MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

JANUARY 12, 2022
SUMMARY MINUTES

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MEETING PURPOSE

The United States (US) Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC) convened a meeting of the Advisory Committee on Immunization Practices (ACIP) on January 12, 2022. The meeting took place remotely via Zoom, teleconference, and live webcast. This document provides a summary of the meeting, which focused on cholera, tickborne encephalitis (TBE), influenza, hepatitis, respiratory syncytial virus (RSV), and pneumococcal vaccines; 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 January 12, 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 3:10 PM Eastern Time (ET) on January 12, 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-2022-0132. 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.

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?" This session focused on Vaxchora® pediatric dose development and the Evidence to Recommendation (EtR) Framework for CVD103-HgR among children and adolescents 2-17 years of age.

Vaxchora® Pediatric Dose Development

James McCarty, MD (Emergent BioSolutions) presented a brief overview of recent studies addressing pediatric dosing volume and palatability of the live attenuated *V.* cholerae vaccine, Vaxchora®. Vaxchora® is composed of 2 packets, or sachets, that are reconstituted in bottled water prior to administration. The first of the 2 packets contains a buffer powder that neutralizes stomach acid and facilitates the passage of vaccine into the intestines. The second packet contains the active component, which is comprised of 2 grams of lyophilized *V. cholerae* CVD103-HgR vaccine strain. Vaxchora® has been evaluated in a Phase 1 study and several randomized double blind placebo controlled Phase 3 and 4 trials in over 4,000 subjects aged 2-64 years of age. Objectives have included safety, immunogenicity, shedding, and clinical efficacy. In the Phase 3 challenge study, seroconversion was noted in most subjects by 7 days after immunization and demonstrated 90.3% efficacy at 10 days and 79.5% efficacy at 3 months, versus placebo against challenge with a virulent strain of *V. cholerae*. A second Phase 3 study documented lot-to-lot consistency and the third Phase 3 study demonstrated a similar immune response in older adults compared with younger adults. A Phase 4 study demonstrated that Vaxchora® is well-tolerated and safe in children aged 2-17 years, with seroconversion occurring in 98.5% of subjects by 10 days post-vaccination—a seroconversion rate that is non-inferior to vaccine in adults.

The pediatric dose development plan was designed to adapt the vaccine to children aged 2-6 years. The primary goals of the product development studies presented during this session were to use the existing approved Vaxchora® formulation as described and to adapt the vaccine to children 2-6 years of age by reducing the administration volume and masking the taste. The methods used were to reduce the administration volume from 100 mL to 50 mL and to investigate the compatibility of different flavoring options and taste masking strategies with Vaxchora®. The first step in the development of the Vaxchora® pediatric dose was to reduce the volume. Several reconstitution methods were tested, including simply adding the buffer and active component to 50 mL of water instead of the 100 mL prescribed for the approved vaccine in adults. Reconstituting the full buffer into 50 mL of water resulted in a pH of 7.16, which is above the release specification. Reconstituting the full buffer and vaccine components directly into 50 mL of water resulted in a slight drop in vaccine potency. An alternative was to reconstitute the buffer in 100 mL of water followed by discarding half and reconstituting the entire active component in the remaining 50 mL of buffered water. In this case, the buffering capacity was below specification and half of the reconstituted buffer was discarded.
When using this method, the Vaxchora® solution remained within the potency specification for at least 15 minutes. The reduction in buffering capacity was deemed acceptable because children have a lower gastric volume and higher gastric pH than adults. This is the dose method

that was used with children 2-6 years of age in the pediatric trial, which resulted in high seroconversion rates and which was approved by the FDA for use in children. It was concluded from these results that the buffer should be kept at the same concentration as the adult formulation and that Vaxchora® is stable when reconstituted in this way in 50 mL of buffer water.

There was an option to add a sweetener (e.g., sucrose or Stevia), which was stirred into the reconstituted vaccine and then the vaccine was consumed within 15 minutes. The next step in the development of Vaxchora® pediatric dose was to investigate the compatibility of different flavoring options and taste-masking strategies. Over-the-counter flavoring agents, such as FLAVORx® or Yummy Meds®, contained propylene glycol which has shown to be bactericidal. Data documented Vaxchora® colony counts well below the lower limits of specification when FLAVORx® was added to the vaccine mixture. During the pediatric study, only PURE VIA Stevia sweetener was used to flavor the vaccine. Therefore, a more thorough study of the compatibility of Vaxchora® with sucrose and different brands of Stevia was performed. Stevia is much sweeter than sugar, so fillers are used to add bulk and the Stevia itself generally accounts for less than 5% of the sweeteners by weight. The strategy in the laboratory was to choose Stevia brands that are available worldwide and contain the most commonly used fillers. An online search showed that the Stevia market is consolidated and dominated by just a few players, including Cargill (makers of Truvia®) and Tate and Lyle (makers of Splenda®). The most commonly used fillers of popular brands are inulin, erythritol, maltodextrin, and dextrose.

Representative brands of Stevia® powder or Stevia® crystals were chosen to include popular brands and the most common filler ingredients. One gram of Stevia®, which is equivalent to 1 packet bought in the store or 4 grams of sucrose were added to 50 mL of reconstituted Vaxchora® and the potency was tested after 15 minutes. Vaxchora® potency was maintained in the presence of sucrose in all brands of Stevia® tested. The conclusion was that Vaxchora® is well-tolerated and likely effective in children aged 2-17 years. Vaxchora® is compatible with up to 4 grams of sucrose or Stevia® sweeteners in a reconstitution volume of 15 mL. It is compatible with Stevia® brands available around the world, including their common fillers. Vaxchora® should not be used with medicine flavorings, such as FLAVORx® or Yummy Meds® due to the presence of propylene glycol.

Discussion Summary

Dr. Hogue (APhA) emphasized that pharmacists are always interested in how they can help pediatric patients take medicines and vaccines, so flavoring is very important. While an image was shown of the reconstitution instructions for the pediatric formulation, there was no mention of whether sweetener could be added to the adult dose. Some adult patients have certain taste aversions as well, so he wondered whether it be acceptable to add sweetener to the adult product or if there were any concerns about doing so. He also requested clarity with regard to whether a pharmacist, nurse, or physician would be able to use an off-the-shelf packet of Stevia, Truvia®, or a similar sweetener, or if the manufacturer would supply a sweetener with the product.

Dr. McCarty said that with the caveat that he did not know the exact language submitted in terms of the label, he knew of no reason that there would be any issues with adding stevia or sucrose to the adult 100 mL mixture based on the laboratory data generated thus far. There are no plans at this time for the manufacturer to provide a sweetener with the product.

Dr. Poehling pointed out that when parents present to a travel clinic, they will sometimes have multiple children in this age group. In terms of product distribution, she could imagine a scenario in which buffer might be added to 100 mL of water and divided into 50 mL to which vaccine would be added for each of 2 children instead of any being discarded. She wondered whether that would be considered to enhance efficiency.

Dr. McCarty clarified that each container of vaccine has 2 sachets, 1 that contains the buffer and the other that contains the vaccine, so 2 sachets of Vaxchora® would still be used to immunize 2 children. Dividing 100 mL into 2 equal 50-milliter containers of buffer solution and adding a complete vaccine sachet into each container should not be a problem.

Dr. Kim (OIDP) observed that while Vaxchora® is anticipated to be recommended for children 2-17 years of, the child and adolescent immunization schedule goes through 18 years of age and the adult immunization schedule begins at age 19. It was not clear where those 18 years of age would fit into the recommendations and whether there were considered to be similar to individuals 16-17 years of age.

Dr. McCarty indicated that the same product was used in the adult studies ≥18 years of age. The data have consistently supported safety and immunogenicity in subjects aged 16, 17, 18, and 19 years. The cutoff and recommendation language would be up to ACIP to determine.

Dr. Schneider (Emergent BioSolutions) added that in accordance with the label, Vaxchora® is indicated for persons 2-64 years of age.

Dr. Daley clarity about whether the amendment submitted to the FDA was only for the purpose of amending the package insert to specify the types of sweeteners that could be used.

Dr. McCarty clarified that the purpose was not only to specify the types of sweeteners that could be used, but also the type of water.

Dr. Lee asked whether there was any intent to create a specific set of sachets for children 2-6 years of age, which could minimize administration errors in high volume clinics.

Dr. McCarty indicated that at this time, the intent is to continue to use the same manufacturing process and formulation.

EtR Framework: CVD103-HgR among Children and Adolescents 2-17 Years of Age

Jennifer Collins, MD, MSc (CDC/NCEZID/DFWED) presented the EtR Framework for CVD103-HgR among children 2-17 years of age. Regarding the background of the WG, in June 2016 ACIP recommended the cholera vaccine CVD103-HgR (renamed Vaxchora®) for adult travelers aged 18-64 years from the US to an area with active cholera transmission. This is the only cholera vaccine licensed for use in the US. In October 2020, the current ACIP Cholera Vaccine WG formed. In December 2020, FDA extended the approved usage of Vaxchora® to include children and adolescents aged 2-17 years. In February 2022, the WG presented background information and the manufacturer presented pediatrics clinical trial data. The current policy question under consideration is. “Should ACIP recommend CVD 103-HgR for children and adolescents aged 2-17 years traveling to an area with active cholera transmission?”

The components of the PICO question include the population of children and adolescents aged 2-17 years traveling to an area with active cholera transmission. The intervention is lyophilized CVD 103-HgR, a single dose, oral, live attenuated bacterial vaccine. The comparison is no cholera vaccine. The WG identified 4 outcomes as the most important for this question, including cholera diarrhea (moderate or severe), cholera diarrhea (any severity), serious adverse events (SAEs), and non-SAEs.

The WG identified the following primary question and sub-questions for the first EtR domain, public health problem:

- ❑ Is cholera among children and adolescents aged 2–17 years traveling to an area with active cholera transmission a public health problem?
  - Are the consequences cholera serious (i.e., severe or important in terms of the potential benefits or savings)?
  - Is cholera urgent?
  - Are many travelers aged 2–17 years from the US affected by cholera?
  - Is cholera related to emerging diseases, antimicrobial resistance, or epidemic potential?
  - Are disadvantaged groups or populations disproportionately/differentially affected by cholera?

Infection with toxigenic *V. cholerae* 01 can cause a range of symptoms. Although most infections are asymptomatic, mild, or moderate, up to 10% of infections manifest as cholera gravis—the most severe form of cholera. Cholera gravis is rapidly fatal if untreated. Fluid management is the primary focus of treatment and rehydration can reduce the fatality rate to less than 1%. However, patients with cholera gravis may require up to 350 ml/kg of fluids within the first 24 hours of illness. Most international travelers from the US do not get cholera because they do not visit areas with active cholera transmission and they have good access to safe food and water. During 2012-2018, there were 64 cholera cases reported in the US. Among these cases, 5 patients (8%) were aged 2-17 years. There were 2 deaths in adults and there were 56 (88%) travel-associated cases. However, national cholera case counts underestimate the true burden of illness given limitations inherent in surveillance for laboratory-confirmed infections. Antibiotic resistance (AR) can occur among the bacteria causing cholera; however, fluids are the mainstay of treatment. Antibiotics are adjunctive therapy in moderate to severe illness. An estimated 1.3 to 4 million cholera cases and 21,000 to 143,000 cholera deaths occur worldwide each year.[1] Cholera epidemics are associated with unsafe water and inadequate sanitation. Secondary cases are rare if sanitation is adequate. Therefore, a US outbreak from a returning traveler is unlikely.

The work group deliberated whether cholera is a public health problem among children and adolescents aged 2-17 years traveling to an area with active cholera transmissions. WG members agreed that cholera is a public health problem for local populations in endemic settings due to unsafe drinking water and inadequate sanitation. However, for travelers from the US, WG members felt that even within cholera endemic areas, the risks for travelers varied by travel destination; travel activities such as tourism versus visiting friends and relatives and access to safe food; water, and sanitation. Apart from the public health question, members noted that cholera may pose a meaningful individual risk for ill travelers with inadequate or delayed access to fluid replacement therapy—even in instances when there is risk of secondary transmission as well. Finally, cholera may become a bigger problem for travelers in the future.

[1] https://www.who.int/health-topics/cholera#tab=tab_1

The WG agreed that having a supply of cholera vaccine for US travelers is important. For the public health problem domain, most WG members felt the determination should be “probably yes,” though some felt it should “probably no” or “varies.” The final WG consensus was “probably yes.”

The WG determined the questions for the next EtR domain, benefits and harms, to be as follows:

- ❑ How substantial are the desirable anticipated effects overall and for each main outcome for the desirable effect?
- ❑ How substantial are the undesirable anticipated effects overall and for each main outcome for which there is an undesirable effect?
- ❑ Do the desirable effects outweigh the undesirable effects?
- ❑ What is the overall certainty of this evidence for the critical outcomes?

The WG categorized the PICO outcomes as benefits and harms. Prevention of cholera diarrhea (moderate or severe) and prevention of cholera diarrhea (any severity) were rated as critical benefits. For harms, SAEs were rated as critical and non-SAEs were rated as important. A systematic review was conducted to identify evidence and use of CVD 103-HgR among children and adolescents aged 2-17 years. Published articles were identified using several databases (PubMed, Embase, and Cochrane Library) and search terms (cholera, *Vibrio cholerae*, CVD 103-HgR, cholera vaccine). Studies were included if they provided data on the current formulation and dose of the vaccine, involved human subjects aged 2-17 years, reported primary data relevant to the efficacy and safety outcomes, and were conducted in cholera non-endemic settings. Titles and abstracts were screened by 2 reviewers. Overall, 571 records were identified and screened and 3 studies were included in the GRADE (Grading of Recommendation Assessment, Development and Evaluation review).

Three articles summarized a Phase 4 randomized double-blind placebo-controlled trial among children and adolescents aged 2-17 years. Results of the clinical trial were presented to ACIP by the manufacturer in February 2021. In summary, the study setting was 7 US sites from July 2017 through December 2019. The sponsor enrolled healthy children and adolescents aged 2-17 years, divided into 3 age cohorts: Cohort 1: 12-17 years; Cohort 2: 6-11 years; Cohort 3: 2-5 years. Participants were randomized using a 6:1 ratio to receive the vaccine at $1x10^9$ CFU vs. 0.9% saline placebo. Participants or parents could request an optional sweetener for palatability, which was PureVia brand Stevia. At least 92% of participants in each study arm chose this. The relevant outcomes addressed included safety and immunogenicity.

Regarding outcomes 1 and 2, cholera diarrhea (moderate to severe) and cholera diarrhea (any severity), no pediatric studies directly assessed vaccine effectiveness (VE). Assessment of these outcomes was based on immunobridging to adults and immune efficacy has been demonstrated. In a separate study, wild-type *Vibrio cholerae* 01 was administered to participants aged 18-45 years following vaccine or placebo. The correlation coefficient between cumulative diarrhea in liters and fold-increase in serum vibriocidal antibodies was -0.75 at 10 days and -0.69 at 3 months. Separately in endemic settings, fold-increases in SVA correlated with protection in both adults and children.

In terms of the GRADE evidence table for cholera diarrhea (moderate to severe) and cholera diarrhea (any severity), 2 randomized control trials (RCTs) were included and the evidence certainty began at Type 1. The WG downgraded the evidence for serious indirectness because efficacy is inferred from immunobridging. The full effects demonstrate that seroconversion was more likely in vaccine recipients than among placebo recipients. The final certainty was Type 2, or Moderate. The GRADE evidence table for SAEs included 2 RCTs and the evidence certainty began at Type 1. No SAEs were attributed to the vaccine in either study. The WG downgraded the evidence for very serious imprecision based on the small sample size to assess SAEs, the small number of events, and the wide 95% confidence intervals that crossed the line of no effect. The final certainty was Type 3, or Low. The GRADE evidence table for non-SAEs was assessed by any solicited AE from study Days 1-8. Again, 2 RCTs were included and the evidence certainty began at Type 1. The WG downgraded the evidence for very serious imprecision based on the wide confidence interval that crossed the line of no effect. The final certainty was Type 3, or Low.

To summarize the GRADE evidence for the critical benefits of cholera diarrhea (moderate to severe), CVD 103-HgR effectively induces SVA seroconversion, an imperfect correlate of protection against cholera. The final evidence was Type 2, or Moderate. For the critical harm of SAEs, none were judged to be related to the vaccine and the final evidence was Type 3, or Low. Finally, the frequency of non-SAEs was not meaningfully different among vaccine versus placebo recipients and the final evidence was Type 3, or Low, for this important outcome. The WG felt that the desirable anticipated effects were moderate, the undesirable anticipated effects were small, and the balance between desirable and undesirable effects favored the intervention, CVD 104-HgR. The overall certainty of this evidence for this critical outcome was Type 3, or Low.

The WG next reviewed the domain of values, for which the following questions were determined:

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

For values, no research evidence was identified. The WG noted that cholera vaccines are optional and individuals can decide whether to get vaccinated based on their values. Therefore, the WG's determination for values was "Don't know."

Turning to the domain of acceptability, the WG considered the following question and sub-questions:

- ❑ Is the intervention acceptable to key stakeholders?
  - Are there key stakeholders who would not accept the distribution of benefits, harms, and costs?
  - Are there key stakeholders who would not accept the costs or undesirable effects in the short-term for the desirable effects in the future?

For acceptability, no research evidence was identified. However, the WG noted that travel medicine providers and medical associations, such as the Infectious Diseases Society of America (IDSA), the American Academy of Pediatrics (AAP), and the Pediatrics Infectious Diseases Society (PIDS) are likely to find it acceptable to administer CVD 103-HgR to children

and adolescents aged 2-17 years traveling to an area with active cholera transmission. The WG's determination for acceptability was "Yes."

The WG determined the following primary question and sub-questions for the domain of resource use:

- Is CVD 103-HgR among children and adolescents aged 2-17 years traveling to an area with active cholera transmission a reasonable and efficient allocation of resources?
  - What is the cost-effectiveness of the vaccination?
  - How does the cost-effectiveness of the vaccination vary in any sensitivity analyses?
  - How does the cost-effectiveness change in response to changes in context, assumptions, model structure, across different studies, etc.?

For research use, no research evidence was identified. A cost analysis was not conducted given the optional nature of the vaccine among travelers. For research use, the WG determination was "Don't know."

