duplicate studies with different titles, studies on non/hypo responders, single arm studies, studies with different schedules/doses of vaccine,

[11] https://www.fda.gov/vaccines-blood-biologics/prehevbrio
[12] Studies that were ultimately included used only Engerix-B out of this list of possible comparators.

review articles, clinical trial registries with no results, studies with vaccine that was not of interest, dose response studies, lot-to-lot consistency studies, vertical transmission studies, therapeutic vaccination, patients with end stage renal disease). In total, 7 RCT studies were ultimately included in the GRADE assessment. Despite the PICO question specifying all US licensed HepB vaccines as comparator vaccines, the 7 included studies that were found to meet the criteria had only Engerix-B as a comparator vaccine out of all possible comparator adult HepB vaccines licensed in the US.

In terms of the GRADE summary of findings based on those 7 studies presented during this session, it is important to note that the GRADE process requires pooling across all available studies and uses an intention-to-treat (ITT) approach rather than per-protocol analysis; the data were not stratified by age group; and all studies considered seroprotection as anti-HB antibody ≥10 mIU/mL, which is a widely used surrogate marker for prevention of HepB infection. This table summarizes the GRADE assessment for all 3 outcomes of interest:

Benefits and Harms: GRADE Summary of Findings Table

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PreHevbrio	Comparator (Engerix-B)	Relative (95% CI)	Absolute (95% CI)		
Hepatitis B Infection (all studies considered seroprotection as anti-HBs ≥10 mIU/mL, between 1-3 months after completion of 3-dose series)												
7	randomized trials	serious[a]	serious[b]	not serious[c]	not serious	none	2929/3500 (83.7%)	1611/2100 (76.7%)	RR 1.07 (1.01 to 1.14)	5,370 more per 100,000 (from 767 more to 10,740 more)	Low	CRITICAL
Severe Adverse Events (e.g. syncope, atrial fibrillation, congestive cardiac failure, death*)												
7	randomized trials	serious[d]	not serious[e]	not serious	serious[f]	none	75/3480 (2.2%)	28/2084 (1.3%)	RR 1.62 (0.50 to 5.22)	833 more per 100,000 (from 672 fewer to 5,670 more)	Low	CRITICAL
Mild Adverse Events (reported up to 6 months after completion of 3-dose series)												
4	randomized trials	not serious	serious[b]	not serious	serious[f]	none	1612/3864 (41.7%)	826/2481 (33.3%)	RR 1.09 (0.76 to 1.55)	3,266 more per 100,000 (from 8,709 fewer to 19,959 more)	Low	IMPORTANT BUT NOT CRITICAL

Explanations CI: confidence interval; RR: risk ratio
a. 3/7 studies contributing to 60% of the weight to the analysis and high risk of bias due to unclear random sequence generation /allocation concealment and blinding (Diaz-Mitoma, Raz, Yap)
b. I^2 = 89%, studies at high risk of bias may contribute to the heterogeneity observed
c. All studies considered seroprotection as anti-HBs ≥10 mIU/mL as a surrogate for prevention of HepB infection
d. 4/7 studies have high risk of bias for randomization/allocation concealment and blinding (Diaz-Mitoma, Etzion, Raz, Yap)
e. I^2 = 67%; heterogeneity due to 2 studies contributing 81% of the weight of this outcome analysis (CONSTANT and PROTECT)
f. 95% CI cannot exclude the possibility of no meaningful difference
*Sudden cardiac death (1 event) was later assessed as unrelated to vaccination, in a participant with history of open-heart surgery and biventricular hypertrophy

For HepB infection assessed via seroprotection, 7 RCTs were included. In the pooled analysis of these studies, 83.7% of participants achieved seroprotection in the PreHevbrio group as compared to 76.7% in the comparison group of single antigen vaccine, which ended up being Engerix-b for all included studies. The relative risk was 1.07. However, the risk of bias was serious as 3 of the 7 studies contributing 60% of the weight to the analysis had high risk of bias due to unclear randomization methods or lack of allocation concealment and blinding. Inconsistency was rated as serious. I^2 being 89% suggests substantial heterogeneity. The indirectness was not serious for the use of seroprotection with antibody level ≥10 mIU/mL as a standard measure of the outcome of HepB infection. This brought the certainty of evidence to low (Level 3). For SAEs, 7 studies were included of which 4 reported no SAEs in either PreHevbrio or the comparator arm. The pooled analysis showed a relative risk of 1.62 with broad interval of 0.50-5.22. The 95% confidence interval cannot exclude the possibility of no meaningful difference, which brought serious imprecision into account. The SAEs in the PreHevbrio group were higher at 2.2% compared to the Engarix0-B group at 1.3%. The risk of bias was serious for unknown randomization method or lack of allocation concealment and

blinding. This brought the certainty of evidence to low (Level 3). Data for mild AEs was abstracted from 4 studies, with and overall risk ratio of 1.09 with the PreHevbrio group showing a higher proportion of participants reporting mild AEs, as compared to the single antigen comparator group with imprecision. With I^2 equal to 89%, the inclusion of studies at risk of bias may contribute to the heterogeneity observed and serious inconsistency. This made overall certainty low (Level 3) for the outcome of mild AEs.

In terms of the benefits and harms conclusions from GRADE, the evidence suggests that the seroprotection conferred by PreHevbrio is non-inferior (little or no difference) compared with seroprotection conferred by Engerix-B. That evidence was established through ITT analysis. PreHevbrio may result in little to no difference in SAEs when compared with those resulting from Engerix-B. PreHevbrio may result in little to no difference in mild AEs when compared with those resulting from Engerix-B.

The WG concluded that the prevention of HepB is a problem of public health importance. The WG concluded that for prevention of HepB infection as measured by seroprotection, the difference in desirable anticipated effects of PreHevbrio compared with those of Engerix B are minimal. The WG judged the differences in undesirable anticipated effects between PreHevbrio and Engerix B to be minimal for the outcomes of SAEs and mild AEs. The WG judged the balance between desirable effects and undesirable effects to favor both PreHevbrio or Engerix-B. The WG deemed the overall certainty of evidence for the critical outcomes to be probably not important. The WG judged the impact of PreHevbrio compared to Engerix-B on health equity to probably have no impact. Based on similarities to the dosage schedule, adjuvant, and vaccine mechanism, the WG perceived the domains of values, acceptability, resource use, and feasibility for PreHevbrio to be comparable with the values, acceptability, resource use, and feasibility of previously approved 3-dose comparator vaccines, which included Engerix-B.

Based on EtR considerations, the balance between PreHevbrio and currently used HepB vaccines is closely balanced. Therefore, the WG judgment on adding PreHevbrio as an option for HepB vaccination of adults was that the desirable consequences clearly outweigh undesirable consequences in most settings. The ACIP Policy Statement for PreHevbrio is:

Recommendation	**PreHevbrio may be used as a HepB vaccine in persons aged ≥18 years recommended for vaccination against HBV infection.**
Additional Considerations	**Persons on hemodialysis, pregnant persons and persons who are breastfeeding are not discussed in this Evidence to Recommendations Framework.** The safety and effectiveness of PREHEVBRIO have not been established in adults on hemodialysis. There are no adequate and well-controlled studies of PREHEVBRIO in pregnant women. Available human data on PREHEVBRIO administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy. Data are not available to assess the effects of PREHEVBRIO on the breastfed infant or on milk production/excretion.

Discussion Summary

Dr. Long observed that for the EtR Framework, the first question pertained to whether the burden of disease is significant, to which the WG answered “yes.” She inquired as to whether this could be interpreted to mean if there were no other vaccines available. If there are 4 or 5 HepB vaccines available, there does not seem to be an unmet clinical need at the moment for more HepB vaccines.

Dr. Wharton responded that in this circumstance in which PreHevbrio is an additional vaccine for indications upon which ACIP already voted, the public health problem domain of the EtR was not necessary to address because the ACIP already weighed in on HepB as a public health problem, as reflected in the recent vote by the committee to recommend HepB vaccination for all adults.

Dr. Ault added that there are 20,000 new HepB cases every year, with $1 billion spent on HepB and about 2 million Americans living with HepB.

Dr. Poehling requested clarification on whether ACIP was intended to vote on this new vaccine, recognizing that it would be included in the same recommendation as the other HepB vaccines.

Dr. Wharton clarified that given the existing ACIP recommendations for vaccination of adults to prevent HepB, the similarity of this product in usage to other licensed products, and the fact that it would not be added to the Vaccines For Children (VFC) program, no vote would be necessary. However, they did want to have public discussion and as documents are updated, this vaccine will be included as an available/acceptable vaccine to use for prevention of HepB in the US.

Dr. Fryhofer (AMA), speaking as an individual practicing physician, recalled that Slide 21 from the December 21, 2021 ACIP presentation from the manufacturer was titled, “Improved immunogenicity in key high-risk groups and investigator-initiated studies" and it specifically mentioned end-stage renal disease (ESRD), human immunodeficiency virus (HIV), and non- or low-responders. She inquired as to whether that type of nuance would be included in guidance regarding this vaccine.

LCDR Weng responded that the WG assessment of the EtR and GRADE question he presented included generally healthy populations. Special populations were excluded from this study. The next term of reference the WG will examine will include some of the populations Dr. Fryhofer mentioned.

MEASLES, MUMPS, RUBELLA (MMR) VACCINE WORKGROUP

Session Introduction

Ms. Lynn Bahta (ACIP WG Chair) introduced this session with a brief background of measles, mumps, rubella (MMR) vaccination in the US. High MMR vaccination coverage has been the major contributor in the US in the elimination of measles in 2000 and rubella in 2004, and a more than 99% reduction in mumps cases. Measles and rubella remain endemic in many parts of the world and mumps is still endemic worldwide. These viruses continue to cause locally acquired and importation-related cases and outbreaks. Between 2016-2021 in the US, data have shown that there have been between 13 to 1,282 cases of measles, between 154 to 6,366 cases of mumps per year (primarily locally acquired), and less than 10 cases of rubella per year (all imported). Currently, there is only 1 licensed MMR vaccine in the US, M-M-R II® manufactured by Merck.

The ACIP MMR Vaccine WG was established to evaluate the safety and immunogenicity of a new candidate MMR vaccine Priorix™ manufactured by GlaxoSmithKline (GSK). The MMR Vaccine WG first met in in January 2022. This WG includes 17 members comprised of ACIP voting members, liaisons, *ex officios*, and CDC experts who represent a broad range of expertise (e.g., epidemiology, vaccine safety, infectious diseases, general medicine, pediatrics, vaccine administration/delivery, public health/surveillance, communications). The WG's Terms of Reference (TOR) are to consider the policy topic of the equivalency and usage of the new MMR vaccine (Priorix™, GSK) compared to the currently licensed MMR (M-M-R II®, Merck). Planned WG activities are to:

- ❑ Review the safety and immunogenicity data for the new and currently licensed MMR vaccines
- ❑ Adjudicate non-inferiority of the vaccine candidate compared to the currently licensed MMR vaccine
- ❑ Consider the new vaccine's use for licensed indications and existing ACIP recommendations for the prevention of measles, mumps, and rubella
- ❑ Consider concomitant use with other childhood vaccines
- ❑ Consider interchangeability of use in the MMR vaccine series
- ❑ Develop MMR vaccine policy options that ACIP may consider for recommendation

This session included a presentation of the data by GSK on the safety and immunogenicity of Priorix™ compared to M-M-R II®. Between now and the June 2022 ACIP meeting, the WG will convene monthly meetings and additional meetings as needed to use the EtR Framework to assess the available evidence. During the June 22-23, 2022 ACIP meeting, the WG will present policy options for consideration by the full ACIP. During that meeting, there will be a possible vote if determined to be necessary and if this candidate MMR vaccine is licensed by FDA. ACIP members were requested to consider the following questions during this session:

- ❑ Do the data presented today support the equivalency of these two vaccines?
- ❑ What additional data would you like to see to consider equivalency and interchangeability?

MMR Safety and Immunogenicity

Dr. Remon Abu-Elyazeed (GSK) presented an overview of GSK's MMR vaccine. The GSK MMR vaccine was first licensed in Germany in 1997 under the trade name Priorix™. It is currently licensed in more than 100 countries worldwide, including all European countries, Canada, and Australia. Over 400 million doses have been distributed worldwide. GSK submitted a Biologics License Application (BLA) to FDA in June 2021. The FDA Action Date is June 2022. For FDA registration, the GSK Clinical Development Program demonstrated that Priorix™ is well-aligned with the ACIP recommendations for M-M-R II® in that it had a non-inferior immune response, comparable safety, and can be used interchangeably in individuals who previously reviewed M-M-R II® or ProQuad®.

The proposed indication for Priorix™ under FDA review is active immunization for the prevention of measles, mumps, and rubella in individuals aged 12 months and older. The proposed dose is 0.5-mL by subcutaneous injection. The first dose is administered at 12 to 15 months of age and the second dose at 4 to 6 years of age. The second dose may be administered before age 4 provided that there is a minimum interval of 4 weeks. For catch-up, the second dose may be administered at 7 years of age and older.

The development plan in support of the BLA consisted of 1 Phase II and 5 Phase III studies. The Phase III studies enrolled over 16,000 subjects, approximately 50% of whom were enrolled in the US. The 5 Phase 3 studies included subjects aged 12-15 months (Studies 160, 161, 162), subjects aged 4-6 years (Study 158), and subjects aged ≥7 years (Study 159). Studies 158, 159, and 160 assessed the immunogenicity, safety, and non-inferiority of Priorix™ at the least potency for the US compared to M-M-R II®. Study 160 also demonstrated manufacturing lot-to-lot consistency. The immune response at the end of shelf-life potency was demonstrated in Study 161, and the maximum potency was assessed in Study 162. In terms of the demographic characteristics for all aggregated studies for the total vaccinated cohort, the demographic profile of the study participants is representative of the ethnically diverse US population and was similar between those who received Priorix™ and M-M-R II®.

Dr. Abu-Elyazeed presented the safety evaluation of Priorix™ post-Dose 1 children aged 12-15 months; post-Dose 2 in children aged 12-15 months who received a second dose 6 weeks after the first dose; post-Dose 2 in children aged 4-6 years; and post-Dose 2 in individuals aged 7 years or older who received Priorix™. All trials assessed the safety endpoints shown in the following table among children and adults receiving 1 or 2 doses of Priorix™:

Event	Time Period
Injection Site Redness, Swelling, Pain	Day 0-3
Drowsiness, irritability, loss of appetite*	Day 0-14
Fever, Rash (including separate categories for measles-rubella like rash and varicella-like rash), parotid gland swelling, any signs of meningism including febrile seizure**, joint pain (arthralgia/arthritis)***	Day 0-42
Unsolicited Adverse Events	Day 0-42
New Onset Chronic Disease	Day 0-180
Adverse Events Prompting a medical visit	Day 0-180
Adverse Events Prompting an ER Visit	Day 0-180
Serious Adverse Events	Day 0- Study End

*drowsiness, irritability and loss of appetite are solicited symptoms in 12–15-month-old children; drowsiness and loss of appetite are solicited symptoms in 4–6-year-olds for only 4 days post-vaccination
** febrile seizures are only solicited in 12–15-month-old and 4–6-year-old children
*** joint pain (arthralgia / arthritis) is only solicited in adults / children 7 years and older

Study 160 was an observer-blinded, non-inferiority, control study in which subjects aged 12-15 months received a first dose Priorix™ or M-M-R II® administered concurrently with US licensed vaccines. The frequency of reported solicited, local, and general AEs was similar in both groups. The most frequently reported solicited local AE in both groups was injection site pain at 26% in Priorix™ and 28% in M-M-R II®. Irritability was the most frequently reported general AE at 63% in Priorix™ and 66% in M-M-R II®. In Study 161, an observer-blind controlled clinical study clinical study, subjects aged 12-15 months received a first dose of Priorix™ or M-M-R II® followed by a second dose of the same vaccine 6 weeks later. Post-Dose 2, the frequencies of reported solicited local and general AEs were similar in both groups and were slightly lower than those reported after the Phase II study.

