MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

SEPTEMBER 29, 2021
SUMMARY MINUTES

TABLE OF CONTENTS

MEETING PURPOSE

The United States (US) Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC) convened a meeting of the Advisory Committee on Immunization Practices (ACIP) on September 29, 2021. The meeting took place remotely via Zoom, teleconference, and live webcast. This document provides a summary of the meeting, which focused on vaccines to prevent tick-borne encephalitis (TBE), zoster, pneumococcal disease, hepatitis B, and orthopoxvirus diseases.

THURSDAY: SEPTEMBER 29, 2021

WELCOME AND INTRODUCTIONS

Dr. Grace Lee (ACIP Chair) called to order and presided over the first day of the 12th ACIP meeting convened in 2021. She introduced ACIP's new Executive Secretary, Dr. Melinda Wharton and shared a brief background about her. Dr. Wharton has held many leadership roles over the years. She received her medical degree from Harvard Medical School, her Masters of Public Health (MPH) from Johns Hopkins University (JHU), completed her training in internal medicine at the University of Michigan, and completed her infectious disease training at Duke University Medical Center before coming to CDC as an Epidemic Intelligence Service (EIS) Officer. She joined CDC's immunization program in 1992 and has had many roles central to ACIP since that time, including Director of the Immunization Services Division (ISD), Acting Director of the National Vaccine Program Office (NVPO), Acting Director of the Immunization Safety Office (ISO), Deputy Director and Acting Director of National Center for Immunization and Respiratory Diseases (NCIRD). In her current role, Dr. Wharton is the Associate Director for Vaccine Policy and Clinical Partnerships of NCIRD. Dr. Lee said she personally has appreciated Dr. Wharton's co-leadership with Dr. Lauri Markowitz of the COVID-19 Vaccine Safety Technical Work Group (VaST WG) over the past year, which has taken a lot of time and dedication from the team. Dr. Lee also discovered that Dr. Wharton loves to ride and has logged in over 369 bike trips and over 3,000 miles as a cyclist. ACIP is grateful that Dr. Wharton agreed to serve as the new Executive Secretary as Dr. Cohn transitions to a new role following her leadership of the ACIP and the important role that she played in shaping national immunization policy during that time.

Dr. Melinda Wharton (ACIP Executive Secretary, CDC) noted that copies of the slides for the day were available on the ACIP website and were made available through a ShareLink™ file for voting ACIP Voting Members, *Ex Officios*, and Liaisons. She indicated that there would be an oral public comment session prior to the vote at approximately 2:35 PM Eastern Time (ET). 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 any other individuals wishing to make written public comments may submit them through https://www.regulations.gov using Docket Number CDC-2021-0075. 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 conflict of interest (COI) waivers. Members who conduct vaccine clinical trials or serve on data

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

Dr. Grace Lee (ACIP Chair) conducted a roll call, during which no COIs were declared and quorum was established. A list of Members, *Ex Officios*, and Liaison Representatives is included in the appendixes at the end of this summary document.

TBE VACCINE

Session Introduction

Dr. Kathy Poehling (ACIP, WG Chair) remined everyone that the Food and Drug Administration (FDA) approved the TBE vaccine, TICOVAC™, on August 13, 2021. Given that no TBE vaccine has been licensed previously in the US, there are no existing ACIP TBE vaccine recommendations. The TBE Vaccine WG was formed in September 2020 to review use of TBE vaccine in US adults and children traveling abroad. The terms of reference for the TBE Vaccine WG 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 vaccination recommendations; and 6) publish an ACIP recommendation in the *Morbidity and Mortality Weekly Report* (*MMWR*). This session focused on a summary of the immunogenicity and safety of TBE vaccine and next steps for the TBE Vaccine WG.

Immunogenicity and Safety of TBE Vaccine & Next Steps

Dr. Susan Hills (CDC/NCEZID) presented on TBE vaccine and its administration, immunogenicity after the primary series, immunogenicity after a booster dose, safety, vaccine effectiveness (VE), and special populations. She reminded everyone that during the October 2020 ACIP meeting, the manufacturers presented summarized information on development of the TBE vaccine, but that she would present a more comprehensive overview of the vaccine's immunogenicity and safety as there had been some changes since that time.

In terms of background, an earlier formulation of a TBE vaccine was first licensed in Austria in 1976. Changes to that formulation over time have included removal of thimerosal and a transition in the origin of the production virus seed to chick embryo fibroblast cells. The current adult formulation of the vaccine was licensed in Europe in 2001 and the pediatric formulation became available in 2003. Because of the manufacturing changes that have occurred, the TBE Vaccine WG has focused on data for the current formulation of the vaccine that has been available since 2001. This vaccine has had extensive use in TBE-endemic countries during the last 20 years, with more than 75 million doses administered. About 2/3 of those doses have been in adults and about 1/3 have been in children. The vaccine is currently marketed in about 30 countries, primarily in Europe.

This vaccine is an inactivated, whole virus vaccine based on the European subtype of TBE virus called the Neudorfl strain. It is produced on chick embryo fibroblast cells and the adjuvant is aluminum hydroxide. There is no preservative and the stabilizer is human serum albumin. The other ingredients and substances used in manufacturing that might be found in the final product include sodium chloride, dibasic sodium phosphate, monobasic potassium phosphate, formaldehyde, sucrose, protamine sulfate, neomycin, and/or gentamicin. The vaccine has an adult dose for persons aged ≥16 years (0.5mL) and a pediatric dose for children aged 1-15 years (0.25mL). Vaccine is supplied in a pre-sealed syringe and is administered intramuscularly (IM). The only difference in the schedule is that the first 2 doses for adults are administered 14 days to 3 months apart and for children the first 2 doses are administered 1 month to 3 months apart. The third dose of the primary series is given 5-12 months later, and a booster dose may be given at least 3 years after the primary series if ongoing exposure or re-exposure to TBE virus is expected.

In terms of immunogenicity after the primary series, it is important to note that there are no vaccine efficacy (VE) trials because the low incidence of disease would make such trials impossible. As a result, vaccine licensure and evidence of protection has been based on immunogenicity end points. TBE virus neutralizing antibodies are believed to confer protection against disease. A 50% neutralizing antibody titer of ≥10 is generally used in vaccine studies to indicate protection. However, no formal correlate of protection has been established and there are no standardized reference reagents available.

The data on immunogenicity after the 3-dose primary series in adults came from initial and follow-up observational studies conducted in Poland[1] among adults 16-64 years of age. In the initial study, the seropositivity rate is approximately 1 month after the final dose of the 3-dose primary series, with 99% among the 416 adults in the study. In a follow-up study,[2] the seropositivity rate 3 years after the final dose immediately prior to the booster dose was 94%. The geometric mean titers (GMTs) showed a moderate decrease between 1 month after the primary series and 2 years after the primary series, but then remained relatively stable until 3 years. Pediatric immunogenicity data after the primary series came from initial and follow-up[3] observational studies conducted in several European countries among children and adolescents 1-15 years of age. In the initial study, the seropositivity rate was approximately 1 month after the final dose of the 3-dose primary series, with 99% among the 360 subjects in the study. In the follow-up study, the seropositivity rate at 3 years after the final dose immediately prior to the booster dose was 98%. Similar to the adult data, the GMTs showed a moderate decrease between 1 month after the primary series and 2 years after the primary series, but then remained relatively stable until 3 years. The pattern was similar for children in all age groups.

To summarize the data from these key studies on immunogenicity among adults and children, the studies showed high seropositivity rates of 99% at 1 month after completion of the 3-dose primary series. High seropositivity rates of at least 94% persisted for 3 years after the primary series, or until immediately prior to the scheduled booster dose. However, there was a moderate decrease in GMTs that mainly occurred initially but little change between Years 2 and 3.

[1] Loew-Baselli A et al. Vaccine 2006; Loew-Baselli A et al. Vaccine 2009
[2] Loew-Baselli A et al. Vaccine 2009
[3] Pöllabauer EM et al. Vaccine 2010; Poellabauer E et al. Vaccine 2019

Key data on immunogenicity in adults after a booster dose administered at 3 years after the final dose of the primary series came from further follow-up of individuals in the adult study[4] mentioned earlier. In this cohort of 232 adults, 100% were seropositive at 1 month after the booster dose. Seropositivity rates of at least 94% were maintained through 5 years after the booster dose. By 10 years after the booster dose, seropositivity rates were still high at 85%. There was a moderate decrease in the GMTs within the first 2 years after the booster dose, with a relatively slow decline from 2 years to 10 years.

The pediatric immunogenicity data after a booster dose were from further follow-up in individuals in the pediatric study described earlier.[5] In this cohort of 172 children and adolescents, 100% were seropositive at 1 month after the booster dose. By 10 years after the booster dose, there was still a high seropositivity rate of 90%. Looking at GMTs over time after the booster dose for children in 4 age groups (1-2 years, 3-6 years, 7-11 years, 12-15 years) similar patterns were seen in all age groups with an initial moderate decrease, followed by a slow decrease through 10 years.

To summarize the key data on immunogenicity after a booster dose among adults and children, the studies showed high seropositivity rates of 100% at 1 month after a booster dose. High rates of at least 85% persisted through 10 years after the booster dose. A moderate decrease in GMTs occurred within the immediate period after the booster dose, followed by a slow decrease through 10 years.

Moving to safety, the safety data for adults came from a study that included almost 3,000 adults 16-64 years of age.[6] Overall, the rates of solicited adverse events (AEs) within 3 days after Dose 1 were 36% for local reactions, 14% for systemic reactions excluding fever, and less than 1% for fever. The percentage of subjects with an AE was highest after Dose 1. These can generally be considered the highest rates of AEs after any dose. There were few severe adverse events (SAEs). The rates of SAEs after Dose 1 were 0.1% for local reactions and 0.03% for systemic reactions. There were no subjects with a severe fever >40ºC. The most common systemic reactions after Dose 1 were fatigue, headache, and malaise, each occurring in 7% or fewer subjects. There were no SAEs considered vaccine-related by the study investigators.

The pediatric safety data[7] came from a study that included 2,417 children and adolescents, age 1 to 15 years. Overall, the rates for solicited adverse events AEs within 3 days after Dose 1 were 25% for local reactions, 20% for systemic reactions excluding fever, and 10% for fever. Similar to adults, the AE rates among children were higher after Dose 1 than after subsequent doses. Again, these can generally be considered the highest rates after any dose. The rates of SAEs after Dose 1 were 0.2% for local reactions and 0.1% for systemic reactions. No subjects had a severe fever >40ºC. While the fever rate overall after Dose 1 was 10%, fever rates were variable by age group and occurred in higher rates among younger children. These ranged from 36% in young children 1-2 years of age to 6% among older children and adolescents. However, most fevers were mild. Among the children 1-2 years of age, the age group most at risk for any fever, 2/3 of all fevers were lower than >38.5ºC and none were >40ºC. In addition, fever rates were substantially lower after subsequent doses, with fever rates of 1% to 2% overall after Doses 2 and 3 of the primary series. The most common solicited systemic reactions in children after Dose 1 were headache reported in 11% overall among subjects 1-15 years of age,

[4] Konior et al. Vaccine 2017; Pfizer
[5] Poellabauer E et al. Vaccine 2019
[6] Loew-Baselli A e al. Vaccine 2006
[7] Pöllabauer EM et al. Vaccine 2010

restlessness reported in 9% of children 1-5 years of age, and fatigue reported in 6% of subjects 6-15 years of age. There were no SAEs considered vaccine-related by the study investigators.

To summarize the key data on safety among adults and children, after Dose 1, solicited local AEs were reported in 36% of adults and 25% of children and adolescents, systemic AEs were 14% in adults and 20% in children and adolescents, and fever rates were variable by age group but were mainly mild and no fever was reported >40ºC. Severe AEs were uncommon. Rates of AEs were highest after the first dose and lower after subsequent vaccine doses.

As mentioned earlier, there are no VE studies for Pfizer's TBE vaccine alone. However, there is a VE study from Austria[8] that has some partially relevant data. The assessment had some limitations because most, but not all, of the TBE vaccine used in Austria during the relevant period was Pfizer's TBE vaccine. It was estimated that about 90% to 95% of vaccine use was Pfizer's TBE vaccine. When TBE occurred in a vaccinated person, there was no information on which TBE vaccine the person had received. In addition, many vaccinated persons would have received the previous formulation rather than the current formulation of the Pfizer TBE vaccine. Finally, effectiveness was measured based on adherence to vaccination according to the recommended primary and booster vaccination schedule used in Austria, but not necessarily that of the US-approved schedule and not at a specific time point after vaccination. Despite those limitations, the data are useful to briefly review. During the period 2000 to 2006, the VE estimate overall was 99%. Effectiveness was high in every age group ranging from 96% to 99%. An updated VE estimate without age specific data covering the period 2018-2020 showed a similar overall VE of 96%.[9]

Regarding information on disease and vaccination among special populations for TBE disease, a limited number of case reports suggest that pregnant women have a similar spectrum of illness to non-pregnant persons. Transplacental transmission of TBE virus has not been established. No studies have assessed the safety or immunogenicity of TBE vaccine in pregnancy. There are some limited safety data available from the manufacturer's safety database. This database is based on reports submitted by healthcare providers (HCP) and others from other sources, so it is more likely to capture data where an AE occurred when vaccine was administered. However, it is also likely to capture only a small proportion of all occurrences of any event, regardless of whether an AE occurred.

During the 45 year period from 1976-2020 when more than 150 million vaccine doses were distributed, 138 reports were submitted to the manufacturer. Of those, 60 related to vaccination of a pregnant woman where neither the mother nor infant experienced an AE. For 48, the mother remained healthy but the infant outcome was unavailable. For 30, an AE was reported in the mother or infant, but there was no distinct pattern of AEs seen in either the mothers or infants. In regard to breastfeeding women and TBE disease, 2 case reports indicated transmission of TBE virus from infected, breastfeeding women to their infants.[10] The outcome was reportedly severe for 1 infant and the other infant was healthy. No studies have investigated the safety of TBE vaccination in lactating women. Limited data are available from the manufacturer's safety database. From 1976-2020, there were 25 reports of a breastfeeding mother being vaccinated for which the manufacturer received a report on the event. In 11 of these reports, follow-up on the infant indicated there was no AE, the infant outcome was unknown in 8 of the reports, and there was an AE in the infant in 6 of the reports that included a

[8] Heinz FX et al. Vaccine 2007
[9] Pfizer, data on file
[10] International Scientific Work Group on TBE (presentation by Jana Kerlik MD)

fever in 3, a rash in 1, and gastrointestinal (GI) symptoms in 2 infants, 1 of whom was hospitalized for colic.

For immunocompromised persons, TBE infection can result in severe illness and these individuals have a higher risk of a fatal outcome. There are limited data[11] on the use of TBE vaccine in persons with altered immunocompetence. In many of the available studies, either a previous formulation of the vaccine or a modified vaccination schedule was used. To summarize overall, immunogenicity results were variable but typically showed a lower response in persons with altered immune status. When an adequate response occurred, development of the response was often delayed. The available safety data suggested this inactivated vaccine was well-tolerated.

In regard to TBE in older persons, it is well-recognized that the incidence and severity of disease are highest in older persons. Most studies on TBE vaccination in older persons show that there are high seropositivity rates after the primary series. In one study, 99% of the 137 healthy elderly adults 70 years of age or older were seropositive at 1 month after completion of the primary series.[12] Some concern has been expressed in publications about the duration of seropositivity over the longer term after the booster dose in older adults, particularly at 5 or more years after the booster dose. However, these data are very limited.[13] One study that followed adults for 10 years after a booster dose had fewer than 10 subjects older than 60 years of age included in the dataset. AE rates in older persons have been shown to be comparable to those in younger persons.[14] There are no data on co-administration of TBE vaccine with other vaccines.

To summarize key points, there are good immunogenicity results following TBE vaccination, with high seropositivity rates within a few weeks of completion of the 3-dose primary series and following a booster dose administered at 3 years. Seropositivity rates are high in both adults and children. The vaccine also has an acceptable safety profile. It is relatively well-tolerated with few severe or local systemic reactions. Its safety profile is similar to many other inactivated vaccines. There are limited data among special populations, but some persons with altered immunocompetence might have a reduced immune response. No major safety issues have been identified among any of the special populations. There are some limitations of the immunogenicity data. In regard to interpretation of the seropositivity data, there is no formal immunologic correlate of protection. In addition, the level of protection from this TBE vaccine based on a European subtype TBE virus for other subtypes of TBE virus transmitted in parts of Eastern Europe and endemic countries further East is unclear. Available data from human and animal studies and the genetic and antigenic similarity between the 3 main TBE virus subtypes suggest that there is likely cross-protection, but data are limited and VE has not been demonstrated.