The main question and sub-questions identified by the WG to assess equity included the following:

- What would be the impact on health equity of CVD 103-HgR among children and adolescents aged 2-17 years traveling to an area with active cholera transmission?
  - Are there any groups or settings that might be disadvantaged in relation to the problem or options that are considered?
  - Are there plausible reasons for anticipating differences in the relative effectiveness of the option for disadvantaged groups or settings?
  - Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the option or the importance of the problem for disadvantaged groups or settings?
  - Are there important considerations that should be made when implementing the intervention (option) in order to ensure that inequities are reduced, if possible, and that they are not increased?

For equity, no research evidence was identified. However, the WG expressed concern for possible inequity, noting that under-served populations may have difficulty accessing and paying for the vaccine. WG members noted that travelers visiting friends and relatives (VFR) travelers in cholera endemic areas are likely at highest risk for illness, but are often uninsured. For other travel vaccines, VFR travelers are often less likely than other travelers to go to travel clinics and receive pre-travel vaccines. The WG determination for equity was that "Varies."

The primary question and sub-questions identified by the WG to assess feasibility included the following:

- Is CVD 103-HgR feasible to implement among children and adolescents aged 2-17 years traveling to an area with active cholera transmission?
  - Is the intervention sustainable?
  - Are there important barriers that are likely to limit the feasibility of implementing the intervention or that require consideration when implementing it?
  - Is access to the vaccine an important concern?
  - Would the vaccine recommendation have any impact on health equity?

- Are there important considerations when implementing the intervention in order to ensure that inequities are reduced, if possible, and that they are not increased?

The WG felt it is likely feasible to administer the vaccine to children and adolescents aged 2-17 years in a travel clinic. The travel clinic study is preferred because the dose preparation is more complicated than routine childhood vaccines. It requires reconstitution in bottled or purified spring water and half the buffer is discarded for children aged less than 6 years of age. Additionally, it may be optimally ingested with specific sweeteners. More than 92% of trial participants used PureVia Stevia with their dose and 89% of study participants consumed the complete vaccine dose. Seroconversion with partial dosing was encouraging. The 69% of participants who consumed less than 50% of the dose and all 7 patients who consumed 50% to 80% of the dose seroconverted. Finally, the recommendation may impact health equity as previously discussed. The WG determination for feasibility was "Probably yes."

This table summarizes the WG's determinations for each of the EtR domains just discussed:

EtR Domain	Question	Work group determination
Public health problem	Is cholera among children and adolescents aged 2–17 years traveling to an area with active cholera transmission of public health importance?	Probably yes
Benefits and harms	How substantial are the desirable anticipated effects?	Moderate
	How substantial are the undesirable anticipated effects?	Small
	Do the desirable anticipated effects outweigh the undesirable effects?	Favors CVD 103-HgR
	What is the overall certainty of the evidence for the critical outcomes?	Low
Values	Does the target population feel the desirable effects are large relative to the undesirable effects?	Don't know
	Is there important variability in how patients value the outcome?	Don't know
Acceptability	Is CVD 103-HgR acceptable to key stakeholders?	Yes
Resource use	Is CVD 103-HgR among children and adolescents aged 2–17 years traveling to an area with active cholera transmission a reasonable and efficient allocation of resources?	Don't know
Equity	What would be the impact of CVD 103-HgR among children and adolescents aged 2–17 years traveling to an area with active cholera transmission on health equity?	Varies
Feasibility	Is CVD 103-HgR feasible to implement among children and adolescents aged 2–17 years traveling to an area with active cholera transmission?	Probably yes

Based on the EtR Framework, the WG considered the balance of consequences and their consensus was that the "desirable consequences probably outweigh undesirable consequences in most settings," given that they had only indirect data to assess the desirable consequences. Finally, the WG consensus was that the type of recommendation should be, "We recommend the intervention CVD 103-HgR for children and adolescents aged 2-17 years traveling to an area with active cholera transmissions."

Discussion Summary

Dr. Poehling noted that at one point, there was mention about how individuals would choose whether to get the vaccine because it is an individual benefit. However, the conclusion was that it should be recommended and there was a choice for shared decision-making. She requested further elaboration to help her better understand the conversations on those 2 choices.

Dr. Collins indicated that the WG spent a long time deliberating how they wanted to rate the specific domain of "public health problem." Some of that is because the EtR Framework was created with the lens of more general vaccines and policies of routine immunization in mind. Travel vaccines are thought of somewhat differently. Overall, the WG felt that they wanted to

recommend the vaccine, but also acknowledged that some people may feel that it does not meet the criteria for being a public health problem in the US. Individual travelers may be at risk and the status of people's individual risk factors (e.g., heart disease, Blood Type O, low gastric acids, partial gastrectomy, other factors) that may increase their potential for experiencing cholera gravis may be unknown. While WG members agreed on recommending vaccine for travelers to endemic areas, they debated extensively whether this meets the criterion of being a public health problem. The proposed language for consideration is a full recommendation for adults aged 18-64 years who are traveling to areas of active cholera transmission.

Ms. Bahta recalled that some of the cholera cases that occurred in the US during 2012-2018 were not travel-associated and requested additional information about whether these were secondary infections acquired from other people who had traveled. In addition, she requested further information about the mention that cholera could become a bigger problem in the future.

Referring to Slide 9, Dr. Collins noted that 64 cholera cases were reported during that 6-year period. Of those, 88% of those were travel-associated. Typically in this surveillance system, they see that other cases were associated with Gulf Coast seafood consumption or swimming in Gulf Coast waters where *Vibrio cholerae* is endemic. Occasionally through surveillance, cases are identified without a particular cause identified. However, she suspects the others were associated with Gulf Coast waters as well. In terms of the potential for becoming a bigger problem in the future, cholera had not occurred in Haiti for a very long period of time until the hurricane in the early 2000s after which there was epidemic cholera in Haiti. Most travelers to the US currently do not travel to cholera endemic areas, but *Vibrio cholerae* has a reservoir. Therefore, it can be hard to predict what areas might become unsafe cholera risk areas over time. It is important to remember that cholera is under-reported in the US and globally.

Dr. Bell requested further information about whether there have been any rare SAEs noted and if so, in general what the reports look like with this vaccine once the vaccine has been used.

Referring to Slide 68, Dr. Collins indicated that they had their colleagues in the Immunization Safety Office (ISO) retrieve data from when the vaccine was approved in 2016 through February 2021. These data were generated using the Bayesian mining process. The only events identified that occurred more commonly with Vaxchora® than with other vaccines related to the fact that this is an oral vaccine that requires people to not eat close to ingestion. People may have consumed food in closer proximity than was recommended. The product administered to patients of an inappropriate age may have been one issue for patients less than 18 years, and theoretically could be an issue for patients ≥65 years of age. That is, some of these seem to be related to administration and not SAEs. Preparation and administration are complicated, which drove part of the WG's discussion about recommending that the vaccine be administered in a travel clinic.

Dr. Sanchez added that clearly, the intent is that this administration of this vaccine in a travel clinic is anticipated to facilitate inherent issues with administration. The WG debated whether this is a public health problem because there are so few cases in the US. However, it may be a public health problem for individuals who are traveling to cholera endemic areas depending upon the lifestyles they choose in those areas. He would prefer to a recommendation rather than shared decision-making because of the AEs of cholera.

Dr. Loehr inquired as to whether Dr. Barnett from the International Society for Travel Medicine (ISTM) could comment on whether ISTM has an opinion.

Dr. Barnett (ISTM) reported that while she did not think it would be used in a travel medicine situation for all traveling children, members of the ISTM would be happy to have this vaccine available to eligible children who will be in an outbreak or other situation in which they may be exposed to cholera.

Dr. Brooks asked how many doses per year of vaccine are utilized currently for individuals ≥18 years of age. Dr. Collins did not have the number of doses administered annually on hand, but indicated that he would try to find out and would circle back to ACIP with that information.

Dr. Grogg (AOA), also an ISTM member, pointed out that many travel medicine clinics have closed because of COVID-19 and the limited supply of Yellow Fever (UF) vaccine. As a pediatrician, he said he was in favor of having a pediatric vaccine and would recommend that the vaccine be available, but the recommendation about administration at a travel medicine clinic may be a barrier.

Dr. Lee thought the context of a recommendation for those who are going to endemic areas made a lot of sense and felt that the shared clinical decision-making was for when the benefit-risk balance to an individual is uncertain. In this case, what is uncertain is the risk based on where someone travels and what is/is not known about the prevalence of cholera in those areas. For those traveling into a high-risk area, it seems like a straightforward recommendation would be worthwhile given what was presented about the benefit-risk balance. Additional clinical considerations or clinical guidance from CDC or ISTM to help clinicians understand the actual risk would be beneficial. She also asked about the durability of immunity, when revaccination would be recommended, and if that information would that be provided in the clinical guidance or in other areas.

Dr. Collins indicated that there would be a clinical considerations presentation during the next meeting prior to any votes. There are no data available about safety or efficacy in preventing cholera with boosters for the current formulation. Little is known about the duration of protection beyond the 3-month period that was evaluated in the oral challenge study in adults aged 18-45 years. ACIP does not currently have a recommendation for adults regarding the use of booster doses and is unlikely to make such a recommendation for children given the limited data.

Dr. Lee emphasized that it would be helpful if there is an opportunity to collect at least immunogenicity data in terms of long-term follow-up.

Dr. Sanchez emphasized that endemic cholera is not reported in many of the developing countries and a lot of cholera outbreaks occurring in endemic countries are not being reported to the World Health Organization (WHO), so they are likely seeing only the “tip of the iceberg.” Therefore, this vaccine will be important as a contributor to travel medicine vaccines.

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 US, there are no existing ACIP TBE vaccine recommendations. The TBE Vaccine WG was formed in September 2020 to

review the use of TBE vaccines in US persons traveling abroad and laboratory workers. The TBE Vaccine WG's Terms of Reference (TOR) are to: 1) review information on TBE, including its epidemiology, clinical presentation, diagnosis, treatment, and outcome; 2) review data on infection risk and burden for travelers and laboratory workers; 3) review data on vaccine safety, immunogenicity, and effectiveness; 4) provide evidence-based recommendation options for ACIP; 5) identify areas in need of further research for informing potential future vaccine recommendations; and 6) publish ACIP recommendations in the *Morbidity and Mortality Weekly Report* (*MMWR*). 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 civilian US travelers, laboratory workers, and US military personnel. In September 2021, the WG presented the immunogenicity and safety of Pfizer's TBE vaccine. The focus of the January 12, 2022 session was on follow-up of ACIP member questions regarding the immunogenicity of 1 or 2 doses of TBE vaccine, the EtR Framework for TBE vaccine for persons who travel abroad and laboratory workers. The plan is to be prepared to have an ACIP vote on vaccine recommendations and finalize the *MMWR* in February 2022 before the next tick season.

Immunogenicity of 1 or 2 Doses of TBE Vaccine

Dr. Susan Hills (CDC/NCEZID) presented some data to follow up on ACIP member questions from the September ACIP meeting. During that meeting, several members commented on the challenges of the TBE vaccine schedule in terms of travelers having sufficient time to finish the primary series of vaccine before travel, given that a minimum of 5 to 6 months are needed to complete the 3-dose primary series. The WG discussed this issue and agreed with this concern. In terms of the seropositivity rates following each of the doses in the primary series in adults, one study[2] showed that after only 1 dose of vaccine right before the second dose was given at 12 days, the seropositivity rates were 52% percent for younger subjects aged 16-49 years and 27% for older subjects aged 50-79 years. Once Dose 2 was administered, seropositivity rates measured 3 weeks later had increased to 97% in the younger age group and 88% in the older age group. Subsequently, at 3 months and 5 months after Dose 2, seropositivity rates had dropped to 71% to 79% for the younger age group and 61% to 65% for the older age group. After Dose 3 was given, seropositivity rates measured 3 weeks later had increased to 99% to 100% in both age groups. While there is no formal TBE correlate of protection, a neutralizing antibody titer of ≥10 is commonly considered to be a surrogate marker of protection. Similar to the seropositivity results, geometric mean titer (GMT) data from the same study were higher in the younger adults compared to older adults. In both groups at 3 weeks after Dose 2, GMTs were moderate. At 3 months and 5 months after Dose 2, the GMTs had dropped and were close to the seropositivity cutoff of 10. When Dose 3 was given, there was a robust response with a 9- to 15-fold increase in GMTs.

Data from a study[3] with children aged 1-11 years with data at 1 and 5 months after Dose 2 and 1 month after Dose 3 show that seropositivity rates decreased only slightly from 100% at 1 month after Dose 2 to 95% at 5 months after Dose 2. Similar to the adult results, the GMTs decreased notably during the same period from 237 initially to only 40 at 5 months after Dose 2. When the third dose was given, the GMTs increased more than 13-fold. Other studies had similar patterns.

[2] Loew-Baselli A et al. Vaccine 2011;29:7307-19/FDA Memo
[3] Pollabauer EM et al. Vaccine 2010;28:4680-5; Prymula R et al. Hum Vaccin Immunother 2012;8:736-42

In summary, after only 1 dose of TBE vaccine, seropositivity rates and GMTs are low. This suggests 1 dose is unlikely to provide much protection for a traveler. After the second dose, seropositivity rates and GMTs initially increase then decrease in the following months. There is clear variability in the response by age group, with lower rates and GMTs in older adults. While there is no correlate of protection for TBE, it is concerning that GMTs are close to the seropositivity cutoff within a few months of the second dose. Administering the third dose of the primary series results in an increase in seropositivity rates and a notable boost in the GMTs, often with a 10-fold or higher increase in GMTs. After considering and discussing these data and findings, the WG concluded that it is important to recommend that a 3-dose primary series be completed prior to a traveler's departure in line with the Food and Drug Administration (FDA)-approved schedule if at all possible. However, the results from studies on immunogenicity after only 1 or 2 doses will be included in the *MMWR* documents to allow healthcare providers (HCP) to counsel individual travelers if they are not able to complete the full series prior to travel.

EtR Framework for Travelers & Laboratory Workers

Dr. Susan Hills (CDC/NCEZID) next provided a very brief reminder of the key information on TBE and TBE vaccine and discussed the evidence the WG considered in drafting the TBE vaccine recommendations. TBE is a flavivirus related to Powassan virus. There are 3 main subtypes of TBE virus (European, Siberian, and Far Eastern) 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.[4] 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 locally 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.[5] The main risk period occurs in the warmer months from April through November when ticks are most active.[6] 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 invasive disease occurs, it can have potentially high fatality rates of 1% to 20% and high sequela rates of 10% to 50%.

The TBE vaccine manufactured by Pfizer as TicoVac™ was approved by the FDA in 2021 for use in persons ≥1 year of age. Although only recently licensed in the US, the current adult formulation (0.5 mL) for persons aged 16 years and above and pediatric formulation (0.25 mL) for children and adolescents up to 15 years of age have 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.

Now turning to the EtR framework and the WG's key considerations for development of draft recommendations for persons who travel abroad. The policy question was, "Should TBE vaccine be recommended for use in persons aged ≥1 year traveling to or residing in TBE risk areas?" The first domain of the EtR the WG addressed was the question, "Is TBE of public health importance?" For this domain, 5 key factors were considered. The first regarded whether is of public health importance for residents of some TBE endemic countries. For example, the median incidence of reported TBE cases in European countries that reported data in 2019 was

[4] https://www.ecdc.europa.eu/en/tick-borne-encephalitis
[5] Dobler et al, Wien Med Wochenschr 2012
[6] Source: https://www.ecdc.europa.eu/en/publications-data/epidemiological-situation-tick-borne-encephalitis-european-union-and-european

1.3 per 100,000 population. Second, TBE cannot be considered an important public health problem overall for US persons traveling to risk areas. With a median of 1 diagnosed case per year among millions of travelers to TBE endemic countries, the estimated risk of TBE is less than 1 case per million trips. However, TBE is an important concern for certain subpopulations of travelers who have itineraries/activities that put them at higher likelihood of receiving a tick bite, or because they plan to live in or travel recurrently to risk areas. TBE can be a very severe disease with variable but potentially high case fatality and sequelae rates and there are no specific antiviral treatments. TBE is more an individual rather than a societal concern. TBE vaccine will be paid for out-of-pocket by most civilian travelers, given that travel vaccines are generally not covered by insurance. TBE vaccine will not be covered under the Vaccines for Children Program (VFC). Therefore, the individual traveler will bear both the cost and the benefits of vaccination. The WG's conclusion on public health importance was that it "varies. For the US traveling population overall, TBE is not a problem of public health importance. However, it is a concern for certain individuals who are at a higher risk of a severe disease, which can result in death or permanent sequelae.

For the second domain of benefits and harms the WG considered the results based on the GRADE assessments and the following questions:

- ❑ How substantial are the desirable anticipated effects?
- ❑ How substantial are the undesirable anticipated effects?
- ❑ Do the desirable effects outweigh the undesirable effects?

The outcomes the WG aimed to assess included protection from disease after the 3-dose primary series, and after a booster dose at 3 years after the primary series. However, there are no efficacy data for TBE vaccine and low TBE incidence would make such trials infeasible. In the absence of efficacy data, the WG reviewed immunogenicity data that noted 2 limitations. While a neutralizing antibody titer of ≥10 is typically used to indicate seropositivity, there is no established immunologic correlate of protection to TBE. Second, the vaccine is based on a European subtype TBE virus, which is 1 of the 3 main TBE virus subtypes and likely has cross-protection against the other 2 TBE virus subtypes transmitted in the Eastern part of the TBE endemic region. The supporting data are limited. To assess initial seropositivity after the primary series, data were identified from 10 studies (7 adult, 3 pediatric). All were observational studies. At 1 month after the primary series, seropositivity rates were 96% or higher in all but 1 study. When subjects in 1 of the adults and 1 of the pediatric studies were followed up at 3 years after the primary series, which is immediately prior to the booster dose, seropositivity rates remained high at 94%. To assess seropositivity after the booster dose, there were 2 studies (1 adult, 1 children). They all were observational studies. At 1 month after the booster dose, seropositivity rates were 100%. At 5 years, they were 94% or higher and at 10 years, seropositivity rates were 85% or higher. Based on these data, the WG considered the desirable anticipated effects to be large.