A subset of subjects was evaluated for local and general AEs in Study 158, an observer-blinded controlled study. In this study, subjects aged 4 to 6 years received Priorix™ or M-M-R II® as a second dose. These children had received an initial dose of M-M-R II® or ProQuad® in the second year of life. In this sub-cohort, the reactogenicity was similar between the Priorix™ and M-M-R II® groups. The most common solicited local AE was pain at the injection site of 41% in both groups. The most common solicited general AE between Day 0 and Day 42 was fever at 24% in the Priorix™ group and 25% in the M-M-R II® group. In study 159, subjects aged 7 years and older received Priorix™ or M-M-R II® as a second dose following pre-administration of a

combined MMR-containing vaccine. The reactogenicity profile was similar between the 2 vaccine groups.

Turning to the immune response data, in agreement with FDA pre-defined endpoints, Priorix™ would infer immunity based on the comparative immunogenicity data with M-M-R II®. In study 160, children aged 12-15 months received a first dose of Priorix™ or M-M-R II® concurrently with hepatitis A (HepA) vaccine and varicella vaccine. Children enrolled in the US also received PCV13 vaccine. The predefined non-inferiority success criteria of the first dose of Priorix™ compared with M-M-R II® were demonstrated in terms of seroresponse rates and antibody geometric mean concentrations (GMCs) to MMR antigen. In study 161, subjects aged 12-15 months received a first dose of Priorix™ or M-M-R II® followed by a second dose of the same vaccine 6 weeks later. In a descriptive analysis in a subset of subjects, the immune response after the second dose was similar between the 2 groups in terms of seroresponse rate, antibodies, and GMC for all antigens.

In study 158, subjects 4-6 years of age received Priorix™ or M-M-R II® as a second dose after an initial dose of M-M-R II® or ProQuad® in the second year of life. Priorix™ and M-M-R II® were given concurrently with DTaP-IPV (diphtheria, tetanus toxoids and acellular pertussis and inactivated poliovirus vaccine) and varicella vaccines in a subset of subjects. The pre-defined non-inferiority criteria were met for seroresponse rate and antibody GMC for all antigens.
In study 159, subjects aged 7 years and older received Priorix™ or M-M-R II® as a second dose after previous administration of a combined MMR vaccine. The pre-defined non-inferiority criteria were met for all comparisons.

Interchangeability with other MMR-containing vaccines is an important clinical consideration. In the development plan, GSK studied the use of Priorix™ after a previous dose of other MMR vaccines. Based on the comparable immunogenicity data in primed subjects who received either MMR vaccine in Studies 158 and 159, Priorix™ can be administered interchangeably with other MMR vaccines received as the first dose. Concomitant use of Priorix™ was evaluated with other routinely administered vaccines including HAVRIX, varicella vaccine, and PCV13 in Study 160 in children aged 12-15 months and KINRIX and varicella vaccine in Study 158 in children aged 4 to 6 years. There was no evidence that Priorix™ interfered with the antibody responses to the antigens in the previously mentioned vaccines compared with immune the responses of M-M-R II® co-administered with these same vaccines.

ACIP recommends MMR vaccination of children as young as 6 months of age in an outbreak setting or prior to international travel. With that in mind, Dr. Abu-Elyazeed shared the results of 2 open-labeled, randomized, controlled Phase III studies conducted in Singapore and India.[13] These studies evaluated the immunogenicity and safety of 2 doses of Priorix™ co-administered with 1 or 2 doses of the GSK varicella vaccine, Varilrix® in healthy infants beginning at 9 months of age. The seroconvergence rate after 1 dose for measles was in the range of 88% to 94% for measles, 83% to 92% for mumps, and 100% for rubella. Nearly all children (> 99%) seroconverted for all antigens after completing the 2-dose vaccination schedule in both studies. The 2 studies concluded that Priorix™ was well-tolerated and immunogenic when administered to children as young as 9 months and 12-15 months of age.

[13] Goh P, Lim FS, Han HH, et al. Infection. 2007;35(5):326-333. http://dx.doi.org/10.1007/s15010-007-6337-z; and Lalwani S, Chatterjee S, Balasubramanian S, et al. BMJ Open. 2015;5(9):e007202. http://dx.doi.org/10.1136/bmjopen-2014-007202.

To summarize the GSK conclusions regarding the safety of Priorix™, the overall safety data collected during Priorix™ development have not identified a safety concern and are comparable to the safety profile of M-M-R II®. Priorix™ is generally well-tolerated in subjects 12-15 months of age, 4-6 years of age, and ≥7 years of age given as a first or a second dose. The safety provides of Priorix™ co-administered through the range of routine childhood vaccinations is comparable to that of the M-M-R II® co-administered with the same vaccine. The safety profile of Priorix™, including at the maximum release potency, is acceptable and comparable to the safety profile of M-M-R II®.

In addition, safety surveillance of Priorix™ outside of the US showed no significant safety concerns and confirmed an acceptable safety profile consistent with the US registration studies.

In summary of the GSK conclusions in regard to the immunogenicity of Priorix™, the clinical trial data demonstrated non-inferiority of the immune responses of Priorix™ compared to M-M-R II® in terms of seroresponse rate and GMCs in children 12-15 months of age after a single dose and in children 4-6 years and individuals ≥7 years of older when Priorix™ is given as a second dose of MMR vaccine. The data supports the dosing schedule recommended by ACIP for MMR vaccination. Priorix™ can be administered interchangeably to individuals who received a previous vaccination with M-M-R II® or ProQuad®. Priorix™ can be co-administered with routine US pediatric vaccines.

In conclusion, the GSK MMR vaccine program has met the development objectives to bring Priorix™ to the US market. From a public health perspective, the availability of a second MMR vaccine would be efficient.

Discussion Summary

Dr. Lee expressed gratitude to GSK for enrolling people at-risk in the clinical trials.

Dr. Daley requested additional information about the term “meningism including febrile seizure” that appeared on several slides in this presentation. In addition, he noted that there were several fibral seizures and wondered whether those were characteristic of what is typically observed following M-M-R II® at 7-10 after vaccination.

Dr. Abu-Elyazeed explained that this refers to meningeal irritation and could include headache, stiff neck, blurring of vision, and/or convulsion. None of the children were diagnosed with meningitis. Fibral seizures were reported as part of meninge irritation within 43 days following each vaccination and there were very few. Among children 12-15 months of age, 16 cases were identified out of 6,441 (0.25%) in the Priorix™ cohort and 7 cases out of 3,361 (0.2%) in the M-M-R II® cohort. Only 5 of the 16 cases (0.08%) were related in the Priorix™ cohort and 5 of the 7 cases (0.14%) were related in the M-M-R II® cohort.

Dr. Daley asked whether there are any estimates of the rate of vaccine-associated fibral seizures following Priorix™ from post-authorization studies elsewhere in the world, and related to that whether there are any estimates of the rate of thrombocytopenia following Priorix™ given post-authorization elsewhere in the world.

Dr. Abu-Elyazeed replied that while he did not have any febrile seizure information in hand, there were no cases of thrombocytopenia following Priorix™ and only 1 case out of 3,395 in the M-M-R II® cohort, representing 3/10,000.

Ms. McNally asked whether there was any difference in reactogenicity when Priorix™ is co-administered or used interchangeably, and how this vaccine might be examined in a younger age group for co-administration with COVID-19 vaccine.

Dr. Abu-Elyazeed indicated that this program started in 2008 and all clinical trials were completed in 2014 before COVID-19, but GSK would consider a study on the co-administration of Priorix™ with COVID-19 vaccine if ACIP wishes them to do so. In terms of reactogenicity when Priorix™ is co-administered or used interchangeably, there was no difference in AEs between the groups who received Priorix™ or M-M-R II® (Slide 8). For interchangeability, the safety profiles in subjects who received either Priorix™ or M-M-R II® following a previous dose showed no difference.

Dr. Kotton observed that there has been limited research over the years in transplant and other immunocompromised pediatric patients to show that it is safe for them, when on very low dose immunosuppression, to receive the current MMR vaccine. She asked whether GSK is studying this and if there is any way of knowing whether this would be similar with Priorix™.

Dr. Abu-Elyazeed responded that Priorix™ has a comparable safety profile to M-M-R II® and can be used in the same way. However, GSK does not have specific data on immunocompromised pediatric patients.

Regarding the Singapore study, Dr. Sanchez asked whether the mothers had received previous vaccination with MMR vaccine or if they had natural infection previously. For the post-Dose 1 and post-Dose 2 data, he inquired as to whether there were data for baseline MMR titers. The role of maternal antibody was somewhat confusing as presented in terms of the effects of these titers.

Dr. Abu-Elyazeed said he would have to review the data again for the studies in Singapore and India to determine whether data were collected from the mothers. The definition used for the "seropositive response rate" was the percentage of initially seronegative subjects with concentration above the seroresponse threshold for each antigen. The seroresponse threshold for measles was 200 mIU/mL, for mumps 10 enzyme-linked immunosorbent assay units (EU)/mL, and for rubella is 10 international units (IU). Those with positive MMR titers were excluded from the analysis.
Dr. Cineas asked whether there are any studies of the use of Priorix™ in adults who are not immune to 1 of the 3 components for adults in other countries.

Dr. Abu-Elyazeed noted that the indication GSK is seeking from FDA, which is under approval, is among individuals aged 12 months and older and for catch-up in older populations. Study 159 included individuals ≥7 years of age. About 36% of the subjects were aged 7-17 years 64 of the subjects were about 18 years of age and older.

Dr. Long recalled seeing the maximum potency in parentheses and asked whether she understood that the same dose was used in all of the studies, and Dr. Daley asked whether it was that potency varies lot-to-lot or that they tried a higher dose.

Dr. Abu-Elyazeed indicated that in terms of the maximum dose, licensure the US requires the minimum and maximum potency required to be immunogenic to be defined. The maximum dose must be safe. Only Study 162 assessed maximum potency and had safety as a primary objective. It is not that potency varies lot-to-lot. They tried higher doses to ascertain the maximum potency necessary to ensure that the dose is sufficient at the end of shelf-life. There

was a wide range from the minimum to maximum potency in this development program. The minimum is defined as end of shelf-life and the maximum is the least potency necessary to ensure that at the end of shelf-life, the potency of the antigen is sufficient. Through this development program, for measles the minimum potency was 3.4 log10 CCID50 and the maximum was 4.5 log10 CCID50. For mumps, the minimum was 4.2 log10 CCID50 and the maximum was 5.7 log10 CCID 50. For rubella, the minimum was 3.3 log10 CCID50 and the maximum was 4.4 log10 CCID50.

Dr. Long observed that only about 1,000 children received the maximum potency. Febrile seizures are not reported spontaneously following receipt of MMR vaccine because they do not occur within a week of vaccination. The recipient has to grow the virus and get the febrile illness that results in the febrile seizure, which occurs in the second week. Parents and doctors do not always associate this with vaccination. The incidence is about 1/1,800 and vaccine-associated febrile seizures are often not identified until studying this prospectively. The numbers Dr. Abu-Elyazeed reported of 1/500 and 1/300 were very high. It did not appear that there was a single study with just MMR vaccine. All were with concurrent administration with 2 or 3 other vaccines that could cause fever and seizures at completely different times. She would like to know the difference in the incidence of seizures depending on what was received concurrently. With only a couple of thousand children in the febrile seizure age range, combined with meningism and febrile seizures that are not the same kinds of events, it was surprising that febrile seizures associated with MMR were not expected to occur at nearly the same frequency with the second dose because the second dose is usually only picking up the 5% or 6% percent who were missed from the first dose. There is robust virus replication in 7% of the population, so it is important to understand what is the same and different.

Dr. Abu-Elyazeed referred to Slide 9, the second dose in children aged 12-15 months. Fever was 32.5% and grade three is 3.5% among Priorix™ recipients and 34.3% among M-M-R II® recipients, or basically no difference. Meningism, including febrile convulsions increased up to 43 days post-vaccination. He can present to ACIP the AEs related to meningism, fever, and fibral convulsion in each of the studies.

Dr. Long said she would like to see febrile convulsions in the second week following immunization and in the first 48 and 72 hours separately since a lot could be going on early on that would wash out any potential differences that might be occurring in the second week.

PUBLIC COMMENT

Overview

The floor was opened for public comment on February 23, 2022 at 2:25 PM ET. Given that many more individuals registered to make oral public comments than could be accommodated during this meeting, selection was made randomly via a lottery. Dr. Lee provided a gentle reminder that the ACIP appreciates diverse viewpoints that are respectful in nature and issue-focused rather than comments directed at individuals. The comments made during the meeting are included in this document. Members of the public also were invited to submit written public comments to ACIP through the Federal eRulemaking Portal under Docket No. CDC-2022-0022. Visit http://www.regulations.gov for access to the docket or to submit comments or read background documents and comments received.

Public Comment

Ms. Leah Russin
Co-Founder/Executive Director
Vaccinate California

Thank you for your time. I know COVID isn't on the agenda for today, but as the parents of a 21-month-old child in the vaccine trial, I want to take a moment and acknowledge the confusion and frustration that we parents are feeling. I have 2 main points, both related to messaging and both of which actually relate to your MMR discussion today. First, when explaining the vaccine approval process, "because that's how we've always done it" isn't good enough. Explain what was considered, why it was rejected, and what's next. Please think as creatively as a scared parent in considering options that need explanation. For example, back in December, Pfizer's first press release indicated that data was strong for 2 doses of 3 microliters for toddlers but not for ages 2 to 5. Why couldn't we have considered authorizing the 2-dose series for toddlers before preschoolers back in December allowing us to have protected at least some of our children through Omicron? "Because that's not the way we do things" isn't a good enough answer. Also, why couldn't Pfizer have trialed a 5 microliter 2-dose series in addition to adding a third dose of 3 microliters? Two vaccines is already asking a lot for families. Again, "because that's not how we do things" isn't good enough. Explain to us why. Don't leave us fumbling around in Facebook groups and WhatsApp chats with hundreds of other parents trying to figure out why what seems obvious to us isn't happening. Second, many physicians and other medical practitioners report that there're uncomfortable and lack confidence discussing vaccines with their patients. You are the experts. You have uniquely delved deep into the data and carefully assessed and weighed the risks of the diseases against the vaccine. I encourage you when you do recommend a vaccine for approval have staff take the time to prepare materials for public dissemination reflecting your collective comments explaining why you personally recommend the vaccine. Your comments during and after voting are often eloquent and compelling, but they're inaccessible to medical professionals that ultimately might benefit from your experience when discussing vaccines with their patients. In honor of Paul Farmer, please continue to push for equitable and easy access for healthcare for all. Thank you again for your time and your service to public health.