In terms of next steps and the TBE Vaccine WG's timeline, the WG plans to present the Evidence to Recommendations (EtR) Framework to ACIP in October 2021 in anticipation of having ACIP vote on TBE vaccine recommendations during the February 2022 ACIP meeting, prior to the next TBE virus transmission season.

[11] Prelog M et al. Vaccine 2008; Zielinski CC at al. Cancer 1986; Panasiuk B et al. Infection 2003; Einarsdottir et al. Vaccine 2021; Harrison et al. NPJ Vaccines 2020.
[12] Wanke et al. Clin Microbiol Infect 2012
[13] Konior et al. Vaccine 2017
[14] Pfizer study 690601

Key Discussion Points

- ACIP requested additional information about the following if/when available:
    - Co-administration of TBE vaccine with other vaccines
    - The larger drop in GMTs as children/adolescents get older (Slide 25)
    - The target audiences for whom a TBE vaccination recommendation might be made in addition to travelers and laboratory workers
    - Optimal dosing intervals, particularly for travelers who may not have received all doses in the series prior to traveling and given that the third dose results in a very strong boost in GMTs
    - Continued clinical trial data and post-marketing effectiveness and safety data, particularly for immunocompromised populations, older adults, pregnant persons, infants, and lactating/breastfeeding women

ZOSTER VACCINES

Introduction

Dr. Camille Kotton (ACIP, WG Chair) introduced the zoster vaccine session, which focused on immunocompromised persons. The recombinant zoster vaccine (RZV) was licensed by the Food and Drug Administration (FDA) in 2017. CDC subsequently adopted the ACIP's recommendation in January 2018. The European Medicines Agency (EMA) approved an expanded RZV indication in August 2020 for adults 18 years of age and older at increased risk for zoster. A Supplemental Biologics License Application (sBLA) was submitted to the FDA in Fall 2020 to support RZV use in immunocompromised persons 18 years of age and older. ACIP began reviewing this earlier in 2021. The FDA approved the expanded RZV indication for use in immunocompromised adults 18 years of age and up in July 2021.

With that in mind, the policy question now before ACIP is as follows:

- ❑ Should adults ≥19 years of age who are or will be immunodeficient or immunosuppressed due to disease or therapy be recommended to receive two doses of the recombinant zoster vaccine for the prevention of herpes zoster and its complications?

- ❑ Including but not limited to:
    1. Hematopoietic stem cell transplant (HSCT) recipients
    2. Patients with hematologic malignancies (HM)
    3. Renal or other solid organ transplant (SOT) recipients
    4. Patients with solid tumor malignancies (STM)
    5. People living with human immunodeficiency virus (HIV)
    6. Patients with primary immunodeficiencies, autoimmune conditions, and taking immunosuppressive medications/therapies

In terms of the PICO question, the population is immunocompromised adults ≥19 years of age. The intervention is whether they should get 2 doses of RZV at least 4 weeks apart. The comparison is no vaccine. The critical outcomes are to prevent herpes zoster (HZ) and consider serious adverse events (SAEs). Important outcomes are to prevent postherpetic neuralgia (PHN), prevent herpes zoster-related hospitalizations, consider the risk of immune-mediated

disease (IMD), consider reactogenicity, determine whether there might be an increased risk of graft versus host disease (HSCT) or graft rejection (SOT).

During the June 2021 ACIP meeting, the WG began to discuss some of these issues in the EtR Framework domains of Public Health Problem and Benefits and Harms. Since the June meeting, the WG has convened 4 meetings and has reviewed and discussed the remaining EtR domains of Values, Acceptability, Feasibility, Resource Use, and Equity. This included an economic assessment of the use of this vaccine in immunocompromised patients 19-49 years of age. The WG also reviewed data on primary care physicians' perspective related to vaccine and looked at a GRADE (Grading of Recommendation Assessment, Development and Evaluation) analysis regarding the use of this vaccine in immunocompromised adults. In addition, the WG has given thought to special considerations for potential use of this vaccine in immunocompromised adults.

This session focused on the economics of immunocompromised 19-49 years of age against HZ in the US, the preliminary EtR analysis regarding the use of RZV in immunocompromised Adults, and next steps.

Economic Assessments Regarding Use of RZV in Immunocompromised Adults 19-49 Years of Age

Dr. Ismael Ortega-Sanchez (CDC/NCIRD) presented on the economics of vaccinating immunocompromised adults in the US against HZ, summarizing key elements and findings of two economic studies that were discussed extensively within the WG. One of these studies was an in-house economic analysis led by Dr. Andrew Leidner from the Immunization Services Division (ISD) at CDC, referred to as the "CDC Model." The second study was conducted by GlaskoSmithKline (GSK), referred to as the "GSK Model."

Although the policy question has been particularly motivating for these economic analyses, given how heterogeneous immunocompromising conditions can be, the economic assessment of this potential recommendation has been quite challenging. Therefore, the approach adopted in both models was to split the policy question by age, 19-49 years, and specific immunocompromising condition. The base case in both models focused on HSCT. To consider the economics of the policy question is to consider the health benefits and costs of vaccination simultaneously to ascertain whether vaccinating immunocompromised adults against HZ is cost-effective. To answer this question, both models used the same comparator of unvaccinated immunocompromised groups 19-49 years of age and focused on the analysis of cost-effectiveness of RZV administration in adults 19-49 years of age with HCST.

In addition to the HCST recipients, the WG has been considering the economics of vaccination in immunocompromised populations. Specifically, the CDC and GSK coincided on modeling one another's immunocompromised populations to include adults living with HIV. The immunocompromised populations for this analysis considered by CDC Model that differed from the groups considered by the GSK Model included multiple myeloma, non-Hodgkin's lymphoma, hematologic malignancies, and autoimmune and other inflammatory disease. The GSK Model considered renal or other solid organ transplant, Hodgkin's lymphoma, and breast cancer.

In general, the models followed similar designs. Both used a static analytical decision-making approach, relied on probabilistic simulation and sensitivity analyses to manage the various data uncertainties, modeled a hypothetical cohort of HSCT recipients 19-49 years of age, used a reasonable timeframe of time of vaccination with 1st and 2nd dose of RZV, used an analytical

horizon of age-specific life expectancy or 30 years, and used a discount rate of 3% (0%-6%). The key difference to mention is that the CDC Model uses a healthcare perspective, given that it focused only on the direct medical costs. The GSK Model used a societal perspective, given that it accounted for the loss of income associated with temporary productivity loss.

Once the models were set, they were set by different types of input and main outcomes including epidemiological data, vaccine characteristics, quality-of-life in specific immunocompromised conditions, health care resource utilization (HCRU) and cost data, indirect cost data (GSK only), and other parameters. The source and specific values and assumptions of these parameters had some overlaps across models, but there were marked differences as well. The full reports with the input data and assumptions from both models were made available to ACIP members. Both models estimated outcomes for uncomplicated HZ cases, HZ with PH, quality-adjusted life-years (QALYs) saved, $/Case saved, $/QALY saved, and number needed to vaccinate (NNV) to avert one case of HZ. The CDC Model also assessed the outcomes of inpatient care of HZ, HZ-associated deaths, and NNV to avert hospitalization and deaths. The GSK model also assess the NNV to avert a PHN case.

Before proceeding, Dr. Ortega-Sanchez briefly reviewed a few economic concepts to help understand the results better. First, the cost of the intervention is basically the cost of a vaccination program. This includes the cost of recommended associated vaccine doses, the cost of administration, and the cost of associated AEs weighted by the probabilities. Second, the savings from the intervention includes changes in the course of illness due to vaccination without vaccination program costs. The net cost of vaccination is usually estimated as the difference between the cost of the intervention minus the savings from the intervention. In this context, it is said that an intervention is cost-saving when the total costs of intervention are less than the total savings from an intervention. One thing to keep in mind is that all cost-saving interventions are also cost-effective, but not all cost-effective interventions are necessarily cost-saving. When an intervention is cost-saving, it will be reflected in the body of a ratio, usually calculated in health economics as the incremental cost effectiveness ratio (ICER). When the value of this ratio is less than zero, it means that preventing one HZ case or one HZ-related hospitalization will save money. In other words, it would be more costly to do nothing because of the potential savings from adopting the vaccination program.

With this concept in mind, it is possible to summarize the most important findings in this model based on 4 measures. The vaccination of the HSCT group was found to be cost-saving by the CDC Model. This is also reflected in the low NNV to vaccinate toward any specific outcome. The costs per QALY findings are generally supported with a simulation and sensitivity analysis. Specifically, 72% of these simulations, including the base case, were found to be cost-saving. Similarly in the GSK Model, based on 2 measures, the vaccination of the HSCT group also was found to be cost-savings. Like the CDC Model, the simulation and sensitivity analysis of the GSK Model found that there are cost-saving results supported by the outcomes of the simulation analysis.

Both models agree that vaccination of HSCT recipients is cost-saving as shown by the cost per QALY, cost per case report, and relatively low NNV to avert a HZ case. It is important to understand what might be driving the variability in the simulations. Particularly influential were the epidemiological and clinical variables. In other words, any changes in either initial VE, HZ incidence rate, or duration of immunocompromised status have a relatively or proportionally higher increasing impact on the base cost per quality value. Regarding the cost-effectiveness of additional immunocompromised populations, the estimates were cost-saving for most of the scenarios when reported cost were less than $100,000 per QALY except the ones for the

autoimmune and inflammatory diseases, with a cost per QALY ranging from $150,000 to $200.000 per QALY depending on the model and specific assumptions.

Given the relatively large population size of people with autoimmune and inflammatory diseases, the WG considered it important to explore more than the health benefits and costs of vaccinating them. If the healthcare costs are lower and incidence is relatively low, such as 11 cases per 1000 person years, the economic value of vaccinating a selective autoimmune/ inflammatory disease group is relatively less favorable. The estimated one reported by Yun et al was about $200,000 per QALY.[15] In a similar fashion and borrowing the threshold analysis in HSCT from the GSK report, it may be possible to corroborate a relatively high cost per QALY in an implicit autoimmune inflammatory scenario. If everything else remains equal from the HSCT scenario, it could be inferred that for an incidence around 11 per 1000 person years, there would be about an 80% reduction in HZ incidence and the cost per QALY would become quite high.[16] It is worth noting that GSK reported $150,000 per quality for an implicit scenario when assuming the starting age as 25 years, incidence of 10 per 1000 person years, 5 years' duration of immunocompromised status, and higher VE.

To summarize, the economic value of recommending RZV could be favorable (e.g., cost-saving) in HSCT patients, with relatively higher HZ incidence and HZ-related healthcare costs combined with reasonable VE. Data from clinical trials support these findings. Yet, the HSCT recipients represent a relatively small population among all immunocompromised groups. For other immunocompromised groups, such as HIV or autoimmune/inflammatory disease groups, the economic value of RZV immunization is less favorable relative to the HSCT patients. This is due to the relatively lower risk of HZ and lower healthcare costs. Some specific autoimmune inflammatory conditions may have even the least favorable estimates, a fact that is heavily dependent upon the underlying risk of HZ. It is important to consider the relatively large patient population size among all immunocompromised conditions.

WG Interpretation of the EtR Benefits & Harms & Resource Use Domains & Next steps

Dr. Tara Anderson (CDC/NCIRD) reviewed the preliminary EtR Framework regarding the use of RZV in immunocompromised adults and next steps. As a reminder, the policy question under consideration is as follows:

- Should adults ≥19 years of age who are or will be immunodeficient or immunosuppressed due to disease or therapy be recommended to receive two doses of the recombinant zoster vaccine for the prevention of herpes zoster and its complications?

- Including but not limited to:
    1. Hematopoietic stem cell transplant (HSCT) recipients
    2. Patients with hematologic malignancies (HM)
    3. Renal or other solid organ transplant (SOT) recipients
    4. Patients with solid tumor malignancies (STM)
    5. People living with human immunodeficiency virus (HIV)
    6. Patients with primary immunodeficiencies, autoimmune conditions, and taking immunosuppressive medications/therapies

[15] Yun et al. 2016. "Risk of Herpes Zoster in Autoimmune and Inflammatory Diseases", Arthritis and Rheumatology 68(9): 2328-2337

[16] Chen, S.-Y., et al., Incidence of herpes zoster in patients with altered immune function. Infection, 2014. 42(2): p. 325-334; Yun et al. 2016. "Risk of Herpes Zoster in Autoimmune and Inflammatory Diseases", Arthritis and Rheumatology 68(9): 2328-2337

In terms of the PICO question, the population is immunocompromised adults ≥19 years of age. The intervention is whether they should receive 2 doses of RZV at least 4 weeks apart. The comparison is no vaccine. The critical outcomes are to prevent HZ and consider SAEs. Important outcomes include prevention of PHN, prevention of HZ-related hospitalizations, consideration of the risk of IMD, consideration of reactogenicity, determination of whether there might be an increased risk of HSCT, determination of whether there might be an increased risk of SOT. This presentation provided an overview of each EtR domain regarding use of RZV in immunocompromised adults, including the available evidence and WG determinations.

First a review of the public health problem, which was presented previously during the June 2021 ACIP meeting. For this domain, the WG was to assess whether HZ in immunocompromised adults is of public health importance. As previously discussed, millions of persons in the US are immunocompromised. In the 2013 National Health Interview Survey (NHIS), approximately 7 million adults self-reported immunosuppression. There are a total of approximately 3 million among stem cell transplant recipients, patients with hematologic malignancies, renal or solid organ transplant recipients, patients with solid-tumor malignancies, and people living with HIV. In addition to these groups, there are approximately 22 million with more than 80 diverse autoimmune and/or inflammatory conditions, such as systemic lupus erythematosus, rheumatoid arthritis, and inflammatory bowel disease. These patients often have underlying immune defects, but generally are not considered frankly immunocompromised unless they are on immunosuppressing treatments.[17]

Importantly, an increasing proportion of immunocompromised patients are likely to be treated with immunosuppressive medications and therapies. Of note, zoster vaccine live (ZVL) was contraindicated for most immunocompromised patients. HZ is common in the general population. There were approximately 1 million cases of zoster per year in the US during the pre-herpes zoster vaccine era.[18] Zoster rates increase with age, with incidence rates ranging from about 2 to 9 per 1,000 persons.[19] As previously noted, the immunocompromised population at higher risk for zoster is substantial, but estimating burden of disease requires a clear understanding of zoster incidence and severity in these groups.

A systematic literature review regarding the risk of zoster in immunocompromised Groups 1-5 was conducted recently.[20] It was noted that the median zoster incidence estimates for these immunocompromised groups exceeded those reported for immunocompetent adults 50 years and older. The incidence rate of zoster ranged between 9 and 95 per 1,000 person years. There was variation in study estimates for the cumulative incidence and the incidence of zoster within each group and between groups. Ultimately, risks within each condition varies due to the underlying disease and therapies received. For stem cell transplant recipients, zoster risk varies depending on the type of the transplant received and complications, such as graft versus host disease, both of which may affect the type and timing of prophylaxis received. For solid-organ transplant recipients, zoster risk correlates with the intensity of immunosuppression, with the highest risk for heart and lung transplant recipients followed by kidney and liver. Solid-organ transplant patients are on lifelong immunosuppressants, while stem cell transplant recipients may be able to discontinue their use. Therefore, risks may vary over time among populations. In this systematic review, it also was noted that zoster complications and severe disease were

[17] See Slides 7 and 79 in Dr. Anderson's slide set for references
[18] Harpaz et al. Prevention of Herpes Zoster, MMWR, June 6, 2008, Vol 57, #5
[19] CDC, unpublished data; Updated from Harpaz et al. Clinical Infectious Diseases, Volume 69, Issue 2, 15 July 2019, Pages 341–344, https://doi.org/10.1093/cid/ciy953
[20] McKay et al. Herpes zoster risk in immunocompromised adults in the United States: A systematic review. CID 2020;71(7):e125–34.

increased in immunocompromised populations. However, the data were insufficient to assess risk by group.