In terms of how substantial the undesirable anticipated effects are, the WG reviewed data on SAEs. In 4 RCTs and 9 observational studies among almost 7,000 adult and pediatric subjects who received at least 1 dose of vaccine in the primary series, there were no vaccine-related SAEs reported. In 3 active post-marketing surveillance studies among almost 2,700 adults and children, there was 1 vaccine-related SAE of a febrile convulsion in a child. The possible contributing factors included rhinopharyngitis, gastroenteritis, and otitis media. Based on these data, the WG considered the undesirable anticipated effects to be "minimal."

Regarding whether the desirable effects outweigh the undesirable effects, the WG noted that there were high seropositivity rates and no serious safety concerns, and that vaccination can prevent a rare but potentially serious and untreatable disease. However, the WG also noted that HCP should discuss the balance of desirable and undesirable effects with individual travelers based on their itinerary and activities. As with any vaccine, rare SAEs can occur. For some travelers, even a low probability of an SAE might be higher than their disease risk. Therefore, vaccination should be targeted to travelers at higher risk for disease. Overall, the WG determined that if the vaccine is used in line with the proposed recommendations, the balance of desirable and undesirable effects "favors the intervention."

The GRADE assessment results were used to determine the overall certainty of the evidence for the critical outcomes. For protection from TBE, the overall certainty of the evidence was 3 (Low). Certainty was downgraded based on results being from observational studies only, and for indirectness because there were no efficacy data. The likelihood of protection from disease was based on seropositivity with no established correlate of protection and there is unconfirmed cross-protection against non-European TBE virus subtype. Certainty was upgraded because of the magnitude of effect. For SAEs, the overall certainty of the evidence was "moderate." Some data were available from RCTs, but evidence was downgraded because of the risk of bias from inadequate blinding.

For the domain of values, 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?

For this domain, 3 studies informed the WG's response. The first study[7] investigated TBE vaccination practices of non-US adults who had traveled to a TBE endemic country. This included travelers from Canada, Germany, Sweden, and the United Kingdom (UK). Among 365 travelers who had engaged in an activity that put them at higher risk of TBE, only 15% had received a vaccine before their trip. The most frequent reason given for lack of vaccination was a perception of insufficient risk. These results suggested that even in a higher risk setting, travelers had variable attitudes toward the value of vaccination. A second publication[8] investigated TBE vaccination rates among residents of Sweden where TBE is endemic and TBE vaccine must be paid for out-of-pocket. TBE vaccination rates were 33% in residents of risk areas and 18% in other areas. This again suggests variable attitudes toward vaccination, even in the context of ongoing risk. The WG reviewed 1 publication of US population perceptions of vaccinations when considering Japanese encephalitis (JE).[9] The WG considered this study because there are many similarities between JE and TBE and JE vaccine and TBE vaccine. These include that the disease risk for travelers is very low, the potential impact of disease is high, both vaccines are safe and effective, and both vaccines are high cost at over $250 per dose. When participants were presented with information describing the low risk of JE but the potentially high consequences of disease, the vaccine immunogenicity and safety, and information on the vaccines cost, the responses from the almost 6,500 participants indicated

[7] Marano C et al. Perceptions of tick-borne encephalitis risk: a survey of travelers and travel clinics from Canada, Germany, Sweden and the UK. J Travel Med 2019;26(Suppl 1):S10–S16

[8] Slunge D. The willingness to pay for vaccination against tick-borne encephalitis and implications for public health policy: Evidence from Sweden. PLoS One 2015;10:e0143875

[9] 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;38:2117–21

43% were very or somewhat unlikely to be vaccinated, 25% were unsure, and only 32% were very or somewhat likely to be vaccinated. When noting factors important in their decision, some valued the availability of vaccine to prevent a disease with potentially serious outcomes and no specific treatment. Others were less likely to value an expensive vaccine with the possibility of rare serious side effects. Based on these findings, the WG determined that it is likely the US traveler population will have variable opinions on whether the desirable effects of vaccination are large relative to undesirable effects. The WG similarly determined that there likely will be important uncertainty or variability in how much people value the vaccine.

Regarding the domain of acceptability of TBE vaccine, no formal evaluation of acceptability was undertaken. However, the WG discussed acceptability for the groups considered to be the key stakeholders, including US travel medicine and other HCP providers. The WG considered that TBE vaccine is likely to be acceptable to US HCP based on the attitudes and practices of European healthcare providers. TBE vaccine has been available in Europe for decades and is actively recommended by European HCP for higher risk travelers to endemic areas. For the public, TBE vaccine recommendations are expected to be acceptable because vaccine availability gives an option, in addition to tick bite prevention measures, for protection from a potentially severe disease. The WG therefore thought the intervention would be acceptable to key stakeholders.

For the domain of resource used, the WG considered whether TBE vaccination is a reasonable and efficient allocation of resources. A cost-effective analysis for TBE vaccination of travelers has not been conducted. Most travel vaccines are not cost-effective. TBE vaccines for travelers are not likely to be cost-effective because the number of US travelers needed to be vaccinated to prevent 1 case is very high. However, the WG noted that cost-effectiveness considerations are less relevant for a travel vaccine when the decision on vaccination is for an individual traveler and not being made for the population as a whole, when vaccine is typically paid for by the traveler themselves and is generally not paid for by insurance, and when the vaccine is not covered under the VFC Program. Cost-effectiveness analyses have been conducted in some endemic areas, but the results have been variable. Programs are often not projected to be cost-effective, with incidence and vaccine cost being important variables in predicting cost-effectiveness. The WG also considered resource allocation issues. Vaccine recommendations targeted to higher risk groups are probably an efficient use of resources, as the financial implications of vaccine purchase will be borne by travelers most at risk of a severe disease who will, therefore, receive the most benefit. However, even among higher risk travelers, there will be variability in whether vaccine purchase is a reasonable allocation of resources based on several factors, including the actual risk of disease, the likelihood of use of other tick prevention measures, and opportunity costs such as buying TBE vaccine versus purchasing travel insurance or other vaccines with available financial resources. The WG also considered under this domain that healthcare costs for management of TBE presenting as neurologic illness are potentially large. Based on these factors, the WG determined that whether TBE vaccination is a reasonable and efficient allocation of resources “varies” depending on the individual traveler.

With respect to the d of equity, TBE vaccine will cost more than $750 for a primary series and will be paid for out-of-pocket by most travelers or by insurers or employers in some cases. Currently, the approach to TBE prevention for US travelers is tick bite prevention measures. Vaccine available would lead to health disparities because some travelers will have the resources to pay for the vaccine or have it paid for and others will not. However, the absolute risk of TBE is low and only a small number of travelers will require vaccinations. Overall, vaccine availability will not cause substantial population disparities. Additionally, the WG noted

that TBE vaccination recommendations cannot address this issue. The WG's conclusion was that the impact on health equity would be "probably reduced" by TBE vaccine availability.

For the domain feasibility, the WG considered whether implementation of TBE vaccination is feasible to implement. While the WG felt that administration of TBE vaccine would be feasible as part of a pre-travel consultation, they felt the key barriers to implementation would be that the primary vaccination schedule requires a minimum of 5 months to complete. Secondly, they felt that many travelers to TBE endemic countries, particularly Europe, are unlikely to consult am HCP before travel or to consult with a non-specialist HCP. There might be a lack of provider understanding about which travelers are at highest risk for TBE and might benefit most from vaccination. To address this, CDC will be posting resources on its website once recommendations are approved. The decision overall was that the intervention is "probably feasible" to implement.

Overall, when considering all the domains of the EtR Framework, the WG determined that the "desirable consequences probably outweigh the undesirable consequences in most settings." Policy option category the WG would opted to propose was that "TBE vaccination for persons who travel abroad should be based on shared clinical decision-making." The WG's draft recommendations for ACIP consideration is:

> *TBE vaccine should be considered for persons aged ≥1 year traveling or moving abroad to TBE endemic areas if they are at risk of TBE virus exposure through engaging in outdoor activities during the transmission season in environments where ticks are likely to be present.*

The recommendations will be accompanied by additional information to ensure that HCP can have informed discussions with travelers about TBE vaccine and disease prevention. This will include information on factors that increase the risk of infection, including a table with detailed information on risk factors for TBE virus exposure; the need for all travelers to take precautions to avoid tick bites; advice to avoid consumption of unpasteurized dairy products; and information on general factors to consider in the decision whether to vaccinate, such as the likelihood of future travel to TBE endemic areas and the rare occurrence of TBE at its potentially high morbidity and mortality.

Regarding the EtR Framework for TBE vaccine use among laboratory workers, TBE virus transmission occurred through virus aerosolization either during laboratory procedures or handling of infected animal waste. Transmission through accidental percutaneous or mucosal exposures is possible. At least 46 laboratory-acquired TBE virus infections were reported globally prior to 1995. Among these, at least 4 occurred among US laboratory workers—all before 1979. Currently, fewer than 10 laboratories in the US work with TBE virus for diagnostic or research purposes. Although research activity might increase with the availability of a vaccine.

The policy question the WG considered was, "Should TBE vaccine be recommended for use in laboratory staff working with TBE virus?" The population for vaccination was considered to be persons working with TBE virus for diagnostic or research purposes and having a scientific understanding of disease and vaccines. The same GRADE assessment for outcomes of vaccination was used as was used for travelers. For the first domain regarding whether TBE is a public health problem, TBE cannot be considered of public health importance overall, given that only 4 cases of laboratory-acquired infection have ever been reported in the US. However, for laboratorians working with TBE virus, there is a risk of a severe disease that can result in death

or permanent sequalae.

For values, the WG considered that scientists are likely to consider the desirable effects to be large relative to the undesirable effects since they will understand the risks of disease and risks and benefits of vaccination. The WG did not think that there is likely to be important variability among scientists. TBE is likely to be accessible to key stakeholders, including occupational health directors, laboratory workers, and other researchers because its availability will improve safety and remove a barrier to research.

For the domain of resource use, the WG felt that TBE vaccination was a reasonable allocation of resources because there are only a limited number of staff working with TBE virus and vaccination is a small cost to pay to avoid the potentially serious impact of a worker becoming infected. The WG thought that equity probably would be increased as TBE vaccine will likely be paid for by employers and will improve safety for staff at occupational risk of a severe disease. The WG also thought that vaccination would be feasible to implement as it will likely build on existing occupational health programs for laboratory workers.

Overall, when considering all of the domains of the EtR Framework, the WG determined that the desirable consequences of TBE vaccinations for laboratory workers clearly outweigh the undesirable consequences in most settings. The policy option category the WG proposed was is that TBE vaccination is "recommended" for laboratory workers. The draft recommendation for ACIP members' consideration is:

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

The recommendations will be presented with additional text to provide clear information for implementation, including noting that a local institutional biosafety committee should undertake a risk assessment of the potential for exposure to TBE virus, considering the type of work to be performed and the biosafety level at which work is being conducted. The vaccination is not required for workers handling routine clinical samples.

In terms of next steps, the WG anticipates asking ACIP members to vote on the TBE vaccine recommendations during the February 2022 ACIP meeting prior to the next TBE virus transmission season. Following the meeting, the *MMWR* documents will be finalized and published.

Discussion Summary

Dr. Lee asked with 20 years and 75 million doses administered whether there are any post-marketing efficacy or safety data available from other countries that could help inform ACIP's decision-making and augment the clinical trial data.

Dr. Hills indicated that there are some VE data, but none are directly relevant to the Pfizer vaccine. There are 2 vaccines available in Europe, one of which is the Pfizer vaccine. Some of the VE data from studies conducted in areas where there is availability of both vaccines are not directly relevant to the Pfizer vaccine. In Austria, 85% to 95% of vaccine use was of the Pfizer vaccine. When the VE study was conducted, VE was higher than 90%. The WG reviewed and discussed those data and were reassured about the high VE. In addition to the limitation of there being 2 vaccines, the schedule used in Austria was slightly different. In terms of safety data, over 75 million doses have been administered over a period of 20 years. While there is no

formal publication, the manufacturer has a safety database that ACIP has seen. However, a limitation is that data reported to the manufacturer are more likely to be those in which an AE or SAE has occurred. CDC has reached out to colleagues in Europe several times to ask if they have any national-level reports or local publications available to which CDC could access. It has not been possible to obtain any additional data from them to date, primarily because they have been actively involved in the COVID-19 response, but they have responded that there is confidence that it is a safe and effective vaccine.

Taking a step back from TBE in particular, Dr. Lee suggested considering a process for how to incorporate data for well-established vaccines into the EtR Framework to assist ACIP with the decision-making process. She reminded everyone that she expressed her opinion previously about shared clinical decision-making versus a recommendation for use. Speaking only for the travel vaccines, she requested that her fellow committee members provide their perspectives on the use of shared decision-making in the context of travel vaccines and when that seems appropriate. Her feeling at this point was that if the benefit/risk balance made sense and high-risk situations could be reasonably defined, it should be a recommendation.

Dr. Poehling reported that the WG had a robust discussion about this and there were pros and cons in all directions. The thought process that led the WG to the draft recommendation was that TBE vaccine is relatively similar to the JE vaccine in that it is recommended for few persons, which is an individual benefit. With that in mind, the thinking was that this would involve shared decision-making. She called upon WG member Dr. Chen, who is a travel medicine specialist, to elaborate further.

Dr. Chen said he had gone back and forth trying to interpret and understand the shared decision-making model versus a recommendation. While he would rather have a unified approach, the WG discussed the variability of risk and how to clearly define that. That is the role of the travel clinic consultation. Although limited data were available, the WG had confidence in the safety of the vaccine and a reasonable belief that it has good efficacy. It is a question of how this recommendation is framed. Is it from the context of a population-wide recommendation in that the population would obtain benefit versus the individual? Many segments of the population that are not traveling and certainly would not receive any benefit. There is a wider context in which many travel vaccines for endemic diseases exist in other countries. The WG has gone back and forth trying to understand, but Dr. Chen thought it would be helpful to address this again in a unified fashion.

Dr. Sanchez agreed that although an individual may have a choice with respect to receiving the vaccine or not, it seemed that ACIP should make a firm recommendation that individuals should receive the vaccine under certain circumstances that pose high risk rather than having shared decision-making. It is always up to the individual to decide whether to receive a vaccine. Given the evidence available and what is being done in countries where TBE is endemic, he thought people deserved a formal recommendation from the ACIP. He asked whether countries such as Austria and others that are administering this vaccine have formal recommendations that the entire population should get it and what age they are receiving TBE vaccine.

Dr. Hills indicated that there is substantial variability in recommendations in Europe for TBE vaccine use and for whom the vaccine is recommended. When there are recommendations, they are variable from country-to-country. Approximately 50% of countries with endemic TBE have recommendations. Austria has a recommendation for the entire population but is the only country with a national recommendation. Germany has a recommendation for vaccination

for persons who live in higher-risk areas in the country, and they define those higher-risk areas. Some countries have a recommendation only for those who are occupationally exposed, while other countries have a recommendation only for those who are going to be undertaking extensive outdoor activities. Recommendations for entire populations are rare. Vaccination recommendations are made in Austria beginning with young children ≥1 year of age. Germany also has a recommendation that begins with young children. Recommendations would be only for adults in countries that recommend the vaccine only for those at occupational risk. Uptake in Austria is over 80%. In other countries, uptake is typically low at about 25%. There is variability in uptake not only due to personal choice, but also because it is not reimbursed in most places and people would have to pay out-of-pocket.

Dr. Brooks recalled that the vaccine is a 3-dose series with a booster and requested further information on duration of protection and when the booster would be needed.

Dr. Hills indicated that following the 3-dose primary series, seropositivity remains high for several years at very good rates. The booster is recommended 3 years after the primary series. After the booster dose is given, seropositivity remains very good for at least 10 years. Again, there is no correlate of protection.

Dr. Kotton noted that she has engaged in a fair amount of travel medicine, predominantly in immunocompromised patients. She was struck by the overall paucity of cases, with only 11 cases in 20 years in civilian travelers and 9 cases in military personnel over a 14-year period. Therefore, her preference would be shared clinical decision-making rather than an official recommendation. While it seemed rare that the vaccine would be warranted and would not be routinely given, she would be happy to have it available for cases in which she feels a patient may be at risk.

Dr. Long thought they were confusing what shared decision-making might entail in this regard. She thinks of shared decision-making in cases when there is a potential difference in how an individual values the vaccine or values having protection. In this situation, the only decision-making would be the level of someone's risk. That might be very difficult to define on a population basis, but not too difficult to define on an individual basis in terms of degree and length of exposure in areas where the virus is endemic. There should be a clear recommendation that those at highest risk should be vaccinated. The difficulty will be in differentiating individuals or making rules that would define high-risk and length of exposure. She thinks of that as individual value rather than shared decision-making and would prefer to make a recommendation that does not result in variability in use of the vaccine.

Dr. Lee agreed with the statement about distinguishing between risk-based recommendations and shared clinical decision-making recommendations.

Dr. Virginia Caine asked whether it is known that at 10 years, GMTs are sufficient for protection or just that there is antibody and lack of clarity about the level of protection.

Dr. Hills indicated that the GMTs were assessed for up to 3 years after the primary series and up to 10 years after the booster dose. Given that there is no formal correlative protection for TBE, it cannot be said definitively that somebody with a particular neutralizing antibody titer is definitely protected. There are no VE data, but it is assumed that a GMT of ≥10 equates with protection. Laboratory workers would be recommended to complete the primary series and consider a booster dose. There may be consideration of potential additional doses for laboratory workers who are working with live TBE virus and have neutralizing antibody titers <10. There

will be additional information for laboratory workers indicating that a local biosafety committee should be involved in considering the level of risk for laboratory workers depending upon the activities they are undertaking. That is considered to be a critical part of consideration for vaccine recommendations for laboratory workers.

Dr. Baker (IDSA) noted that some viral vaccines that are recommended as a 3-dose primary series. Given the data shown on serology after the second dose, she wondered whether any data were available on someone who has received 2 doses and were then exposed whether in terms of whether that might prevent disease. Knowing that there is no correlate of protection, she asked whether there is any hint that if someone has a reasonable GMT after 2 doses they might be protected based on serology. In addition, she asked if/how insurance might be impacted with shared decision-making versus recommendation.