Ms. Sarah Barry
Independent Pro-Vaccine Advocate

Hello and thank you ACIP. My name is Sarah Berry and I'm an independent pro-vaccine advocate. Because these meetings are well-attended and listened in by anti-vaccine activists, I think it's very relevant to talk about attitudes towards vaccines in general and I'm going to read off a comment that an anti-vaccine activist made about me in regard to past public comments I have made to ACIP. "Sara is insane. Every chance she gets she goes on about how parents abuse their autistics by trying to help them in any ways possible. We should just accept them and their suffering as normal. It's absolutely disgusting." I mention this comment because it is clear evidence that anti-vaxxers are incapable of adequately defending themselves from my specific form of criticism. And I need not just ACIP, but every pro-vaccine person in the world, to know this. I have indeed given public comments to ACIP about the dangerous and yes abusive cures for autism that anti-vaxxers have created. Since the person who called me insane clearly did not listen to the facts that I have shared in previous public comments, I will go over some of them again because again, this is something the anti-vaxxers are scared of and that's important when we talk about vaccines. First, Kerri Rivera. She sold a book called "Healing the Symptoms Known as Autism." A careful review of her book shows it is a manual that teaches parents how

to force their children to drink bleach. Other methods in the book detail how to give bleach baths and even bleach enemas. Second Mark Geier. He lost his medical license for experimenting on autistic children by giving them dangerously high doses of a drug called Lupron. To get approval for his experiment, he created and oversaw an Institutional Review Board along with his son, his wife, and other associates. It's an obvious breach of basic medical ethics and if any vaccine manufacturer attempted such a thing, anti-vaxxers would rightly use it as an example of corruption. When it's one of their own, however, they look away. Lastly, Andrew Wakefield. Whenever anybody says his name, I want the next sentence to be about what happened to Jack Piper. If you don't know about Jack Piper, I will tell you. As per Wakefield's experimental protocol, Jack Piper was subjected to a colonoscopy that ended up piercing his bowel 12 times. He was 5 years old and had to stay in intensive care for 2 weeks. He also suffered multiple organ failures and even developed epilepsy. Even so, Andrew Wakefield is still a hero to the anti-vaccine community. Two of the biggest anti-vaccine voices are Robert F. Kennedy, Jr. and Del Bigtree. When it comes to people like Kerri Rivera and Mark Geier, I challenge Kennedy and Bigtree to think about how they have personally failed to call out the unethical and dangerous actions I have described today. If my comments calling out this failure are disgusting to anti-vaxxers, then so be it. I will not back down because I know that my method of talking about this situation is the way to solve the anti-vaccine misinformation crisis. Thank you again ACIP.

Dr. Grace Lee
ACIP Chair

Thank you for your comments. I just want to interject for a moment that we are very much interested in hearing public comments about the votes. I want to recognize that there are many challenges out there with communication and what not. Our preference is to use public comments to focus in on the issues at hand and, again, not to focus on individuals as opposed to the issues. Thank you very much.

Mrs. Barbara Loeppke
Loeppke Professional Services

Good afternoon, Chairwoman Lee and the Committee. My name is Barbara Loeppke. I'm a mother, grandmother, and advocate. Something good has occurred with the COVID vaccine and that is that more of the American public has started attending the FDA and CDC meetings online and taking an interest in what you do. This also means though that they're asking more questions. I've been asked to present a few of those today and perhaps you can address these now or in the future. One concern I've been told is that adverse events seem to be diluted by the listing of redness at the injection site and pain at the injection site as the most common complaint. This makes other more concerning adverse events get bumped down the list and not mentioned. This is something the public expects from the manufacturer, but the public believes the CDC is working for them and they'd like to know more about the adverse events than just the redness caused by the puncture of a needle. As the committee continues to give their COVID vaccine recommendations in the future, can you tell the public when Comirnaty will actually be used in the US? Some were under the impression that they're getting the actual licensed product when they're still getting the emergency authorized version. Is Comirnaty not used in the US yet due to the VIPP process? And if it isn't, when will it be? Have you detected a signal on new suicidal ideations from the COVID vaccine? A quick search of VAERS showed over 900 entries in the report and so far, I don't believe this has been mentioned in any of the meetings. Can you tell us how many reports of death from the COVID vaccines are currently being held back for review? Could you go through the process in one of the meetings of how a

vaccine comes before the committee? I think there's a lot of people that would like to know that answer. And finally, just as we can't give you legal advice about the meetings and shutting down a public comment, neither can anyone else who is not a licensed attorney in the US. With more of the public attending online each time, it would likely further diminish the image of the CDC, and currently in the last couple of days, that's been diminished with reports that there's been data held back. Thank you so much for your time. We appreciate the work you put in and we await your responses to a few of the questions the public has.

Marla Dalton, PE, CAE
Executive Director/Chief Executive Officer
National Foundation for Infectious Diseases

Good afternoon. I am Marla Dalton, Executive Director and CEO of the National Foundation for Infectious Diseases, or NFID. On behalf of NFID, as a longstanding partner CDC, we appreciate the valuable work of ACIP in guiding US immunization policy and protecting public health through the ongoing review and analysis of vaccine safety and efficacy data. Recommended vaccines help protect individuals of all ages from serious diseases including flu, pneumococcal disease, hepatitis B, and measles among others. And although annual flu vaccination is important for everyone age 6 months and older, adults aged 65 and older are at greater risk of flu-related complications, including hospitalization and death. Yet, despite the availability of safe and effective vaccines to help prevent disease, immunization rates remain suboptimal across populations for nearly all recommended vaccines in the US. This problem has only been exacerbated by the COVID-19 pandemic, with routine vaccinations declining significantly across all age groups. These declines are dangerous to public health. We can no longer delay life-saving vaccines and we must address the concerning decline in vaccination rates. Low immunization rates contribute to poor health outcomes and they carry a high price tag for society as a whole. The US spends an estimated $26.5 billion annually treating adults with flu, pneumococcal disease, shingles, and pertussis. NFID urges additional action to ensure that all populations are vaccinated as recommended. We must work together to help protect individuals and society as a whole. It is not enough to have safe and effective vaccines. We must ensure these vaccines are used as intended. Thank you all for the important work you do to protect public health and for your tireless and dedicated service.

Ms. Clarissa Garcia
Executive Portfolio Lead
Patient Education Programs
American Heart Association

I'm Clarissa Garcia, our Executive Portfolio Lead for Patient Education Programs. On behalf of the American Heart Association (AHA), I welcome this opportunity to publicly share comments with the ACIP. The COVID-19 pandemic has affirmed that chronic diseases and infectious diseases are inextricably linked. We offer these comments about recommendations to strengthen influenza vaccination guidance as essential for protecting health and preventing adverse outcomes equitably. In El Paso Texas, we observed lower than average influenza-related hospitalization rates, in part due to our CDC funded outreach efforts over the past 2 seasons. We believe decreased rates were a direct result of a mix of the following: Consumer and healthcare professional education and mobilization, community access, the distribution of high-dose influenza vaccine, and COVID-19 mitigating measures such as mask wearing and social distancing. The AHA supports operationalizing the Vaccine for Adults program that is a federally funded, nationwide, evidence-based adult vaccination program in the United States. The program focuses on vaccinating under-served racial and ethnic communities, Medicaid

beneficiaries, and adults aged 65 years or older. Specifically, the AHA supports the availability of the high- dose influenza vaccine for seniors during influenza season in hospitals, clinical care settings, community pharmacies, and other locations that get vaccines to people. The AHA endorses rapid ACIP reviews of all relevant science related to influenza vaccines—standard and high dose. Enhanced availability of high-dose and standard-dose influenza vaccines creates a unique opportunity to explore disparities in standard-dose influenza uptake against racial and ethnic groups in addition to analyzing the structural and systemic factors affecting access to high quality vaccination services. The AHA aligns its recommendations regarding influenza vaccine with ACIP recommendations and revises recommendations to align with updates from ACIP. The American Heart Association will do its part to improve equitable influenza vaccine access and uptake with an emphasis on educating both the consumer and healthcare professionals. Our message is to administer the most effective influenza vaccine based on age and underlying medical condition. We will be submitting more comprehensive written documents for consideration. I thank you for your time today.

Dorit Reiss, JD
Professor of Law
University of California
Hastings College of the Law

Thank you. My name is Dorit Reiss. I'm a Professor of Law at the University of Hastings College of the Law. Thank you again for the opportunity to comment. You've heard a lot about issues and messaging, so I want to start by saying that one of the good things about this committee is the high-level transparency where the data good or bad is presented in such transparent ways. To give just one example of the many wonderful presentations we've seen today, the careful examination of the studies and the comparative assessment of vaccines involve not just the clear discussion of the data, but also the limitations of it. And that's been true throughout. So, I know your committee and its staff work really hard to make data accessible and transparent, and I know you came up with some creative great ideas, for example your previous illustration of the benefits of influenza vaccine. And I wanted to thank you for your efforts with transparency. I appreciate them and I know a lot of people do. I also want to remind the committee that generally, the people who are subject to your recommendations are lay people and won't come in with a preference between vaccine or an opinion and depend on doctors to join you. I want to echo Ms. Russin's recommendation that some handout or some information summary of the wonderful comments made by the committee might be helpful to doctors in giving points to people in why they should get this vaccine. I know you have a lot to do. I know you've done a lot. I would consider whether there's a way for you to also put out summaries of the important points that the committee made in support of a recommended vaccine. I also want to echo Dr. Dalton's points about the importance of emphasizing routine vaccines. And I was glad that this meeting gave attention to them, because we know we have a problem. We know that COVID that has interrupted our life in so many ways and also interrupted immunization rates across the board. And it's time to put an emphasis on that. And finally, I want to encourage you to respond to public comment. As I said in the past, I think you can legally and legitimately move through these comments but understand where you'd you hesitate to do this. But if you want to preserve oral comments, I want to encourage the committee to post [unclear] advantage at least for routine meetings. I know that before you've made an effort to increase transparency by, for example, making sure people are notified about public commenting beforehand and putting the agenda up. I appreciate your efforts. I know it's been a rough 2 years. But putting the slides up in advance will help people make the public comments more meaningful. In this case, the MMR slides were still not up this morning, so I hope that improves. Thank you again for all your work.

THURSDAY: FEBRUARY 24, 2022

AGENCY UPDATES

Centers for Disease Control and Prevention

Dr. Posner presented an update on behalf of CDC. Beginning with staffing announcements, he reported that Dr. Rima Khabbaz would be retiring from CDC following 38 years of service. She has been the Director of the National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) for the last 5 years. Upon her retirement at the end of March 2022, Deputy Director, Dr. Christopher Braden, will take over as Acting Director for NCEZID. Dr. Althea Grant-Lenzy is currently serving as the Acting Deputy Director for Science within NCIRD. In this role, she leads special cross-cutting projects that connect and improve the Center's surveillance, epidemiology, laboratory, and data science programs and is very involved in the transition activities with the response.

In terms of COVID vaccine implementation updates, CDC provides daily updates on COVID-19 vaccine distribution and administration on the CDC COVID Data Tracker website.[14] As of February 22, 2022, more than 686 million doses have been delivered, more than 549 doses have been administered, and more than 214 million individuals have been fully vaccinated. Subsequent to the recommendation for the Pfizer BioNTech COVID-19 vaccine for children aged 5-11 years, more than 9.2 million individuals in that age group have received at least 1 dose of the COVID vaccine. Updated guidance has been posted for the extended intervals to the mRNA COVID-19 vaccine primary series. The interim Clinical Considerations are in the process of being updated and other CDC web pages and materials reflect this and should be updated shortly.

Moving to current efforts on maintaining childhood vaccination coverage, provider ordering of publicly purchased vaccine for FY22 has decreased 70% compared to FY19 orders in FY2020. Non-influenza vaccine orders decreased by 15% overall, with a significant drop in vaccines administered to children and adolescents. Influenza vaccine coverage as of January 8, 2002 for children aged 6 months to 17 years is approximately 50%, which is almost 3 percentage points lower than the previous season. CDC has developed information for parents and providers, such as the Well Child Visit and Recommended Vaccination Communications Campaign[15] that encourages parents to prioritize the need to catch-up their children on routine childhood vaccinations. CDC issued a number of Calls to Action in August 2020, October 2020, and March 2021 to address decreases in routine childhood immunization to numerous partners, immunization programs, and providers.

Seasonal influenza activity resumed in the 2021-2022 season. Influenza activity increased over the fall and through the week ending December 25, 2021, but then began to decline. In the last week or so, there was a slight increase in influenza activity. Influenza activity is difficult to predict, such that influenza may continue to circulate for a number of weeks. The majority of influenza virus this season is expected to be A(H3N2). Preliminary data suggest that VE against currently circulating A(H3N2) viruses may be reduced this season. However, vaccination still likely offers protection—including against serious influenza illness and death. Influenza

[14] https://covid.cdc.gov/covid-data-tracker/#datatracker-home
[15] https://www.cdc.gov/vaccines/parents/visit/vaccination-during-COVID-19.html

vaccination coverage is lower this season compared to last season, especially among certain higher risk groups such as pregnant people and children. Racial and ethnic disparities persist, with lower vaccination rates among non-Hispanic Black adults and Latino adults compared to non- Hispanic White adults. Getting an annual influenza vaccine is the best way for people to protect themselves, their loved ones, and their communities against influenza. CDC continues to recommend influenza vaccination as long as school activities continue. In terms of seasonal influenza vaccine distribution for the 2020-2022 season, vaccine manufacturers have projected that they will provide as many as 188 to 200 million doses of influenza vaccine for the US market. As of February 11th, approximately 175 million doses of influenza vaccine have been distributed.

Regarding measles and rubella elimination reverification, the Pan American Health Organization (PHAO) annual meeting of Measles, Rubella, and Congenital Rubella Syndrome Elimination Regional Monitoring and Verification Commission took place in November-December 2021. Noted declines in surveillance were reported in nearly every country in the region. The decline in measles and rubella in suspected cases in 2020 was reported as likely being due to decreased importations and social distancing, which may lead to a false sense of security in the region. The US was verified as sustaining elimination. All countries in the region (including Brazil, which lost status in 2019 and Venezuela, which was added to 2018) were certified as having maintained measles and rubella elimination. In response to measles among Afghan evacuees, the US Government (USG) implemented a rapid response to quickly interrupt measles virus transmission among Afghan evacuees in 2021 during Operation Allies Welcome (OAW) in which CDC provided immediate guidance for OAW-implementing partners to prevent measles transmission among evacuees on a domestic and international basis due to an ongoing outbreak and low vaccine coverage in Afghanistan, as well as close living quarters during the process of evacuating people into the US. After measles cases were confirmed, a CDC directive on September 14, 2021 called for mass vaccination for measles, mumps, rubella, and varicella that reached approximately 100% of coverage, followed by a 21-day quarantine period. Also called for was a pause in evacuation flights and administration of vaccine for polio and COVID-19. This effort limited measles cases to just 47 among the 70,000-plus Afghan evacuees without any deaths or community infection. According to preliminary data, a total 49 measles cases were reported in the 5 jurisdictions in 2014.

Dr. Lee thanked CDC for continuing to manage the unbelievable range of activities and responsibilities the agency has. It is important to remember how much CDC is doing to protect the health of the population in addition to addressing the pandemic. She highlighted and thanked CDC for continually updating the guidance on COVID-19 vaccines, particularly the updates on the interval issue. In addition, she expressed congratulations to Dr. Khabbaz and extended well wishes to her on behalf of the entire committee.

Centers for Medicare and Medicaid

Ms. Hance presented the CMS update from the Medicaid perspective. Building on Dr. Posner's comments, she emphasized that CMS also is committed to working to increase immunization rates for COVID-19 and influenza vaccines, and appreciates that CDC has made themselves available to speak to different groups within CMS. For example, CDC spoke during CMS's recent monthly call with state Medicaid Directors during which they highlighted changes pertaining to COVID-19 vaccinations. In January, CDC gave a presentation to the Children's Health Insurance Program (CHIP) State Plan Directors that highlighted COVID-19 vaccines and the important need to continue to promote catch-up of pediatric immunizations. CMS will

continue to look for opportunities to amplify those messages, and greatly appreciate CDC's support and willingness to speak regularly to the Medicaid and CHIP state staff.