Regarding available data for PHN, approximately 6% to 10% of immunocompromised patients experienced PHN versus about 4% overall in administrative claims databases.[21] Between 6% and 45% experienced PHN across immunocompromising conditions and studies.[22] Approximately 3% of immunocompromised patients experienced disseminated zoster, but it is exceedingly uncommon in healthy persons.[23] Between 10% and 17% mortality has been associated with disseminated zoster among renal transplant recipients.[24],[25] About 8% of stem cell transplant recipients with zoster are hospitalized[26] versus less than about 1% of overall Medicare beneficiaries with zoster.[27] Better evidence of the incidence of zoster complications and severity in immunocompromised populations is needed to inform economic and zoster vaccine policy analyses.

Regarding the risk of zoster in immunocompromised Group 6, there is a study evaluating the risk of zoster in autoimmune and inflammatory diseases.[28] In this study, the authors determined that there is an approximately 2- to 4-fold higher risk of zoster in patients with autoimmune and inflammatory conditions than in healthy individuals. It was noted that the risks varied across conditions and by age groups and age-standardized zoster incidence rates varied, with the highest rates in patients with systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), and rheumatoid arthritis (RA). Another recent study identified similar results with an approximately 1.5-fold higher risk of zoster for unvaccinated Medicare beneficiaries with autoimmune conditions versus those who are not immunocompromised.[29]

As previously noted, for some autoimmune conditions such as SLE, IBD, and RA, the risk of zoster is about 2- to 4-fold higher. Importantly, age-specific incidence rates among persons 21-50 years of age can be comparable to, or substantially higher than, corresponding rates in healthy adults greater than 60 years of age. The impact of immunosuppressive treatments is another consideration for these patients. The standard of care is for patients to be on one or more immunocompromised drugs, the duration of which could be months, years, or lifelong. In addition, it is not possible to define high-risk subgroups based on anticipated drug treatments, including disease-modifying anti-rheumatic drugs, glucocorticoids, and biologics since they are very different from condition to condition and even over time for individual patients based on their response, tolerability, and other factors.

[21] Chen et al. Incidence of herpes zoster in patients with altered immune function. Infection 2014; 42(2): 325–34
[22] McKay et al. Herpes zoster risk in immunocompromised adults in the United States: A systematic review. CID 2020;71(7):e125–34
[23] McKay et al. Herpes zoster risk in immunocompromised adults in the United States: A systematic review. CID 2020;71(7):e125–347
[24] Rommelaere et al. Disseminated varicella zoster virus infection in adult renal transplant recipients: Outcome and risk factors. Transplantation Proceedings. 2012; 44(9): 2814-2817
[25] Kirnap et al. Prevalence and outcome of herpes zoster infection in renal transplant recipients. Exp Clin Transplant. 2015; Apr;13 Suppl 1:280-33
[26] Winston et al. Inactivated varicella zoster vaccine in autologous haemopoietic stem-cell transplant recipients: an international, multicentre, randomised, doubleblind, placebo-controlled trial. Lancet (London, England) 2018; 391(10135): 2116–27
[27] Izurieta et al. Effectiveness and duration of protection provided by the live-attenuated herpes zoster vaccine in the Medicare population ages 65 years and older. CID 2017;64(6):785–93
[28] 1Yun et al. Risk of Herpes Zoster in Autoimmune and Inflammatory Diseases. Arthritis & Rheumatology 2016;68(9):2328-2337
[29] Izurieta et al. Recombinant Zoster Vaccine (Shingrix) real-world effectiveness in the first two years post-licensure. Clinical Infectious Diseases, 2021;, ciab125, https://doi.org/10.1093/cid/ciab125

Important points from WG discussions included that immunocompromised populations are very heterogeneous across and within groups and among individuals over time. The risk of zoster and its complications is generally higher in immunocompromised populations, although there is variability across and within groups. It is not feasible to define every possible immunocompromising condition and medication combination. It is important to consider broad recommendations and provider guidance for immunocompromised populations. The WG has extensively reviewed these and other findings and concluded that zoster and its complications in immunocompromised adults is of public health importance.

Moving to the benefits and harms domain, the WG sought to answer questions regarding how substantial the desirable anticipated effects are for each main outcome, how substantial the undesirable anticipated effects are for each main outcome, and whether the desirable effects outweigh the undesirable effects. A table with the information sources and inclusion/exclusion criteria for the systematic review, as well as additional criteria for the GRADE review may be found on Slide 19 of Dr. Anderson's slide set. For benefits, the population was sub-setted into those who received 2 doses of RZV. For harms, all who received at least 1 dose of RZV were evaluated. In terms of evidence retrieval, a flow diagram with details of the evidence retrieval for all records included in the evidence synthesis is included on Slide 20 of Dr. Anderson's slide set. A total of 19 studies were included in the evidence synthesis and 9 studies were included in the review of evidence and grade analysis since they included a comparator group. There were 7 randomized control trials (RCTs) and 2 cohort studies across several immunocompromised populations, including patients with hematologic malignancies, renal transplant recipients, solid tumor patients, HSCT recipients, patients living with HIV, patients with immune-mediated diseases, patients with IBD, and Medicare beneficiaries with immunocompromised and autoimmune conditions.

The benefits outcomes included in the overall GRADE analysis included the critical outcome of preventing HZ and the important outcomes of preventing PHN and HZ-related hospitalization. The harms outcomes included the critical outcome of SAEs and the important outcomes of immune-mediated disease, graft versus host disease, graft rejection, and Grade 3 reactogenicity. For the first benefits outcome of prevention of HZ, using the efficacy population, the VE estimates ranged from 68% to 100%. Estimates were generally higher in younger adults within a population and lower for autologous stem cell transplant recipients. Of note, VE in immunocompetent adults is about 90% to 97% depending upon age. The 2 peer-reviewed cohort studies (Izurieta 2021 and Kahn 2021) reported VE among autoimmune and immunocompromised Medicare beneficiaries of 68% and 64.1%, respectively. Khan et al looked at VA patients with IBD and found adjusted hazard ratios of 0.41% for those over 60 years of age who were non-steroid users and 0.34% for those who were steroid users and a hazard ratio of zero for the 50 to 60 year old group since no cases were reported.

Using the efficacy population for studies reporting immunogenicity, the table Slide 25 shows the vaccine response rate for both humoral and cell-mediated immunity (CMI) across the 6 included RCTs. These studies showed that there was a vaccine response. Starting with humoral immunity, response rates ranged from a low of 65.4% to a high of 96.2% at 1 month after the last dose. This decreased somewhat at the 12-month evaluation mark, with response rates ranging from a low of 51.5% to a high of 91.7%. Placebo response rates were very low, from 0 to 6.4%. Corresponding to adjusted geometric mean ratios (GMRs) ranging from 14 to 42.2 for 1 month after the second dose and 8.81 at 12 months after the second dose. For CMI, response rates ranged from a low of 50% to a high of 93% at 1 month after the last dose, decreasing to a low of 17.6% and a high of 66.7% 12 months after the last dose. Again, placebo rates were low.

Looking at the GRADE Evidence Table for the outcome of preventing HZ, the evidence type for the RCTs started at Type 1. No serious risk of bias was identified and there were no concerns for inconsistency or imprecision. The body of evidence was downgraded for indirectness due to not comprising data on all relevant populations under the recommendation. The VE estimates range from 68.2% to 98.5%, with an overall certainty of Type 2, or moderate certainty. For RCTs containing immunogenicity data, the risk of bias was not serious and there were no concerns with inconsistency or imprecision. However, the body of evidence was doubly downgraded for indirectness due to both studies not comprising the range of populations under consideration for the outcome and also a surrogate outcome. Humoral adjusted GMRs range from 14 to 42.2 and the CMI adjusted GMR ranged from 9.94 to 17.26 measured at 1 month after vaccination. This evidence was graded Type 3, or low certainty. For cohort data, the evidence type started at Type 3. There were no serious concerns with risk of bias, inconsistency, or imprecision, but the studies were downgraded due to indirectness and upgraded due to a strong association observed among those over 50 years of age. The hazard ratio for those with 2 doses of RZV compared with placebo was zero for persons 50-60 years of age and 0.39 for those over 60 years of age. The evidence was graded Type 3, or low certainty.

For the outcome of SAEs, 7 randomized studies evaluated multiple immunocompromised populations. Overall, SAEs were fairly balanced between the vaccine and placebo groups. Using the harms population, or those who received at least 1 dose of RZV, there was a risk ratio of SAEs ranging from 0.79 to 1.99. It is important to note that this population is significantly ill, so a high proportion of SAEs in both the vaccine and placebo group are not unexpected. However, the SAEs related to vaccination were much less common, ranging from 0.33% to 1.6% in the vaccine group and 0.36% to 0.76% in the placebo group. Looking at the GRADE Evidence Table for SAEs, the evidence type started at Type 1. The body of evidence was downgraded only for indirectness. The proportions of RZV and placebo recipients experiencing SAEs are noted in the table, with risk ratios ranging from 0.79 to 1.99, but generally representing a similar proportion of SAEs in both groups. The body of evidence was graded with a certainty of Type 2, or moderate certainty.

For the outcome of graft rejection, one study was included. This study looked at renal transplant patients receiving daily immunosuppression with stable renal function, free of allograft rejection or multiple organ transplants or potential immune-mediated diseases. There were 4 cases of graft rejection in the vaccine group (3%) and 7 in the placebo group (5.3%), for a calculated risk ratio of 0.57. There also were 3 studies with no comparator that were included in the evidence synthesis, but not formally included in the GRADE analysis. Barghash and L'Huillier found no evidence of graft rejection, while Hirzel found that 6.1% of participants experienced rejection among a population of lung transplant patients. Of note, these rejection episodes were classified as unrelated to vaccination. Looking at the GRADE Evidence Table for graft rejection, the RCT began in evidence level of 1 and was downgraded for indirectness due to only including renal transplant patients and for imprecision due to small counts of included cases. The final evidence type was Type 3, or low certainty.

To summarize the GRADE results for benefits and harms, the body of evidence for benefits shows relatively high VE across these heterogeneous immunocompromised populations, ranging from 68.2% to 90.5%. For preventing PHN and zoster-related hospitalizations, there was just one study that but reported VE of 89% and 85%, respectively. For harms, SAEs were common and balanced in both the vaccine and placebo groups, with risk ratios ranging from 0.79 to 1.99. SAEs attributed to vaccination were rare. Immune-mediated diseases were not shown to be increased for those in the RZV group. There was little data on graft versus host disease and graft rejection, with one RCT each showing no increased risk of rejection. Finally,

RZV was noted to be reactogenic with increased reported local and systemic reactions in the RZV group. Of note, limited data for some harms outcomes highlights the need for additional research, as well as provider counseling for these patients. For example, there may be counseling regarding appropriate timing of vaccination for some immunocompromised patients.

Upon review of these data, the WG concluded that the desirable anticipated effects of RZV in immunocompromised adults are large and that the undesirable anticipated effects are small. Overall, the WG concluded that the desirable effects outweigh the undesirable effects, which favors the intervention of 2 doses of RZV at least 4 weeks apart.

In the domain of values, the WG sought to answer whether the target population (e.g., immunocompromised adults) feel that the desirable effects of RZV are large relative to the undesirable effects, and whether there is important uncertainty about, or variability in, how much immunocompromised adults value the main outcomes. There are limited published data, zoster vaccination is increasing in general and RZV series completion rates are high. Though there is currently no ACIP recommendation, immunocompromised patients recognize the increased risk of zoster and many already have received RZV as noted in a large study of Medicare data where nearly a million patients met the study definitions of autoimmune and immunocompromised and received RZV.

To summarize the domain of values, many immunocompromised patients desire the ability to receive RZV to prevent zoster and its complications. In fact, many already are pursuing vaccination with RZV as part of regular care as shown in the Medicare analysis mentioned earlier. The WG anticipates that more immunocompromised patients would pursue vaccination for zoster if recommended by ACIP and their provider. Upon review of these data, the WG concluded that immunocompromised adults probably feel that the desirable effects of RZV vaccination are large relative to the undesirable effects and that there is probably not important uncertainty or variability in how much immunocompromised adults value the main outcomes.

In terms of the domain of acceptability, the WG sought to answer the question regarding whether RZV is acceptable to key stakeholders working with immunocompromised adults. While there are limited published data, primary care physicians' perspectives were captured and published in a recent University of Colorado Denver knowledge, attitudes, and practices (KAP) survey. Important points from WG discussions included the heterogeneity of immunocompromised populations, the reality that is not feasible to define every immunocompromising condition and therapy combination, and that an age-based recommendation is preferred since this will provide the most actionable guidance for clinicians and patients.

The objectives of the noted survey were to assess among primary care physicians serving adults regarding RZV; their current practices, attitudes, knowledge, and barriers to recommending RCV; and the likelihood of recommending RZV to immunocompromised patients among physicians who had not previously recommended the vaccine to these patients. Physicians in existing Vaccine Policy Collaborative Initiative (VPCI) sentinel networks were surveyed. Family physician (FP) and General Internist (GIM) results were combined with any differences highlighted. Regarding physician strength of recommendation for RZV and different types of patients 50 years and older, recommendations for healthy adults, adults anticipating a bone marrow or solid-organ transplant, and adults on low-dose methotrexate were consistent with current ACIP recommendations, with 70% to 96% strongly recommending or recommending RZV, but not strongly. Among patients without an ACIP recommendation, the strength of recommendation for RZV varied considerably by age and health status, with 67%

strongly recommending or recommending RZV, but not strongly for adults 50 years of age and older with HIV to 42% strongly recommending or recommending RZV, but not strongly for adults 50 years and older who were receiving immunosuppressive therapy for a bone marrow or solid-organ transplant. Of note, 27% to 42% of respondents noted they defer to a subspecialist for these immunocompromised populations 50 years of age and older.

Among adults 18-49 years of age with immunocompromising conditions, 31% of respondents noted strongly recommending RZV or recommending but not strongly, while only 4% noted strongly recommending RZV or recommending but not strongly for healthy adults 18-49 years of age. Among physicians who would not recommend RZV to immunocompromised patients, the likelihood of recommending RZV to a range of immunocompromised patients 18 years of age and older was very likely for 40% to 48% of respondents. Percentages also were similar for somewhat likely, somewhat unlikely, and very unlikely responses. These responses were based on how likely a respondent would be to recommend RZV to an immunocompromised patient within the first 6 months of an approval and without input from a subspecialist. These results highlight the importance of provider guidance for vaccination of immunocompromised patients.

In summary, given highly specialized care and increased zoster risk among immunocompromised populations, the WG noted that vaccination is favored if there are no safety concerns. As previously noted, additional safety data is a research need. However, the WG considered the currently available evidence to be acceptable. Importantly, many physicians are recommending RZV to patients with immunocompromised conditions despite the lack of a recommendation from ACIP. Of note, physicians need more direction on which patients are eligible for RZV, including the substantial minority who would be unlikely to recommend RZV to various immunocompromised patients even if it were licensed, recommended, and covered by insurance for them, without input from a subspecialist. Overall, the WG anticipates that acceptability in RZV vaccination in immunocompromised adults would increase with FDA approval and an ACIP recommendation. Upon review of the data, the WG concluded that use of RZV in immunocompromised adults is acceptable to key stakeholders.

Moving to the feasibility domain, the WG sought to answer the question regarding whether RZV in immunocompromised adults would be feasible to implement. There also are limited data published for this domain other than some information from the previously noted KAP survey. Important points that were considered by the WG included that immunocompromised populations are very heterogeneous across and within groups and among individuals over time; it is not feasible to define every possible immunocompromising condition and therapy combination, so it is important to consider broad recommendations and provider guidance for immunocompromised groups; and an age-based recommendation is preferred since this will provide the most actionable guidance to clinicians and patients.

To briefly summarize WG discussions, delivery of RZV is complicated by delivery at different locations. As previously noted, physicians need more direction on which of their patients are eligible for RZV. It also is anticipated that identification of immunocompromised patients (e.g., based on immunosuppressive medications) and standing orders will be concerns in the pharmacy setting. Although implementation is addressed at the jurisdiction and provider levels, the WG noted that decisions support guidance (e.g., for electronic health records, immunization registries, et cetera) would be helpful. The WG concluded that use of RZV in immunocompromised adults is feasible to implement.