Dr. Hills indicated that there are some VE data, but not specifically for the Pfizer vaccine given the availability of more than 1 vaccine in Europe. While there are no data to look closer at what the considerations might be, it is known that seropositivity rates are variable by age. Older persons do not have seropositivity rates or neutralizing antibody titers as high as younger people, so age would be one factor to consider. Another factor would be the time point after the second dose (e.g., 1 month, 5 to 6 months, et cetera). It is somewhat nuanced, but there are no data to answer this definitively. It is known that people who receive 2 doses who may be traveling during the subsequent TBE virus transmission season likely would have seropositivity. Given the various nuances in terms of age, how long somebody may be traveling, and that their neutralizing antibody titers might decrease over time, the WG was not willing to make a recommendation for just 2 doses for travelers. However, this type of information will be provided so that HCP can refer to that when counseling travelers.

Dr. Lee pointed out that other issues that are relevant to travel vaccines are equity, access, and affordability. Recognizing how the current system is, ACIP should not be asking individuals for any particular disease to have out-of-pocket costs if they are at high risk for that illness or are hospitalized upon return from travel. While this is a basic issue that cannot be fixed through recommendations, ACIP should recognize that equity, access, and affordability are driving issues that likely would contribute to shared clinical decision-making around the use of TBE vaccine. While they do not want cost to be a factor in someone's decision, practically it could be. This particular category is challenging because it means different things to different people. Her hope was to use a consistent approach to thinking about the framework for when the vaccine is appropriate to use and advocating for something that clarifies whether there is a benefit. In the case of a high risk of vaccine AEs or perhaps inconsistent or incomplete effectiveness, she does believe it would be appropriate recommend shared clinical decision-making. However, ACIP should be consistent with its risk-based recommendations from the past for routine and travel vaccines.

Dr. Barnett (ISTM) asked whether there are now or will be data about shortened dosing intervals for last-minute travelers and observed that this vaccine differs somewhat from other travel vaccines. Travelers to Europe do not typically go to travel clinics for preparation. Therefore, perhaps a wider range of providers should be asked for advice about this vaccine. She agreed with all who said that the recommendations will need to be very clear and specific about who would be at greatest risk and would need this vaccine. The JE vaccine recommendations were written with that in mind, but that vaccine is given primarily in travel clinics. ACIP needs to wrestle with the issue of whether 2 doses would be sufficient for a traveler who is leaving in 6 weeks, because the provider will be grappling with the issue of whether 2 doses is better than no doses.

Dr. Hills reiterated the concern about 2 doses in terms of variability by age. Some clinicians may not be comfortable telling an older person that they will have very good protection for 6 months after the second dose. A person who is traveling for 8 months as opposed to 1 month is going to have variable seropositivity over that period. This was one of the WG's considerations for the importance of receiving the third dose if at all possible. The FDA-approved schedule is for 3 doses. All of this information will be made very clear in the *MMWR* documents.

Dr. Daley emphasized that if possible, ACIP should strive for consistency in the way they approach vaccines recommended for international travelers. It seemed to him that clinical decision-making was not designed or intended for this purpose. It was striking that there were different interpretations of clinical decision-making among WG and ACIP members, implying that there also would be different interpretations by providers and patients. To him this boiled down to what he would say to the patient in front of him who self-identifies as going to a high-risk area, so he was leaning toward "recommended."

Dr. Poehling noted that one of the conversations the WG had was that some people will present who will be able to get only 2 doses before departing the US. Those who are going to be in an endemic area for a long time can get their third and booster doses in that nation.

Dr. Hills presented some additional data that may help the ACIP members understand why the WG proposed "shared clinical decision-making." Referring to Slides 103, 104, and 107, she pointed out that the problem with proposing a "recommendation" was that it would be difficult to define high-risk groups and then make a recommendation for those groups without the conversation happening between the traveler and the HCP. There are no apparent cutoffs in terms of age, duration of travel, undertaking high-risk activities, et cetera that would make sense to include in recommendations. For the 11 US travelers with TBE, the median duration of travel was 18 days or roughly 2.5 weeks. The range of travel duration was from 7 days up to 2 months. What did appear to be more important than duration were the activities in which travelers were involved, but there was still variability within that whole group. Activities were unavailable to for 3 of the 11, but the remaining 8 travelers all reported activities that put them at higher risk for the tick bites (3 hiking, 2 substantial outdoor exposure in rural areas, 1 camping, 1 fishing, 1 trail running). While activities were important, they did not define the whole group. Given the small number of cases, the WG was reluctant to recommend anyone going to go to Europe who thinks they might hike once to be vaccinated. This led to the WG's consideration that it would be better to propose shared clinical decision-making, so that the provider can have a discussion with the traveler. The WG also considered whether the vaccine should be recommended to everyone moving to a TBE endemic country to take up residence since the increased duration of time in an endemic area might increase their risk. However, it is more related to their activities than their duration of travel. Unlike mosquitoes, one must go into a tick habitat to be exposed to ticks. The vast majority of people who are traveling to Europe are not going to be at risk. Again, even the European recommendations are not uniform—even for those living in areas with TBE virus transmission. There are some major limitations with trying to estimate the TBE risk for US travelers to Europe or China. Multiple assumptions had to be incorporated because some of the data needed for the calculation were lacking. Percentages were not available for all travelers to Europe who visit at least 1 TBE endemic country, visit an endemic area within a TBE endemic country, and/or undertake an activity that might put them at exposure to the risk of exposure to ticks. Acknowledging the major limitations up front and thinking about all travelers to Europe, including Russia and China, the risk is about 1 TBE case per 37 million US citizen trips to Europe and China overall. That is clearly a major underestimate because many countries in Europe have no transmission or only sporadic transmission. Though

many travelers would not be at risk, they have to be included in the denominator for that estimate. If the information is incorporated that 78% of trips are during the TBE virus transmission season, which is supported by some survey data from the National Travel and Tourism Office (NTTO), and an assumption that 50% of trips involve travel to at least 1 TBE endemic area within Europe or China, the risk is 1 case per 15 million trips for travelers to endemic areas during the transmission season. Picking up on an earlier comment that ACIP wants to make sure that the recommendations are targeting the appropriate travelers since the risk for US travelers is minimal, it is going to be impossible to define clearly which travelers might need to be vaccinated. Based on the NTTO survey data that say about 15% of travelers to Europe will be exposed to ticks based on undertaking certain activities (e.g., camping, hiking, hunting, fishing, visiting a national park, visiting rural areas, et cetera), the risk comes down to 1 case per 2 million trips for travelers who visit an endemic area within a TBE endemic country during the transmission season and undertake an at-risk activity. If the assumption is included that there might be 10 times as many TBE cases occurring than are diagnosed, which is unsupported by data, this may be an overestimate. CDC is the only place in the US where diagnostic testing for TBE is done and the agency receives only about 10 to 15 samples per year for testing. Incorporating that assumption, the risk is 1 per 219,000 trips for travelers who visit an endemic area within a TBE endemic country during the TBE transmission season. The available data were highly influential in the WG's desire to propose shared clinical decision-making rather than potentially misleading the traveling population by suggesting that everyone going to Southern Germany, for example, may want to be vaccinated. A lot of factors are likely to go into shared decision-making in addition to a traveler's specific itinerary, such as their intended activities, individual personal perception, tolerance of risk, et cetera.

Dr. Loehr emphasized that they should make a distinction between risk and the recommendation for the vaccine. If someone has a high enough risk, they probably should get the vaccine and he was willing to recommend that. Talking about shared decision-making to decide whether someone has a certain amount of risk is not what he considers to be the concept of shared decision-making in the ACIP arena. His concept of shared decision-making in the ACIP arena is situations in which the risk/benefit analysis of the benefit of the vaccine are so close that reasonable people would make different decisions. If they were arguing about shared decision-making being about risk, that was not what he thought they should be arguing about. They should be talking about recommending the vaccine for those who are at risk.

Dr. Bell agreed with the importance of ACIP being clear in their thinking about when to recommend shared clinical decision-making, and she agreed with the overall concept. In this situation, the more she listened to Dr. Hills and the point that Dr. Kotton made, it was not entirely clear to him that they actually could characterize the risk clearly. It sounded in some ways like this is a rare enough disease that there is not a good understanding of the variables about who should get this vaccine and who should not. Perhaps there may be an argument for emphasizing other prevention strategies versus vaccination. She agreed with the points made about differentiating between making a recommendation in the context a travel vaccine when the risk is clear. Based on the information presented, a narrow population would be impacted.

INFLUENZA VACCINE

Session Introduction

H. Keipp Talbot, MD, MPH (ACIP, WG Chair) introduced this session, the focus of which was on influenza vaccines for older adults. She reported that recent WG activities have included ongoing discussions of the systematic review of influenza vaccines for older adults referred to as "enhanced vaccines" and examination of the evidence for high-dose inactivated, adjuvanted, and recombinant vaccines. She reminded everyone that while influenza vaccine is often thought of as one vaccine, it is actually a different vaccine each year with 4 different strains. There also are different manufacturing methods, which makes influenza vaccines complex.

Influenza Vaccines for Older Adults

Dr. Lisa Grohskopf (CDC/NCIRD) presented on influenza vaccines for older adults in terms of the burden of influenza among older adults aged 65 years and older (though some studies may have slightly different age ranges), influenza vaccine efficacy/effectiveness among older adults, challenges in comparing influenza vaccines, and an initial overview of the retrieved findings from the systematic review. She explained that the presentation of the systematic review would be split between 2 meetings due to the large amount of content. Adults ≥65 years of age have long been recognized as being at increased risk of severe illness, hospitalization, and death from influenza and were among the groups that have been included since one of the very first recommendations made by the federal government in the US for routine vaccination of the civilian population. While there had been periodic recommendations previously for pandemics, the *Surgeon General's Recommendation for Influenza Immunization—United States, 1960*[10] was published as a follow-on to everything that occurred during the 1957 pandemic. Adults ≥65 years of age were among the 3 groups addressed in the report and have remained a focus since that time.

Based on surveillance data for the last 4 seasons (2016-2017 through 2019-2020) with substantial influenza activity from FluSurv-NET, a surveillance system for laboratory-confirmed influenza-associated hospitalizations that is updated weekly during influenza season, the highest burden of cumulative hospitalization is borne by persons ≥65 years of age compared to younger adults. Data from the 2013-2014 season through the 2019-2020 season illustrate that even though this age group does tend to have the highest burden, there is variability from season-to-season in terms of severity. To some degree, though not completely fool-proof, it can be assumed generally that H3N2 seasons are likely to be more severe and may be associated with more hospitalizations. H1N1 seasons tend to be somewhat milder, though not always.
If you can hit the next slide. The 2018-2019 season was interesting in that it had an early H1N1 prominence and then about midway changed to H3N2, with cumulative hospitalizations increasing around the February/March timeframe. Older adults were at highest risk for influenza-related deaths in the population during H3N2 predominant seasons.

[10] Burney LE, Public Health Reports, October 1960, Vol. 75(10), page 944

Moving to influenza vaccine efficacy/effectiveness among older adults, this population also tends to be a group for which vaccines do not work as well as in younger age groups. Data from the CDC US Flu VE Network summarizing the overall VE for seasons 2011-2012 through 2019-2020 reflect striking differences between those 65 years and older group and the general population.[11] Fortunately, there are many doses of influenza vaccine among a variety of brands and types. While there were 13 unique brands at one time, this season there are 9. This is due largely to phase-out of trivalent vaccines with one B strain over the last few years in favor of quadrivalent vaccines with 2 B strains. All 9 of the vaccines currently available are quadrivalent for the first time. Persons ≥65 years of age are eligible to receive a vaccine from 8 of the 9 available formulations based strictly on FDA-approved age indications. The only exception is the FluMist® Quadrivalent, which is licensed only for persons aged 2-49 years.

For purposes of the upcoming discussion, the focus was on 3 types of vaccines that are of particular interest for the systematic review. These include Fluad® Quadrivalent and its trivalent predecessor Fluad® licensed for persons 65 years of age and older, Fluzone® High-Dose Quadrivalent and its trivalent predecessor Fluzone® High-dose also licensed for persons 65 years of age and older, and Flublok® Quadrivalent and its trivalent predecessor Flublok® licensed for persons 18 years of age and older. The high-dose inactivated influenza vaccine (HD-IIV3 or Fluzone® High-Dose) was approved in the US in 2009. It was replaced with HD-IIV4 Fluzone® High-Dose Quadrivalent after that new vaccine was approved in 2020 and was first available for the 2020-2021 season. This vaccine contains 4 times the quantity of hemagglutinin per vaccine virus compared with standard-dose inactivated vaccines. That is 60µg per virus as opposed to 15µg, which is to address the issue that those 65 years of age and older tend not to respond as well to influenza vaccines. HD-IIV3 demonstrated superior efficacy to standard-dose FluZone® (SD-IIV3) in a randomized clinical trial conducted among approximately 32,000 participants aged ≥65 years over the 2 influenza seasons of 2011-2012 and 2012-2013. Subsequently, HD-IIV4 was approved after demonstrating non-inferior immunogenicity to HD-IIV3 for the 3 viruses common to both vaccines, and superior immunogenicity to the additional B viruses not present in the trivalent comparators.

The MF59-adjuvanted inactivated influenza vaccine is the US's only adjuvanted influenza vaccine. For this discussion, there are aIIV3 (Fluad®) and aIIV4 (Fluad® Quadrivalent). Though aIIV3 was approved in the US in 2016 and initially available in the 2016-2017 season, it was in use in Europe as early as 1997. aIIV4 was approved in 2020. While both vaccines were available in the 2020-2021 season, only aIIV4 is currently available. This vaccine contains the lipid-in water adjuvant MF59 as a means to help promote a stronger immune response in people 65 years of age and older. The quadrivalent version was licensed on the basis of favorable safety compared with Tdap in a randomized trial of 6,740 persons ages ≥65 years over 2 seasons (Northern Hemisphere 2016-2017 and Southern Hemisphere 2017). For this particular trial, the primary efficacy endpoints were not met as 88% of viruses from culture-confirmed influenza cases in the aIIV4 arm were antigenically mismatched. Efficacy was higher against illness that was defined by a higher fever.

FluBlok® and Flublok® Quadrivalent are recombinant influenza vaccines (RIVs). The recombinant trivalent, RIV3, was first approved in 2013. It was not licensed for persons 65 years of age and older right away. Initially. It was approved for persons 18-49 years of age. Within about a year, persons ≥50 years of age were added. RIV4 was approved in 2017 and was available alongside RIV3 for 1 season before a switch was made to RIV4, which has been the

[11] https://www.cdc.gov/flu/vaccines-work/past-seasons-estimates.html

only RIV available since 2018-2019. RIV4 is a somewhat unique vaccine in that it does not use influenza viruses in its manufacture. It contains hemagglutinin, which is the primary antigen that is responsible for promoting and neutralizing antibody response. Instead of getting that from actual influenza viruses, it is produced by recombinant technology without the use of influenza viruses or eggs. The main efficacy study was conducted with RIV4, which demonstrated efficacy relative to SD-IIV4 in a randomized study conducted among approximately 8,600 persons aged ≥50 years over the 2014-2015 season.

HD-IIV4 (Fluzone® High-Dose Quadrivalent), aIIV4 (Fluad® Quadrivalent), and RIV4 (Flublok® Quadrivalent) have been available in the US for a number of seasons. There are studies supporting the relative benefits of each. The ACIP has not yet made a preferential recommendation for any of these vaccines over any other vaccines. The recommendation is that any IIV or RIV vaccine is appropriate as long as it is an age-appropriate vaccine, and that vaccination should not be delayed to find a specific vaccine when an appropriate vaccine is available. For the last several seasons, there has been discussion in the literature in terms of the studies supporting the relative benefits and the fact that the number, size, and designs of these studies vary. The guidance also has pointed out that comparisons among these 3 vaccines against one another versus laboratory-confirmed influenza outcomes are limited. More recently with the advent of the quadrivalent formulations of these more enhanced vaccines, the guidance also points out that most of the accumulative evidence focuses on HD-IIV3 and aIIV, which are now exclusively available as quadrivalent formulations for which limited research and data have accumulated.

There are a number of challenges inherent in comparing different influenza vaccines with one another. Chief among these is that many elements of influenza vary and can cause VE to vary in any given study. These include varying circulating virus types and subtypes, constant virus mutations and varying degrees of match each season, and the fact that neither of these can be predicted ahead of the season. Influenza vaccine viruses are generally chosen by the World Health Organization (WHO) for the Northern Hemisphere in late February and the FDA meets about that in March. This allows sufficient lead time for vaccine to be produced when the season starts in the Fall. Since these viruses are constantly on the move, this is difficult sometimes to predict in some seasons. There also are host factors such as age/immunosenesence, chronic medical conditions that can interfere with VE, past influenza illnesses and exposures and their impact, and previous vaccination history. For this discussion, most important are viral factors and the simple fact that it is not possible to predict what the influenza is going to be like from season- to-season.

In addition to the fact that VE varies from season-to-season, VE is not static from one season to the next. In addition to variance in the general VE of an influenza vaccine, the relative VE (rVE) of influenza vaccines compared to one another also varies. Comparing the same 2 vaccines in one season and then the next might not have the same result as illustrated by this example of an analysis of CMS data by Izurieta et al:

	Relative VE compared with egg-based SD-IIV4		
Vaccine	**2017-18**	**2018-19**	**2019-20**
HD-IIV3	**9.0 (7.2, 10.6)**	**4.9 (1.7, 8.1)**	**6.8 (3.3, 10.1)**
aIIV3	**3.9 (1.4, 6.3)**	**7.7 (3.9, 11.4)**	**8.2 (4.2, 12.0)**
RIV4	**-**	**-**	**13.3 (7.4, 18.9)**
ccIIV4	**11.0 (7.9, 14.0)**	0.8 (-4.6,5.9)	2.8 (-2.8,8.2)

Izurieta et al have performed 3 consecutive analyses of CMS data for 2017-2018, 2018-2019, and 2019-2020 seasons.[12] These datasets included 12-13 million people aged 65 years and older each season. The analyses compared multiple vaccine types against one another. Because this is a retrospective cohort study, it was not practical to have a laboratory-confirmed influenza outcome. Instead, the primary outcome was VE against influenza-associated hospital encounters, including inpatient stays and emergency department (ED) visits. Other outcomes also were analyzed for each of the 3 papers, which were defined by International Classification of Diseases, Ninth Revision (ICD-9) influenza codes. For 2017-2018 versus 2018-2019 versus 2019-2020, there was some variability in the point estimate of the rVE from one season to the next. These were all rVE for each vaccine against an egg-based SD-IIV4 vaccine. Of note, there were insufficient uptake of RIV4 in the CMS system to be able to generate a reliable VE estimate for the first 2 seasons. Given the influenza activity in 2020-2021, there probably will not be similar estimates from the CMS system or the Flu VE Network. But this is all to just illustrate that relative VE varies as well.