On February 11, 2022, CMS issued an updated Medicaid COVID-19 Toolkit that addresses Medicaid policy for coverage and reimbursement of COVID-19 vaccines. That is available on the Medicaid.gov website. On December 2, 2021, CMS announced that state Medicaid agencies are now required to cover vaccine counseling visits when a vaccine is not administered for most children enrolled in Medicaid up to age 21 under the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) program. Because of this change, CMS will now consider certain COVID-19 vaccine counseling visits for children and youth to be COVID-19 vaccine administration. For those visits, state expenditures can be federally matched at 100% during the coverage period under the ARP.

Food and Drug Administration

Dr. Fink presented the FDA update, reporting that there were no new EUAs or vaccine approvals since ACIP last met. FDA continues its active and ongoing review of several submissions for EUAs for COVID-19 vaccines, as well as reviews of BLA and supplemental BLA (sBLA) applications for various COVID and non-COVID vaccines. FDA expects to be able to provide updates on regulatory actions related to some of these ongoing reviews the next time ACIP convenes. In the meantime, FDA also continues to be actively engaged with public health authorities and international regulatory authorities to work out considerations and policies to address emerging data related to the COVID-19 pandemic, as well as the needs for further development and authorization of COVID-19 vaccines to address the pandemic.

Health Resources and Services Administration

Dr. Rubin presented the update for HRSA from the Division of Injury Compensation Programs. The National Vaccine Injury Compensation Program (VICP) continues to process an increased number of claims. In FY21, petitioners filed 2057 claims with the VICP. Nearly $208.3 million was awarded to petitioners. Approximately $36.5 million was awarded for attorneys' fees and costs, which includes compensated and dismissed cases. In FY22, petitioners filed 327 claims with the VICP as of February 1, 2022. Nearly $82 million was awarded to petitioners, including attorneys' fees and costs. As of February 22, 2022, the VICP had a backlog of 1462 claims alleging vaccine injury that are awaiting review. As of February 1, 2022, the Countermeasures Injury Compensation Program (CICP) has received 6540 claims alleging injuries and deaths from COVID-19 countermeasures have been filed. This included 3700 claims alleging injuries from COVID-19 vaccines. More information about the CICP can be found on the HRSA website.

Indian Health Services

Dr. Clark presented the IHS update. Like other healthcare delivery systems, the IHS continues to confront the challenges of the current pandemic and its impact on both routine and SARS-CoV-2-specific immunization efforts. As it has done since September 2020, the IHS COVID-19 Vaccine Task Force coordinates the distribution and administration of COVID-19 vaccines agency-wide, including at federal direct care facilities, tribal health programs, and urban Indian organizations that have elected to receive vaccines through the IHS jurisdiction. In collaboration with federal, tribal, and urban Indian organization partners, the IHS Vaccine Task Force efforts support an efficient system of distribution, prioritization, communication, administration,

data management, and safety monitoring for approved and authorized COVID vaccines across 356 federal, tribal, and urban facilities. The IHS has prioritized equitable access to COVID vaccines throughout Indian country. As of February 21, 2022 within the IHS jurisdiction, over 2.7 million COVID-19 vaccines were distributed and over 2.1 million vaccines were administered by participating federal, tribal, and urban facilities. According to current CDC tracking data, among the estimated 2.1 million people served at IHS facilities, 41% are fully vaccinated and 28% of those fully vaccinated have received a booster dose. IHS will continue its efforts to maximize COVID vaccine coverage rates, especially among the most vulnerable members of the Tribal communities it serves.

Across its 3 surveillance systems to date, IHS COVID vaccine safety monitoring has demonstrated a reassuring safety profile consistent with other national vaccine safety surveillance systems. The IHS routinely collaborates with the CDC and engages with Tribal leaders in support of vaccine confidence among the American Indian/Alaskan Native (AI/AN) service population. Routine tracking of IHS pediatric immunization coverage indicates the decline in vaccine coverage for children and adolescents, which has been amplified by the COVID-19 pandemic. Beginning in Spring 2021, the IHS initiated a pediatric immunization initiative called "Safeguard our Future: Protect Tomorrow, Vaccinate Today."[16] Communication strategies have included blog posts, a parent toolkit, and educational webinars to highlight the topic and to share best practices. Meanwhile, information technology tools and training sessions have helped users to identify and reach out to patients missing recommended vaccines. In addition, IHS facilities have been invited to participate in a quality improvement project targeting changes in immunization workflow to support improved and sustained pediatric vaccination coverage. During the 2021-2022 influenza season, the IHS immunization program continues to organize educational webinars, disseminate ACIP influenza vaccine recommendations, coordinate supply chain logistics, and distribute facility resources in support of the Influenza Immunization Action Plan. The IHS immunization program is planning to leverage COVID-19 vaccination strategies for the efficient implementation in its service population of new and expanded adult pneumococcal, zoster, and HepB vaccine eligibility recommendations by the ACIP.

National Institutes of Health

Dr. Beigel from National Institute of Allergy and Infectious Disease (NIAID) presented the NIH update, reporting that the COVID-19 work over the last few months has been very interesting in terms of defining immune correlates of protection for COVID-19. NIAID researchers and collaborators found that levels of binding and neutralizing antibodies to the spike protein correlated with the degree of VE in the Phase III mRNA-1273 COVID-19 vaccine trial, which was published about a month ago. The results of the heterologous COVID-19 booster vaccine trial also were published. The antibody responses have been previously presented to ACIP and formed the basis of heterologous booster vaccines. The publication provides additional details, additional time points, and a description of T cell-mediated responses to the heterologous booster vaccines—a critical part of evaluating these vaccines. As part of that trial, neutralizing antibodies to the Omicron variant were assessed and it was found that most homologous and heterologous combinations increased humoral immunity to Omicron. Additional work has been done to improve COVID-19 vaccine immunogenicity in immunocompromised populations. A new trial has begun to assess the antibody response to additional doses of an mRNA vaccine in kidney and liver transplant recipients. This study is unique because it is

[16] https://www.ihs.gov/sites/newsroom/themes/responsive2017/display_objects/documents/SafeguardOurFutureVaccineToolkitforParentsandFamilies.pdf

testing whether an additional dose of mRNA alone or with concurrent reduction of immunosuppressive medication will improve antibody response. An NIH-funded study found that vaccinating women against SARS-CoV-2 in mid- to late-pregnancy could provide infants with some degree of protection against COVID-19 through 6 months of age. There continues to be work on pandemic preparedness, including a workshop on pandemic preparedness in November 2021. The *NIAID Pandemic Preparedness Plan*[17] was issued in December 2021 for future public health emergencies caused by infectious diseases. There also continues to be work toward universal coronavirus vaccines. Details of these and several additional updates were provided in a written summary.

Office of Infectious Disease and HIV/AIDS Policy

Dr. Kim presented the OIDP update on behalf of the National Vaccine Program Office (NVPO), OIDP, and the Office of the Assistant Secretary for Health (OASH). Along with contributors from a number of federal agencies, OIDP prepared a draft *Vaccine Schedule Implementation Plan* as a companion document to the *National Strategic Plan for the United States | 2021–2025*[18] released in 2021. The implementation plan outlines federal actions in support of national vaccination goals. Soon there will be a Federal Register Notice (FRN) for a 30-day public comment period, for which Dr. Kim invited feedback. Work is underway to strengthen the case with transitioning 3 developmental objectives and immunizations to core objectives in Healthy People 2030. These developmental objectives are to: 1) increase the proportion of women who get the Tdap vaccine during pregnancy; 2) increase the proportion of information systems that track immunizations across the lifespan; and 3) increase the proportion of adults aged ≥19 years who get recommended vaccines. OIDP particularly welcomes information exchange from its partners who work on composite adult vaccination data. With the new ACIP universal HepB vaccine recommendation for adults aged 19-59 years that is pending publication in the *MMWR*, OIDP is working with CDC and other partners that are interested in promoting HepB vaccination in routine preventive adult care and will be assisting with promotional activities. The National Vaccine Advisory Committee (NVAC) turned 35 this year. The February 11-12, 2022 NVAC meeting covered several timely topics on vaccines, including prohibiting discrimination in COVID-19 vaccination programs, COVID-19 VE, expanding Immunization Information Systems (IISs), and vaccine safety. The next NVAC meeting will be June 15-16, 2022.

PNEUMOCOCCAL VACCINES

Session Introduction

Dr. Katherine Poehling (ACIP WG Chair) introduced the pneumococcal vaccines session, beginning with a review of current pneumococcal recommendations in children. PCV13 is routinely recommended as a 4-dose series at 2, 4, 6, and 12-15 months—sometimes known as a 3+1 schedule. PCV13 catch-up options are for healthy children through 59 months of age and children with underlying conditions through 71 months. In terms of PCV13 and PPSV23 for children 24-71 months of age with underlying conditions, the recommendation is to complete the PCV13 series followed by PPSV23 ≥8 weeks after the last PCV13. Children who are immunocompromised or with sickle cell disease or asplenia can receive a second dose of PPSV23, which is recommended 5 years after the first dose of PPSV23. To put this into context, this table shows the underlying conditions in immunocompetent, functional or anatomic asplenia, and immunocompromised risk groups:

[17] https://www.niaid.nih.gov/sites/default/files/pandemic-preparedness-plan.pdf
[18] https://www.hhs.gov/sites/default/files/HHS-Vaccines-Report.pdf

3) Children aged 24–71 months with underlying medical conditions

Risk group	Underlying conditions	Complete PCV13 dose	PPSV23	
		Recommended	Recommended	Revaccination 5 years after 1st dose
Immunocompetent	Chronic heart disease	X	X	
	Chronic lung disease	X	X	
	Diabetes mellitus	X	X	
	Cerebrospinal fluid leaks	X	X	
	Cochlear implants	X	X	
Functional or anatomic asplenia	Sickle cell disease/other hemoglobinopathies	X	X	X
	Congenital or acquired asplenia	X	X	X
Immunocompromised	Congenital or acquired immunodeficiencies	X	X	X
	Chronic renal failure/nephrotic syndrome	X	X	X
	Hematologic malignancy	X	X	X
	Generalized malignancy	X	X	X
	Solid organ transplant	X	X	X

PCV13 and/or PPSV23 is recommended for children 6-18 years of age with underlying conditions. For these children, 1 dose of PPSV23 is recommended for children with chronic heart/lung disease, or diabetes. If never received, 1 dose of PCV13 is recommended followed by PPSV23 ≥8 weeks for children with immunocompromising conditions, cerebrospinal fluid (CSF) leak, or cochlear implants. For children with immunocompromising conditions, a second dose of PPSV23 is recommended ≥5 years after the first PPSV23 dose. The following table illustrates recommendations for children aged 6-18 years with underlying medical conditions:

4) Children aged 6–18 years with underlying medical conditions

Risk group	Underlying conditions	Complete PCV13 dose	PPSV23	
		Recommended	Recommended	Revaccination 5 years after 1st dose
Immunocompetent	Chronic heart disease		X	
	Chronic lung disease		X	
	Diabetes mellitus		X	
	Cerebrospinal fluid leaks	X	X	
	Cochlear implants	X	X	
Functional or anatomic asplenia	Sickle cell disease/other hemoglobinopathies	X	X	X
	Congenital or acquired asplenia	X	X	X
Immunocompromised	Congenital or acquired immunodeficiencies	X	X	X
	Chronic renal failure/nephrotic syndrome	X	X	X
	Hematologic malignancy	X	X	X
	Generalized malignancy	X	X	X
	Solid organ transplant	X	X	X

The reason the Pneumococcal Vaccine WG is working on this now is due to anticipated PCV15 licensure in the first quarter of 2022 and anticipated PCV20 licensure in the second quarter of 2023. Given this, the policy questions proposed by the WG are:

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

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

It is important to note that the WG is not currently considering any change in the recommended pneumococcal vaccine dosing or schedule. This session included presentations on the epidemiology of pneumococcal disease and pneumococcal vaccine coverage in US children; PCV15 Phase 3 study results in children; GRADE and EtR for PCV15 use in US children; and a summary of next steps.

Epidemiology of Pneumococcal Disease and Pneumococcal Vaccine Coverage in US Children

Mr. Ryan Gierke (CDC/NCIRD) began with a brief background on the spectrum of pneumococcal disease. Pneumococcus is transmitted through airborne droplets from person-to-person. It can be colonized or carried in the nasopharynx and then spread locally to the ears to cause otitis media or sinusitis. It also can be aspirated and cause pneumonia. Pneumococcus can also infect the blood and cause septicemia. These different infections can be characterized into noninvasive and invasive disease. Invasive pneumococcal disease (IPD) is a less frequent, less severe form of illness. Noninvasive disease is more frequent. In children, otitis media is one of the most common forms of pneumococcal disease.

Mr. Gierke then reviewed current pneumococcal vaccine coverage in children, recent IPD data assessing the impact of PCV13 on IPD burden and serotype distribution, IPD burden caused by serotypes covered in the new conjugate vaccines (PCV15 and PCV20), what is known to date regarding the impact of PCV13 on all-cause pneumococcal pneumonia among children, recent estimates of pneumococcal pneumonia incidence, the impact of PCV13 incidence estimates and serotype distribution among acute otitis media (AOM), and serotype distribution of pneumococcal carriage among children.

As a reminder of the current pneumococcal vaccines in use and the serotypes covered by each, PCV13 pneumococcal conjugate vaccine covers 13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) and is routinely recommended for all children aged less than 2 years. A dose is given at 2, 4, and 6 months of age with an additional dose at between 12-15 months of age. A catch-up option is recommended through age 4 in healthy children or age 5 among children with certain medical conditions. PCV13 also is recommended for children aged 6-18 years with certain medical conditions. Additionally, PPSV23 polysaccharide vaccine has 23 serotypes (the 13 from PCV13 plus 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F) and is recommended for children aged 2 years and older with certain medical conditions. Coverage of pneumococcal conjugate vaccine among children has remained consistent in recent years, with over 90% of children receiving 3 doses and over 80% receiving 4 doses by 24 months of age.

No declines were observed in birth years 2017-2018 compared to 2015-2016.[19] Although data for birth year 2018 are considered preliminary, CDC will continue to monitor this.

In terms of the impact of PCV13 on pediatric IPD incidence and serotype distribution, data on IPD are obtained from the Active Bacterial Core surveillance (ABCs). ABCs provides population-based surveillance at 10 sites across the US. Cases are defined as "pneumococcus isolated from a normally sterile site." Isolates are serotyped at reference laboratories using whole genome sequencing, Quellung, or PCR. For this analysis, serotypes were grouped by vaccine-type and serotype 6C was grouped with PCV13 types due to the cross-protection provided by the 6A antigen. Regarding IPD incidence rates in children and adult age groups, incidence is highest among older adults and also is high among children under 5 years of age. Incidence is low for children aged 5-17 years, with approximately 25% of cases in this age group having a medical condition that is an indication for PCV13.

Looking at the incidence rates of IPD among children under 5 years of age from 2007-2019,[20] rates of PCV13-type IPD in children declined sharply after the introduction of PCV13 in 2010. Comparing 2007-2008 rates to the 2018-2019 rates, there was an almost 90% reduction in PCV13-type IPD. This resulted in a 67% reduction in overall IPD over the same time period. However, declines and PCV13-type IPD rates plateaued after 2013 at around less than 2 cases per 100,000. This trend continued on through 2019. Rates of non-PCV13 serotypes remained relatively stable over this time period. No replacement disease has been observed by non-vaccine serotypes in children at this time. Examining IPD rates for individual serotypes and PCV13 plus 6C among children less than 5 years of age from 2011-2019, rates of IPD declined for many PCV13 serotypes after PCV13 introduction in children. However, reductions were not seen in serotypes 3 or 19F. Together, these 2 serotypes accounted for almost 80% of the remaining PCV13-type disease in 2018-2019. Serotype 9A has declined substantially, but still accounts for about 14% of remaining disease. For older children aged 5-18 years, serotypes 3 and 19F make up most of the remaining PCV13-type disease in this age group, accounting for around 65% of remaining disease. Rates of 19A still accounted for 21% of remaining disease in 2018-2019.