For the domain of resource use, the WG sought to answer the question pertaining to whether RZV in immunocompromised adults is a reasonable and efficient allocation of resources. As noted in Dr. Ortega-Sanchez's previous presentation summarizing the economics of vaccinating immunocompromised adults 19-49 years of age against zoster in the US, vaccination with RZV was cost-saving for the base case of HSCT recipients in both the GSK and CDC models. Some scenarios also were cost-saving or ranged in dollars per QALY of $10,000 to $208,000 depending upon the scenario. As noted by Dr. Ortega-Sanchez regarding base case HSCT patients, the economic value of RZV appears to be favorable or cost-saving. This is influenced by higher zoster incidence and zoster-related healthcare costs and reasonable VE. Of note, the base case represents a smaller proportion of the immunocompromised patient population. For scenarios focused on other immunocompromised patient groups, such as patients living with HIV or patients with autoimmune and inflammatory conditions, the economic value of RZV vaccination is less favorable relative to HSCT patients given their lower risk of zoster, severe outcomes, and lower healthcare costs. Notably, some autoimmune and inflammatory conditions may have the least favorable estimates of RZV use depending on the underlying risk of zoster. Importantly, patients with autoimmune and inflammatory conditions represent a larger proportion of the immunocompromised patient population.

Overall, given the highly specialized care and resources typically invested for the base-case and other immunocompromised populations, the WG did not consider cost-effectiveness assessments to be a main driver for decision-making. Upon review of these data, the WG concluded that use of RZV in immunocompromised adults is a reasonable and efficient allocation of resources.

With regard to the equity domain, the WG considered what the impact of RZV would be on health equity. The NHIS captures zoster vaccination data, including data for ZVL and RZV. Overall in 2018, zoster vaccination coverage among adults ≥50 and ≥60 years was 24.1% and 34.5%, respectively. White adults ≥50 and ≥60 years had higher coverage compared with Blacks, Hispanics, and Asians. An analysis using 2010-2019 NHIS data found that in general, race, ethnicity, household income, education level, and health insurance type were significantly associated with receipt of zoster vaccinations among adults 65 years of age and older. The WG anticipates an ACIP recommendation would increase access overall, given that it would increase the scope of the population eligible to be vaccinated and would ensure coverage under the Affordable Care Act (ACA). However, there likely will still be challenges with uptake, given the previously noted race/ethnicity, household income, education level, and insurance disparities and out of pocket costs. Upon review of these data, the WG concluded that health equity probably would be increased.

Turning now to the overall EtR summary in terms of the domains, the WG determined that HZ in immunocompromised adults is of public health importance. The desirable anticipated effects of RZV use in immunocompromised adults are large and the undesirable effects are small, which favors the intervention. Immunocompromised adults probably feel the desirable effects of vaccination with RZV are large relative to the undesirable effects and that there is probably not important uncertainty or variability in how patients value these outcomes. Use of RZV in immunocompromised adults is acceptable to key stakeholders, feasible to implement, a reasonable and efficient allocation of resources, and health equity probably would be increased. Therefore, the WG concluded that the desirable consequences of vaccinating immunocompromised adults with RZV clearly outweigh the undesirable consequences in most settings and ultimately would recommend the intervention.

With respect to special considerations for use of RZV in immunocompromised adults and next steps, the RZV package insert contraindications, warnings, and precautions are summarized here:

- **Contraindications:** History of severe allergic reaction to any component of the vaccine or after a previous dose of SHINGRIX.

- **Warnings and Precautions:**
  - In a post-marketing observational study, an increased risk of Guillain-Barré Syndrome (GBS) was observed during the 42 days following vaccination with SHINGRIX.
  - Syncope (fainting) can be associated with the administration of injectable vaccines, including SHINGRIX.

- **Pregnancy:**
  - Package Insert: The data are insufficient to establish if there is vaccine-associated risk with SHINGRIX in pregnant women.
  - WG Discussion: Do not recommend pregnancy testing prior to vaccination; if known pregnancy, delay vaccination (given lack of data)

- **Breastfeeding:**
  - Package Insert: Data are not available to assess the effects of SHINGRIX on the breastfed infant or on milk production/excretion; The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SHINGRIX and any potential adverse effects on the breastfed child from SHINGRIX or from the underlying maternal condition.
  - WG Discussion: Similar to most other vaccine recommendations, do not recommend delaying vaccination

- **Individuals with a History of GBS:**
  - Update Vaccine Information Statement (VIS) "Risks of a vaccine reaction" section per FDA package insert warning
  - Providers and patients should discuss potential risk

- **Individuals who have Received the Varicella Vaccine Series:**
  - Laboratory testing is not recommended to confirm vaccine-induced immunity

- **Individuals with no History of Varicella or Varicella Vaccine:**
  - RZV not indicated for prevention of primary varicella infection
  - Laboratory testing not recommended to confirm naïve
  - Limited safety data

In terms of next steps, the WG looked forward to the day's discussion of the preliminary EtR and special considerations for use of RZV in immunocompromised adults. The WG will then discuss any ACIP feedback during subsequent WG meetings and will finalize the EtR, and anticipates presenting the final EtR and holding a vote during a future ACIP meeting.

Key Discussion Points

- ACIP requested additional information about the following if/when available:

    - The impact of natural disease-related zoster, breakthrough wild-type disease due to decreased vaccine efficacy, and varicella vaccine in populations younger than 49 years of age
    - Disseminated disease, including life-threatening disease such as encephalitis, pneumonitis, and potentially devastating outcomes, particularly people in their 20s, 30s, and 40s who are immunocompromised who have significant rates of zoster
    - If/how having multiple locations for vaccine delivery contributes to health equity
    - The importance of a vaccine registry for adults and information about how vaccine status information will be transferred so that primary care physicians and the subspecialists knows what happens in outside delivery settings, including information about states that are inputting zoster vaccinations for adults into their registries
    - Development of communication materials that are clear and available to providers and patients
    - Driving factors for the inequalities that exist today in zoster vaccination coverage and what can be done proactively to reduce the inequality to the extent possible
    - Autoimmune and inflammatory conditions in terms of data that could separate out the underlying conditions versus the medications that patients are taking, recognizing the difficulty in and potential complication of breaking it down into every combination
    - Individuals on Medicare over 65 years of age who could not cover the vaccine costs out of pocket and the percent on Medicare Advantage or Medicare Part D plans that do not cover this vaccine
    - Gaps in the US in terms of insurance coverage and how to think about vaccine programs that do address equity
    - More safety data regarding individuals without a history of varicella or varicella vaccine who receive RZV
    - The concept of checking antibodies for those who were not previously vaccinated, recognizing that the WG discussed the challenges with laboratory testing and reliability of the results
    - Co-administration of RZV with other vaccines, recognizing that there are no current concerns with RZV co-administration with other adult vaccinations

- The American Immunization Registry Association (AIRA) commented on zoster vaccine, especially if administered in the pharmacy setting. All of the existing Immunization Information Systems (IISs) can actually accept adult data. In 2019, about 60% of adults had an IIS record. AIRA anticipates that this number has increased significantly over the past 9 months. They recently tested 57 IISs to find out if they could accept a zoster vaccine, and all 57 reported back that they can. Most pharmacies are connected to local IIS systems and are submitting information.

- ACIP pointed out that the cautionary note about breastfeeding might be confusing to physicians because of the previous ZVL product. The WG will consider revising the language to make it less negative.

- Some concern was expressed that it seems that ACIP is always speculating in terms of the impact on health equity. However, it is important to remember that the environment that causes the health equity is no different:

    - It is difficult to believe that a new indication or a new population is not going to encounter all of the same inequalities that populations encountered prior to such recommendations.
    - It is known that that people are getting the vaccine although it is not currently recommended by ACIP. Perhaps some of these individuals are already paying out-of-pocket. A full ACIP recommendation could ensure that coverage and access would be more equitable, recognizing that there is still an under-insured population where this needs to be addressed.

- There was support for starting the age range at 18 years of age rather than 19 years of age, which seemed odd to some ACIP members. Dr. Anderson noted that the adult schedule begins at 19 years of age, which was the rationale for focusing the policy question beginning with this age.

PNEUMOCOCCAL VACCINES

Introduction

Dr. Kathy Poehling (ACIP, WG Chair) framed the conversation for the pneumococcal vaccines session. As a reminder, 2 pneumococcal vaccines are currently licensed in the US. One is the 23-valent pneumococcal polysaccharide vaccine (PPSV23) and the other is the 13-valent pneumococcal conjugate vaccine (PCV13). There also are 2 new pneumococcal vaccines, a 20-valent pneumococcal conjugate vaccine (PCV20) by Pfizer that was licensed for use in adults aged ≥18 years on June 8, 2021[30] and a 15-valent pneumococcal conjugate vaccine (PCV15) by Merck that was licensed for use in adults aged ≥18 years on July 16, 2021.[31] Policy options for PCV15 and PCV20 use are being evaluated separately and each PCV15 and PCV20 will be compared to the current recommendations.

Currently, there is no recommendation for persons 19-64 years of age without chronic or high risk medical conditions. Persons 19-64 years of age with chronic medical conditions are recommended to receive PPSV23. Persons 19-64 years of age with a cochlear implant or cerebrospinal fluid (CSF) leak are recommended to receive PCV13 and PPSV23 in series. Those with immunocompromising condition in this age group are recommended to receive PCV13 and PPSV23 in series, with PPSV23 repeated after 5 years. Persons ≥65 years without chronic or high risk medical conditions or with chronic medical conditions are recommended to receive PCV13 based on shared clinical decision-making and PPSV23 for all. Persons ≥65 years with a cochlear implant, CSF leak, or immunocompromised condition are recommended to receive PCV13 and PPSV23 in a series.

[30] https://www.pfizer.com/news/press-release/press-release-detail/us-fda-approves-prevnar-20tm-pfizers-pneumococcal-20-valent
[31] https://www.merck.com/news/merck-announces-u-s-fda-approval-of-vaxneuvance-pneumococcal-15-valent-conjugate-vaccine-for-the-prevention-of-invasive-pneumococcal-disease-in-adults-18-years-and-older-caused-by-15-serot/

One of the components that the WG is striving for is to simplify the risk- and age-based recommendations. There are 2 age-based recommendations currently and the goal is to have a single age-based recommendation whether it be at ≥50 years of age or ≥65 years of age and the same risk-based recommendation across chronic medical conditions, cochlear implants, CSF leak, and immunosuppressing conditions. The target age group for the age-based recommendation will determine the ages that are eligible for the target population for the risk-based recommendations.

In June 2021, the WG presented the cost-effectiveness analysis and public health impact and the GRADE/EtR for use of PCV15 and PCV20 in older adults. The feedback received from the full ACIP was incorporated into the comparison of cost-effectiveness analyses and GRADE/EtR for use of PCV15 and PCV20 in adults with underlying conditions. This is in preparation of an ACIP vote in October 2021. Since the June 2021 ACIP meeting, the WG has reviewed an updated cost-effectiveness analysis based on feedback and added models with ≥50 years of age or ≥65 years of age cohorts. Key inputs were updated for the base-case, which included waning of PCV, modifying the VE assumptions, and vaccine costs. An additional one-way sensitivity analysis was performed for lower VE for PCV20 and higher vaccine coverage for PCV only use. In addition, the WG discussed risk-based use of PCV15 and PCV20, reviewed the new cost-effectiveness analysis findings, and revisited the policy options.

Each vaccine was considered with and without PPSV23 at 2 age groups, ≥50 years of age and ≥65 years of age, and risk-based for persons 19-49 years of age. Originally, 8 policy options were under consideration for the PCV options considered for cost-effectiveness analysis. To reiterate a point that Dr. Ortega Sanchez made earlier, cost-savings means that the intervention improves health outcomes and is a lower cost than the current recommendations. Looking at persons ≥50 years of age cohort in the PCV only option, the WG found worse health outcomes than the current recommendations in most scenarios proposed in the CDC and Merck models. When they looked at persons ≥50 years of age for the PCV15 and polysaccharide vaccine, there were worse health outcomes than the current ones for the CDC model and improved health outcomes and increased cost in the Merck model. Looking at persons ≥65 years of age for PCV15, found health outcomes were found than the current recommendations for the CDC model and cost-savings were found in the Merck model. The last consideration for persons ≥65 years of age was PCV15 and PPSV23. In this model, cost-savings were found in the CDC model and improved health and increased cost were found in the Merck model. Therefore, the WG selected the option that consistently yielded improved health outcomes compared to the current recommendation, which was to focus on PCV15 + PPSV23 in persons ≥65 years of age.

For the PCV20 options under consideration for persons ≥50 years of age and ≥65 years of age, a variety of results were found for persons ≥50 years of age from cost-savings to worse health and lower costs compared to the current recommendations for the CDC model, and improved health and increased cost in the Merck and Pfizer models. For PCV20 at ≥65 years of age cost-savings were found in the CDC and Pfizer models and between cost-savings to improved health and increased cost in the Merck model depending on the scenario. To summarize, PCV20 use at ≥65 years of age was cost-saving in most models. PCV20 use at ≥50 years of age resulted in improved health outcomes in most scenarios and was cos-saving in some CDC models.

The WG next considered PCV20 in series with polysaccharide vaccine. For persons ≥50 years of age, this was found to be cost-saving in the CDC model and improved health and increased cost in the Merck and Pfizer models. At ≥65 years of age it was cost-saving in the CDC model and improved health and increased cost in the Merck and Pfizer models. The WG went further and evaluated PCV20 and what happened the polysaccharide vaccine was added and found

that adding PPSV23 yielded better health than PCV20 use alone but with increased cost, making it economically less efficient. For these reasons, the WG selected the two options for PCV20 use alone since PCV20 use alone yielded better health compared to the current recommendations in most scenarios. Therefore, the policy options currently under consideration for the October ACIP meeting are as follows:

PCV15 Age-based:
- Should PCV15 be routinely recommended to US adults ≥65 years in series with PPSV23?

PCV15 Risk-based:
- Should PCV15 in series with PPSV23 be recommended for US adults aged 19-64 years with chronic medical conditions* or immunocompromising conditions**

If age-based PCV20 recommendation at age ≥50 years:
- Should PCV20 be routinely recommended to US adults aged ≥50 years?
- Should PCV20 be recommended for U.S. adults aged 19-49 years with chronic medical conditions* or immunocompromising conditions**?

If age-based PCV20 recommendation at age ≥65 years:
- Should PCV20 be routinely recommended to US adults aged ≥65 years?
- Should PCV20 be recommended for US adults aged 19-64 years with chronic medical conditions* or immunocompromising conditions**?

*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

The target populations for the age-based recommendation will determine the target populations for the risk-based recommendation. During this session, ACIP heard presentations on a summary of the economic models assessing pneumococcal vaccines in the US, an EtR summary of risk-based PCV15 and PCV20 use in US adults, and considerations for use of PCV15 and PCV20 in adults.

Summary of Economic Models Assessing Pneumococcal Vaccines in US Adults

Dr. Andrew Leidner (CDC/NCIRD) presented on 3 economic models (CDC, Merck, Pfizer) that assessed the use of pneumococcal vaccines in the US. The objective of a cost-effectiveness model is to estimate a cost-effectiveness ratio (CER) that compares the costs and outcomes of two vaccination strategies. The CER captures the change in cost divided by the change in outcomes when a new intervention is compared to an alternative. While a variety of outcomes can be considered in a cost-effectiveness analysis, the primary outcome for this presentation was QALYs. The policy questions being considered for the new pneumococcal vaccines are fairly complicated in that there are age-based, risk-based, and combined components to the considerations. For one of the vaccines, there are currently two different options for age-based considerations. With this in mind, the results presented during this session were organized to first discuss the assessment of the age-based analysis, then the risk-based analysis, and finally combined age-based and risk-based vaccinations in one policy package.

In terms of the CDC model, following the June ACIP presentation based on further review of evidence and further discussions with the WG, several inputs were revised. These revisions were applied to the base-case model settings and included reduced duration of waning protection for PCV, increased initial VE for PPSV23 against invasive pneumococcal disease (IPD) among healthy and chronic medical condition (CMC) populations, and reduced initial VE assumptions for all vaccines among immunocompromised populations. Based on these changes, strategies that use PPSV23 would be expected to become slightly more favorable following the updates to the CDC model.