The challenges in comparing multiple vaccines with one another and the fact that VE varies raises some considerations when reviewing the literature. Data from one or a few seasons in any given study might not generalize to all or most seasons. Ideally, data from high-quality, randomized studies conducted over as many seasons as possible are preferred for making health policy decisions. Unfortunately, common study designs, including randomized studies, are associated with some tradeoffs. Randomized studies generally provide the highest quality data in terms of being able to control for potential biases and confounding. They are generally less feasible to conduct over successive seasons, and they are rather expensive due to large sample sizes. While there are examples of RCTs performed over 2 to 3 seasons, conducting them longer than that is typically not practical. Although these studies are less subject to bias and create higher quality data, they are not as feasible to conduct over multiple seasons as observational studies. There are networks in the US like the Flu VE Network and the Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN) that assess hospitalized influenza among adults, Influenza Monitoring Vaccine Effectiveness (I-MOVE) in Europe, and the Canadian Primary Care Sentinel Surveillance Network (CPCSSN). These and other networks use observational methods to examine VE over sequential years. While observational studies are more feasible to conduct over successive seasons using similar methods, they also are more subject to bias, produce lesser-quality data, and can be constrained by uptake of the vaccine(s) of interest.

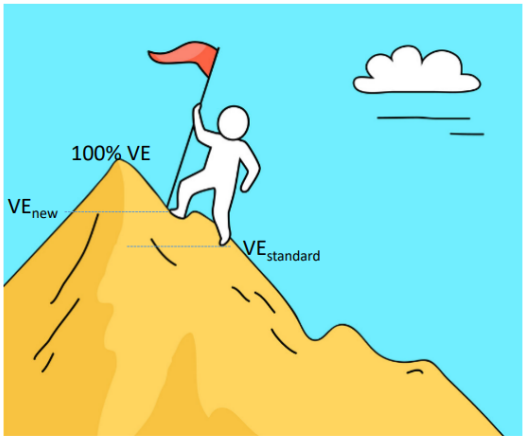
To this a little further to illustrate some of the issues that the WG has observed in the context of the literature they are reviewing, considering observational designs means dealing with more variability in study designs, differences in outcomes and analytic methods, and other tradeoffs. Most of what the WG is dealing with in their particular realm of retrieved papers are retrospective cohort studies and a lower proportion of case-control studies. An advantage of the case-control studies is that generally, they have laboratory-confirmed outcomes. A drawback with these studies is that they often have smaller sample sizes and event counts. For example, the sample sizes might be in the hundreds to thousands. Retrospective cohort studies make up the bulk of the observational studies the WG has been reviewing. An advantage with these is that they potentially can have very large sample sizes in the tens of thousands to millions. The Izurieta CMS analyses mentioned earlier included 12-13 million people per season, which is a sizable number of observations. A disadvantage of retrospective cohort studies is that they are probably not practical to carry out a study like this and expect to have laboratory-confirmed influenza outcomes. These generally include diagnostic code-defined outcomes that are less

[12] JID 2019;220:1955-1964; JID 2020;222:278-287; CID 2021;73(11):e4251-e4259

specific and have greater potential for misclassification and bias than there would be with a laboratory-confirmed influenza study.

Before summarizing the literature, Dr. Grohskopf elaborated on considerations regarding the meaning of rVE, given that it is another one of the challenges associated with comparing vaccines. Although the WG's review includes studies of the vaccines of interest against no vaccine, placebo, and non-influenza control vaccines that would generate an absolute VE for those vaccines, those studies are somewhat in the minority. While the WG will be summarizing those with all of the EtR Framework tables and with the materials that will be presented during the next ACIP meeting, the WG is considering rVE estimates since they are assessing this from a policy standpoint. The formula for rVE is shown here, with VE is illustrated by a graphic courtesy of Dr. Jill Ferdinands:

$$\text{Relative VE} = \frac{VE_{new} - VE_{standard}}{1 - VE_{standard}} * 100\%$$



One of the interesting qualities of this particular calculation is that for any given fixed difference between the new vaccine and the standard vaccine is represented by the mountaineer's stride as he is climbing up the mountain. For any specific fixed difference in new versus standard VE, what the relative VE calculates out to be will depend on how high he already is up the mountain. VE is relative, varies, and it will be associated with baseline VE. In each of 3 scenarios, the difference between the standard vaccine VE and the new vaccine VE is 20% or 0.2. Starting with a baseline VE of 20% calculates outs to a rVE of 25%. If you start out with that same difference between the 2 vaccines with a baseline VE of 40%, rVE would be 33%. Beginning with a baseline of 75% with a difference of 20% would result in rVE of 80%.

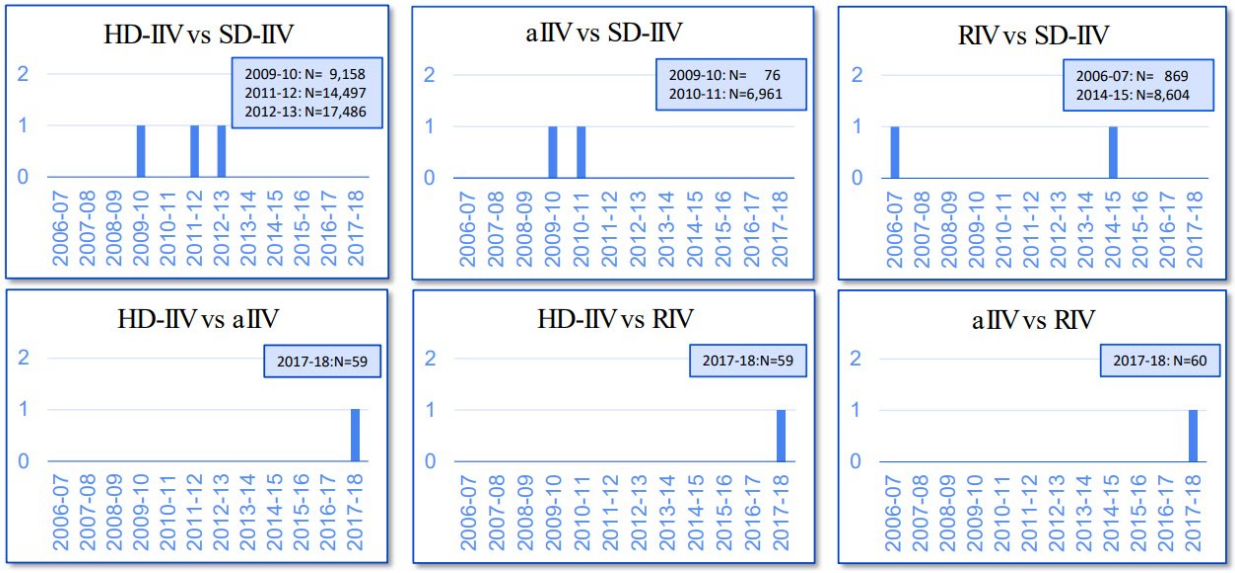
Some considerations for rVE specifically when dealing with a disease state for which baseline VE varies from season-to-season are: 1) the higher the effectiveness of the standard (comparator) vaccine, the higher the rVE for the same increase in absolute VE (i.e., the size of the relative VE depends on the starting point); and 2) it is difficult to compare rVE from different seasons when the VE of the comparator vaccine varies by season.

Now turning to an overview of the first part of the retrieved literature for the systematic review of influenza vaccines for older adults. The review question regards whether the relative benefits and harms HD-IIV, aIIV, and RIV as compared with one another and with other influenza vaccines favor the use of any one or more of these vaccines over other age-appropriate influenza vaccines for persons ≥65 years of age. In terms of the PICO elements, the population is adults ≥65 years of age. The interventions of interest include HD-IIV, aIIV, and RIV either US-licensed or similar in formulation or manufacturer to US-licensed formulations. Comparators include other trivalent or quadrivalent vaccines (US-licensed or similar in formulation and manufacture to US-licensed vaccines), non-influenza control vaccine, placebo, and no vaccine. After a great deal of discussion in 2019 and leading into 2020, the WG selected a total of 8 outcomes, 4 efficacy/effectiveness and 4 safety outcomes. The efficacy/effectiveness outcomes include outcomes that apply to all viral types and subtypes and are influenza illness, influenza-associated outpatient or ED visits, influenza-associated hospitalizations, and influenza-associated deaths. Safety outcomes include any solicited systemic AEs of Grade 3 or higher, any solicited injection site AEs of Grade 3 or higher, any SAEs, and Guillain–Barré syndrome (GBS).

A total of 6 bibliographic databases were searched as far back as 1990, given that the WG felt that to encompass the pre-licensure period for the 3 vaccines of interest, the beginning of the range should be set at the time of Fluad® licensure in Europe in 1997. The earliest references they could find scoping PubMed for MF59 were around 1995. They buffered that with an additional 5 years to 1990. There were 2 search strategies used, the first that searched articles in general and the second for review articles alone in order to be able to look for potentially missed articles in the bibliographic references of those reviews. A total of 3 searches were conducted in February 2020, February 2021, and most recently in the beginning of September 2021 to update the literature as it was published. A total of 10,808 references initially were found. An additional 160 were identified through a search of bibliographies of review articles or through reports that were forwarded on after screening to full-text review. After removing duplicate reports, that number is 799. The WG has 10,169 subjected title abstract screens, of which 6,624 were deemed not relevant. A fairly large number of 3,545 went to full-text review, given that previous reviews revealed that it can be very difficult sometimes to make a judgement based on a title and an abstract. Thus, the WG erred on the side of reviewing full-text when in doubt. Of the 3,545 reports that went to full-text, 3,468 were excluded. Amazingly among all of the articles the WG requested, the library was unable to locate only about 15. They ended up with 77 included reports, which comprised 34 individually randomized studies, 2 cluster randomized studies, and 41 observational studies.

None of the randomized studies address outpatient medical visits or deaths, which fits with the design of these studies. This is not a real-life activity as part of a clinical trial. Most of these studies were designed such that people signed up for the trial, received their vaccine, and were asked to report on such things as instances of respiratory illness—using some criteria so that they could be swabbed. The primary outcome for most of these studies is influenza illnesses. A relatively small number have an outcome of hospitalizations. There are just 4 studies for hospitalizations, which include 2 high-dose versus standard-dose comparisons, 1 cluster-randomized study, and 1 high-dose versus quadrivalent comparison. There is 1 cluster-randomized trial looking at adjuvanted versus standard-dose vaccine.

This set of charts attempts to illustrate VE data dispersed over multiple seasons in individually-randomized studies. For each of the 6 vaccine comparisons here, without regard to whether they are trivalent or quadrivalent, there is a histogram that shows the number of studies on the x-axis and the seasons on the y-axis. The small blue box in the upper right-hand corner provides an idea of the number of participants in those studies:



Notably, none of the columns in the bar charts go above 1 and there is not broad representation of seasons for the most part in these individually-randomized studies. The 2 outcomes are influenza illnesses and influenza-associated hospitalizations. To summarize the HD-IIV versus SD-IIV comparisons, there were 2 studies from Diaz/Granados (2013) and Diaz/Granados (2014). There are a lot of similarities in the designs of these 2 studies. They both compare HD-IIV3 with SD-IIV3. The Diaz/Granados 2013 study was initiated during the 2009-2010 pandemic, which led to the consequence that there was circulating virus which was much different from what was anticipated to circulate, and there were no matched positive viruses isolated from cases. Therefore, it is not possible to draw inferences from that study. There also is a fairly wide confidence interval for the VE estimate.

The similarly designed Diaz/Granados 2014 study began in the 2011-2012 season and also includes the 2012-2013 season, so it is a 2-season study. It also compares HD-IIV3 to SD-IIV3. This study had nearly 32,000 people enrolled, with approximately 15,900 in each group. The primary outcome for this study was PCR or culture-confirmed influenza-like illness (ILI) due to any viral type or subtype. There are separate estimates for each of the 2 seasons and a combined estimate for both seasons combined, which was the main finding reported in their abstract. A relative VE of 24.2% for the combined seasons, which was statistically significant based on the confidence interval. There were two other ILI definitions used in the analyses for this paper that were somewhat more general than the previous one. One was a modified CDC ILI definition in that the temperature criterion was lowered somewhat because older adults tend not to be as likely to have a fever response with infectious diseases, including influenza. There also was an estimate for that definition for both seasons, as well as for a third definition of respiratory illness, which is the most general definition. That definition was used to trigger people getting swabbed and investigated to determine whether they had influenza. Comparing just the point estimates for those 3 definitions going from more specific to less specific, the point estimate of the VE decreases.

For the influenza illness outcome for aIIV compared to SD-IIV, there were 2 studies. Both were individually-randomized trials. Song 2013 was conducted during the 2009-2010 season. It is a relatively small study of only 76 subjects. The paper indicates that they asked people with symptoms of ILI to return to be swabbed, with ILI confirmed by a virologic testing. The specific nature of that virologic testing was not specified. Unfortunately, this study is not informative in that no laboratory-confirmed influenza was observed during follow-up. The second study by Frey et al., 2014 was conducted during the 2010-2011 season. This was the major safety study for this vaccine versus SD-IIV inactivated unadjuvanted vaccine. Roughly 7,000 people were enrolled in this study. While this study assessed ILI, it used a symptom-defined definition and no laboratory confirmation was performed. The relative VE was 9 and it was not statistically significant.

There is 1 other aIIV RCT by Beran et al., which is not a rVE study. It was a study of aIIV compared to Tdap as a non-influenza control vaccine. This included roughly 6,700 people. The primary outcome was PCR-confirmed ILI due to any viral type or subtype associated with protocol-defined ILI. For that primary outcome, the efficacy endpoint was not reached. VE was 19.8 with a confidence interval that spans the null. Again, this illustrates that when definitions are changed, VE looks different. There is also a modified CDC-defined ILI, similar to what was in the Diaz/Granados paper, and a WHO-defined ILI, which is probably the most specific definition of the 3. This study did have higher point estimates, with statistically significant results for those outcomes.

There are 2 papers for RIV versus SD-IIV, Keitel (2009) and Dunkle (2017). Keitel et al. (2009) was a pre-licensure study examining RIV3 versus SD-IIV3. This study had an ILI outcome similar to other designs that asked people to present for testing, in this case with culture rather PCR. This study had a relatively small number of culture-confirmed ILI cases, so rVE was not calculated. There was 1 instance out of 436 in the RIV3 group for 0.2% and 2 in the SD-IIV3 group for 0.55%. The larger study, Dunkle et al. (2017), was one of the major studies for licensure of RIV4. This study was conducted over the 2014-2015 season and compared RIV4 to SD-IIV4 among 8,600 people. The primary outcome was ILI associated with PCR-confirmed influenza. This study enrolled people 50 years of age and older, so it has a slightly different age range than most of the other studies the WG is reviewing. This study had a statistically significant rVE of 30%. The rVE for those ≥65 years was 17% and was not statistically significant. Overall, for the broader population, there is some evidence of improved efficacy among older adults.

For comparisons of the vaccines of interest (HD-IIV, aIIV, and RIV) against each other, there was 1 individually-randomized study by Belongia et al (2020) that was conducted over the 2017-2018 season. This was primarily an immunogenicity study, the efficacy outcome was exploratory, and the sample size is small. There were 99 subjects, with 29 each in the HD-IIV and aIIV groups and 30 in the RIV. The study does provide some data on laboratory-confirmed influenza. This study will be pooled with other results that are compatible for pooling. In this study, there were 8 instances of PCR-confirmed ILI, 1 in the HD-IIV, 3 in the aIIV group, and 4 in the RIV group.

Looking now at influenza-associated hospitalizations, a topic of discussion in the WG for many years, it is obviously very important to prevent all influenza. This is particularly important in older populations because older adults can become quite ill. Hospitalization is an important milestone and marker for severe illness. There have been a lot of questions about how well influenza vaccines prevent severe illness. For this particular outcome, the WG identified studies that differ from the studies just shown. There are 2 individually-randomized trials and 2 cluster-randomized

trials. The individually-randomized trials are both comparisons of HD-IIV compared to SD-IIV. There is 1 cluster-randomized trial of HD-IIV compared to SD-IIV and 1 of aIIV versus SD-IIV. No more than one season is represented at a time.

Beginning with the individually-randomized study by Diaz/Granados 2015, this is a supplementary analysis of the Diaz/Granados 2014 data—the large 32,000-person RCT conducted over the 2011-2012 and 2012-2013 seasons. That study and its original outcomes did not include influenza-associated hospitalizations. However, it did include all-caused hospitalizations. This analysis used a method to try to get an idea of hospitalizations that possibly were related to influenza. It involved examination of SAEs from Diaz/Granados 2014 for which primary terms were adjudicated as possibly being related to influenza and divided up into 4 categories: Influenza Events, Pneumonia Events, Asthma/Bronchial Events, and Other Respiratory Events. These seem to be the most likely to be potentially be applied to an influenza illness event. Three were not statistically significant results for any of these, though the point estimates indicate that point estimates below 1 are good in terms of some diminished likelihood of influenza-associated hospitalization with a high-dose vaccine. The category of Pneumonia Events was statistically significant, but was not a primary study outcome. These events were adjudicated before study unblinding.

Vardeny et al (2021) is 3-season study (2016-2017, 2017-2018, and 2018-2019) that examined HD-IIV3 compared to SD-IIV4. This is an interesting study in that the criteria for admission are less based on age than they are on previous history of cardiac or congestive heart failure (CHF) hospitalizations. Therefore, this study has a somewhat broader age range. The interquartile age range is 58-74 years for both groups. The primary outcome were not influenza-related hospitalizations. It was more cardiovascular-related hospitalizations. As described in the supplementary methods for the protocol, a group of clinicians examined hospitalizations and determined whether they were primarily due to influenza or primarily due to pneumonia. There is not a rate ratio or risk ratio calculated for these comparisons, just p-values. Comparing the proportion or percent of events in each group for pneumonia or influenza, neither is statistically significant.