To review the current pediatric IPD burden among PCV15 and PCV20 serotypes, the serotypes covered by new conjugate vaccine PCV15 include those in PCV13 plus 22F and 33F. PCV20 includes the serotypes in PCV13 and PCV15 plus serotypes 8, 10A, 11A, 12F, and 15B. For analysis purposes, PCV15 non-PCV13 included serotypes 22F and 33F; PCV20 non-PCV15 included serotypes 8, 10A, 11A, 12F, and 15B; and PPSV23 non-PCV20 included serotypes 2, 9N, 17F, and 20. Looking at incidence of IPD among children less than 5 years of age grouped by conjugate vaccine-type from 2011-2019, PCV13-type IPD decreased after PCV13 introduction in children. In 2018-2019, incidence was about 1.5 cases per 100,000 population. PCV15 non-PCV13 serotypes and PCV20 non-PCV15 serotypes have remained relatively stable. In 2018-2019, incidence due to these serotypes was 1.2 and 1.6 cases per 100,000 respectively. For children aged 5-18 years, incidence of PCV13-type IPD also decreased since PCV13 introduction in younger children. However, there was more variability in the older ages that is likely due to the smaller rate of disease. In 2018-2019, PCV13-type IPD incidence was 0.5 per 100,000 population . PCV15 non-PCV13 serotypes and PCV20 non-PCV15 serotypes have remained relatively stable. In 2018-2019, incidence due to these serotypes was 0.2 and 0.3 per 100,000 population respectively. From 2018-2019, PCV13 serotypes still account for around 20% to 35% of IPD in children. PCV15 non-PCV13-type disease accounted for an

[19] https://www.cdc.gov/mmwr/volumes/70/wr/mm7041a1.htm
[20] Active Bacterial Core Surveillance (ABCs) Report Emerging Infections Program Network Streptococcus pneumoniae, 2019. Available: SPN_Surveillance_Report_2019.pdf (cdc.gov)

additional 16% to 17% of IPD. PCV20 non-PCV15 type disease accounted for 13% to 15% of IPD, while PPSV23 non-PCV20 accounted for 1 to 5% of IPD. Nonvaccine-types accounted for 32% to 46% of disease in children.

To review data on the impact of PCV13 on all-cause and pneumococcal pneumonia and estimated incidence of pneumonia in children, Mr. Gierke first reviewed the findings from recent studies examining the impact of PCV13 on pneumonia in children. An analysis of US insurance claims data comparing years 2008-2009 versus 2014 found a 17% to 35% reduction in rates of all-cause pneumonia among children depending on age group, with the largest reductions among children less than 2 years of age.[21] A study analyzing US healthcare claims data for 2007-2009 compared to 2011-2012 found a reduction of 17% to 21% in all-cause inpatient pneumonia depending on age group. However, no reductions were observed in older children aged 5-17 years. The same study assessed changes in pneumococcal pneumonia, finding 40% and 51% reductions among ages <1 and 5-17 years respectively. However, there were no significant reductions among children aged 2-4 years.[22]

Estimates of pneumonia among children can have a wide range for several reasons, including the data sources used, the time period examined, the definition of pneumonia used, and the age of the populations. A recent publication of 2014 US insurance claims data estimated the rate of all-cause pneumonia among children to be around 1300 to almost 4000 episodes per 100,000 person years, depending on the age group.[23] The lowest rates were among children aged 5-17. Based on recent national inpatient sample data,[24] estimates of inpatient pneumonia among children ranged from around 87 to 680 cases per 100,000 population based on age group, with the lowest rates among children 5-17 and higher rates among the younger ages. Studies examining pneumococcal pneumonia incidence among hospitalized children under 5 years of age using data from years 2011-2012 found a range of 6-18 cases per 100,000 population.

A recent study examining the impact of PCV13 on AOM in children that analyzed US insurance claims data from years 2008-2014 found a 14% reduction in AOM among children ≤1 year of age. Older age groups did not have significant reductions in AOM over the same time period.[25] Estimates of AOM-like pneumonia can have a wide range for several reasons (e.g., data sources used, time period, definition used, and age of population). A recent publication of 2014 US insurance claims data estimated the incidence of AOM among children <5 years of age to be approximately 30,000 to almost 50,000 episodes per 100,000 person years, depending on age group.[26] In a prospective cohort study of children at Rochester, New York, *Streptococcus pneumoniae* (*S. pneumoniae*) was isolated from 24% of children aged 6-36 months with clinically diagnosed AOM.[27] The same study from Rochester reported serotype distribution among children with pneumococcal AOM from 2015-2019. Based on specimens collected by either nasopharyngeal swab (NP) or middle ear fluid sample by tympanocentesis, serotype distribution among AOM cases were similar, with PCV15 non-PCV13 serotypes accounting for between 6% to 8% of AOM in this population.[28]

[21] Tong BMC 2018
[22] Simonsen Lancet 2014
[23] Simonsen et. al. lowest, Jain et. al. highest
[24] National Inpatient Sample, 2018-2019
[25] Tong et al, BMC 2018
[26] Adapted from Tong BCM 2018
[27] Kaur EJCMID 2022
[28] Adapted from Kaur BCM 2022

Comparing the serotype distribution of pneumococcal AOM cases found in the Rochester area to the serotype distribution among IPD cases in the New York State ABC surveillance area, which includes Rochester, a greater proportion of non-vaccine serotypes were observed to be causing AOM compared to IPD. PCV15 non-PCV13 serotypes contribute to around 6% to 8% of AOM compared to 18% of IPD in the New York ABC surveillance area.[29] The Rochester prospective study of children with AOM also examined NP carriage of pneumococcus among healthy children in 2015-2019. Children in the Rochester area aged 6-9 months were enrolled and followed through 36 months of age having NP swabs taken during routine well-child visits. Serotype distribution for pneumococcal carriage in the New York study and additional unpublished carriage data was available courtesy of a study conducted by the Georgia Emerging Infections Program (EIP).[30] The EIP study was among children aged 6-59 months presenting to a children's hospital emergency department (ED) in the Atlanta area for any reason. Consenting children had an NP swab taken at the time of visit. The serotype distribution of pneumococcal carriage in children was similar in these 2 distinct geographic areas. In both study populations, there was a greater proportion of non-vaccine serotypes compared to serotypes causing AOM and IPD. PCV15 non-PCV13 serotypes contributed to 3% to 4% pneumococcal carriage in children in these populations compared to around 6% to 8% of AOM and 16% to 17% of IPD.

In conclusion, overall IPD and PCV13-type IPD incidence has plateaued among children <5 years of age since 2013-2014. Incidence of IPD caused by PCV15 serotypes also has remained stable. In older children 5-18 years of age, overall IPD rates are small and even a few cases can impact trends. Among cases in this age group, 25% had a medical condition that was indicated for PCV13. After pediatric PCV13 introduction, all-cause and pneumococcal pneumonia showed modest declines among children and the impact varied by age group. Burden estimates of all-cause and pneumococcal pneumonia varied across studies. Serotype distribution among pneumococcal pneumonia is unknown in children. AOM after pediatric PCV13 introduction saw modest declines among children, with less impact among older children. The burden of AOM in children remains high, with pneumococcus contributing to a quarter of clinically-diagnosed disease. AOM and IPD data show that 2 additional serotypes included in PCV15 cause 8% to 17% of remaining pneumococcal disease in children <5 years of age.

Discussion Summary

Dr. Hahn (CSTE) noted that the definitions for "noninvasive" versus "invasive disease" were somewhat counterintuitive. COVID-19 and other respiratory diseases are usually defined by severity. Therefore, it would be worth a more in-depth discussion about why pneumonia would not be considered invasive disease.

Mr. Gierke explained that colonization of the nasopharynx generally precedes disease. That can lead to aspiration, which can cause pneumonia. Pneumonia can be invasive or noninvasive, because after causing pneumonia, it also can go on to cause septicemia. For the purpose of this analysis, invasive and noninvasive pneumonia were grouped together. However, there is a much higher proportion of noninvasive pneumonia than invasive.

Dr. Daley asked what serotypes were responsible for the largest proportion of AOM in the 85% not caused by identified serotypes in the Rochester study.

[29] Adapted from Kaur BCM 2022; IPD from ABCs 2015–2019
[30] Adapted from Kaur BCM 2022; Data curtesy of GA EIP, unpublished

Mr. Gierke indicated that based on that study, an uptick was noticed in 35B, 15B/C, and 23B after PCV13 introduction. For children <5 years of age, 15C is one of the top non-vaccine-types. If grouped together 15B and 15C would be the top serotypes. In addition, 23B is also seen in a lot of AOM cases, and 23B and 35B are both ranking as the highest non-vaccine types among children for both IPD and AOM.

PCV15 Phase 2/3 Study Results in Children

Dr. Natalie Banniettis (Merck Research Laboratories, Merck & Co.) presented a high-level clinical overview of pneumococcal polysaccharide 15-valent conjugate vaccine (V114, VAXNEUVANCE) that included an overview of the rationale for development of V114, the Phase 3 pediatric clinical development program, immunogenicity results, safety results, supportive studies, and brief conclusions from the supportive studies and the integrated analysis of preterm infants. Since the advent of PCVs, the incidence of IPD among children has decreased considerably, mainly due to reductions in vaccine-type disease.[31] However, serotype 3, which is included in PCV13, persists and is one of the top serotypes causing IPD in US children <5 years of age in the post-PCV era.[32] One can also appreciate the relative increase of non-vaccine types, such as 22F and 33F included among the leading serotypes causing IPD. As such, new PCVs targeting additional serotypes have the potential to further reduce IPD burden among children.

V114 was developed to expand vaccine coverage to 2 serotypes not targeted by currently licensed pediatric PCVs, 22F and 33F, while maintaining or improving upon immune responses to current vaccine serotypes shared with PCV13 to help sustain the progress achieved to date and ensure the safety profiles comparable to licensed PCVs. In 2019, Breakthrough Therapy Designation was granted by the US FDA for the V114 pediatric indication, with priority review by both US FDA and Health Canada underscoring the public health value of V114. Importantly, the availability of V114 would introduce a second supplier to the US market, which will increase the availability of PCVs for the US population and globally. Of note, V114 was licensed in adults in July 2021. The anticipated date for the pediatric submission is April 1, 2022.

The V114 pediatric clinical program was designed to target pediatric populations in which PCV vaccination is indicated and to generate a robust safety and immunogenicity profile for V114 in children through 17 years of age. The Phase 3 program includes 9 Phase-3 studies comprised of approximately 8500 participants of whom about 5300 received V114. These 9 Phase-3 studies include 3 pivotal studies in infants evaluating 3+1 dosing in protocol V114-029 and 2+1 dosing in protocols V114-025 and V114-026, the latter of which is still ongoing. There are 3 supportive studies evaluating PCV in infants and catch-up vaccinations through 17 years of age, as well as a large safety study in infants. There are 3 studies in special populations at increased risk for IPV, including children with sickle cell disease, children who live with HIV, and hematopoietic stem cell transplant (HSCT) recipients—a study that is ongoing. Another ongoing study in the program is protocol V114-032, the AOM efficacy study.

Safety and tolerability evaluation in the program was based on solicited, non-solicited, and SAEs. Immunogenicity was evaluated using validated pneumococcal electrochemiluminescence (ECL) and multiplex opsonophagocytic activity (OPA) assays. The ECL was bridged to the WHO reference enzyme-linked immunosorbent assay (ELISA). Evaluation was based on

[31] US CDC ABC Surveillance Network, 1998-2017
[32] Epidemiology of IPD following 18 years of PCV use in the US; Pilishvili et al, CDC

serotype-specific antibody responses including IgG response rate ≥0.35 µg/mL, IgG GMC, and serotype-specific OPA GMTs. In infants, immunogenicity was measured 30 days post-primary series immediately prior to the toddler dose and 30 days following the toddler dose. In children aged 2 years and up, immunogenicity was assessed immediately before and 30 days following vaccination with a single dose of PCV. Of note, the higher burden of disease in infants under 1 year of age in comparison to older children underscores the need for strong vaccine-induced immune responses in this age group. As such, the demonstration of non-inferior immune responses to the standard of care licensed vaccine after the infant series at post-does 3 is a regulatory requirement for the pediatric indication when licensing new PCVs in the US.

Transitioning now to the features of Phase 3 Pivotal Study Protocol V114-029. Protocol 029 was designed to evaluate the safety and immunogenicity of V114 PCV schedule administered at 2, 4, 6, and 12-15 months of age (3+1 dosing regimen) among 1720 healthy infant participants who were randomly assigned in a 1:1 ratio to receive V114 or PCV13. The study also evaluated the co-administration with licensed pediatric vaccines. Vaccination report cards were reviewed at study visits and via telephone contacts at Day 15 after each vaccination, and at 6 months after the last PCV dose. The primary safety objective was the evaluation of safety and tolerability of V114 with respect to AEs. The primary immunogenicity objectives were the non-inferiority evaluation of IgG response rates and GMC ratios. The secondary immunogenicity objectives included a descriptive evaluation of OPA GMT and non-inferiority evaluation of antigen-specific response rates to the co-administered vaccines. Additionally, a superiority evaluation was conducted for responses to the unique serotypes 22F and 33F and the shared serotype 3.

In regard to the primary objective of IgG response rates after the third dose, a conclusion of non-inferiority of V114 to PCV13 was based on the difference in the proportion of responders between the arms being less than 10 percentage points. V114 met non-inferiority for all 13 shared serotypes. As per regulatory requirements, responses for the unique serotypes in the V114 group were compared with the lowest observed response rate in the PCV13 group, excluding serotype 3. Serotype 23F was 92%, so V114 met non-inferiority for the 2 unique serotypes. In regard to the primary objective of IgG GMC post-dose 3, a conclusion of non-inferiority of V114 to PCV13 was based on the lower bound of the 95% confidence interval for the GMC ratio being greater than 0.5. V114 met non-inferiority for 12 out of the 13 shared serotypes, narrowly missing the pre-defined criterion for serotype 6A with a 95% confidence interval lower bounds of 0.48. For the unique serotypes, for regulatory requirements IgG GMCs for the V114 groups were compared with the lowest observed IgG GMC in the PCV13 group excluding serotype 3, which in this case was serotype 4 at 1.4 µg/mL, so V114 met non-inferiority in this case as well. In terms of the toddler dose, V114 met non-inferiority criteria for all 13 shared serotypes based on IgG GMC at post-dose 4 with all lower bounds greater than 0.5. Similarly for the unique serotypes, V114 met non-inferiority based on IgG GMC at post-dose 4.

Transitioning from the primary non-inferiority objectives to the secondary superiority objectives starting with the post-dose 3 response rates for the unique serotypes, a conclusion of superiority of V114 to PCV13 was based on the difference in the proportion of responders between the arms being greater than 10 percentage points. Comparing responses of V114 directly to responses of PCV13, V114 met superiority criteria for both unique serotypes. For IgG GMC for the unique serotypes, a conclusion of superiority was based on the lower bound of the GMC ratio being >2 or at least double. V114 met superiority criteria at both post-dose 3 and post-dose 4. Regarding the shared serotype 3 and response rates at post-dose 3, the superiority criterion

was based on the difference in response rates being greater than zero. With a lower bound of 12.1, V114 met the superiority criterion for serotype 3. When looking at serotype 3's IgG GMCs for post-dose 3 and post-dose 4 time points, superiority was based on the lower bound of the ratio being greater than 1.2. V114 met superiority here as well.