Looking at the results from the combined analysis from two versions of the CDC model, one with the inputs used from the June presentation and the second with the updated inputs, the combined age-based and risk-based assessment for PCV20 strategies did not qualitatively change. These results remained in the cost-saving quadrant of the cost-effectiveness plane. The assessment of PCV15 with PPSV23 in series became more favorable because the value of the cost-effectiveness ratio declined as would be expected given the updated input values. For the PCV15 + PPSV23 strategies, the cost per QALY gained declined by about $50,000 in the updated version. In both the June version and the updated version, this strategy would be found to have higher costs and higher QALYs relative to current recommendations.

Moving on to an overview of the available models, with 3 models and such a complicated policy deliberation, there would be no way to present all of the inputs and completely describe all of the models in one presentation. Therefore, a few selected model characteristics were presented that captured some of the most important attributes and differences between the models and also informed the discussion of the results. The results from the CDC and Pfizer models were organized around one base-case. The Merck model results were reported from 4 different scenarios, each of which had a different set of assumptions for VE. For this reason, the Merck model results appeared in this presentation as a range that represented the 4 VE scenarios. One of the characteristics described how the models accommodated transitions from lower risk status to high risk status. An example of a risk that transitioned would be a model that started with an individual who was healthy and allowed that individual to transition or to be diagnosed with a CMC condition at a later point in the model. The CDC and Pfizer model included these kinds of transitions and the Merck model did not. Generally speaking, allowing for the model population to develop higher risk conditions would increase the projected burden of disease and would lead to a lower cost-effectiveness ratio. Since the Merck model did not include these kinds of risk state transitions, the Merck model might be expected to produce higher estimates than the other two models.

Additional model characteristic inputs related to VE PCV VE serotype 3 (ST3) lower than other serotypes and PPSV23 VE against pneumonia greater than 0%. For these characteristics, the Pfizer model base-case used assumptions where PCV was equally effective for ST3 as it was against other serotypes and assumed no VE for PPSV against pneumonia. In general, these two assumptions would make the Pfizer base-case more favorable to PCV-focused strategies relative to the other two models. The CDC model used a different comparator for the risk-based analysis than the other two models. The CDC model compared risk-based use of a new vaccine with age-based use of that same new vaccine. In contrast, the Merck and Pfizer models compared risk-based use of the new vaccine with risk-based use of the currently recommended vaccines. Both approaches provided useful information about the value of risk-based vaccinations, but this difference in the approaches between the CDC model and the other two models will limit the extent to which the results can be compared across all three models in the risk-based analysis. All three models include sensitivity analyses. From the sensitivity analyses,

important inputs were identified, including VE for initial VE and waning protection, indirect effects from a possible pediatric program using a new vaccine, and the incidence of pneumonia.

Moving on to the results. In terms of the age-based results for PCV20 at age 65 and age 50, when the age of vaccination was set at age 65 years, the models were fairly consistent. The CDC and Pfizer models were cost-saving in their base-case. The 4 scenarios from Merck yielded a range that included cost-savings and went up to $39,000 per QALY gained. When the age of vaccination was set to 50 years old, the results across the models were less consistent. Of note, the CDC model found lower costs and lower QALYs in the base-case. While this estimate projects lower health than the current recommendations, the estimated economic value could be considered okay because the numeric value indicates that for every 1 QALY lost, $5.3 million dollars could be saved.

Looking at some scenarios from the CDC model that will help put this result into more context, the estimated cost for the Pfizer model for vaccinations at age 50 was $18,000 per QALY gained. This is a health improving result. The Merck model estimated a cost per QALY gained that ranged from $174,000 to $514,000 per QALY gained. Again, that result was health improving. As mentioned in the model overview section, the Merck model did not include transitions to higher risk levels and assumed more favorable VE assumptions for PPSV in some of their scenarios. These assumptions are believed to contribute to the differences in results for that strategy.

In terms of additional results from the CDC model, there were three main takeaways. The first was that across the scenarios for PCV20 vaccination at age 65, all scenarios indicated cost-savings. This is a very consistent and stable result for this strategy. The second take away was that the results assessing age 50 vaccinations were less consistent across scenarios. However, 3 of 5 were health improving and 2 of 5 were cost-saving. The last takeaway was that when comparing the strategies at age 65 and at age 50, the strategy at age 65 would be preferred from a strictly economic perspective based on the results from this model. At age 65, there were more scenarios with improved health and cost-saving results. That said, some scenarios at 50 years old indicated that health may not be improved. However, that finding was not stable and under a few different assumptions this strategy may be health improving and may be cost-saving.

Staying with the age-based analysis but switching gears from PCV20 to PCV15 and PPSV23 in series, this vaccine series at age 65 yielded cost- savings in the CDC model. In the Merck model, it yielded a cost per QALY in the mid $200,000 range. As discussed previously, these differences appear to be related to differences in how the two models incorporated risk transitions, vaccine coverage assumptions, and VE assumptions. Merck provided a sensitivity analysis that tried to use similar vaccine coverage assumptions as the CDC model, which estimated cost-savings. Taking a closer look at some scenarios from the CDC model, the results were quite consistent for the use of the series at age 65, with 4 scenarios improving health and yielding cost-savings.

Now moving to the assessments of risk-based vaccinations beginning with use of PCV20 in adults 19-64 years of age and adults 19-49 years of age. As mentioned in the model overview section, the CDC model conducts a different kind of analysis than the Merck and Pfizer models. The CDC model conducted an incremental analysis that compared the use of PCV20 at younger ages to the use of PCV20 at the age of 65 and 50. By contrast, the Merck and Pfizer models assessed the use of PCV20 in a risk-based setting relative to current risk-based recommendations. Because of the different analytical approaches, the CDC result was not

directly comparable to the Merck and Pfizer results. However, all of the results indicated the health would be improved with higher costs. In the Pfizer model, the results included potential pediatric indirect effects. When indirect effects were removed, the adults 19-49 years of age risk-based estimate was cost-saving. Results were not available for the adults 19-64 years of age risk-based only analysis without indirect effects, which was why the indirect effects were shown. When the results were compared within each model, the cost-effectiveness ratio in the 19-49 year old strategies were generally higher than the 19-64 year old strategy. This was true for all three models. For example, the $483,000 per QALY at 19-49 years was greater than $292,000 per QALY at age 19-64 in the CDC model.

Instead of looking at just risk-based strategies in isolation, the risk- and age-based strategies were combined in the same analysis and assessed as a combined policy strategy. When the age threshold was set to 65 years, the combined assessment was found to be cost-saving in both the CDC and Pfizer models. When the age-based vaccinations occurred at age 50, the CDC model remained cost-saving and the Pfizer model had a cost of $11,000 per QALY gained. The potential pediatric indirect effects were not included for the Pfizer results, which is consistent with the CDC base-case model assumption.

Switching gears from PCV20 to PCV15 and PPSV23 in series, the risk-based analysis and combined age- and risk-based analysis were included for the CDC model. Notably, the risk-based strategy improved health and had higher costs in all of the models. However, the same caution as before applies with regard to comparing results across models due to the difference in approaches. The final cost-effectiveness ratio for the combined strategy in the CDC model was $338,000 per QALY gained.

There was one other model in the research literature by researchers at the University of Pittsburgh that was published in the summer in the *American Journal of Preventive Medicine* (*AJPM*).[32] This model looked at age-based recommendations at age 65 only. In addition, this model focused on assessing the value of vaccinations for healthy and CMC populations. There were no immunocompromised populations and there was no risk-based analysis in this study. Thus, the focus of this study was much more limited in scope than the CDC, Pfizer, and Merck models discussed during this presentation. In addition, the Pittsburgh model included several assumptions that made the result less variable than the models summarized earlier. However, this model was included because it was on topic and was published in a peer-reviewed journal. It provides helpful context in that the study's focus, assumptions, and results could be thought of as an upper bound on the likely value of these age-based vaccinations. It is, therefore, reassuring that these results indeed had higher cost-effectiveness ratios than were found in the other models reviewed during this session.

To summarize the range of cost-effectiveness estimates highlighted during this presentation, values across models were fairly consistent in one analysis of PCV20 use at age 65, but were less consistent in other analyses. This was due to differences across the model structural choices and input uncertainty. A couple of the important inputs that were explored in sensitivity analyses included initial VE and waning protection and indirect effects from a possible pediatric vaccination program. AEs were not included in the CDC, Pfizer, and Merck models, but they were included in the Pittsburg model. Comparisons across models were made even more challenging for this policy consideration than what might be more typical for models presented

[32] This study was not reviewed by the ACIP economics review team but was peer-reviewed for publication in *American Journal of Preventive Medicine*. Citation: Smith, Kenneth J., et al. "Higher-Valency Pneumococcal Conjugate Vaccines: An Exploratory Cost-Effectiveness Analysis in US Seniors." American Journal of Preventive Medicine (2021).

to ACIP just because of the number of policy options that were initially considered and the number of different vaccines that were involved. Any time a single modeling framework is being used to address such a heterogeneous policy context, it is going to make cross-model comparisons very challenging generally speaking.

To summarize the results of the age-based use of PCV20, PCV 20 at age 65 was health improving across all age-based results and most estimates were cost-saving. There were three scenarios in the Merck model that were not cost-saving. In those scenarios, vaccination was estimated to cost $39,000 per QALY or less. PCV20 at age 50 was health improving in many results, but not all. The Pfizer model and Merck model base-cases indicated health improvements in the main analysis. The CDC model indicated health improvements in 3 of 5 scenarios. The Pfizer model and Merck model did not indicate cost-savings, but estimated a cost of $18,000 per QALY for Pfizer and a range from $173,000 to $513,000 per QALY gained in the Merck model. The CDC model indicated cost-savings in 2 of 5 scenarios.

In summary of the risk-based and combined analyses for PCV20, improved health was indicated in all risk-based strategies and models. For risk-based use of PCV20 in persons 19-64 years of age, the assessments indicated a broad range of possible value from $11,000 per QALY to $292,000 per QALY gained. However, when risk-based vaccinations were combined with age-based vaccinations, assessments indicated cost-savings in 2 of 2 models. For risk-based use of PCV20 among persons 19-49 years of age, assessments indicated a broad range of values. Combined age and risk-based assessments indicated more favorable value, while the CDC model indicated cost-savings. The Pfizer model indicated costs of $11,000 per QALY gained in the combined analysis.

Moving from PCV20 to PCV15 and PPSV23, in the age-based analysis, improved health was indicated in all main results with cost-savings indicated by the CDC model in 4 of 4 scenarios. In the risk-based analysis, improved health and higher cost was indicated in all main results. Risk-based only strategies yielded a broad range of possible values from $250,000 to $656,000 per QALY gained. The combined age- and risk-based assessments indicated values that were more favorable than risk-based alone. The CDC model was $338,000 per QALY gained in the combined analysis.

EtR on Risk-Based Use of PCV15 and PCV20 in Adults, Considerations for Use of PCV15 and PCV20 in Adults, and Next Steps

Dr. Miwako Kobayashi (CDC/NCIRD) presented the data and WG's interpretation on the risk-based use of 15-valent and 20-valent pneumococcal conjugate vaccines in adults using the EtR Framework Before proceeding with the presentation on the risk-based recommendation, Dr. Kobayashi provided a summary of the WG's interpretation of each domain for the age-based recommendations that were updated since the June ACIP meeting after additional cost-effectiveness analysis results just presented by Dr. Leidner became available. The PCV15 and PCV20 Policy Options currently being considered follow:

- PCV15 Policy Option
  - Should PCV15 be routinely recommended to US Adults aged ≥65 years in series with PPSV23?

- PCV20 Policy Option:
  - Should PVCV20 be routinely recommended to US adults aged ≥50 years?
  - Should PCV20 be routinely recommended to US adults aged ≥65 years?

The comparison groups are different based on the age groups being considered. To summarize the updated WG interpretation on use of PCV15 in series with PPSV23 in adults aged ≥65 years, the WG believed the new intervention would prevent more disease against the 2 additional serotypes that are not included in PCV13. There may be improved protection against serotype 3 disease, the most common PCV13 type disease. However, the WG has only immunogenicity data and uncertainties on clinical impact remain. Routine use of PCV15 in series with PPSV23 would be a simplified recommendations compared with current PCV13 use based on shared clinical decision-making. In the updated CDC model, the intervention was cost-saving, meaning it yielded better health outcomes and lower costs compared with the current recommendations. Conversely, some WG members believed routine use of PCV15 and PPSV23 series would be more likely to disadvantage those with limited access to vaccines and maybe less acceptable and feasible for some providers. The WG determined that the balance between desirable and undesirable consequences is closely balanced or uncertain.

To summarize the WG's updated interpretation on use of PCV20 in adults aged ≥65 years, the WG believed the new intervention would prevent more disease against the 7 additional serotypes that are not included in PCV13. This would be a simplified pneumococcal vaccine recommendation that likely would be more acceptable to stakeholders and more feasible to implement. The WG believed that this may increase vaccine coverage compared with the current recommendations. This intervention was health-saving across all cost-effectiveness analysis models reviewed and was cost-saving in most. In contrast, the clinical significance of the lower immunogenicity observed compared with PCV13 is unknown. The non-inferiority criteria were met in Phase 3 trials. The impact of losing coverage against 4r PPSV23 serotypes is also unknown. The WG determined that the desirable consequences clearly outweigh the undesirable consequences in most settings.

In terms of the WG's updated interpretation on the use of PCV20 in adults aged ≥50 years and older focusing on differences for adults ≥65 years, the WG believed that lowering the age-based recommendation may improve vaccine coverage in adults 50-64 years of age with underlying conditions that are more prevalent in certain populations. In general, risk-based vaccine recommendations have resulted in lower vaccine coverage. Therefore, this intervention may be more equitable. The intervention would provide more opportunity to vaccinate adults before they develop conditions that increase their risk of disease. The intervention would be health-improving in many cost-effectiveness analyses and cost-saving in some. Conversely, the vaccine may not provide sufficient protection later in life due to waning of immunity when risk of pneumococcal disease increases. In some CDC scenarios, the intervention resulted in worse health outcomes. Since this is a new age group, some WG members believed that this intervention could have initial implementation challenges. The WG group determined that the desirable consequences probably outweigh the undesirable consequences in most settings.

For the risk-based recommendations, the target population would be those who do not meet the age criteria for the age-based recommendation but are currently recommended to receive pneumococcal vaccines due to their underlying conditions (e.g., CMC, cochlear implant, CSF leak, immunocompromising conditions). According to the NHIS, approximately 90% of adults 19-64 years of age who are eligible for the current risk-based pneumococcal vaccine recommendations have chronic medical conditions. The PICO question for PCV15 use is, "Should PCV15 in series with PPSV23 be recommended for US adults aged 19-64 years with

chronic medical conditions or immunocompromising conditions?" The population is US adults aged 19-64 years with chronic medical conditions or immunocompromising conditions. The intervention is 1 dose of PCV15 followed by PPSV23. The comparison is PPSV23 only for adults with chronic medical conditions or PCV13 use in series with PPSV23 in adults with immunocompromising conditions. Outcomes considered as critical by the WG included vaccine type IPD (VT-IPD), vaccine type non-bacteremic pneumococcal pneumonia (VT-NBPP) deaths, and SAEs. The two PICO questions for PCV20 use are, "Should PCV20 be routinely recommended to US adults aged 19-49 years with chronic medical conditions or immunocompromising conditions?" and "Should PCV20 be routinely recommended to US adults aged 19-64 years with chronic medical conditions or immunocompromising conditions?" The intervention is 1 dose of PCV20. The comparison and the outcomes are the same as those for PCV15. As a reminder the EtR Framework consists of the following seven domains: Public Health Problem, Benefits and Harms, Values, Acceptability, Feasibility, Resource Use, and Equity. The available evidence is usually assessed for each policy question. However, given the overlap in available evidence for the 3 questions being considered, the WG reviewed the 3 questions in parallel for each EtR domain.

For the public health problem domain, the WG sought to answer the question regarding whether pneumococcal disease is of public health importance in adults aged 19-64 years with chronic medical conditions or immunocompromising conditions. Pneumococcal disease can be divided into IPD (e.g., meningitis, bacteremia, and bacteremic pneumonia) and non-invasive disease. IPD occurs less frequent but involves a severe form of illness, while non-invasive disease is a more frequent form of illness. After PCV13 was introduced in children in 2010, PCV13-type IPD incidence declined in adults with chronic medical conditions and immunocompromising conditions. Risk-based use of PCV13 in series with PPSV23 was recommended for adults with immunocompromising conditions in 2012. However, PCV13 IPD incidence in adults with immunocompromising conditions remained stable. This trend is similar to what was observed after routine use of PCV13 in series with PPSV23 was recommended for adults aged ≥65 years and older in 2014.[33] Based on these findings, ACIP voted to change the PCV13 recommendation in 2019.