The last 2 studies for this proportion of the WG's initial findings were cluster-randomized studies by Gravenstein et al (2017) of HD-IIV3 versus SD-IIV3 and McConeghy et al (2020) of aIIV3 versus SD-IIV3. These studies were conducted in a network of approximately 823 nursing homes in the US. Randomization was is based on the level of the facility, so some facilities received HD-IIV, some received SD-IIV, some received adjuvanted, and some received unadjuvanted. The outcomes were pneumonia and influenza-coded hospitalizations, both of which showed a statistically significant decreased risk of that particular outcome. It is not a lab-confirmed outcome, but it is some evidence toward hospitalization.

In summary of the randomized studies, the WG has data available comparing HD-IIV and RIV versus SD-IIVs against laboratory-confirmed outcomes. They also have relatively more limited comparisons of aIIV versus SD-IIV against laboratory-confirmed influenza outcomes. Comparisons of HD-IIV, aIIV, and RIV with one another are limited to 1 small study as an exploratory endpoint. Within each vaccine comparison, a limited number of seasons are represented. This is a potential limitation considering that influenza vaccine VE varies so much. The WG has no data on laboratory-confirmed influenza hospitalizations. The estimates on hospitalizations from individually randomized studies do not come from primary analyses.

Discussion Summary

Dr. Poehling asked whether she was correct in understanding that the subcutaneous influenza vaccine was not recommended for persons aged ≥65 years and if so, why it was not included.

Dr. Grohskopf indicated that the intradermal vaccine has not been marketed in the US for several seasons. It was in around 2011 in the US. FluZone intradermal and FluZone intradermal quadrivalent were only approved for persons aged 18-49 years, which had to do with the populations in which it was studied. One issue with the intradermal vaccine is that the immune cells that are the targets are in a pretty specific layer and there is potentially some thinning of skin with age. There is a version of that vaccine with a higher antigen dose that is licensed in other countries for person 65 years of age and older. That was a higher antigen dose. Here, there was FluZone® intradermal with 9µg of antigen per virus, which is lower because not as much is needed for intradermal as is needed with an intramuscular, which had 15µg. There was a version licensed for older adults in other countries that had 15µg.

Dr. Long noted that it was somewhat difficult to keep a running tally about what the preponderance of evidence shows. She asked whether Dr. Grohskopf could say, understandably with lots of exceptions, that there was suggestion across the studies that the vaccines particularly formulated for older adults showed increased efficacy.

Dr. Grohskopf said the best way to answer that was that there is variability. This was intended to be a brief overview. During the February meeting, the intent would be to discuss the meta-analysis.

Dr. Caine asked whether any demographic and socioeconomic data would be provided since it is known that Black persons had the highest influenza-associated hospitalization rates across all of the last 10 influenza seasons. There also is a higher level of chronic medical illness among Black persons compared to their White counterparts.

Dr. Grohskopf indicated that the studies identified by the WG do not evaluate race as a primary variable, but most of them do examine race, particularly the CMS studies and the larger observational studies. All of the clinical trials will provide some discussion of the demographic data. All of the studies have various sub-analyses. For example, they may break the ages down into different groups. She did not immediately recall whether any of them performed specific analyses by race or ethnicity, but the WG can definitely start by looking at the make-up of these studies to try to delve into that further.

Dr. Talbot added that there is not a lot of diversity in these studies. The COVID-19 vaccine studies in adults over 65 years of age were some of the first to be better diversified. There is a lot more work to be done in that area in the influenza studies, and there is unlikely to be significant data to pull out of the studies identified.

Dr. Bell made a general overall comment about this whole enterprise that had been begun looking at rVE, presumably with the idea of considering a preferential recommendation. She personally would appreciate a very robust discussion and examination of what the threshold for a preferential recommendation would be. While she recognized that it is all speculation, she anticipated that it would be easier for her to think about her vote on a topic like this if she has a clear understanding of at least what the experts and the WG think the implications of such a recommendation might be.

HEPATITIS VACCINE

Session Introduction

Kevin Ault, MD (ACIP WG Chair) introduced this session, which focused on evaluation of the use of a 3-antigen HepB vaccine candidate (PreHevbrio™) for adult vaccination. The FDA approved PreHevbrio™ on November 30, 2021.[13] In terms of background, 2022 is the 40th anniversary of the original Hepatitis B (HepB) vaccine. The rate of new infections in the US in the past 40 years has decreased by 90% because of these vaccines. The ACIP voted on November 3, 2021 to expand HepB coverage through a universal adult vaccination recommendation. Manufactured by Variation BioTechnologies Inc. (VBI Vaccines, Inc.), the indication for PreHevbrio™ is for prevention of infection caused by all known subtypes of the HepB virus in adults 18 years and older.

Safety & Immunogenicity of a 3-Antigen Hepatitis B Vaccine, PreHevbrio™

Dr. Francisco Diaz-Mitoma, MD, PhD (VBI Vaccines Inc.) present on the safety and immunogenicity of PreHevbrio™. As a new entrant to the US, he took a moment to introduce the company. VBI Vaccines, Inc. is a biotechnology company. Their first product is PreHevbrio™, a recommended HepB vaccine approved by FDA. VBI Vaccines, Inc. has a pipeline composed of several prophylactic and therapeutic vaccine candidates targeting different infectious diseases and cancers. This is a global company with its corporate headquarters in Cambridge, Massachusetts; research and development headquarters in Ottawa, Canada; and fully owned manufacturing and research facility in Rehovot, Israel where the HepB vaccine candidate is produced.

HepB remains a persistent US health problem that will require a new solution. There are numerous challenges with HepB, including suboptimal surveillance, low awareness of infection, and vaccine uptake rates that have been persistently low at around 25%. Additionally, there has been an increase in acute cases of 11% in recent years with changes in the incidence and epidemiology, with half of cases occurring in adults 30-49 years of age. Despite these challenges, there is renewed focus on HepB with ACIP's vote for the universal vaccine recommendation and further surveillance guidelines. Additionally, the HHS has called for a 90% reduction in cases by 2030. To achieve these goals, new public health tools are needed.

To highlight the general features of the HepB virus that are relevant to the PreHevbrio™, as with other envelope viruses, the HepB virus has 3 main components: its genetic material, a capsid or core, and the envelope. The envelope has 3 distinct surface proteins: Small HBsAg envelope protein (S), Medium HBsAg envelope protein (Pre-S2), and Large HBsAg envelope protein (Pre-S1). The Pre-S proteins have a critical functional role in the recognition of the virus cell receptor. B cell epitopes present in the Pre-S domain elicit potent antibodies against the small S antigen, resulting in seroprotection against infection in HepB susceptible populations. In terms of features that differentiate PreHevbrio™vaccine from others on the market, all available vaccines express the small S antigen. PreHevbrio™ is the only vaccine with a full set of envelope antigens, which is believed to lead to the potent immune response resulting in increased seroprotection. The Pre-S proteins have a critical functional role in the recognition of

[13] https://www.fda.gov/vaccines-blood-biologics/prehevbrio

HepB virus cell receptors. VBI Vaccines, Inc. believes that the immune epitopes present in the Pre-S domain elicit that potent immune response that results in protection against infection. PreHevbrio™ is the only vaccine expressed in mammalian cells. The other vaccines are expressed in yeast. PreHevbrio™ contains a common adjuvant, aluminum hydroxide, which has a good safety record and is also used in the standard-of-care vaccines. The adult dose contains 10µg of antigen. In terms of the significance of these differentiating features and why it matters, the benefits are 3-fold. First, unlike currently available HepB vaccines containing the small S, the antigens in PreHevbrio™ vaccine resemble the naturally occurring mammalian glycosylation with a similar glycosylation pattern and properly folded proteins representing linear and confirmational B cell epitopes able to elicit efficient immunogenicity. Second, Pre-S1 and Pre-S2 regions are significantly more immunogenic at T and B cell levels than S. Pre-S1 and Pre-S2 antigens can overcome non-responsiveness to S through expanded T cell epitopes and distinct regulation pathways. The efficiency of the Pre-S1 to elicit that immune response in non-responders highlights the additional benefit of a vaccine with these components. Several animal model studies support these findings in terms of the pre-antigen confirmation, the mammalian cell derivation, and confirmed benefits that result in an increased protection. The Pre-S1 and Pre-S2 T helper and B cell epitopes result in antibodies that are required to prevent infection by all HepB virus genotypes. While the overall effect of vaccine escape mutants is likely low, emergence of drug resistant mutants with alterations in “a” determinant of S protein is of some concern, Pre-S1 and pre-S2 epitopes may help reduce emergence of vaccine escape mutants and may reduce risk of HBV infection caused by escape mutants.

The 3-antigen HepB virus (HBV) vaccine has an extensive history. The US Phase 3 program delivered 2 pivotal studies, PROTECT and CONSTANT, that were designed to achieve licensure in adults in the US, Europe, and Canada. These were initiated at the end of 2017 and were completed in 2020. The US FDA approved PreHevbrio ™ on November 30, 2021 for the prevention of infection caused by all known subtypes of HBV in adults aged 18 and older. The American Medical Association (AMA) Current Procedural Terminology (CPT®) Panel established unique CPT code for the 3-antigen HepB vaccinee (90759). The vaccine was designed and initially produced at the Weizmann Institute in Israel. Since 1989, 23 clinical studies have been performed in children and adults, resulting in initial market authorization in 2000 in Israel, where it currently has preferential adult recommendations for certain patients or groups. Approximately 750,000 individuals have received a vaccine in Israel where the vaccine is licensed in 3 dose formulations:

- 2.5 µg & 5 µg HBsAg/0.5 mL (neonates, infants, and children)
- 10 µg HBsAg/1 mL (adolescents and adults)
- High-dose 20 µg HBsAg/1 mL formulation, which also has been evaluated in several clinical studies

The Phase 3 clinical program was comprised of the 2 pivotal studies, PROTECT and CONSTANT, which assessed immunogenicity and safety in comparison to the most frequently used standard-of-care vaccine. The PROTECT study was published in *Lancet Infectious Diseases* in May 2021 and the CONSTANT study was published by the *JAMA Network* on October 11, 2021. The PROTECT study is a multi-center double-blind randomized control study conducted in 28 community clinics and academic hospitals in the US, Greenland, Canada, and Belgium. The study enrolled 1607 participants with an age range of 18-90 years. The co-primary endpoints are non-inferiority in adults aged 18 and older and superiority in adults 45 years of age and older. Secondary endpoints included safety, tolerability, and antibody concentration, kinetics of the seroprotection rate, and immunogenicity in subgroups. The CONSTANT study is a double-blind 4-arm lot-to-lot consistency study with a control. The study and size were

expanded to complete the safety database requirements. Randomization was to 4 arms, with 1 arm receiving the control vaccine and 3 arms receiving the candidate vaccine, with a total of 2800 participants. The age range was 18-45 years. The primary endpoint was the geometric mean concentration (GMC) of antibodies across the 3 vaccine lots. Secondary endpoints were safety, tolerability, reactogencity, and seroprotection rate.

In terms of breakdown and subgroup distribution for the PROTECT study, 82% of the age cohort was older than 45 years. In PROTECT, 43% of participants were enrolled in the US. The US-based is racially and ethnically diversity. There is good representation of African American and LatinX populations. In addition, 40% of the patients were enrolled in Europe and 16% in Canada. Of the participants, 95% completed the study. The CONSTANT enrolled 2838 participants from 35 study sites, with 27% in the US and 70% in Europe. There were more participants from Europe, especially Finland. In Finland, HepB universal pediatric vaccination was only recommended in 2016, allowing the investigators to enroll a younger cohort aged 18-45 years. All volunteers in this study were healthy and all potential participants with chronic health conditions were excluded, including people with a body mass index (BMI) higher than 30.

A critical endpoint of the pivotal program was to confirm the safety of the 3-antigen vaccine observed in previous clinical studies. The integrated safety analysis identified no unexpected reactogenicity. The vaccine was associated with increased rates of mild to moderate injection site pain, tenderness, and myalgia. This reactogenicity generally resolved without intervention in 1 to 2 days. There was no increase in reactogenicity over the 3-dose vaccine schedule and there were lower rates of vaccine discontinuation. The rate of unsolicited AEs was similar in both vaccine arms. There were no unexpected safety signals and there were no unusual patterns or concerning clusters of SAEs. There was no increased rate of medically attended adverse events (MAAEs) or new onset of chronic illness (NOCI) in comparison to the controlled vaccine arm.

Summarizing the safety data across both Phase 3 studies, there was a high completion rate in both studies and the most common finding was local reactogenicity that resolve with no intervention. There was no difference in MAAEs between vaccine groups. SAEs were uncommon with both vaccines and there was no clustering of AEs. There were 2 SAEs reported as possibly related, a severe gastroenteritis in PROTECT and an ankyloglossia (tongue-tie) in CONSTANT that upon independent review it was determined not to be vaccine-associated. There was 1 death in the CONSTANT study to a participant randomized to the PreHevbrio™ arm. The autopsy ruled that the death was due to pre-existing hypertrophic heart disease.

The PROTECT and CONSTANT studies analyzed the immunogenicity of PreHevbrio™ vaccine and the standard-of-care control. The co-primary endpoints were met 4 weeks after the third vaccination. These co-primary endpoints were based on the comparison between arms of the seroprotection rate represented by 10 milli-international units per milliliter (mUI/mL) units per milliliter of antibodies against the surface antigen, which represents protection against infection. The first endpoint, non-inferiority in adults of all ages, was demonstrated with a between group difference of 14.9% in all adults in the per protocol set. This difference was sustained and slightly increased in the second endpoint and statistical and clinical superiority of PreHevbrio™ was demonstrated in older adults with a between group difference of 16% in the full analysis set.

There was a difference in seroprotection rates between subgroups of interest. This improvement was sustained regardless of age, diabetes, or BMI. There are additional analysis showing that the improvement in seroprotection and antibody concentration were sustained regardless of alcohol consumption, smoking, gender, race, ethnicity, and/or geographic jurisdiction. Higher seroprotection rates were achieved with PreHevbrio™ after 2 and 3 doses in comparison to the control. In the PROTECT study, the difference after 2 doses was pronounced, with 87% versus 39% seroprotection rates. In the CONSTANT study, PreHevbrio™ also achieved higher levels of seroprotection after 2 doses than the control at 90% versus 51%. Moreover, the seroprotection rate was higher for PreHevbrio™ than the control at both time points and in all age cohorts. The seroprotection rate was higher after 1 dose and more than double after 2 doses with PreHevbrio™ than with the control vaccine. In addition, the durability of seroprotection was higher with PreHevbrio™ than with the control in all adults. The immunogenicity results of the CONSTANT study demonstrated a rapid and consistently high rate of seroprotection and higher concentration of antibodies than were achieved with PreHevbrio™ in young adults who were compared to the control vaccine. The primary endpoint of consistency was met.

PreHevbrio™ has expansive real-world experience, highlighted by 3 investigator-initiated studies in populations where there is particular concern from low or non-response to HepB vaccines in which PreHevbrio™ was able to circumvent non-response in the majority of patients. These 3 published studies demonstrate the benefits of a more potent HepB vaccine. Patients with end stage renal disease (ESRD) or human immunodeficiency virus (HIV) are particularly at risk of HepB virus exposure and the standard-of-care requires frequent serology testing. Often there is no seroprotection after a standard-of-care vaccination. In the renal failure study, these patients did not respond to a double dose of Engerix-B®. After 3 doses of PreHevbrio™ vaccine, a seroprotection rate of 86% was achieved versus the control of 56%. Similarly, in the HIV positive patients, a high seroprotection rate was observed after 3 dose of the 3-antigen vaccine of 84% versus historical controls of 17% to 53%. In the third study, adults who did not respond to more than 3 doses of conventional yeast-derived HBV vaccines, achieved a seroprotection rate was 87% after 1 dose of PreHevbrio™.

To summarize, the safety profile of PreHevbrio™ is comparable to Engerix-B® and consistent with a 20-year known history and usage of the 3-antigen PreHevbrio™ HepB vaccine. There are higher rates of protection in all adults and robust immunogenicity across age cohorts. In particular, for older adults in whom immunosenescent is a concern, am improved response was observed in the studies of people 45 years of age and older and people 55 years of age and older. There was a rapid onset of protection for all ages and all time points. In particular, 90% of participants in the study aged 18-45 years reached seroprotection after 2 doses. Nearly half of all cases of HepB are occurring in this population of increased concern. There is improved immunogenicity in key high-risk population. Those with chronic conditions often have a suboptimal response to vaccine, but there was improved seroprotection for people with both diabetes and obesity following receipt of PreHevbrio™. There is a renewed focus on HepB with new immunization and screening guidelines. These efforts will require new approaches and PreHevbrio™ is a public health tool to help achieve these goals.

Discussion Summary

Dr. Ault asked whether VBI Vaccines, Inc. has any data on PreHevbrio™ that are specific to pregnancy.

Dr. Diaz-Mitoma indicated that there were a handful of pregnancies in the study for whom no AEs were observed during the study. As part of their full licensure commitment, they are developing a protocol now that will be presented and submitted to the FDA as a pregnancy registry. Otherwise, there is limited experience thus far with pregnancy.

Dr. Sanchez noted that it seemed like PreHevbrio™ also has been used in neonates and is currently being used in Israel in neonates and infants. In addition, it seemed to him that S, Pre-S1, and Pre-S2 are distinctly different proteins.

Dr. Diaz-Mitoma explained that this is one of the main differentiating features of PreHevbrio™ vaccine. PreS1 is the largest protein that is approximately 226 amino acids in length. There is a unique overlapping region that is about 100 amino acids and there is a common region for the small S. Similarly with Pre-S2, there is a very specific domain that is around 50 amino acids that is very specific for the Pre-S2 domain. A characteristic of these Pre-S domains is that they contain very potent T cell helper and B cell epitopes. In terms of the experience with the neonate in Israel, the vaccine has been used as a birth vaccine for the last 20 years and it continues to be used in neonates and in children. It has been used extensively in pediatrics. In terms of the legacy studies, there are 23 clinical studies in addition to the 3 pivotal Phase 3 studies. Of the 23 studies, 12 are in neonates or children. There is extensive literature about the use of this vaccine in Israel. In terms of FDA approval for newborn vaccination, VBI Vaccines, Inc. currently has a waiver from FDA for the pediatric indication and they remain open to further development, especially if there is interest from investigators who use them in populations where there is a need for an enhanced HepB vaccine.

Dr. Cineas requested a list of the groups for whom the PreHevbrio™ vaccine is recommended in Israel.