In terms of co-administered vaccines, all lower bounds met non-inferiority criteria. Additionally, for the IgG GMC to pertussis, V114 met non-inferiority with lower bounds of the ratios being greater than 0.67 for each evaluated pertussis antigen. When considering each of the 15 serotypes in V114 and all the concomitant antigens assessed, V114 met 73 out of 74 individual immunogenicity hypotheses in Protocol 029. Furthermore, a descriptive evaluation of functional activity at post-dose 3 and post-dose 4 demonstrated generally comparable OPA GMTs for the shared serotypes and higher GMTs for the unique serotypes in V114 recipients as compared with PCV13.

The pediatric V114 program was designed to generate a robust safety database to characterize the safety profile of V114 in the pediatric population. This presentation focused on the 7 studies included in the initial US filing with one Phase-2 and 6 Phase-3 studies. These 7 studies encompass approximately 7200 children aged 6 weeks to 17 years, of whom approximately 4800 received V114. About 6100 were infants enrolled at 6-12 weeks of age, of whom about 4300 receive V114. Older children through 17 years of age receiving a single dose of PCV were enrolled in 3 studies.

Regarding the integrated Phase 3 safety results pooled across Protocol 31, the safety study, Protocol 029, 2 pivotal studies, and Protocol 027, the interchangeability study, the baseline characteristics and demographics of participants included in the integrated safety analysis are comparable between the groups. Notably, the population was diverse with regard to race and ethnicity. In terms of the integrated safety summary with about 3000 in the V114 group and nearly 1500 in the PCV13 group, V114's safety profile was generally comparable to that of PCV13. The proportion of participants with AEs (e.g., injection sites, systemic and vaccine-related AEs, and SAEs) were generally comparable between the groups. Solicited events accounted for the majority of all AEs and vaccine-related AEs in both groups. In both groups, the majority of AEs were mild or moderate in intensity with a duration of 3 days or less. There were no discontinuations due to vaccine-related AEs in the integrated analysis. Vaccine-related SAEs of pyrexia were reported for 2 participants in the V114 group. The events were considered mild and moderate in intensity, and both resolved in 3 days. A total of 4 deaths were reported, 2 in each group and none of which were deemed to be vaccine-related by the investigators. The distribution of maximum body temperatures for the integrated analysis also was generally comparable between intervention groups, with the majority being afebrile 7 days post-vaccination. Of those with temperatures greater ≥104.4^{0}F, the majority were less than 101.3^{0}F in both groups.

To briefly summarize the key conclusions for the supportive studies that were evaluated descriptively, Protocol 027 is a study of interchangeability, otherwise known as switch or mixed dosing, when the series is initiated with PCV13. Protocol 024 is a study of catch-up vaccination through 17 years of age, with age-appropriate regimens of 3, 2, or a single dose of PCV. Protocol 023 is a study in children with sickle cell disease aged 5-17 years receiving a single dose of PCV. Protocol 030 is a study in children living with HIV aged 6-17 years receiving a single dose of PCV followed sequentially by PPSV23. Infants born prior to 37 weeks gestational age were integrated for descriptive analysis. The integrated preterm population presented are comprised of approximately 290 preterm infants. The youngest gestational age enrolled

in the V114 group was 27 weeks and the distribution of gestational ages between groups was comparable, with a median gestational age of approximately 36 weeks.

The overall safety conclusions from the supportive studies and the integrated preterm infant analysis were that V114 is well-tolerated and safe in these populations. The overall immunogenicity conclusions were that V114 is immunogenic to all 15 serotypes, both quantitatively and qualitatively, with comparable responses for the shared serotypes and higher responses for the 2 unique serotypes as compared with PCV13. The key conclusions of the V114 pediatric clinical program are that in children with an unmet medical need in pneumococcal disease prevention, V114 is well-tolerated, with a safety profile that is consistent with licensed PCV. V114 induces robust immune responses to the 13 serotypes shared with PCV13 without significant loss of immunogenicity. V114 is superior to PCV13 for the shared serotype 3 and the unique serotypes 22F and 33F, which are of high public health importance. Therefore, V114 has the potential to significantly address the burden of remaining pneumococcal disease due to vaccine-types and leading non-vaccine-types in children.

Discussion Summary

Dr. Haupt, Head of Vaccines and Infectious Diseases and Medical Affairs for Merck, thanked the ACIP Pneumococcal Vaccines WG for all of the efforts that were undertaken to ensure a comprehensive review of all the evidence supporting the recommendation for PCV15 in children. Additionally, Merck recognizes that there have been major efforts by the ACIP and CDC to consider the PCV15 pediatric conditions so quickly following all of the work that was just done and is still ongoing for the adult pneumococcal vaccine recommendations. That all has been done in the context of the additional work related to the COVID-19 pandemic. Based on timeline presented during this session and assuming licensure, a vote for the PCV15 vaccine in children could occur during the June 2022 ACIP meeting. As noted, Merck submitted the data file to the FDA in the third quarter of 2021. The FDA granted Merck a priority review and established a date of April 1, 2022. Therefore, Merck expects licensure by April 2022. That is important as the critical criterion for priority review is that a medicine or vaccine addresses an unmet medical need. Including serotypes 22 and 33F in the PCV15 vaccine that are not included in PCV13 offers opportunity to address diseases caused by these serotypes and with a superior immunological response in serotype 3, may provide some protection against serotype 3 as well. Merck will continue to support the WG as they review all the data that are needed to inform the vote that is upcoming.

Referring to Slide 20, Dr. Poehling requested additional information about the interpretation of the differences between the post-dose 3 and post-dose 4 responses.

Dr. Banniettis responded that the interpretation was that there was no significant difference after the third dose with *Haemophilus influenzae* (Hib), but V114 met non-inferiority for Hib-PRP at post-dose 4. Thus, the responses were comparable between the 2 arms. The plot shows the ratio between V114 and PCV13.

Dr. Fink further explained from a regulatory approach to this non-inferiority testing. There are statistical criteria for non-inferiority testing and then each statistical criterion is associated with a clinical understanding or assessment. In a non-inferiority analysis, what FDA would consider to be a clinically meaningful non-inferiority finding could, in a separate statistical analysis, be a statistically significant difference that FDA does not find to be clinically meaningful. FDA considers meeting the non-prespecified non-inferiority criterion to be clinically meaningful and would not consider what might be said to be a statistically significant difference. With the caveat

of multiplicity control, FDA would not consider the apparent statistically significant difference to be clinically meaningful from a regulatory perspective.

Regarding Slide 25, Dr. Poehling requested additional clarification about the 2 pyrexia SAEs and the 4 deaths that were not considered to be vaccine-related.

Dr. Banniettis clarified that the 2 pyrexia events for the first the onset occurred the same day as Dose 1. Maximum body temperature was reported as 100.4^{0}F and concomitant vaccines included rotavirus vaccines, Hib, and combination vaccines with DTaP, IPV, and HepB. The second serious events of fever in the V114 group had onset on the same day as Dose 3. Maximum body temperature was reported as 102.9^{0}F. Concomitant vaccines were OPV and a combination vaccine with DTaP, Hib, and HebB. Among the 4 deaths that were deemed unrelated, 2 deaths occurred in the V114 group, 1 occurred on Day 2 relative to Dose 3 due to congenital heart disease, and 1 death occurred on day 110 relative to Dose 4 due to cranial cerebral injury after a car accident. Of the 2 deaths in the PCV13 group, the first was on Day 25 relative to Dose 1 from cardio-respiratory arrest due to sudden unexplained infant death, and the second death occurred on day 185 relative to Dose 2 from complications of head injury and septic shock.

Dr. Daley asked what caused the fevers to be designated as vaccine-related SAEs and whether a fever of 105^{0}F was reported among vaccine recipients and V114.

Dr. Banniettis indicated that the SAE designation was based on specific criteria, one of which is hospitalization. The 2 pyrexia events were admitted to the hospital and therefore they constituted SAEs. Regarding the temperatures, the proportion of participants reporting a maximum body temperature greater than 104^{0}F were low in both groups. Temperatures greater than or equal to 105.8^{0}F were reported in 0.2% in each intervention group.

Dr. Lee commented that fever distribution for Doses 1, 2, and 3 looked fairly comparable. However, the height of the fever for Dose 4 seemed somewhat different in the V114 group compared to PCV13. That time period tends to be the height of background rates for febrile seizures, which has been observed before with concomitant PCV13 and influenza vaccines. With that in mind, she wondered whether those with a temperature greater than 104^{0}F seemed qualitatively different, whether there have been any associated febrile seizures, and whether any of these children received concomitant influenza vaccine.

Dr. Banniettis responded that apart from post-Dose 4 fevers greater than 105.8^{0}F, the temperature distribution was relatively comparable between the groups. It is important to remember what the concomitant vaccinations that are given with Dose 4 included MMR and varicella vaccines. In regard to the difference between the arms, it just a difference of 0.2% and there is not anything specific to explain that in this particular situation. It also is important to point out that the sample size for V114 was approximately 2800 and the sample size for PCV13 was around 1300, which may explain the discrepancy. The rate of febrile convulsions in the pediatric program was 0.3% in the V114 arm and 0.2% in the PCV13 arm. These particular events were not associated with febrile seizures. Influenza vaccine was not administered concomitantly during the pediatric program.

GRADE and EtR for PCV15 Use in US Children

Ms. Jennifer Farrar (CDC/NCIRD) presented the WG's interpretation on the use of 15-valent pneumococcal conjugate vaccine in children using the EtR Framework. After discussion with the Pneumococcal Vaccine WG, 2 PICO questions were decided for PCV recommendations:

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

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

Both policy questions compare PCV15 to the current vaccine recommendations and review the outcomes of vaccine-type IPD ,vaccine-type pneumonia, vaccine-type AOM, deaths due to vaccine-type pneumococcal disease, and SAEs following immunization. As a reminder, the EtR Framework consists of 7 domains: Public Health Problem, Benefits and Harms, Values, Acceptability, Feasibility, Resource Use, and Equity. This presentation focused on the domains Public Health Problem, Benefits and Harms, Values, and Equity. Available evidence is usually assessed for each policy question. However, given the overlap in available evidence for the 2 questions being considered, the WG reviewed the 2 questions in parallel for each EtR domain.

Regarding whether pneumococcal disease is of public health importance in children, AOM is one of the most common reasons for outpatient care in children[33],[34] and *S. pneumoniae* is one of the most common bacterial causes of AOM. However, administrative data have shown AOM and pneumonia rates in children have decreased over time. IPD rates decreased after PCV introduction in children, but young children are at increased risk of pneumococcal disease. Among children less than 5 years of age, overall PCV13-type IPD incidence has plateaued since 2013-2014. The incidence of IPD caused by the unique PCV15 serotypes also has remained stable during this time. The 2 additional PCV serotypes caused 17% of IPD in 2018-2019. Overall IPD rates in children aged ≥5 years have remained small and 25% of IPD in children aged 6-18 years was in children with immunocompromising conditions. The WG determined that pneumococcal disease is of public health importance in children.
For the benefits and harms domain, the WG reviewed each policy question and covered several questions:

- How substantial are the desirable anticipated effects for vaccine-type IPD, vaccine-type nonbacteremic pneumococcal pneumonia, vaccine-type acute otitis media, and deaths from vaccine-type disease.
- How substantial is the undesirable anticipated effect for SAEs?
- Do the desirable effects outweigh the undesirable effects?
- What is the overall certainty of this evidence for the critical outcomes in terms of effectiveness and safety of the intervention?

The search strategy included reviewing evidence for PCV15 from clinicaltrials.gov, PubMed, and additional resources provided by vaccine manufacturers and subject matter experts (SMEs). An initial 71 studies were identified. After deduplication and exclusion, 7 were included

[33]Tong BMC Health Services Research 2018
[34] Lewnard CID 2021

for GRADE. No PCV15 studies directly assessed VE against the critical outcomes. There were 5 RCTs identified that evaluated PCV15 efficacy and/or safety in healthy children. All 5 studies were compared to those who received PCV13. The study by Platt in 2020 (V114-008) was a Phase 2 RCT that compared 2 different lots of PCV15 with PCV13 using a 3+1 schedule. Study V114-029 by Merck was a Phase 3 RCT in the pivotal study for PCV15, which was presented in-depth earlier in this session. As a reminder, this study evaluated PCV15 compared to PCV13 using a 3+1 schedule, as well as concomitant vaccine administration with other routine immunizations. Study V114-027 by Merck evaluated product interchangeability with using PCV13 and PCV15. Study V114-024 by Merck evaluated catch-up schedules at different ages using PCV15. The fifth study, V114-031 by Merck was an RCT focused on safety and tolerability in healthy infants that was stratified between full-term and pre-term infants. Infants were given either PCV15 or PCV13 at 2, 4, 6, and 12-15 months of age.

Regarding routine use in healthy children, PCV15 was non-inferior to PCV13 for all 13 shared serotypes post-dose 4. Post-dose 3 PCV15 was non-inferior to PCV13 for 12 of 13 shared serotypes, with serotype 6A missing the non-inferiority criteria. PCV15 had statistically significant higher immune responses for serotypes 3 and 22F and 33F—the 2 serotypes unique to PCV15. Immune responses for PCV15 were higher compared to PCV13 for serotype 3 and the unique PCV15 serotypes. The certainty assessment was not serious for all criteria except indirectness, which was downgraded to serious due to the absence of data on correlates of protection for some of the critical outcomes considered. The overall certainty of evidence was therefore 2 or Moderate.

The WG determined that the desirable anticipated effects of routine PCV15 use are moderate. Considerations discussed by the WG include that no PCV15 studies directly assessed clinical outcomes. Additionally, there are knowns such as the clinical implications of improved immunogenicity against serotype 3. However, PCV15 provides additional coverage for 2 additional serotypes compared with PCV13 if the improved immune response against these 2 serotypes translates to clinical effectiveness. There were 5 RCTs that evaluated safety regarding PCV15 use in healthy children compared with PCV13 use. There were 5 SAEs reported following immunization in the intervention group across all 5 studies. A pooled estimate observed a higher risk for SAEs among the PCV15 group compared to the PCV13 group. However, this was not significant. Regarding the certainty assessment, all criteria were deemed not serious except precision, which was downgraded to serious due to few events of the outcome being reported. The overall certainty of evidence was 2 or Moderate. Therefore, the undesirable anticipated effects of routinely using PCV15 were determined to be minimal.

Balancing the desirable and undesirable effects, the WG determined that routine use of PCV15 was favorable compared with the current recommendation. It should be noted that the vote was split between “favors intervention” and “favors both.” Some WG members thought the option “favors intervention” gave the impression that the WG was proposing a preferential recommendation when the intention was to assess whether PCV15 could be used as an option in addition to PCV13. Based on the certainty assessment during GRADE, routine use of PCV15 was 2, moderate, for both effectiveness and safety of the intervention.