In 2017-2018, approximately 50% of the remaining PCV13-type IPD in adults aged 19-64 years with chronic medical conditions or immunocompromising conditions was due to serotype 3. Despite the decline in PCV13-type incidence in 2017-2018, adults with chronic medical conditions or immunocompromising conditions had 4 to 9 times higher risk of all IPD and 4 to 7 times higher risk of PCV13-type IPD compared with adults without these conditions. The two additional serotypes included in PCV15 but not in PCV13 comprised 11% to 13% of the remaining IPD burden in adults aged 19-64 years with chronic medical conditions or immunocompromising conditions. The 7 additional serotypes included in PCV20 but not in PCV13 comprised 27% of remaining IPD burden.[34] According to a retrospective analysis of two US healthcare repositories, adults aged 18-64 years with chronic medical conditions had 4 to 5 times higher rates of pneumococcal pneumonia hospitalizations. Adults with immunosuppressing conditions had 11 to 18 times higher rates compared with adults with these conditions.[35]

The WG determined that pneumococcal disease is of public health importance in adults aged 19-64 years with chronic medical conditions or immunosuppressing conditions.

[33] ABCs 2007-2018
[34] ABCs and NHIS, 2017–2018
[35] Pelton et al. CID 2019

For the domain of benefits and harms, the WG sought to answer how substantial the desirables anticipated effects are for VT-IPD, VT-NBPP, and deaths from vaccine-type disease; how substantial the undesirable anticipated effects are for SAEs; and whether the desirable effects outweigh the undesirable effects. Although a GRADE analysis of the evidence was performed for PCV15 and PCV20, the WG used a broad search strategy to identify relevant evidence on PCV13 and PPSV23 for background for the age-based policy options presented to ACIP in June. The WG leveraged a prior literature review from the age-based review for 2019-2021 that yielded 923 citations. An additional search was performed to identify literature published during January 2012-March 2019, restricting the search to those with immunocompromising or chronic medical conditions, which yielded 471 citations. The WG also contacted manufacturers for unpublished data. After screening and full text review, 5 Phase 2 studies were identified. Of these, 2 studies were on PCV15 and 3 were on PCV20. All were immunogenicity studies and did not assess VE against the critical outcomes.

First to review evidence on PCV15, the 2 Phase 3 RCTs compared the immunogenicity of PCV15 with PCV13, both given in series with PPSV23. Study V114-017 compared adults aged 18-years who were Native Americans in good health with non-Native Americans who had chronic medical conditions. PCV13 and PPSV23 were given 6 months apart. Study V114-018 targeted adults 18 years and older with HIV. PCV13 and PPSV23 were given 8 weeks apart. Overall, those who received PCV15 in series with PPSV23 had higher GMTs compared with those who received PCV13 in series with PPSV23 in most serotypes shared with PCV13. The differences were significant for 1 serotype in 1 study. The certainty of evidence was moderate as there are no established correlates of protection and the impact of these findings against the critical outcomes is unknown. As presented in previous ACIP meetings, PCV15 has shown improved immunogenicity against serotype 3 compared with PCV13 when measured 30 days after PCV15 administration. However, the improved response against serotype 3 was less noticeable when measured after PPSV23 receipt.[36] Looking at the opsonophagocytic activity (OPA) GMTs 30 days after PCV and 30 days after PPSV23, the GMTs were generally lower for serotype 3 compared with other serotypes. Similar findings were observed in B114-018.[37]

The WG determined that the desirable anticipated effects of PCV15 use in series with PPSV23 is moderate. Some WG members believed that the incremental benefit of this intervention may be large in those with chronic medical conditions who are currently recommended to receive PPSV23 only, assuming improved VE in PCV15 compared with PPSV23. Added benefit maybe greater if PCV15 provides improved protection against serotype 3 disease based on immunogenicity data. The clinical benefits remain unknown. On the other hand, PCV13 type disease declined from pediatric indirect effects and learning from the experiences from routine PCV13 use in series with PPSV23 in adults aged 65 years and older, some thought that the added benefit maybe small. PCV15 provides protection against 2 additional serotypes compared with PCV13, which comprised 11% to 13% of remaining IPD burden. For harms, neither study reported any SAEs that were associated with the vaccines. The certainty of evidence was moderate because the sample size might have been small to observe any vaccine-associated events. Therefore, the undesirable anticipated effects of using PCV15 in series with PPSV23 was determined to be minimal. Balancing the desirable and undesirable effects, the WG determined that using PCV15 in series with PPSV23 was favorable compared with the current recommendations.

[36] Please see GRADE summary tables for details
[37] Merck February 2021 ACIP presentation, *Serotypes not included in PCV13, OPA: opsonophagocytic activity

For PCV20, the WG reviewed the evidence for the two questions together since the same studies were reviewed for GRADE. There were 2 Phase 3 and 1 Phase 2 RCTs identified. All 3 studies excluded adults with immunocompromising conditions and none specifically targeted adults with underlying conditions. In the 2 studies that used PCV13 in series with PPSV23, the 2 vaccines were given 1 month apart. The first comparison was PCV20 compared with PCV13 for the 13 shared serotypes. Across all included studies, PCV20 recipients had lower responses by GMT and percent seroresponders in most shared serotypes. However, PCV20 met non-inferiority criteria for all 13 shared serotypes by GMT ratio. In 1 Phase 2 RCT, data on PCV20 response to the 13 shared serotypes compared with the response after receipt of both PCV13 and PPSV23 as opposed to PCV13 only were available. PCV20 recipients had lower responses in all 13 serotypes by GMT and percent seroresponders compared with those who received both PCV13 and PPSV23. Of note, the interval between PCV13 and PPSV23 that was used in the study was different from what is currently recommended.

The next comparison is PCV20 compared with PPSV23 for the 7 shared serotypes. Across all studies, PCV20 recipients had higher GMTs and percent seroresponders in all serotypes except for serotype 8. In a Phase 3 trial, PCV20 met non-inferiority criteria for 6 of 7 shared serotypes based on GMT ratio. Non-inferiority was not met for serotype 8. The last comparison is immunogenicity of PCV20 in adults aged 18-49 years compared with adults aged 60-64 years. In one Phase 3 trial, GMTs and percent seroresponders in adults aged 18-49 years were higher for most of the 20 serotypes and the non-inferiority criteria were met for all 20 serotypes by GMT ratio in a Phase 3 trial.

The certainty of evidence was low since correlates of protection are not established, so the impact of these findings against the critical outcomes are unknown. Also, the studies targeted generally healthy adults and did not include immunocompromised persons so they are not representative of the population considered for the policy options. The WG determined that the benefits of PCV20 use in adults aged 19-49 years or 19-64 years with chronic medical conditions or immunocompromising conditions are large. PCV20 contains 7 additional serotypes compared with PCV13, which comprised 27% over remaining IPD. Some WG members thought that a simplified recommendation may improve vaccine coverage. Some WG members expressed concerns about the lower immunogenicity observed compared with PCV13. However, PCV20 response met non-inferiority criteria in Phase 3 trials, so the clinical significance is unknown. Also, PCV13-type disease declined from pediatric indirect effects, so the impact on remaining PCV13-type disease may be small. Some WG members expressed concerns about fewer serotypes covered by PCV20 compared with PPSV23. However, the cost-effectiveness analysis showed improved health outcomes compared with the current recommendations. There were no vaccine-related SAEs reported in the included studies. The certainty of evidence was moderate because the sample size might have been small to observe any vaccine-associated SAEs. The undesirable anticipated effects from use of PCV20 was determined to be minimal. In balancing the desirable and undesirable effects, the WG determined that both PCV 20 interventions were favorable compared with the current recommendations.

For the domain of values and preferences, the WG sought to answer questions regarding whether the target population feels that the desirable effects are large relative to the undesirable effects and whether there is important uncertainty about, or variability in, how much people value the main outcomes. The WG performed a PubMed search on US studies published in the past 5 years in adults who qualified for the current risk-based pneumococcal vaccine recommendations. The search identified 1 online cross-sectional survey study conducted between March-April 2019 that assessed vaccine related beliefs, reasons for hesitancy, external influences on vaccination, and prior vaccination. Residents in Tennessee aged 19-64 years with risk-based indications were enrolled. The study population was mostly female, white, non-Hispanic, and had at least some college education. The most common qualifying conditions were current smoker, asthma, and diabetes. Of the participants, 19% indicated that pneumococcal vaccine was offered to them in the past 5 years. More than 90% indicated that vaccines can prevent serious disease and one-third were reluctant, hesitant, or resistant to a recommended vaccine. The common reasons were not knowing it was needed, fear of needles, or concerns about safety. The odds of vaccine hesitancy or resistance were greater in minorities, those believing others like them do not need to get vaccinated, and/or those recalling negative media about vaccines.

For PCV15 use in series with PPSV23, the WG agreed that adults probably feel that the desirable effects from vaccination are large relative to undesirable effects. PCV13 and PPSV23 have been used in series in and are considered safe. Some WG members believed that acceptance of pneumococcal vaccines is higher than for other vaccines. The WG determined that most adults with conditions that increased the risk of pneumococcal disease would value individual protection from vaccination. For the second question, the WG determined that there is probably important uncertainty or variability. Some WG members believed that increase in recommended vaccine doses in adults with chronic medical conditions was an important source of uncertainty or variability. However, the WG determined that most adults probably would perceive that the desirable effects outweigh the undesirable effects. For PCV20 use, the WG also agreed that adults probably feel that the desirable effects from vaccination are large relative to undesirable effects. For the second question, the WG determined that there was probably not important uncertainty or variability. The WG acknowledged that there may be some uncertainties in how changing recommendations from PPSV23 only to PCV20 only or from PCV13 in series with PPSV23 to PCV20 would be perceived. However, the WG determined that most adults probably would perceive that the desirable effects outweigh the undesirable effects.

Moving to the domain of acceptability, the WG considered whether the option is acceptable to key stakeholders. In June, the WG summarized findings from 3 surveys to assess the acceptability of the age-based options. There were 2 HCP surveys and 1 survey targeting members of the Association of Immunization Managers (AIM). The WG also reviewed findings from another HCP survey conducted by Merck in August that targeted physicians, physician assistants, and pharmacists who provide or administer pneumococcal vaccines. Responders preferred a simplified pneumococcal vaccine recommendation and potentially the same recommendation across age and risk groups. There were mixed responses on the use of PCV in series with PPSV23. A single vaccine was preferred over a sequential vaccine regimen in the Merck survey. Routine PCV and PPSV23 use was the most preferred among provided options in the survey by Pfizer. Implementation and communication challenges and health equity concerns were expressed in the AIM survey, since a recommendation with 2 different vaccines requires capturing the correct vaccination history or having adults return to complete the vaccine series. In the Merck survey, respondents were asked to select 2 hypothetical vaccine profiles with different attributes and levels. Immunogenicity in total additional coverage of serotypes

associated with remaining pneumococcal disease yielded the highest probability of preference.[38]

The WG interpreted that whether recommending PCV15 in series with PPSV23 is acceptable to key stakeholders varies. Some members believed that this recommendation may add more burden to providers since PCV and PPSV23 series would be offered to a larger group of people than the current recommendation. On the other hand, some believed that aligning the recommendations for adults with chronic medical conditions and immunocompromising conditions would be a simplification of recommendations. Also, cost-effectiveness analyses showed that the new intervention would prevent more disease compared with the current recommendation. The WG interpreted that recommending PCV20 probably would be acceptable to key stakeholders. The WG believed that this would be a simplification of current risk-based recommendations. The cost-effectiveness analyses showed that the new intervention would prevent more disease compared with the current recommendation.

Turning to the domain of resource use, the WG sought to answer whether the option is a reasonable and efficient allocation of resources. As shown in the previous presentation by Dr. Leidner, cost-effectiveness analyses that assessed the risk-based use for PCV15 in series with PPSV23 improved health and increased costs, with a broad range of cost-effectiveness ratios reflecting the differences in model structure and assumptions. The CDC model assessed the combined impact of the age and risk-based intervention and indicated that the values were more favorable than the risk-based intervention alone. The WG's opinion was initially split between probably no and probably yes, but the members eventually determined that the additional health benefits from the new intervention were potentially sufficient to outweigh the additional cost associated with the intervention. Cost-effectiveness analyses that assessed the risk-based use of PCV20 showed improved health with a broad range of possible values, but generally favored risk-based use of PCV20 in adults aged 19-64 years with chronic medical conditions or immunocompromising conditions compared with use in adults aged 19-49 years. Models that assess the combined impact of age and risk-based interventions indicated more favorable values and the interventions were cost-saving in some scenarios. The WG determined that recommending PCV20 would be a reasonable and efficient allocation of resources. Additional health benefits from the new intervention were considered to be sufficient to outweigh the additional cost associated with the intervention. Also, some of the combined age and risk-based assessments would be cost-saving.

In terms of impact on health equity, the WG presented in June that pneumococcal vaccine coverage in adults aged 19-64 years with risk-based indications has been low compared with adults 65 years of age and older with age-based recommendations. By race and ethnicity, the Hispanic population has significantly lower coverage compared with the white population. One study reported the influence of social determinants of health (SDOH) on vaccine uptake and time to pneumococcal vaccination. The study utilized nationwide convenience samples of commercial insurance claims data from 2013-2016. Adults aged 18-64 years with no prior pneumococcal vaccination before diagnoses of risk-based indications were included. Among them, 25% were vaccinated within 1 year of diagnosis of risk-based indications. Odds of vaccination were lower among areas of higher poverty, areas with limited internet access, and adults not receiving a seasonal influenza vaccine. Time from diagnosis of risk-based indications to vaccination was lower in rural communities and communities with less internet access.[39]

[38] AIM survey 2021; Pfizer HCP preference survey 2021; Merck survey 2021
[39] Gatwood et al. Vaccine 2021

The WG determined that recommending PCV15 in series with PPSV23 probably would have no impact on equity. Some members thought that alignment of the recommendation for adults with chronic medical conditions and immunocompromising conditions may increase vaccine coverage, prevent more disease, and reduce disparity in vaccine-type disease. Others believed that a routine PCV and PPSV23 series recommendation would be more likely to disadvantage populations with limited vaccine access. The WG determined that PCV20 use probably would increase health equity. A single risk-based vaccine recommendation may increase vaccine uptake and reduce disparity in vaccine-type disease. Some members believed that introduction of any new effective adult vaccine may decrease equity, at least in the short-term, disadvantaging those who have limited vaccine access or lack of awareness of the new recommendation.

Regarding the domain of feasibility, the WG considered whether the options would be feasible to implement. The WG determined that recommending PCV15 in series with PPSV23 probably would be feasible. The PCV13 and PPSV23 series is currently recommended for immunocompromised adults. Extending the vaccine series recommendation to adults with chronic medical conditions would result in a larger number of people targeted for the vaccine series, which may increase logistical and financial burdens. The WG determined that recommending PCV20 for either group would be feasible.

To summarize the WG's interpretation of all of the EtR Framework domains, differences were noted in the domains of benefits and harms, values, acceptability, resource use, equity, and feasibility. In terms of whether PCV15 should be recommended in series with PPSV23 for persons aged 19-64 years with chronic medical conditions or immunocompromising conditions, the WG's interpretation was that the desirable consequences probably outweigh the undesirable consequences in most settings compared to current recommendations. The perceived benefits were from simplification of the current risk-based recommendations and the potential to prevent more vaccine type disease by recommending PCV15 in series with PPSV23 for adults with chronic medical conditions. Given that adults with chronic medical conditions comprised approximately 90% of the target population and are currently recommended to receive PPSV23 only, some WG members believed that the new recommendation may be less acceptable to providers and potentially the target population, and less feasible to implement compared with the current recommendations. The impact on the prevention of serotype 3 disease remains unknown. If there is increased protection against serotype 3 disease, then the benefits from use of PCV15 would be greater. For the two PCV20 options, the WG determined that the desirable consequences clearly outweigh the undesirable consequences in most settings.