Dr. Diaz-Mitoma indicated that the vaccine has preferential use for healthcare workers, frontline responders, persons with ESRD, persons who are HIV-positive, and/or patients who have immunosuppression.

Dr. Kotton observed that the data looked good for ESRD and HIV, but wondered whether there are subgroups with organ transplants, more severely immunocompromised patients, patients receiving rituximab, and/or other highly challenging patients.

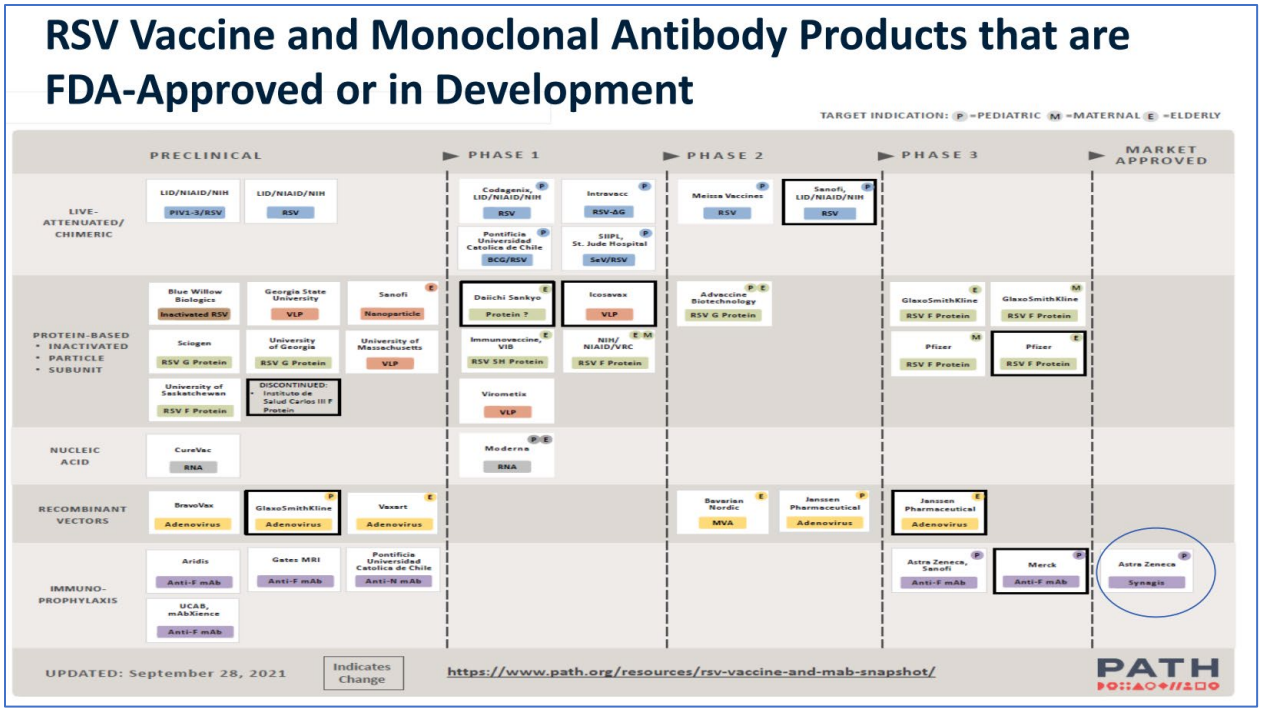
Dr. Diaz-Mitoma indicated that there have been very small investigator-initiated studies in transplant recipients, especially those with very profound immunosuppression like liver transplants in whom the results also have been positive. The higher dose formulation has been used in these studies. There is very limited information on the subgroups Dr. Kotton mentioned.

Dr. Lee asked whether there are post-market safety surveillance data available from other countries and whether the FDA approval includes a statement about pregnant women.

Dr. Diaz-Mitoma explained that the main observations they have are from the periodic safety reports that have been submitted every 2 or 3 years to the Minister of Health in Israel over the last 15-20 years. Clustering of SAEs has not been observed in any of those reports. The FDA approval excludes pregnancy.

MATERNAL/PEDIATRIC RESPIRATORY SYNCYTIAL VIRUS (RSV) WG

Sarah S. Long, MD (ACIP WG Chair) introduced the newly formed Maternal/Pediatric RSV WG. In term of the purposes of this WG, RSV is a major cause of lower respiratory illness, particularly among infants and children and among older adults and adults with chronic medical conditions. RSV vaccine and monoclonal antibody development has progressed in the past decade with over 40 candidate vaccines and monoclonal antibodies currently in development. The target populations for whom these products are intended include infants and young children, pregnant women, and older adults. It was the CDC's decision to create 2 WGs. A different WG will consider older adults and immunocompromised persons. The new Maternal/Pediatric RSV WG will consider recommendations for use of RSV vaccines and monoclonal antibodies targeting protection of children aged <18 years. The goals of the Maternal/Pediatric RSV WG will be to: 1) review the epidemiology and burden of RSV disease in children and pregnant women; 2) review the efficacy immunogenicity, safety, and cost-effectiveness of RSV vaccines and newly developed monoclonal antibody products in pregnant women and children; 3) provide evidence-based recommendations regarding use of RSV vaccines and newly developed monoclonal antibody products in pregnant women and children; and 4) identify areas in need of further research for informing potential future vaccine and monoclonal antibody recommendations. Here is a snapshot of the products that are FDA-approved or in development:



The only approved product is the monoclonal antibody palivizumab, which is costly, is given in 5 doses, and has only modest benefit in even preventing hospitalizations. It has been available since 1998. The kinds of vaccines that are under study include live-attenuated/chimeric, protein-based, nucleic acid, and recombinant vector vaccines. The WG will focus on those that are in Phase 3 or later trials. Note that the products are marked with either E, M, or P. These represent the target populations. E is for elderly populations, M signifies maternal immunization, and P is for pediatric preparations. The WG anticipates that a Biologics License Application (BLA) will be submitted for a monoclonal antibody and 2 vaccines within the next 12 to 16 months.

The WG includes 2 other members of ACIP, 8 *ex officio* members, and 5 liaison members along with an elite group of expert consultant and CDC staff. The WG has convened calls from October 2021-January 2022 during which the members have reviewed the burden and epidemiology of RSV, reviewed the US RSV surveillance systems and definitions of RSV infection and disease, and began to discuss potential components of cost-effectiveness considerations for RSV vaccines and monoclonal products. Upcoming activities will be to review the safety and efficacy with manufacturers of the developing vaccines and monoclonal antibodies, review RSV seasonality data in relation to potential recommendations for timing of administration of either of these types of products, review the results of cost-effectiveness models, present the data to the ACIP, and apply EtR Framework for each product. The first vote by ACIP is not expected until 2023.

Discussion Summary

Dr. Chen emphasized that this would an exciting set of discussions for the future for an area that has long been hindered. He asked whether the WG has or would be discussing the unusual RSV surge that occurred during the past summer, what the epidemiology was during the coldest parts of the seasons, and what was observed last year—recognizing that these are COVID-19 times.

Dr. Long indicated that the WG had not discussed the potential reasons for this very aberrant season specifically. As far as their deliberations for use of products, the next 12 months will be very important in terms of assessing whether RSV revert back to its more typical epidemiology. All of that will affect recommendations and will be very important in terms of if/how it coincides with an RSV season.

PNEUMOCOCCAL VACCINE

Session Introduction

Katherine Poehling, MD, MPH (ACIP WG Chair) introduced the Pneumococcal session. The Pneumococcal Vaccines WG's terms of reference are to: 1) review current data including efficacy, effectiveness, immunogenicity, epidemiology, and cost-effectiveness of pneumococcal vaccines and assess the strength of the evidence; 2) review current recommendations considering up-to-date evidence; and 3) revise or update recommendations for pneumococcal vaccine use as needed. As a reminder, ACIP voted on 2 recommendations for the use of PCV14/PCV20 during the October 2021 meeting as follows:

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

Adults aged 19–64 years with certain underlying medical conditions or other risk factors who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown should receive a dose of pneumococcal conjugate vaccine (either PCV20 or PCV15). When PCV15 is used, it should be followed by a dose of PPSV23.*

*Alcoholism, chronic heart/liver/lung disease, diabetes, cigarette smoking, chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, human immunodeficiency virus infection, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplants, congenital or acquired asplenia, sickle cell disease, or other hemoglobinopathies, CSF leak, or cochlear implant.

Much of the WG's current focus is on the anticipated licensure in children, with PCV15 licensure expected in the first or second quarter of 2022 and PCV20 licensure expected in the second or third quarter of 2023.

Updates from the Pneumococcal Vaccines WG

Miwako Kobayashi, MD, MPH (CDC/NCIRD) pointed out that the language voted on during the October 2021 ACIP meeting that Dr. Poehling described focused on adults who have not previously received the pneumococcal conjugate vaccine or whose previous vaccination history is unknown. Additional clinical guidance the WG proposed that was not part of the vote included the following:

Clinical Guidance on the PCV15–PPSV23 Interval

- When PCV15 is used, the recommended interval between PCV15 and PPSV23 is ≥1 year. A minimum interval of 8 weeks can be considered for adults with an immunocompromising condition*, cochlear implant, or cerebrospinal fluid leak to minimize the risk for IPD caused by serotypes unique to PPSV23 in these vulnerable groups.

*chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, human immunodeficiency virus infection, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplants, congenital or acquired asplenia, sickle cell disease, or other hemoglobinopathies, CSF leak, or cochlear implant

Clinical Guidance for Those Who Previously Received PPSV23 Only

- Adults who have only received PPSV23 may receive a pneumococcal conjugate vaccine (either PCV20 or PCV15) at least 1 year after their last PPSV23 dose.

Clinical Guidance for Those Who Previously Received PCV13 (with/without PPSV23)

- The WG is in favor of providing an opportunity to administer higher-valent PCVs to those who have already received PCV13 (with/without PPSV23).
- The incremental public health benefits of providing PCV15 or PCV20 to adults who have received PCV13 only or both PCV13 and PPSV23 have not been evaluated by the ACIP.

- The *MMWR* Policy Note expected to be published on January 28, 2022 does not include a recommendation on PCV15/PCV20 use in adults who previously received PCV13 (with/without PPSV23).

The WG plans to conduct an evaluation on higher-valent pneumococcal conjugate vaccines for adults who previously received PCV13 for consideration by the ACIP in the future. Therefore, the proposed language for clinical guidance for adults who receive PCV13 with or without PPSV23 is as follows:

> *The incremental public health benefits of providing PCV15 or PCV20 to adults who have received PCV13 only or received both PCV13 and PPSV23 have not been evaluated. These adults should complete the previously recommended PPSV23 series.*

The WG has started reviewing data on PCV15 use in children in anticipation of FDA licensure of PCV15 for children as early as April 2022 and PCV20 licensure anticipated in 2023. Currently, PCV13 is recommended for routine administration for all children <2 years of age, catch-up vaccination for children aged <5 years of age who missed their recommended doses, and children aged 2-18 years for certain medical conditions in series with PPSV23.[14]

The proposed policy question being considered by the WG is, "Should PCV15 be recommended as an option for US children who are recommended to receive PCV13?" In the months leading to the vote, the Pneumococcal WG plans to review the immunogenicity and safety of PCV15 use in children; the epidemiology of pneumococcal disease and vaccine-preventable disease burden for invasive pneumococcal disease (IPD) and non-IPD; and the expected public health impact and cost-effectiveness of PCV15 use in terms of the estimated direct/indirect effects in children and the impact on health equity. The WG will use the GRADE and EtR Framework to summarize the evidence. During the February 2022 ACIP meeting, the WG plans to present data on pediatric pneumococcal disease epidemiology, findings from Phase 2 and 3 PCV15 studies in children, and part of the EtR Framework and GRADE. During the June 2022 ACIP meeting, the WG plans to present a summary of the cost-effectiveness analysis and the remainder of the EtR Framework. An ACIP vote on recommendations for use of PCV15 in children is anticipated after expected licensure and when deemed appropriate by ACIP.

Discussion Summary

Dr. Kotton requested clarification about what would be included in the *MMWR* if there is no recommendation for people who previously had a conjugate vaccine. Clinicians are left with a lot of questions about whether they should/should not be giving the vaccine.

Referring to Slide 13, Dr. Kobayashi indicated that because the WG had not had the opportunity to present data on use of the higher-valent conjugate vaccines to the ACIP yet for consideration for a vote, the language they are currently planning to include in the upcoming *MMWR* is:

> Clinical Guidance for Those Who Previously Received PCV13 (with/without PPSV23)
>
> *The incremental public health benefits of providing PCV15 or PCV20 to the adults who have received PCV13 only or both PCV13 and PPSV23 have not been evaluated. These adults should complete the previously recommended PPSV23 series.*

[14] *MMWR* 2010 (59); RR-11; *MMWR* 2013 (62); 521–524

Dr. Poehling pointed out that it is important to review the history of how this occurred. The WG worked hard to simplify the pneumococcal recommendations, recognizing that simplified recommendations would increase coverage and equity. They also worked hard to get a timely vote after the licensure. During the October 2021 ACIP meeting, it was mentioned by multiple persons and there was discussion about immunocompromised and elderly populations. At that time, these conversations were truncated and it was understood that the WG could fill in the gaps on some of these questions by including the information in Clinical Considerations. That ACIP meeting was jam-packed, the schedule was tight, and there were many votes. Following that meeting, the WG met and developed recommended Clinical Considerations. In the review process, it became clear that the vote language was more restricted than intended. The WG met on January 11, 2022 and unanimously felt that enabling access to newer pneumococcal conjugate vaccines is important for immunocompromised, high-risk, and elderly populations and that the proposed language creates clinical barriers and decreases both access and equity. At the same time, the WG recognized there are many naïve persons who need this vaccine. Moving forward, the WG proposes to quickly identify and evaluate the available data and present this information to the ACIP to fill in this gap. She requested input on any specific data that the WG should include in such a presentation.

Dr. Lee noted that there was a distinction in her mind between people who have received PCV13 only. She approached this from a pediatric perspective in which clinicians have to think about the immunization schedules for immunocompromised persons in particular in terms of whether someone is due for PPSV23 and if they should receive a polysaccharide vaccine or a conjugate vaccine as the boost in that instance. That might be a different question than people who already have received PCV13 and PPSV23 and she asked whether the WG was thinking about those in the same or a different way.

Dr. Poehling indicated that the WG talked about all of those, but was told that they could not move forward with what was presented yet.

Dr. Goldman (ACP) said that speaking as an individual practice internist, he had several concerns with the policy of not allowing for an additional pneumonia dosage of the new conjugate vaccine for those who have been previously vaccinated for 3 reasons: 1) the best interest of the patient, 2) logistical issues, and 3) the confusion that this will create in messaging with the policy. As an internist and primary care physician (PCP), the most important patient is the one right in front of him. While public health and resource concerns are necessary, he is more interested in what is most beneficial to that patient. Many patients have received either PCV13 with/without PPSV23 and may have received them at such a significant interval in the past that they are aging into a category for an additional dosage or are facing imunosenescence and are left unprotected at an older age. This reinforces the need for repeat vaccination. He does not believe it is in the best interest of the patient not to offer them an additional conjugate vaccine that will allow for additional protection. This is a case in which the harms are minimal, the vaccine is safe and effective, and permissive or shared clinical decision-making is appropriate. Many health care systems and physicians may have chosen the path to give only PCV20 over the PCV15/23 combination. To suggest now that they have to go back to an additional dose of PCV23 may create the impossible tasks of acquiring and stocking multiple vaccines, and patients will not be able to get fully protected. It is similar to when ACIP decided to allow for Tdap to be interchangeable with TD and allow only one vaccine to be able to be stocked. The previous confusion created by multiple schedule changes with pneumonia made it difficult for frontline physicians to implement. The hope was that this new vaccine schedule would keep it simple and allow for better vaccine uptake. He encouraged the committee to allow for an additional dose of conjugate vaccine to those who have previously had PCV13

with/without PPSV23, with either a permissive recommendation or a shared clinical decision-making recommendation. He believes this will allow for improved protection against pneumonia, reduce the individual risk of disease, and save lives.

Dr. Long said that considering the unanimous wish of the WG that this not be put in the *MMWR* and Dr. Poehling's statement that she is willing to do the hard work to try to bring this to the ACIP in a little over a month's time, she favored not including a statement at all about this situation of those who are not previously naïve for one more month until ACIP is able to assess the data more carefully. They all felt that it was the wrong direction to continue these individuals on the PPSV23 route when there is PCV20. They have said those who are naïve could receive either PCV15 or PCV20 and that if they got PCV15, it should be followed by PPSV23. She did not see how this was different from that, except that there would be nobody who could want to then give someone who had receive PCV13 PCV15 followed by PCV23. What would make the most sense and would restore the understanding and faith of practitioners in the pneumococcal vaccine recommendations would be to provide flexibility to use either PCV20 or PPSV23 in those who previously received PCV13.

Dr. Kotton agreed with the comments from Drs. Goldman and Long and thought there should be flexibility and clarity. Already, the majority of clinicians she meets with do not understand the recommendations that were made years ago for PPSV23 and PCV13. When she brings up PCV15 and PCV20, they are further confused. There are data to suggest that there would not be harm in giving additional doses of conjugate vaccine. It is known from surveys and other sources that many Americans who are at high-risk for pneumococcal disease remain ill-protected. The ACIP should not increase barriers toward providing protection, but rather should provide clinicians flexibility and significant clarity in the guidelines.

Dr. Fryhofer (AMA), speaking as a practicing physician, applauded the WG and ACIP for simplifying this pneumococcal recommendation, because there are now higher-valent conjugate vaccines. She thinks this will be much easier to implement and much easier to explain to those administering these vaccines. Previously, there were some groups of patients who would receive another dose of PPSV23 once they turned 65 years of age if it had been at least 5 years since they had had a PPSV23. She requested clarification on whether there is no reason now for anyone to receive more than a single PPSV23 moving forward.

Dr. Kobayashi confirmed this to be correct. Under the new recommendation, people who receive PCV15 are not recommended to receive repeated doses of polysaccharide vaccine at this point. However, this language refers those who received PCV13 to the existing recommendation. What that means is that if they are due for another polysaccharide vaccine, that is what they should get

Dr. Posner emphasized that recommendations must be based on the evidence reviewed. The issues people raised during this discussion highlighted the importance of moving quickly to review the evidence and appropriately consider any changes to the recommendations.