The WG identified 2 RCTs evaluating PCV15 use in children with underlying medical conditions compared with PCV13 use. The first study, V114-023, evaluated 1 dose of PCV15 in children with sickle cell disease. The second study, V114-030, evaluated PCV15 in series with PPSV23 in children living with HIV. Regarding PCV15 use in children with underlying medical conditions, post-PCV dose, PCV15 had higher immune responses versus PCV13 for 6 to 7 PCV13 shared serotypes and unique serotypes 22F and 33F across both studies. In one study that assessed

PCV use in series with PPSV23, post-PPSV23 dose, PCV15 plus PPSV23 had numerically higher immune responses versus PCV13 plus PPSV23 for 3 of 13 shared PCV13 serotypes, but not for unique serotypes 22F and 33F. When assessed for certainty of evidence, 2 of the criteria were downgraded. Indirectness was downgraded to serious due to the absence of data on correlates of protection for some critical outcomes considered, and imprecision was downgraded due to small sample size. Therefore, the overall certainty of evidence was 3, or Low. The WG determined that the desirable anticipated effects of PCV15 use in children with underlying medical conditions is moderate.

WG discussions regarding this question were similar for both routine use in children less than 2 years of age and use among children with underlying medical conditions. As a reminder, no PCV15 studies directly assessed clinical outcomes. The WG was split between "moderate" and "large," with some uncertainty around the added benefit from PCV15 use, not just from additional serotypes, but also improved immune response against serotype 3. Additionally, there are unknowns such as the clinical implications of improved immunogenicity against serotype 3. However, as mentioned previously, PCV15 provides additional coverage for 2 additional serotypes compared with PCV13 if the improved immune response against these 2 serotypes translates to clinical effectiveness. In PCV15 use among children with underlying medical conditions, no SAEs following immunization were reported in either study. Regarding the certainty assessment, all criteria were deemed not serious except imprecision, which was downgraded twice to very serious, once due to no events of the outcome being recorded and again for very small sample sizes. Therefore, the overall certainty of evidence was 3, or Low.

The undesirable anticipated effects of using PCV15 in children with underlying medical conditions was determined to be "minimal." Balancing the desirable and undesirable effects, the WG determined that using PCV15 in children with underlying medical conditions was favorable compared with the current recommendation. As was discussed for routine use, it should be noted that the vote was split between "favors intervention" and "favors both." Some WG members thought the option "favors intervention" gave the impression that the WG was proposing a preferential recommendation when the intention was to assess whether PCV15 can be used as an additional option to PCV13. Based on the certainty assessment during GRADE, routine use of PCV15 in children with underlying medical conditions was 3, or Low, for effectiveness and 3, or Low, for safety of the intervention.

In terms of the domain of values and preferences, the WG considered the following questions:

- ❑ Does the target population feel that the desirable effects are large relative to undesirable effects?
- ❑ Is there important uncertainty about or variability in how much people value the main outcomes?

Data on values and preferences of PCV5 use in children were not identified. However, the WG looked at vaccination coverage for 3 or more doses of PCV by 24 months of age and found high vaccination coverage of 92.4%, demonstrating that the target population probably feels that the desirable effects of PCV vaccination outweigh the undesirable effects. The WG interpretation was split evenly between "probably yes" and "yes." For PCV15 use, the WG agreed that the target population probably feels that the desirable effects from vaccination are large relative to undesirable effects. The WG split in responses likely was due to the small potential added impact of PCV15 use over PCV13 use and not over the uncertainty about whether the vaccine is able to prevent serious pneumococcal disease. For the second question, the WG determined

that there is “probably not important uncertainty or variability” in how people value the main outcomes.

For the last domain of equity, the WG considered what the impact would be on health equity. To answer this question, the WG looked at unadjusted IPD rates using ABCs data from 2008-2019 in 2-year increments for children less than 5 years of age, those 5-18 years of age, and for different serotype groupings. For all serotypes, rates decreased during and after 2010 in both age groups and were sustained over time except in Black children 5-18 years of age. However, it is important to note the small IPD rates in children aged 5-18 years. Rate ratios comparing Black and White children decreased from the start to the end of the study period in children less than 5 years of age but not in children 5-18 years of age, although both sets of rates went down. Decreases in overall rates were driven by decreases in PCV13 serotypes. Overall decreases in PCV13-type IPD in all groups were observed from the start to the end of the study period. Rate ratios in children less than 5 years of age decreased over the study period, but in children 5-18, ratios did not, although rates went down in both groups. Non-PCV13 rates remained fairly stable over time in White children but decreased from 14 per 100,000 to 8 per 100,000 in Black children less than 5 years of age, causing the rate ratio to decrease. Rates went up in Black children 5-18 years of age, although the rates were much smaller compared to younger children. There were not big differences by race in the PCV15 non-PCV13 serotypes at any point over the study period.

In conclusion, racial differences in PCV15 non-PCV13-types were quite small. PCV13 resulted in large reductions in IPD in both age groups across races. Regarding equity in Native American and Alaska Native children, IPD rates among Native American children less than 5 years of age decreased after PCV13 use, but rates remained approximately 4-fold higher than in children of all races.[35] Data on Alaska Native children showed that Alaska Native infants had a 1.6-fold higher rate of otitis media-associated outpatient visits compared to all infants[36] and Native American and Alaska Natives experienced cyclical outbreaks due to serotype 12F,[37] which is not included in PCV13, but is included in PPSV23. Regarding equity in vaccination coverage, foreign-born children aged 19-35 months of age had significantly lower coverage rates compared to US-born children.[38] Comparing PCV coverage rates for 4 or more doses, fewer Native American children aged 19-35 months were up to date when compared to White children in a study in North Dakota.[39] Looking at National Immunization Survey (NIS) data from 2020, PCV coverage of 4 or more doses by 24 months of age is low among children who are uninsured, Black, non-Hispanic, living in a non-metropolitan statistical area (MSA), or living in the lowest federal poverty level. The WG determined that recommended PCV15 probably would increase equity. It should be noted that the WG was split in responses, with some voting for “probably no impact,” which is likely due to uncertainty regarding whether PCV15 use will improve health equity compared to PCV13 use.

In summary, the WG determined that pneumococcal disease is of public health importance in children. Regarding benefits and harms, the WG determined that desirable anticipated effects are moderate and undesirable anticipated effects are minimal. The WG determined that using PCV15 was favorable compared to PCV13. But as previously noted, the option “favors intervention” gave the impression that a preferential recommendation was being proposed when the intention was to assess whether PCV15 can be used as an option in addition to PCV13. The

[35] Littlepage et al, 9th International Meeting on Indigenous Child Health, 2021
[36] Singleton et al. PIDJ 2018
[37] Zulz et al. JCM 2012
[38] Varan, AK et al. 2017. J Immigr Minor Health
[39] Woinarowicz, M & Howell, M. 2020. Public Health

overall certainty of evidence regarding VE for routine use in children less than 2 years of age was 2 or Moderate. Indirectness was downgraded once to serious due to lack of data on correlates of protection for some critical outcomes considered. Regarding children 2-18 years of age with underlying medical conditions, overall certainty for VE was 3, or Low. Indirectness was downgraded once to serious due to absence of data on correlates of protection for some critical outcomes considered, and imprecision was downgraded once to serious due to small sample size. Overall certainty for safety was 2, or Moderate, for routine use in children less than 2 years of age, with imprecision downgraded once to serious due to few events of the outcome being recorded. For children with underlying medical conditions, overall certainty of evidence for safety was 3, or Low. Imprecision was downgraded twice to very serious, once due to no events of the outcome being reported, and again for very small sample sizes. Regarding values and preferences, the WG agreed that the target population probably feels that the desirable effects from vaccination are large relative to undesirable effects. Additionally, the WG determined that there is probably not important uncertainty or variability in how people valued the main outcomes. Lastly, the WG determined that recommending PCV15 probably would increase equity.

Discussion Summary

Miss Bahta requested additional information about the discussion of determining that equity would be increased and whether that was because there would be another product that could be used.

Dr. Kobayashi clarified that the WG responses were split across the options. The option that had the highest number of votes was the one that was presented—that probably equity would be increased. The thought was that though the incidence in IPD rates between Black and White populations due to the 2 additional serotypes included in PCV15 was different, it provides an opportunity to prevent more disease with the additional serotypes included. By having that product and preventing more disease, the thought was that there would be an opportunity to prevent more disease in general and that there is a possibility that this might improve equity. She emphasized that there were opinions suggesting different options as well. The option of “probably increased” comprised the majority of opinions.

Dr. Sanchez expressed surprise about the suggestion that it would be an optional rather than a preferential recommendation. With 2 additional serotypes, a good safety profile, and immunogenicity data that are supportive of a benefit, it seemed that there would be an option for a preferential recommendation. With PCV15, it is possible that PCV13 would not be manufactured anymore at some point.

Dr. Poehling pointed out that to have a preferential recommendation, there would need to be a comparison of clinical outcomes and the WG had only immunogenicity data. For that reason, the WG acknowledged the data and that there would be an option.

Dr. Daley asked whether the WG discussed any concern about the idea that 2-month-olds may get a high enough fever that they present for medical care and have a septic workup. Obviously, there was a lot of supportive data and the differences were small. He was just struck by 2 aspects of the prior presentation. One was that there were 2 SAEs in the PCV15 group and the reason they were deemed serious was because the children had a fever and then presented and were admitted to the hospital for that fever. There were 0 fevers in the PCV13 group. Even recognizing that the sample sizes were different, it seems like there might be some imbalance

and somewhat higher fever in the older children that potentially could lead to febrile seizures. It seemed like an area to which additional attention should be paid.

Drs. Kobayashi and Poehling indicated that the WG did not specifically discuss this point. Dr. Poehling added that the WG did not see a difference between PCV13 and PCV15 in those young children, so that also drove that decision.

Dr. Maldonado (AAP) commented that whatever the outcome of this vote in the future, the Committee on Infectious Diseases (COID) of the AAP agreed with and approved of using the remaining pneumococcal vaccination doses and that no changes to dosing or schedules would be needed. She also emphasized that the equity data are not new and have been persistent over many years that underserved, diverse, and vulnerable populations tend to have lower vaccination rates for the 3+1 schedule and COID/AAP are appreciative of and recommend the strong consideration to leave the dose/schedule intact at this point.

Summary and Next Steps

Dr. Miwako Kobayashi (CDC/NCIRD) presented the Pneumococcal Vaccines WG's next steps. As discussed during this session's presentations, the policy questions on PCV15 use in children are:

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

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

Evidence reviewed by the WG and presented to ACIP during this session included data on the epidemiology of pneumococcal disease and vaccine-preventable disease burden for IPD, pneumonia, and AOM; immunogenicity and safety data of PCV15 in children from Phase 2/3 studies; and the GRADE and EtR framework to summarize the evidence and the WG interpretation on the EtR domains of the public health problem, benefits and harms, values, and equity. In future WG meetings, WG members will review the expected public health impact and cost-effectiveness of PCV15 use in children and will summarize the WG's interpretation of the remaining EtR domains of resource use, acceptability, and feasibility and will update the WG's interpretation for other domains, if indicated.

The WG also will review data to inform clinical guidance for PCV15 use, such as use of PCV15 in children who are incompletely or completely vaccinated with PCV13. Additional data will be summarized and presented during the June ACIP meeting, along with policy options on PCV15 use in children for consideration for a vote if the product is licensed for use. The following questions were posed for ACIP's consideration:

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

Discussion Summary

Ms. McNally asked for this particular recommendation whether PCV15 would be considered as an option to PCV13 for pneumococcal conjugate vaccine administration and if it would be up to the provider to determine which product to carry. In addition, she wondered how parents would be educated about the difference in order to be able to determine what they want to select for their children.

Dr. Kobayashi indicated that the WG is still reviewing the remainder of the EtR domains and are happy to raise these questions for discussion. There are precedents with other vaccines such as human papillomavirus (HPV) in which different valency vaccines have been on the market, so this situation would not be unique to the pneumococcal conjugate vaccine.

Dr. Sanchez added that the question of which vaccine to carry depends on whether there is a preferential recommendation. Given that there is no invasive data, it does not make much sense on a practical basis to have a preferential recommendation. He thought ultimately providers would want to know that it may be an option to use one or the other, but that there may be benefits otherwise to including more serotypes.

Dr. Long indicated that as a member of this august WG, she had not commented. However, she thought she understood how the ACIP members were thinking. It is important to remember that the majority of IPD currently occurring is due to serotypes that are in the currently available vaccine. That is, this vaccine theoretically increases coverage for 17% of invasive disease. What is not known as serotypes continue to be added are the potential impact and/or unintended consequences on colonization or on the serotypes for which there already is good clinical evidence of superb efficacy with the existing vaccine. In terms of the equity issue, there are only 4300 infants in the safety studies. This raised the same considerations and concerns she raised earlier regarding the critical questions about high fevers in the PCV15 group that would not be explained by concurrent MMRs since these were fevers in the first week. Therefore, there is more work to do. As far as equity is concerned, it seems that there would need to be a lot more antibody to serotype 3 in addition to the 2 additional serotypes in PCV15 to have the expected clinical impact. That is a complete unknown. Looking at who is getting IPD with the 2 additional serotypes, it would be expected to see more common occurrence in Black compared with White populations, as all IPD was before there were pneumococcal conjugate vaccines. She would not be in in favor of preferentially approving a vaccine just because it contains more serotypes. It is unknown whether there may be a “tipping point” for what happens in the ecology of the nasopharynx because pneumococcus had had a spot there forever. Until these vaccines are in use, it is unclear what replacement might occur. Therefore, she thought caution would be in order. Parents would not need to make a decision about what is best for their children if ACIP ultimately voted that these 2 pneumococcal conjugate vaccines are not different enough to make one preferred over the other. Instead, doctors would carry what works best for their practice.

Dr. Loehr noted that when there was a new HepB vaccine, ACIP did not vote on it because it was fit into the schedule. It seemed that because this was not a new PCV13 vaccine, ACIP would need to vote to approve it and recommend how it should be used.

Dr. Kobayashi confirmed that Dr. Loehr’s observation was correct.

Dr. Lee agreed that the policy questions seemed very appropriate. She noted that the high-risk populations and the data that was determined to be Level 3 made sense to her, but asked if the WG discussed whether those differences were felt to be meaningful for high-risk children. She clarified that her question was less about the GRADE itself and more about the potential difference in immunogenicity, at least for a subset of those serotypes and whether that had any clinical meaning to the WG members to suggest that ACIP should think about it differently for the high-risk population versus the healthy population.

Dr. Kobayashi indicated that there were no specific concerns raised among WG members about whether this vaccine would work differently in this population. However, that was based on the available data for this population suggesting that the efficacy might be comparable to what is observed from PCV13 use in this population. The WG also reviewed data on the VE of PCV13, which were limited among children with an underlying condition.

In terms of vaccines in general, Dr. Maldonado acknowledged the polio vaccine workers who were killed in Afghanistan the previous week as part of their unrelenting service to the world and children throughout the world in their efforts to eradicate polio.