In terms of next steps, the WG will review the available data to evaluate the interval for PCV15 use in series with PPSV23 and review the available data to draft guidance on use of PCV15/PCV20 for adults who already received PCV13 or PPSV23. At this time, the WG is not considering revaccination strategies. The following questions were posed for ACIP consideration and discussion:

1. Does the committee agree with the policy options being proposed for the October ACIP meeting?
2. Are there additional data the committee would like to see before deciding on policy options?

Key Discussion Points

- Following Dr. Leidner's modeling presentation:

    - PCV20 at age 50 might need more consideration. That scenario had waning of 15 years, so it is possible to concede that if a dose is received at age 50, hypothetically one could receive a dose at age 65. It does not necessarily seem like an either/or. The WG could consider whether a booster would be needed at age 65 if there was an age 50 policy and could look at age 65 in a separate analysis at a separate time. In 15 years, there could be new pneumococcal vaccines with a different manufacturing process that may offer additional options.
    - Dr. Poehling indicated that the WG did not consider any re-vaccination strategies in any of the modeling scenarios.
    - It would be beneficial to have more information about the estimated cost of each vaccine type, which Dr. Leidner indicated he would provide to ACIP.
    - It would be beneficial to look more broadly at an adult vaccination program for specific age groups, with modeling to assess the potential impact on some of the economic impacts and the cost-effectiveness of some of these vaccines. One of the greatest successes of the childhood platform is the ability to co-administer vaccines at specific ages.
    - Dr. Ault indicated that the Adult Vaccine Schedule WG plans to discuss the adult schedule during the October ACIP meeting.
    - New pneumococcal recommendations should be developed through the lens of how to make this as easy as possible for patients and providers.

- Following Dr. Kobayashi's presentation on EtR for risk-based use of PCV15 and PCV20 in adults:

    - It sounded to some ACIP members like the question might be for each of the vaccine candidates compared to current recommendations, so perhaps ACIP could start by deliberating on age-based recommendations.
    - Due to the complexity of the pneumococcal vaccines, several members suggested that it would be very important to consider the potential for a vaccine platform at 50 years of age, given that other vaccines are recommended at that time.
    - The WG did weigh the untoward immunologic effects of polysaccharide vaccine and the blunted ability to boost those. Beyond what the WG anticipates as the efficacy associated with immunogenicity, they did consider the probable disadvantage for the general population of potentially everybody receiving polysaccharide as part of the 50 year old group of vaccines. There are still some unknowns about some of the data, but there are data suggesting that there may be some issues with blunting with future vaccination when polysaccharide vaccines given first before the next vaccine.
    - One of the biggest frustrations and difficulties physicians have regards the confusing risk-based pneumonia recommendations. Simplification based on age has the potential to improve vaccine uptake, equity, and overall health. The individual risk versus the societal risk also must be weighed in discussing PCV13 in that the individual may still get benefit even though the population may not see it because of indirect effects. Lowering the age of a pneumococcal recommendation and making it more universal may help the individual and society, improve uptake, and improve equity.

- It is important to keep in mind that ACIP can only deal with the vaccines in front of them, not future vaccines.
- Giving the vaccine at age 50 has the potential to allow people to respond before they develop a medical condition or experience immunosenescence that may interfere with response to vaccines.
- It was not clear to some ACIP members that what was proposed would be less complicated than the existing recommendations.
- It would be beneficial for ACIP to be able to hear an overview of educational information that would be made available for patients to understand the recommendations; however, it was noted that this could be difficult without having a clear understanding of what the recommendations would look like.

Public Comments

The floor was opened for public comment during the September 29, 2021 ACIP meeting at 2:35 PM ET. Given that many more individuals registered to make oral public comments than could be accommodated during this meeting, selection was made randomly via a lottery. The comments made during the meeting are included here. Members of the public also were invited to submit written public comments to ACIP through the Federal eRulemaking Portal under Docket No. CDC–2021–0075. Visit http://www.regulations.gov for access to the docket or to submit comments or read background documents and comments received.

Mr. Robert Blancato
National Association of Nutrition and Aging Services Programs

Thank you for another opportunity to present to you. My name is Bob Blancato, representing the National Association of Nutrition and Aging Services Programs (NANASP). First, I commend ASIP for the extraordinary work you have done through the pandemic—work that has certainly saved lives. My point is simple and straightforward. Please, during this meeting, recommend the use of 2 new and improved pneumococcal vaccines so they can be used in time for this upcoming slew of pneumonia season, especially for older adults. I make this request together with the National Council on Aging (NCOA), National Alliance for Caregiving (NAC), National Caucus & Center on Black Aging, Inc. (NCBA), Generations United, Caregiver Action Network, Vietnam Veterans of America (VVA), and the Women's Institute for a Secure Retirement (WISER). The earlier presentation by the Pneumococcal WG makes an extremely strong case that at least for the 65 plus population you could, in fact, approve the vaccines today. Both of these new and improved vaccines were approved by the FDA this summer. In addition, both have shown early positive results that they can be administered together with the flu vaccine. A more active influenza and pneumonia season is inevitable as our nation slowly returns to more normal social interaction in various settings. Pneumonia is inextricably linked to the flu. Pre-pandemic and 1.5 million persons per year sought care from hospital emergency departments due to pneumonia. Death from these two diseases once was the 9th leading cause of death in the United States. Another compelling reason to recommend approval now is CDC's own guidance that pneumonia vaccines can be administered along with COVID vaccines. As more Americans, especially older Americans, either get their first or second dosages or their boosters, it would be such a convenience to have them both done on the same visit. Another new but critical consideration for having the most current vaccines is data from a study of 5,000 older adults, which showed that persons 65-75 who received the pneumococcal vaccine reduced the risk of developing Alzheimer's Disease by 30%. When this panel approved pneumococcal vaccine in 2014 followed by a decision by CMS to provide coverage, it led to almost a doubling of older adults on Medicare getting pneumococcal vaccines. I urge ACIP to move with the same

incredible speed that it has throughout the pandemic, and this time expedite the approval of these new and improved pneumococcal vaccines. Just as your work has been pivotal to more than 213 million Americans having received at least one COVID-19 vaccine, deciding to recommend approval today for these pneumococcal vaccines could result in millions of older adults getting this critical vaccine. Finally, recommending this vaccine addresses another important public health issue, preventing further social isolation of older adults. A tragic pandemic should not be followed by a twindemic later this year and early next. That can be averted by ASIP moving today to approve vaccines that could prevent this deadly disease from impacting older adults. Thank you very much.

Ms. Elisha Malanga
Chief of Staff
COPD Foundation

My name is Alicia Malanga and I am pleased to be able to represent the COPD Foundation and highlight the written comments submitted to the ACIP by our Chief Medical Officer. The COPD Foundation is dedicated to preventing COPD, bronchiectasis, and nontuberculous mycobacterial (NTM) lung disease, and seeking cures while improving lives and advocating for all affected. The COPD Foundation represents more than 16 million Americans diagnosed with COPD and countless more at risk. We strongly support the work of the ACIP and are grateful for the critical efforts required in the group. My purpose today is to strongly advocate for a simplified age-based vaccine recommendation for the prevention of pneumococcal disease, including pneumococcal pneumonia in adults. While well-intentioned, the current recommendations including shared clinical decision-making has generated confusion. In addition, under the current recommendations, individuals with chronic underlying conditions, including COPD, under the age of 65 are not addressed. Overall, individuals with COPD have more pneumonia, suffer from more severe episodes of pneumonia, and experience more hospitalizations, greater burden, and worse outcomes compared to those without COPD. Sentiment around pneumonia on COPD360social, the foundation's community of over 51,000 individuals, highlights the fear of getting pneumonia and the hope that it can be prevented. We understand that from the July 2021 ACIP meeting, there has been a demonstrated cost-effectiveness of PCV20 without the pneumococcal polysaccharide vaccine in individuals 50 and over and in individuals 65 and over. The data also suggests a demonstrated cost-effectiveness of PCV15 without the pneumococcal polysaccharide vaccine in individuals 65 and over. These data strongly support the COPD Foundation's request that the ACIP implements a simplified age-based pneumococcal vaccine recommendation. That also includes a risk-based recommendation for individuals of chronic underlying conditions, including COPD, who do not meet the age requirement of 50 or 65, respectively. Now more than ever, vaccines and protecting lung health are essential. We need to ensure that we equip our community with clear vaccine guidelines that incorporate at-risk populations, including those with COPD. Thank you for the opportunity to share the impact of your recommendations. We stand ready to assist in providing additional information.

Mr. Burton Eller
Legislative Director
National Grange

Good day. To raise our concern about the continued threat from COVID-19 in combination with what is expected to be an active influenza and pneumonia season this fall and winter, National Grange President Betsy Huber recently wrote an opinion piece in *The Hill* laying out the unique challenges rural Americans face and why they could be especially vulnerable during the upcoming flu season. Some of these include that a quarter of rural residents live in counties with high mortality rates due to underlying medical conditions. Additionally, it is harder for rural residents to access care as 181 rural hospitals have closed permanently in the US since 2015 and nearly 1 in 5 rural Americans continue to have limited access to high speed and broadband, prohibiting virtual physician visits. Certainly more challenging for those in rural America, we know that keeping up with routine checkups and vaccinations could mean life and death for so many vulnerable Americans. With the FDA's recent approval of two new vaccines for pneumonia, which cover more variants of the virus that currently available vaccines, our communities are eager to gain access to this broader protection. We have already heard from several of our members expressing their hopes that the new vaccines are available before the upcoming flu and pneumonia season, including from one individual who lost their older brother to pneumonia at age 40. We implore this committee to expedite this process and ensure the at-risk population and vulnerable Americans across the country ages 50 and older will have access to the most effective vaccines before the flu and pneumonia season is underway. We thank you for the ongoing commitment to protecting Americans against COVID-19 and appreciate all of the progress that has already been made in insuring access to effective preventative vaccines to protect ourselves. Just as we are laser-focused on increasing COVID-19 vaccination rates, we remain diligent in ensuring that we are using every tool available to protect against pneumonia. Thank you.

Rita Kuwahara, MD, MIH
Primary Care Internal Medicine Physician
Health Policy Fellow
Georgetown University

Thanks for the opportunity to speak today. My name is Dr. Rita Kuwahara. I'm a Primary Care Internal Medicine Physician and Health Policy Fellow at Georgetown University. I'm here today to provide evidence for why an updated recommendation for universal adults Hepatitis vaccination is not only a crucial step to protecting the health of my patients and community, it is an issue of health equity and gives us the essential tool we need to significantly increase the current adult Hepatitis C vaccination rates of only 25% and finally eliminate Hepatitis C in the US. As a physician, I'd like to urge you to vote in favor of recommending universal adult Hepatitis C vaccinations. We are a critical time in our nation's history with the ongoing COVID-19 pandemic, the surging opioid epidemic, and widening racial health disparities. Seeking now to improve the public health of our nations will have long lasting effects on the health outcomes of each person in our country. Up to 2.4 million people in the US are chronically infected with Hepatitis C and 1 in 4 people with Hepatitis C will develop liver cancer and liver failure and/or cirrhosis. Liver cancer only has an 18% 5-year survival rate. Prior to COVID-19, regions of our country most affected by the opioid epidemic had alarming rises in acute Hepatitis C of up to 100% to 700%. The opioid epidemic has resulted in further rises, with 36% of all new acute Hepatitis C infections in the US attributed to the opioid epidemic. Hepatitis C is vaccine-preventable and we have highly effective vaccines so there should not be a single new infection of Hepatitis C in our nation. However, since only 25% of adults are vaccinated, we are seeing

continued rises in infections and we must do everything in our power to prevent additional outbreaks within the opioid epidemic and COVID-19 pandemic. As a primary care physician, my number one priority is optimizing the health of my patients. Ending the transmission of vaccine-preventable infectious diseases is paramount to achieving this. When I see patients in clinic, I'm caring for individuals with increasing complex health and social needs. With the current risk-based approach to Hepatitis C vaccinations, it makes it impossible to have automatic alerts to vaccinate patients, leaving our most vulnerable patients without protection against Hepatitis C and associated liver cancer. Hepatitis C disproportionately affects communities such as Asian Americans and Pacific Islanders, African Immigrants, incarcerated individuals, and persons who inject drugs (PWID) who may not have the knowledge and empowerment to ask for the Hepatitis C vaccine. If universal vaccination is recommended, we would not have this problem to create automatic alerts for all of our patients are protected. In a survey of internal medicine physicians I conducted at my community health center, we found that none of the surveyed physicians knew that the adults Hepatitis C vaccination rates is only 25%, so vaccines were rarely ordered. Since every unvaccinated person is at risk of infection, we must increase provider awareness to protect the health of our most vulnerable patients and prevent outbreaks in our communities through increased vaccinations through recommendations for universal adults Hepatitis C vaccination, which can also allow us to finally end Hepatitis C. Thank you.

Ms. Katherine Falk
Vaccine Advocate and Parent

I'm Katherine Falk, a parent and vaccine advocate in Oakland California. Thank you again for all your hard work. I wish this time was about vaccines other than those against COVID-19. I cannot speak to the data on the vaccines you're discussing. I'm glad that you're discussing them, because of all the focus on COVID-19, we still can't lose sight of the many other preventable diseases out there. Speaking of which, it would be nice if it wasn't just left to the market to drive the timeline of the development of new vaccines. We could use a more effective flu vaccine and it would be wonderful if that childhood scourge respiratory syncytial virus (RSV) could be prevented with a vaccine, too. And while I know you're not talking about COVID-19 vaccines today, I hope that when the data on younger children arrives on your doorstep, you'll be able to review and approve it as efficiently as possible without sacrificing the thorough work you always do to assess risks and benefits. But I'm mainly here today to tell you I shouldn't be here. I want to reiterate Mr. Nurenberg's and Professor Reiss's prior comments. Anti-vaccine advocates take advantage of this oral public comment opportunity to disseminate rapid fire disinformation so they can reuse their audio clips and marketing social media campaigns. You had a demonstration of this just last week when one of the public commenters rattled off a bunch of death reports with zero evidence of causation and misused information recommending that people take Ivermectin, engaged in conspiracy theorizing, and advertised his blog free of charge on this forum all in the space of three minutes. This is, to put it mildly, unhelpful. While it's important to let members of the public weigh in, we could also do so in writing. There is no benefit to giving an opportunity to grandstand to people who cite their unverified reports and scare people into leaving themselves and their families and communities unprotected from disease. Nobody should pretend that we public commenters are actually sitting on the ASIP panel as equal meeting participants. Maybe when you get some free time, you can look at changing the comment format. I will also reiterate that I hope the committee is given the resources and opportunity to communicate clearly and widely to the public about vaccines, vaccine science, and the vaccine approval process. There is a lot of work to do. Thank you.

Michaela Jackson, MS, MPH
Prevention Policy Manager
Hepatitis B Foundation

My name is Michaela Jackson. I am the Prevention Policy Manager for Hepatitis B Foundation. Today we urge ACIP to recommend universal Hepatitis B vaccinations for all adults. Earlier this year, a new study by the Hepatitis B Foundation and partners found that 2.4 million Americans are living with Hepatitis B—a number that is greater than was previous estimated. When this number is considered along with the recent rise in the acute Hepatitis B cases and the low adult Hep B vaccination rate, it is clear that Hep B remains a problem in the US despite highly effective vaccines. Considering that, it is imperative that the committee recommends universal vaccination for all adults instead of limiting it to those 59 years of age and under. The most recent Hepatitis surveillance report shows that adults 60 and older have seen a slight but steady increase in Hep B cases since 2014. This rise is particularly concerning in view of the COVID-19 pandemic, as many essential public health services and facilities were closed for extended periods of time. We know that current risk guidelines are ineffective and missed opportunities to vaccinate can be expensive. The CDC Division of STD Prevention reported that new sexually transmitted Hep B cases accounted for $46 million in direct medical costs in 2018—a significant number for a disease that can be prevented. Furthermore, research shows that people who experience liver complications that can occur in Hep B patients, such as decompensated liver, liver cancer, or liver transplant accrue the highest annual healthcare cost in the US. With a lack of clear surveillance and a lack of universal screening combined with underreported Hep B cases, this means that along with chronic Hepatitis B patients, those wo are unaware that they have recovered from an acute case can still be at risk for activation and potential liver problems later in life. Universal prevention is the best way to keep costs low for both the government and the individual. In a time when public health is facing the culmination of many long-standing battles, this battle that can be easily won. The Hepatitis B community feels strongly about a universal recommendation as a priority that cannot be delayed. We wait in anticipation for the committee's final vote this October. I'd like to thank the committee for continuous efforts to better public health and your time today. Thank you.