Dr. Zimmerman (APTR) speaking as an educator and practicing physician, agreed with Drs. Goldman and Long and emphasized that that intent of the WGs on which he has been privileged to serve for many years was simple recommendations and flexibility. He expressed his hope that this could be resolved quickly.

Dr. Hogue (APhA) stressed that everything published that potentially could be changed again in February is going to create confusion no matter how clear and precise they think they are being.

He fully supported everything his colleagues said previously. Providers must be allowed flexibility and there should be caution about putting anything in print that could lead to more confusion among practitioners and patients just a month later. He applauded ACIP's simplification in the Fall meeting, which has been well-received.

Dr. Loehr said that if he was understanding the position of several people, they were asking for flexibility to give PCV20 to someone who has had PCV13 alone or PCV13 plus PPSV23 in the past. They also would like to have this decision made quickly. Based on the timeline Drs. Poehling and Kobayashi outlined, there would not be an ACIP vote until June 2022. While he appreciated Dr. Goldman's strong recommendation to provide flexibility, he was not comfortable making that kind of decision without data.

PUBLIC COMMENT

Ms. Katherine Falk

I'm Katherine Falk, a parent and vaccine advocate in Oakland, California. I thank the Committee again for all your hard work, including am absolutely crazy number of meetings. I first wanted to reiterate Dr. Stanley Plotkin's January 4 written comment on the importance of the flu vaccine. In this time of epidemic Omicron COVID, it is important that people be vaccinated against influenza so that they do not need to seek medical care, which is in short supply. Moreover, influenza itself can kill and disable. There has also been a lot of talk about comorbidities lately. A person can live with a comorbidity for a long time only to be felled by a contagious illness, whether it's COVID, flu, pneumonia, or a combination. So, I'm glad to see pneumococcal and influenza vaccines for older adults on the agenda. I'm also really excited to see RSV vaccines on the agenda. I know it's a threat to older adults and people with compromised immunity, but I also think of this blog I used to follow—remember blogs?—called The Spohrs Are Multiplying.[15] The family's first child was born prematurely with compromised lungs and died before her second birthday. In her short lifetime, she suffered many illnesses, including RSV. It is shocking to me that a virus that causes so much misery still has no vaccine, and I'm sure hoping that's about to change. On a personal note, my 15-year-old daughter came down with COVID this week. She got infected, likely at school, before we had time to get her a booster. If anyone hearing this thinks it's just a cold still, they're going to get an earful from me. But as miserable as yesterday was, I was pleasantly surprised this morning to find that she's feeling a bit better. The vaccine didn't prevent infection and maybe the booster would have if we'd had time, but those 2 doses she got last year do seem to be doing what they're supposed to do—prevent the worst outcome. Thank you.

Joan Edelstein

I'm Joan Edelstein, Professor of Nursing and Faculty in the School Nurse Credential Program at California State University Sacramento. I'd like to thank the Committee for its tireless efforts in expertly evaluating and transparently communicating the science behind all the Committee's recommendations in spite of the many professional and political challenges during this pandemic. We in public health have been concerned about a twindemic since 2020 and are now

[15] https://thespohrsaremultiplying.com/

facing what is referred to as “flurona.” Primary prevention is always critical to an effective public health strategy. School-located vaccine clinics, for which school nurses are key partners and leaders, should be a priority for the CDC, which recommends influenza school-located vaccine clinics on its website. The National Association of City and County Local Health Officers (NACCHO) has a wealth of information on their website. They know that private medical sectors as well as public health clinics have limited capacity and are often unable to vaccinate the expanded population to the degree that school-located vaccine programs are. That is especially true in this pandemic. The advantages of doing this include an increased number of vaccinated children; improved efficiency and cost-saving from a public health perspective; increased access to students who are from minority families, minority groups, the economically disadvantaged, and families whose primary language is not English; reduced absenteeism for both vaccinated and unvaccinated students; and reduced absenteeism for staff and teachers. The National Association of School Nurses (NASN) notes that reaching high vaccination coverage of school-aged children and their families, as outlined in Healthy People 2020 and 2030, is an important public health objective. School nurses are in a critical position to create awareness, influence action, and provide leadership in the development of school-located vaccine programs, according to NASN. School nurses are trusted professionals within the school and community settings and can play a pivotal role in the success of these clinics, which historically have been shown to enhance vaccination rates and are one reason vaccination against polio was so effective. These statements are all supported by data. Both flu and COVID vaccines can be given in the same school clinics to students, staff, families, and community. The CDC should include in their recommendations that school nurses be actively included in assessment planning, policy/program development, implementation, and evaluation of both vaccine programs and mitigation efforts. Rather than continuing to ignore these traditionally female school nurse positions, the CDC should take the lead in recognizing the importance of including school nurses in vaccine campaigns and enjoining state, county, and city health departments to partner with school nurses at the county, district, and school levels to carry out this critical task of getting our public health population vaccinated. I thank you so much for the time and the opportunity to speak.

Ms. Elizabeth Ditz
Vaccinate California

Good afternoon Committee members and thank you for your tireless service, which I deeply appreciate. My name is Liz Ditz and I live in San Mateo County, California. I’m speaking for myself, but I am a donor to Voices For Vaccines, which is a grassroots parent organization advocating for high vaccine uptake. I’m also involved with a very large Facebook group, Vaccine Talk, an evidence-based discussion forum that has nearly 80,000 members worldwide; and the Redwood City Woman’s Club with over 100 members, most over 65. I am the COVID-19 Committee Chair for the last group. I have data on flu vaccine uptake in the Women’s Club. Since I started talking about COVID via email in March 2020, more of our members reported going to get their flu vaccines in the fall of ‘20 and ‘21. Nagging works in this setting. With respect to the pneumococcal vaccine changes, I have a primary care provider who is a family medicine doctor. However, I get my flu vaccine and the Moderna booster at my local big box grocery store that has a pharmacy because it’s more convenient—walking distance as opposed to a 30-minute drive. The rub is I have to inform my primary care provider with the vaccine records from the big box store. Is there no easier way to do this? The developing pneumococcal recommendations will be of interest to both the Facebook group and my women’s group. One thing that has been a consistent pattern in both Vaccine Talk and the Women’s Club is how confusing they have found the messaging about vaccine recommendations. This committee has nothing to do with non-pharmaceutical interventions, so I won’t go there. But in that area, too,

government messaging has been very confusing. As a panel discussion showed, the new pneumococcal vaccine recommendations are confusing even to experts. As the workgroup continues to develop recommendations, may I suggest they also consider very carefully the messaging around who should get which vaccine and when? This is an area where expert advice from science communicators and public communications experts would be extremely valuable. These are two groups that have been underused since March 2020. Thank you again for all your hard work.

Ms. Kathleen Cameron
Pharmacist & Public Health Professional
Senior Director, Healthy Aging
National Council on Aging

Good afternoon. My name is Kathy Cameron. I'm a pharmacist, public health professional, and Senior Director of the Center for Healthy Aging at the National Council on Aging, or NCOA. I appreciate the opportunity to provide comments today on behalf of NCOA, older adults, their family members, and caregivers. NCOA is a respected national leader and trusted partner to help people aged 60-plus live with health and financial security. We believe every person deserves to age well. Vaccines are a vital part of aging well, and NCOA is committed to ensuring access for older adults and caregivers using public benefits. We also provide accurate and timely information about vaccines to our constituents. We recognize and commend the tremendous workload that ACIP has taken during the past 3 years, and we thank you for your dedication. I would like to address the issue of expanding access to pneumococcal vaccinations for as many Americans as possible, building on your previous discussions today. Last fall, we were disappointed when despite strong arguments from some voting members, the Committee chose to limit access to newly FDA-approved vaccines to combat additional strains of pneumococcal disease to those 65 years and older and those with pre-existing conditions aged 19 to 64. Widening the availability of these pneumococcal vaccines to those 50 and older would give a needed boost to the fight against yet another respiratory disease. We hope that ACIP will consider lowering the recommendation to adults 50 and older, many who are family caregivers themselves or work in healthcare and social service settings with older adults. CDC data shows that these new vaccines have the potential to save lives, are cost-effective, and could positively address health disparities. Existing vaccines cover roughly 40 of the approximately 90 strains of serotypes of pneumococcal disease. The new vaccines will increase the number of strains covered and offer greater protection, particularly for older Americans and those with chronic conditions that put them at greater risk for contracting pneumococcal disease. Many Americans have fallen behind on routine vaccinations throughout the pandemic, and we must do all we can to help fix this problem. Offering clear-cut, prompt, and simple recommendations on pneumococcal vaccines is imperative to staving off another wave of respiratory illnesses that could further tax not only an individual's personal health, but our wider healthcare system. We urge ACIP to issue the recommendation guidance for the newly approved pneumococcal vaccinations as soon as possible as our nation continues to battle respiratory illnesses at a rate never seen. Strong and clear-cut recommendations from the CDC are critical each year, but more so this flu and pneumonia season as experts are predicting it could be more serious than last year. Thank you again for the opportunity to provide comments.

Ms. Lindsay Clarke, JD

Health Education and Advocacy
Alliance for Aging Research

Good afternoon. I'm Lindsay Clark, Senior Vice President of Health Education and Advocacy at the Alliance for Aging Research. The Alliance is a leading nonprofit organization dedicated to accelerating the pace of scientific discoveries and their application to improve the experience of aging and health. Today's agenda includes many issues of importance to older adults, and we urge the Committee to consider the following as you continue your discussions. First, we applaud the Committee's October recommendation for pneumonia vaccines. The simplifying and streamlining of the recommendations should help to eliminate confusion and improve uptake of the vaccines. To that point, while the Alliance strongly supports high-quality shared decision-making. We feel that the shared decision-making recommendations for the pneumonia vaccines are overly complex and we're concerned that they could pose a barrier to care or could become a check-the-box activity. Standards for shared decision-making should offer patients and providers understandable information about trade-offs among treatment options and facilitate the incorporation of patient preferences and values into the medical plan. Additionally, streamlined recommendations should aim to provide more definitive guidance for clinicians based on the patient's health status and access to care. Second, we urge the Committee to explicitly encourage older adults to receive high dose or adjuvanted influenza vaccines when available. The 2020-2021 recommendations avoid recommending enhanced influenza products over the standard dose flu shots for adults aged 65 and older despite evidence of superior efficacy. The recommendations should encourage older adults to seek out enhanced vaccines to better protect their health, particularly amid the continuing COVID-19 pandemic and the disease's disproportionate impact on the aging population. While we acknowledge that any influenza vaccination is better than no influenza vaccination, ACIP recommendations should make a stronger statement in favor of enhanced vaccines for older adults. Finally, the Alliance is encouraged by the significant vaccine clinical development for RSV and older adults, and we're glad to see the Committee tackling this important topic. While many people often discuss RSV in terms of impacts on the pediatric population, RSV is also recognized as a significant concern for older adults. Older adults are at greater risk for serious complications from the disease due to weakened immune system, and RSV can be especially life threatening for those with chronic heart or lung disease. Each year, more than 177,000 older adults are hospitalized and 14,000 die from the infection. Beginning this important discussion in advance of any new product approvals establishes an important foundation for timely recommendations, as well as builds awareness and consensus about the need to protect older adults from RSV. Thank you so much for the time and opportunity to comment.

Dr. Kelly Moore, MD, MPH
Chief Executive Officer
Immunize.org

Good afternoon. I'm Dr. Kelly Moore, CEO of immunized.org, a nonprofit supporting frontline vaccinators and immunization coalitions through educational resources and advocacy. I'm also a former member of the ACIP. First, thank you to everyone involved with ACIP for the quality of this transparent, evidence-informed policymaking process. Today I'd like to offer a few thoughts about preferential recommendations. I believe the public's health and public confidence in vaccination improves when the ACIP makes justifiable preferential recommendations based on solid evidence of distinctly superior performance and they are diminished when clear

distinctions are disregarded. The exact threshold for justifying a preference depends on the specific disease and vaccines and questions, and I'm not getting into that here. Well-informed members may reach different conclusions about what is justified depending on their values and points of view. But the concerns I often hear from those who are reluctant ever to express a preference include: *What if we express a preference that there isn't enough supply for everyone? Will it look bad if something unexpected happens later and we must change our policy? What if we express a preference that financially disadvantages another manufacturer and can lead to the discontinuation of a non-preferred product?* For what it's worth, here's a bit of my own thinking about these concerns and the ultimate importance of expressing preferences when justified. First, the ACIP must consider supply and implementation issues, but I believe the highest priority is for ACIP to make the best recommendations for the health outcomes of vaccine recipients. Within reason, initial supply is less critical than making it clear what is preferred if it's available and how to prioritize if necessary. This gives purchasing organizations, busy clinicians, and vaccine recipients clarity. As a "chicken and egg issue," supply and access are issues most likely to resolve as a consequence of preference, not ahead of it. When the ACIP acts on the best available evidence, but unforeseen circumstances necessitate a later change, as we've done before, that's not a flaw of the ACIP. It's a feature. Judge the evidence and don't let speculative what ifs result in decision paralysis. Finally, when ACIP prioritizes vaccines that produce substantially better health outcomes, that incentivizes vaccine innovation to further improve vaccine effectiveness. It's hard to justify innovation and effectiveness research if vaccines with widely disparate performance are consistently treated equally from a policy standpoint. It's my hope that when questions of preference arise, ACIP and CDC will be willing to appropriately acknowledge significant advances in ways that encourage the further pursuit of superior vaccines in the best interest of the public's health. Thank you.

Mr. Mark Gibbons
President/CEO
RetireSafe

Good afternoon. This is Mark Gibbons. I'm the President/CEO of Retire Safe. Retire Safe is an advocacy organization which endeavors to give voice to the multifaceted concerns of middle age and older adults. Needless to say, healthcare issues constantly top that list, particularly the last 2 years when the pandemic has dominated the conduct of all of our lives. Thanks to the spectacular work of researchers and scientists from the public and private sectors, though we are in a challenging fight, we have effective tools at hand to treat, combat, and advance prevention of COVID. We absolutely cannot step away from this effort and we must also continue research so as to be ready for any future variants. But it is equally urgent that we continue to battle diseases that before COVID were taking a huge toll in suffering and loss of life, such as pneumonia, RSV, and influenza. It was in 2018 when 64% of the adults 65 and older had received a pneumonia vaccine—a promising increase from only 48% in 2000. However, considering that about 1 in 20 people who contract pneumonia will die, that percentage is not nearly high enough. We also know that many Americans have fallen behind on routine vaccinations throughout the pandemic, a trend we must work to reverse. Again, thanks to the advancements in science and the commitment of this Committee, older Americans and those deemed at risk will have access to powerful, new innovative vaccines to protect against pneumonia. It is our belief that broad coverage for those most vulnerable communities will have the greatest impact against this deadly disease. While we would have liked to see eligibility extended to those aged 50 and older, we urge broader access for Americans 16 to 64 with serious adverse conditions. By offering clear, simple, and broad clinical guidance on who should receive the new pneumonia vaccines and when they should get them, providers will be able to make better recommendations for their patients. Then more eligible Americans will be

empowered to take this important step to protect their health. As we continue to face the ongoing threat of COVID-19 coupled with the flu and pneumonia season, all Americans who are eligible for the new pneumonia vaccines deserve access as soon as possible. We are grateful for this Committee's ongoing efforts to protect all Americans—especially its elders. We do hope the Committee will, in the future, consider lowering the recommendation to adults aged 50 and older. For our part, we will continue to educate and inform our communities in important steps that we can take to protect ourselves. Thank you for your time.

CERTIFICATION

Upon reviewing the foregoing version of the January 12, 2022 ACIP meeting minutes, Dr. Grace Lee, ACIP Chair, certified that to the best of her knowledge, they are accurate and complete. Her original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

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ACRONYMS USED IN THIS DOCUMENT

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ABCs	Active Bacterial Core Surveillance
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
aIIV	Adjuvanted Influenza Vaccine
AE	Adverse Event
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
APhA	American Pharmacists Association
ASTHO	Association of State and Territorial Health Officers
BLA	Biologics License Application
CDC	Centers for Disease Control and Prevention
CMS	Center for Medicare and Medicaid Services
COI	Conflict of Interest
CPCSSN	Canadian Primary Care Sentinel Surveillance Network
CPT®	Current Procedural Terminology
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
ED	Emergency Department
ESRD	End-Stage Renal Disease
ET	Eastern Time
EtR	Evidence to Recommendation
EVs	Enhanced Vaccines
FDA	Food and Drug Administration
GBS	Guillain-Barré Syndrome
GMC	Geometric Mean Concentration
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
HAIVEN	Hospitalized Adult Influenza Vaccine Effectiveness Network
HCP	Healthcare Personnel / Providers
HD-IV	High-Dose Influenza Vaccine
HHS	(Department of) Health and Human Services
HIV	Human Immunodeficiency Virus

HRSA	Health Resources and Services Administration
ICD-9	International Classification of Diseases, Ninth Revision
IDSA	Infectious Disease Society of America
IHS	Indian Health Service
ILI	Influenza-Like Illness
I-MOVE	Influenza Monitoring Vaccine Effectiveness
IPD	Invasive Pneumococcal Disease
MAAE	Medically-Attended Adverse Events
MASO	Management Analysis and Services Office
MMWR	*Morbidity and Mortality Weekly Report*
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization Canada
NAPNAP	National Association of Pediatric Nurse Practitioners
NASN	National Association of School Nurses
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCIRD	National Center for Immunization and Respiratory Diseases
NCOA	National Council on Aging
NFID	National Foundation for Infectious Diseases
NIH	National Institutes of Health
NMA	National Medical Association
NTTO	National Travel and Tourism Office
OIDP	Office of Infectious Disease and HIV/AIDS Policy (OIDP)
PCP	Primary Care Provider/Practitioner
PCR	Polymerase Chain Reaction
PHAC	Public Health Agency Canada
PICO	Population, Intervention, Comparison, Outcomes
PIDS	Pediatric Infectious Disease Society
rVE	Relative Vaccine Efficacy
RCT	Randomized Controlled Trial
RIV	Recombinant Influenza Vaccine
RSV	Respiratory Syncytial Virus
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
TBE	Tickborne Encephalitis
US	United States
USG	United States Government
VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VFC	Vaccines For Children
WG	Work Group
WHO	World Health Organization