CERTIFICATION

Upon reviewing the foregoing version of the February 23-24, 2022 ACIP meeting minutes, Dr. Grace Lee, ACIP Chair, certified that to the best of her knowledge, they are accurate and complete. Her original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

ACIP MEMBERSHIP ROSTER

CHAIR
LEE, Grace M, MD, MPH
Associate Chief Medical Officer for Practice Innovation
Lucile Packard Children's Hospital
Professor of Pediatrics, Stanford University School of Medicine
Stanford, CA
Term: 8/4/2021 – 6/30/2023

EXECUTIVE SECRETARY
WHARTON, Melinda, MD, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, GA

MEMBERS
AULT, Kevin A, MD, FACOG, FIDSA
Professor and Division Director
Department of Obstetrics and Gynecology University of
Kansas Medical Center
Kansas City, KS
Term: 10/26/2018 – 6/30/2022

BAHTA, Lynn, RN, MPH, CPH
Immunization Program Clinical Consultant
Infectious Disease, Epidemiology, Prevention & Control Division
Minnesota Department of Health
Saint Paul, Minnesota
Term: 7/1/2019 – 6/30/2023

BELL, Beth P, MD, MPH
Clinical Professor
Department of Global Health, School of Public Health
University of Washington
Seattle, WA
Term: 7/1/2019 – 6/30/2023

BROOKS, Oliver, MD, FAAP
Chief Medical Officer
Watts HealthCare Corporation
Los Angeles, CA
Past President, National Medical Association
Term: 7/26/2021 – 6/30/2025

CHEN, Wilbur H, MD, MS, FACP, FIDSA
Professor of Medicine
Center for Vaccine Development and Global Health
University of Maryland School of Medicine
Baltimore, MD
Term: 12/23/2020 – 6/30/2024

CINEAS, Sybil, MD, FAAP, FACP
Associate Professor of Medicine, Pediatrics, and Medical Science (Clinical)
The Warren Alpert Medical School of Brown University
Associate Program Director
Brown Combined Residency in Internal Medicine and Pediatrics
Providence, RI
Term: 7/28/2021 – 6/30/2025

DALEY, Matthew F, MD
Senior Investigator
Institute for Health Research, Kaiser Permanente Colorado
Associate Professor of Pediatrics
University of Colorado School of Medicine
Aurora, CO
Term: 1/4/2021 – 6/30/2024

KOTTON, Camille Nelson, MD, FIDSA, FAST
Clinical Director, Transplant and Immunocompromised Host Infectious Diseases
Infectious Diseases Division, Massachusetts General Hospital
Associate Professor of Medicine, Harvard Medical School
Boston, MA
Term: 12/23/2020 – 6/30/2024

LOEHR, Jamie, MD, FAAFP
Owner, Cayuga Family Medicine
Ithaca, New York
Term: 7/26/2021 – 6/30/2025

LONG, Sarah S, MD
Professor of Pediatrics
Drexel University College of Medicine
Section of Infectious Diseases
St. Christopher's Hospital for Children
Philadelphia, Pennsylvania
Term: 12/24/2020 – 6/30/2024

MCNALLY, Veronica V, JD
President and CEO Franny
Strong Foundation
West Bloomfield, Michigan
Term: 10/31/2018 – 6/30/2022

POEHLING, Katherine A, MD, MPH
Professor of Pediatrics and Epidemiology and Prevention
Director, Pediatric Population Health
Department of Pediatrics
Wake Forest School of Medicine
Winston-Salem, NC
Term: 7/1/2019 – 6/30/2023

SÁNCHEZ, Pablo J, MD
Professor of Pediatrics
The Ohio State University – Nationwide Children's Hospital
Divisions of Neonatal-Perinatal Medicine and Pediatric Infectious Diseases
Director, Clinical & Translational Research (Neonatology)
Center for Perinatal Research
The Research Institute at Nationwide Children's Hospital Columbus, Ohio
Term: 7/1/2019 – 6/30/2023

TALBOT, Helen Keipp, MD
Associate Professor of Medicine
Vanderbilt University
Nashville, TN
Term: 10/29/2018 – 6/30/2022

EX OFFICIO MEMBERS

Centers for Medicare and Medicaid Services (CMS)
HANCE, Mary Beth
Senior Policy Advisor
Division of Quality, Evaluations and Health Outcomes
Children and Adults Health Programs Group
Center for Medicaid, CHIP and Survey & Certification Centers
for Medicare and Medicaid Services
Baltimore, MD

Food and Drug Administration (FDA)
FINK, Doran, MD, PhD
Deputy Director, Clinical, Division of Vaccines and Related Products Applications
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration
Silver Spring, MD

Health Resources and Services Administration (HRSA)
RUBIN, Mary, MD
Chief Medical Officer
Division of Injury Compensation Programs
Rockville, MD

Indian Health Service (IHS)
CLARK, Matthew, MD, FAAP, FACP
Physician
Chair, IHS National Pharmacy & Therapeutics Committee
Durango, CO

Office of Infectious Disease and HIV/AIDS Policy (OIDP)
KIM, David, MD, MA
Director, Division of Vaccines, OIDP
Office of the Assistant Secretary for Health
Department of Health and Human Services
Washington, DC

National Institutes of Health (NIH)
BEIGEL, John, MD
Associate Director for Clinical Research
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases (NIAID)
Bethesda, MD

LIAISON REPRESENTATIVES

American Academy of Family Physicians (AAFP)
ROCKWELL, Pamela G, DO
Associate Professor, Department of Family Medicine, University of Michigan Medical School
Medical Director, Dominos Farms Family Medicine
Ann Arbor, MI

American Academy of Pediatrics (AAP)
MALDONADO, Yvonne, MD
Senior Associate Dean for Faculty Development and Diversity
Professor of Pediatrics and Health Research and Policy
Chief, Division of Pediatric Infectious Diseases
Stanford University School of Medicine
Stanford, CA

American Academy of Pediatrics (AAP)
Red Book Editor
KIMBERLIN, David, MD
Professor of Pediatrics
Division of Pediatric Infectious Diseases
The University of Alabama at Birmingham School of Medicine
Birmingham, AL

American Academy of Physician Assistants (AAPA)
LÉGER, Marie-Michèle, MPH, PA-C
Senior Director, Clinical and Health Affairs
American Academy of Physician Assistants
Alexandria, VA

American College Health Association (ACHA)
CHAI, Thevy S., MD
Director of Medical Services
Campus Health Services
University of North Carolina at Chapel Hill Chapel Hill,
NC

American College Health Association (ACHA) (alternate)
MCMULLEN, Sharon, RN, MPH, FACHA
Assistant Vice President of Student & Campus Life for Health and Wellbeing Cornell Health
Ithaca, NY

American College of Nurse Midwives (ACNM)
HAYES, Carol E., CNM, MN, MPH
Lead Clinician
Clinical Quality Compliance and Management
Planned Parenthood Southeast Atlanta, GA

American College of Nurse Midwives (ACNM) (alternate)
MEHARRY, Pamela M., PHD, CNM
Midwifery Educator, Human Resources for Health
In partnership with University of Rwanda and University of Illinois, Chicago

American College of Obstetricians and Gynecologists (ACOG)
ECKERT, Linda O, MD, FACOG
Professor, Department of Obstetrics & Gynecology
Adjunct Professor, Department of Global Health
University of Washington
Seattle, WA

American College of Physicians (ACP)
GOLDMAN, Jason M, MD, FACP
Affiliate Assistant Professor of Clinical Biomedical Science, Florida Atlantic University, Boca Raton, Florida
Private Practice
Coral Springs, FL

American Geriatrics Society (AGS)
SCHMADER, Kenneth, MD
Professor of Medicine-Geriatrics Geriatrics
Division Chief
Duke University and Durham VA Medical Centers
Durham, NC

America's Health Insurance Plans (AHIP)
GLUCKMAN, Robert A, MD, MACP
Chief Medical Officer, Providence Health Plans
Beaverton, OR

American Immunization Registry Association (AIRA)
COYLE, Rebecca, MSEd
Executive Director, AIRA
Washington, DC

American Medical Association (AMA)
FRYHOFER, Sandra Adamson, MD
Adjunct Associate Professor of Medicine Emory
University School of Medicine
Atlanta, GA

American Nurses Association (ANA)
RITTLE, Charles (Chad), DNP, MPH, RN Assistant
Professor, Nursing Faculty
Chatham University, School of Health Sciences
Pittsburgh, PA

American Osteopathic Association (AOA)
GROGG, Stanley E, DO
Associate Dean/Professor of Pediatrics
Oklahoma State University-Center for Health Sciences
Tulsa, OK

American Pharmacists Association (APhA)
HOGUE, Michael D., PharmD, FAPhA, FNAP
Dean and Professor of Loma Linda University School of Pharmacy
Director, Center for Interprofessional Education & Practice
Loma Linda, CA

Association of Immunization Managers (AIM)
HOWELL, Molly, MPH
Immunization Program Manager
North Dakota Department of Health
Bismarck, ND

Association for Prevention Teaching and Research (APTR)
ZIMMERMAN, Richard, MD, MPH
Professor
University of Pittsburgh School of Medicine
Department of Family Medicine and Clinical Epidemiology
Pittsburgh, PA

Association of State and Territorial Health Officials (ASTHO)
SHAH, Nirav D, MD, JD
Director
Maine Center for Disease Control and Prevention
Augusta, ME

Biotechnology Industry Organization (BIO)
ARTHUR, Phyllis A, MBA
Senior Director, Vaccines, Immunotherapeutics and Diagnostics Policy
Washington, DC

Council of State and Territorial Epidemiologists (CSTE)
HAHN, Christine, MD
State Epidemiologist
Office of Epidemiology, Food Protection and Immunization Idaho
Department of Health and Welfare
Boise, ID

Council of State and Territorial Epidemiologists (CSTE) (alternate)
LETT, Susan, MD, MPH
Medical Director, Immunization Program
Division of Epidemiology and Immunization
Massachusetts Department of Public Health
Boston, MA

Canadian National Advisory Committee on Immunization (NACI)
DEEKS, Shelley, MD, MHSc, FRCPC, FAFPHM
Deputy Chief Medical Officer of Health, Department of Health and Wellness, Nova Scotia
Associate Professor, Dalla Lana School of Public Health, University of Toronto
Chair, National Advisory Committee on Immunization
Halifax, Nova Scotia

Infectious Diseases Society of America (IDSA)
BAKER, Carol J., MD
Professor of Pediatrics
Molecular Virology and Microbiology
Baylor College of Medicine
Houston, TX

International Society for Travel Medicine (ISTM)
BARNETT, Elizabeth D, MD Professor of
Pediatrics
Boston University School of Medicine
Boston, MA

National Association of County and City Health Officials (NACCHO)
ZAHN, Matthew, MD
Medical Director, Epidemiology
Orange County Health Care Agency
Santa Ana, CA

National Association of County and City Health Officials (NACCHO) (alternate)
DUCHIN, Jeffrey, MD
Health Officer and Chief, Communicable Disease
Epidemiology and Immunization Section
Public Health - Seattle and King County
Professor in Medicine
Division of Allergy and Infectious Diseases
University of Washington School of Medicine and School of Public Health
Seattle, WA

National Association of Pediatric Nurse Practitioners (NAPNAP)
STINCHFIELD, Patricia A, RN, MS, CPNP
Director
Infectious Disease/Immunology/Infection Control
Children's Hospitals and Clinics of Minnesota
St. Paul, MN

National Foundation for Infectious Diseases (NFID)
SCHAFFNER, William, MD
Chairman, Department of Preventive Medicine
Vanderbilt University School of Medicine
Nashville, TN

National Foundation for Infectious Diseases (NFID) (alternate)
DALTON, Marla, PE, CAE
Executive Director & CEO
National Foundation for Infectious Diseases (NFID)
Bethesda, MD

National Medical Association (NMA)
WHITLEY-WILLIAMS, Patricia, MD Professor and Chair
University of Medicine and Dentistry of New Jersey Robert Wood
Johnson Medical School
New Brunswick, NJ

Pediatric Infectious Diseases Society (PIDS)
O'LEARY, Sean, MD, MPH
Associate Professor of Pediatrics
Pediatric Infectious Diseases
General Academic Pediatrics
Children's Hospital Colorado
University of Colorado School of Medicine

Pediatric Infectious Diseases Society (PIDS) (alternate)
SAWYER, Mark H, MD
Professor of Clinical Pediatrics
University of California, San Diego School of Medicine
San Diego, CA

Pharmaceutical Research and Manufacturers of America (PhRMA)
ROBERTSON, Corey, MD, MPH
Senior Director, US Medical, Sanofi Pasteur
Swiftwater, PA

Society for Adolescent Health and Medicine (SAHM)
MIDDLEMAN, Amy B, MD, MSEd, MPH
Professor of Pediatrics
Chief, Section of Adolescent Medicine
University of Oklahoma Health Sciences Center
Oklahoma City, OK

Society for Healthcare Epidemiology of America (SHEA)
DREES, Marci, MD, MS
Chief Infection Prevention Officer & Hospital Epidemiologist
ChristianaCare
Wilmington, DE
Associate Professor of Medicine
Sidney Kimmel Medical College at Thomas Jefferson University Philadelphia, PA

ACRONYMS USED IN THIS DOCUMENT

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ABCs	Active Bacterial Core Surveillance
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
aIIV	Adjuvanted Influenza Vaccine
AE	Adverse Event
AESI	Adverse Event of Special Interest
AHA	American Heart Association
AHIP	America's Health Insurance Plans
AI/AN	American Indian/Alaskan Native
AIM	Association of Immunization Managers
AIRA	American Immunization Registry Association
AMA	American Medical Association
AOA	American Osteopathic Association
AOM	Acute Otitis Media
APhA	American Pharmacists Association
AR	Adverse Reaction
ARI	Acute Respiratory Illness
ASTHO	Association of State and Territorial Health Officers
BLA	Biologics License Application
CDC	Centers for Disease Control and Prevention
CHIP	Children's Health Insurance Program
CICP	Countermeasures Injury Compensation Program
CMS	Center for Medicare and Medicaid Services
COI	Conflict of Interest
CSF	Cerebrospinal Fluid
CSTE	Council of State and Territorial Epidemiologists
DFO	Designated Federal Official
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DVA	Department of Veterans Affairs
ECL	Electrochemiluminescence
ED	Emergency Department
EIP	Emerging Infections Program
ELISA	Enzyme-Linked Immunosorbent Assay
EMR	Electronic Medical Record
EPSDT	Early and Periodic Screening, Diagnostic and Treatment
ESRD	End-Stage Renal Disease
ET	Eastern Time

EtR	Evidence to Recommendation
EUA	Emergency Use Authorization
EVs	Enhanced Vaccines
FDA	Food and Drug Administration
FRN	Federal Register Notice
GBS	Guillain-Barré Syndrome
GMR	Geometric Mean Ratio
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
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
HSCT	Hematopoietic Stem Cell Transplant
IDSA	Infectious Disease Society of America
IHS	Indian Health Service
IIS	Immunization Information System
IPD	Invasive Pneumococcal Disease
IV	Intravenous
MMWR	*Morbidity and Mortality Weekly Report*
MSA	Metropolitan Statistical Area
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization Canada
NAPNAP	National Association of Pediatric Nurse Practitioners
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHS	National Center of Health Statistics
NCIRD	National Center for Immunization and Respiratory Diseases
NFID	National Foundation for Infectious Diseases
NHSN	National Healthcare Safety Network
NIH	National Institutes of Health
NIS	National Immunization Survey
NMA	National Medical Association
NP	Nasopharyngeal Swab
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
OASH	Office of the Assistant Secretary for Health
OAW	Operation Allies Welcome
OIDP	Office of Infectious Disease and HIV/AIDS Policy (OIDP)
OPA	Opsonophagocytic Activity
PHAO	Pan American Health Organization
PCP	Primary Care Provider/Practitioner
PCR	Polymerase Chain Reaction
PHAC	Public Health Agency Canada
PICO	Population, Intervention, Comparison, Outcomes
PIDS	Pediatric Infectious Disease Society
RCT	Randomized Controlled Trial
RIV	Recombinant Influenza Vaccine

SAE	Serious Adverse Event
SAHM	Society for Adolescent Health and Medicine
sBLA	Supplemental Biologics License Application
SD-IIV	Standard-Dose Unadjuvanted Influenza Vaccines
SHEA	Society for Healthcare Epidemiology of America
SME	Subject Matter Expert
SVs	Standard Vaccines
US	United States
USG	United States Government
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VFC	Vaccines For Children
VICP	National Vaccine Injury Compensation Program
VSD	Vaccine Safety Datalink
WG	Work Group
WHO	World Health Organization