Mr. Jan Manuel Cubero Jimenez
Public Policy Intern
RetireSafe

Greetings everyone. My name is Jan and I am speaking on behalf on RetireSafe. RetireSafe is a non-profit organization whose mission is to educate and advocate on behalf of older Americans on issues including Social Security, Medicare, health, retirement, and financial well-being. I speak not only as a Public Policy Intern, but as a son of two parents nearing retirement age and the grandson of three grandparents who are eager to spend time with their children and grandchildren, as well as enjoy their retirement outside of their homes. Currently, there are 70 million Americans over the age of 60 with immune system decline as part of aging, as well as the prevalence of chronic disease comorbidities. Many of them are particularly vulnerable to infectious diseases such as influenza, pneumococcal pneumonia, and of course COVID-19. Vaccines for these and other conditions can truly be a matter of life or death, and we are grateful for the continued work of the ACIP to evaluate and approve critical vaccines for COVID-19. RetireSafe has a long history of informing and educating American seniors of the important role vaccines play in maintaining long-term health, and our members are committed to taking the steps necessary to protect against preventable illnesses. While we are encouraged by the progress made toward vaccinating older Americans against COVID-19, we are increasingly concerned that experts are predicting the flu and pneumonia season to be more serious than

last year now that states across the country are relaxing COVID-19 restrictions. In the US, it is estimated that more than 150,000 hospitalizations from pneumococcal pneumonia occur each year and about 5% to 7% of those who are hospitalized from it will die. Given the increased morbidity for older Americans and in light of the two new and improved vaccines for pneumonia, we are particularly focused on what is being done to ensure we are doing everything possible to protect America's seniors. These new vaccines offer even greater protection against life-threatening disease for some of the most vulnerable in our population, but only if they have access to them. We are urging this committee to consider expediting the votes on these vaccines for adults aged 50 and older ahead of this year's flu and pneumonia season. In closing, I would like to share what we heard from one gentleman living in San Antonio, Texas named Joe Velasquez. Mr. Velasquez is a 78-year-old diabetic who wrote to us that he is eager for access to these new vaccines because he is not only concerned about protecting himself, but also his family members, including his daughter who suffers from ALS and her husband who has severe asthma. We are hopeful that Joe and the millions of other seniors across the country who will desperately want to protect themselves ahead of this year's flu and pneumonia season will have access to the best tools to do so. Thank you for the opportunity to speak and thank you so much for your time.

Richard M. Haupt, MD, MPH
Head
Global Medical Research for Infectious Disease
Merck

I am Rick Haupt. I am head of Global Medical Research for Infectious Disease at Merck. I want to thank the ACIP for the opportunity to make a public comment. I also want to thank the WG for their great efforts in supporting recommendations for adult pneumococcal vaccinations. I had some remarks prepared for today's presentation, but before I do that, very quickly I just wanted to address something that came up and that is the issue of immune tolerance. We have data with revaccination with the polysaccharide going out to 5 years that shows no evidence of hyper-responsiveness, so I'm concerned of this issue of immune tolerance taking on a bigger role than it should be. We'd be glad to share that data with you, the WG, in the future. But I couldn't let that pass. My comments regarding today, we really appreciate the changes that were made to the health economic model based on scientific evidence and feedback received in the June meeting. We are disappointed that the work was excluded from the strategy and age-based recommendations. Based on our analysis, the PCV-only strategy was cost-savings in the 65 years of age and older across all scenarios, including the scenario that incorporated most of the CDC assumptions. As presented today, both policy options proposed by the WG in adults 65 years of age are economically favorable and cost-saving. It's important to note that they do have different profiles. A single vaccination covering 20 PCV types or a sequential PCV15 + polysaccharide regimen that has broader coverage is robust. I'd also note that PCV15 is the only vaccine that has generated complex clinical data in immunocompromised and at-risk populations. Consideration of both policy options by the ACIP allows healthcare providers to have the opportunity to select the most appropriate regimen considering the profile of the individual being vaccinated. Also consistent with the desire of the WG to ensure simplified recommendation that would ensure better coverage and avoid confusion among healthcare providers, we suggest that both the 50 and 65 age-based recognitions consider the PCV15/ polysaccharide sequential regimen, as well as the PCV20/polysaccharide policy regimen. Different recommendations in 50- and 65-year-old age groups may lead to more confusion of healthcare providers and as noted earlier, may necessitate the need for booster doses at age 65 or even possibly earlier. And then my last comment, and I think it was good to see this as the next step by the WG, the intervals for the PCV polysaccharide sequential regimen in the at-risk

and age-based categories are different. It's 8 weeks in immunocompromised individuals and it's a year or more in immunocompetent individuals. Merck has generated safety and immunogenicity data that demonstrates that the polysaccharide vaccine can be given as early as 4 weeks following a PCV dose in immunocompetent adults and we respectfully request that the WG consider harmonizing the timing of those intervals in the sequential recommendation in both categories in the effort to simplify the recommendations and likely facilitate series completion. So again, thank you to the WG and the ACIP for all their efforts in the adult policy world. We look forward to working with the WG as they begin deliberations in the pediatric pneumococcal vaccine, which is coming after this adult adventure ends in October. Thank you very much.

Dr. Alejandro D. Cané
North America Chief
Scientific and Medical Affairs
Vaccines Division
Pfizer North America

Good afternoon, everyone. My name is Alejandro Cané. I am the American Chief for Vaccines in Pfizer North America. Thank you very much for the opportunity to speak with you today. We would like to provide some brief comments and an update on our clinical development product for PCV20 adults. Firstly, I would like to remind you that approximately 30% of our subjects under 65 years of age in our Phase 3 clinical trial had a chronic medical condition. Secondly, during today's presentation of the EtR Framework, when providing a summary assessment of the certainty for evidence of PCV20 effectiveness, some WG members expressed concerns about the lower immunogenicity observed for PCV20 versus PCV13 recipients. We would like to reiterate that PCV20 immune responses met the criteria for all of the shared stereotypes in PCV13 and also for all of the shared stereotypes with PCV23, except for stereotype A. That, as you know, fulfills all the criteria required by the FDA for approval. Third. regarding the uncertainty noted around potential future effectiveness of PCV20, we also would like to point out that a similar immunogenicity pattern was significant in the population when moving from PCV7, which we are now approving to be effective against pneumococcal pneumonia, to PCV13. PCV13 was shown to be highly effective at the individual and population levels. While there is no corollary of protection in adults, PCV20 is being compared to a vaccine with proven efficacy, which is similar to the process we follow with PCV13 evaluation. Specifically, a large randomized clinical trial conducted in Maryland among adults 65 years of age and older demonstrated that PCV13 is efficacious against IPD and non-invasive pneumonia for vaccine stereotypes, including stereotype 3. These are supported by similar results from several subsequent effectiveness studies. Therefore, PCV20 will likely have similar efficacy to PCV13. It is also important to point out that these transitions from PCV7, now from PCV13 to PCV20, are being made for a vaccine made by the same manufacturer using the similar processes and the unique technologies of the prior vaccine with proven efficacy. We would like to reassure the ACIP that we are committed to conducting a complete effectiveness study of the PCV20 allowed in the US population once the recommendations become final. Of course, we look forward to sharing the results of this study with the ACIP sometime in the future. Finally, I really would like to say thank you again for the opportunity to speak with you today and thank you for your careful and transparent consideration of the evidence for pneumococcal vaccines, especially when in the midst of the pandemic response. Thank you again, Dr. Lee.

HEPATITIS B VACCINES

Introduction

Dr. Kevin Ault (ACIP, WG Chair) reminded everybody that this is part of a larger effort as outlined by HHS to eliminate hepatitis B in the US, so the question pertaining to whether all unvaccinated adults should receive hepatitis B vaccination will be an ongoing discussion in this and upcoming ACIP meetings. During the February ACIP meeting, the WG presented the background and economic evaluation. The topics for the June 2021 meeting were rescheduled to this September ACIP meeting, including the HepB-CpG (HEPLISAV-B®) post-marketing surveillance study and the EtR Framework plus GRADE, in anticipation of having a vote during the regularly scheduled October ACIP meeting.

HepB-CpG Post-Marketing Surveillance Study

Dr. Katia Bruxvoort (Kaiser Permanente Southern California) presented the final results of the post-licensure vaccine safety study of a 2-dose hepatitis B vaccine, HEPLISAV-B® focused on acute myocardial infarction (AMI) compared to ENGERIX-B®. HEPLISAV-B® is a 2-dose vaccine administered at 0 and 1 month and ENGERIX-B® is a 3-dose vaccine administered at 0, 1, and 6 months. HEPLISAV-B® has a novel TLR 9 agonist adjuvant, cytosine-phosphate-guanine class C (CpG-C). ENGERIX-B® has an alum adjuvant. In pre-licensure clinical trials, HEPLISAV-B® generated higher and earlier seroprotection compared to ENGERIX-B®. But in a single clinical trial, there was a numerical "imbalance" in AMI that occurred randomly with no relationship to vaccine administration at lower than expected incidence rates. However, this imbalance prompted that a safety study be required as part of HEPLISAV-B® licensure.

Thus, the Kaiser Permanente Southern California (KPSC) Department of Research and Evaluation came on board to conduct this real-world post-licensure safety study with the objective of comparing the occurrence of AMI in recipients of HEPLISAV-B® and recipients of ENGERIX-B®. In July 2017, FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) voted 12 to 1 that the HEPLISAV-B® safety data supported licensure. The original Prescription Drug User Fee Act (PDUFA) date was extended to November 2017, while the details of the required post-marketing safety study were worked out. The Biologics License Application (BLA) was approved in November 2017 and ACIP recommended HEPLISAV-B® for use in adults in February 2018. The recommendation was published in April 2018. This allowed KPSC to begin planning for implementation of HEPLISAV-B® and to begin using HEPLISAV-B® in August 2018.

KPSC is a large, diverse, integrated healthcare system serving 4.7 million members with diverse racial, ethnic, and socioeconomic backgrounds. There are 15 medical centers spread over Southern California, each with a hospital and surrounding medical office. These centers administer large number of vaccines every year. KPSC also has a comprehensive electronic health record (EHR) system, which captures details of patient care, and vaccines are offered proactively at every visit and during walk-in clinic visits. Electronic alerts are in place, which help identify patients who can benefit from vaccinations. This includes an alert for hepatitis B vaccinations for patients with diabetes.

KPSC's used a non-randomized design in which HEPLISAV-B® became the only hepatitis B vaccine available in family and internal medicine departments at 7 of the 15 KPSC medical centers. The other 8 medical centers continue to use ENGERIX-B® in family and internal medicine departments. This was a real-world study, so hepatitis B vaccines were administered as part of the routine care delivery from August 2018-October 2019. Individuals were passively followed through their EHRs for 13 months after the first dose administered during the study accrual period, which was the index dose. The primary outcome was the first occurrence of definite or probable Type 1 AMI as defined by the Fourth Universal Definition of Myocardial Infarction during the 13 month follow-up period after the index date. Potential AMI were then identified by International Classification of Diseases-10-Clinical Modification (ICD-10-CM) diagnosis codes from in-patient care or emergency department (ED) visits with the same or next day death. Documentation of potential AMI events for hospitals outside of KPSC was captured from claims. All events were adjudicated by two cardiologist reviewers who were masked to the vaccine group and to each other. The results were reviewed by an independent data monitoring committee.

To adjudicate AMI events, cardiologist reviewers were asked to use the Fourth Universal Definition of Myocardial Infarction (MI) to classify potential AMI events as: Definite AMI, Probable AMI, Insufficient Information, or Not AMI. For definite or probable AMI, reviewers were asked to determine the type of AMI. Cases with disagreement from two cardiologist reviewers went to a third reviewer as a tiebreaker. Cases with disagreement from all three reviewers were considered indeterminant. This was a non-inferiority study designed to rule out a doubling of the rate of AMI in HEPLISAV-B® versus ENGERIX-B® recipients. A Cox proportional-hazards model was used with inverse probability of treatment weighting (IPTW) to assess the degree of control then balance in the characteristics between the vaccine exposure groups. A wide range of covariates and characteristics were considered, including: socio-demographics, diabetes in the prior year, AMI in the prior year, cardiovascular disease (CVD) risk factors and medications in the prior year, other co-morbidities in the prior year, and receipt of concomitant vaccines with hepatitis B vaccine.

Several additional analyses were performed. These included sensitivity analyses using the alternative methods of propensity score-adjusted and -stratified Cox proportional-hazards model and traditional multi-variable Cox proportional-hazards regression. Sensitivity analyses were performed for all types of AMI events and confirmed Type 1 AMI plus indeterminate events, which are the cases with disagreement from all three adjudicators. Subgroup analyses were performed stratifying the cohort by age group and subgroup, including: age <50 years at index dose, age ≥50 years at index dose, diabetes in the year prior to index dose, hypertension in the year prior to index dose, receipt of concomitant vaccination, index dose as first hepatitis B vaccination, and index dose as subsequent hepatitis B vaccination.

Now to look at vaccine accrual by dose for HEPLISAV-B® and ENGERIX-B® recipients for those who received only 1 dose, 2 doses, or 3 doses during the accrual period from August 2018-2019 and with subsequent doses accrued through November 2020. Overall, there were 31,183 individuals who received at least 1 dose of HEPLISAV-B® and 38,442 individuals who received at least 1 dose of ENGERIX-B®. In terms of presenting standardized differences comparing a distribution of the wide range of characteristics we looked at between HEPLISAV-B® and ENGERIX-B® recipients before and after IPTW, KPSC has very large sample sizes in its studies, so they use standardized differences inside of P-values. The standardized difference greater than 0.10 is considered a significant difference. Standardized differences were small before IPTW and showed no significant differences between the two vaccine groups except for

race/ethnicity. After IPTW, there was a good balance of all characteristics between the two vaccine groups.

Looking at rates of AMI during the follow-up period for HEPLISAV-B® and ENGERIX-B® recipients, there were 74 potential AMI events in the HEPLISAV-B® group and 70.3% were confirmed to be Type I AMI events. In the ENGERIX-B® group, there were 128 potential AMI events with 55.5% confirmed to be Type I AMI events. The AMI rate was 1.67 per 1000 person years for HEPLISAV-B® recipients and 1.86 per 1000 person years among ENGERIX-B® recipients. In terms of the final study results concerning the rate of Type I AMI events in recipients of HEPLISAV-B® versus ENGERIX-B®, the adjusted hazard ratio for the primary analysis was 0.92 for the Cox model with IPTW. The 95% confidence interval was 0.63 to 1.32, so there was no evidence of a significant difference in the rate of Type I AMI comparing HEPLISAV-B® and ENGERIX-B® recipients. In addition, the upper bound of the confidence interval was less than 2.0, so a doubling of the rate can be ruled out and the null hypothesis can be rejected.

In the sensitivity analyses using different analytic approaches, consistently similar results were found. In the sensitivity analyses using alternative outcomes for all type of AMI events and the confirmed Type I AMI plus the indeterminate events, slightly lower adjusted ratios were found that also included 1.0. Similarly in all of the stratified and subgroup analyses, no evidence was found of a higher rate of AMI in HEPLISAV-B® recipients compared to ENGERIX-B® recipients.

This study has multiple strengths and limitations. This was a real-world observational study in which hepatitis B vaccine is administered as part of routine healthcare delivery. Like all observational studies, there is potential for measured and unmeasured confounding. However, a wide range of socio-demographic and clinical covariates were considered and IPTW was used to adjust for confounding. Pre-defined stratified and sub-group analyses and sensitivity analyses using alternative analytic approaches and outcome definitions were performed, for which consistent results were found. Misclassification of the vaccine exposure was possible, but the investigators checked to ensure that manufacturer and lot number descriptions matched the brand names and also conducted chart review of doses with potential discrepancies. Misclassification of the AMI outcome also was possible; however, all potential events were adjudicated by at least two cardiologist reviewers. There were more events from claims outside of the KPSC health system in the ENGERIX-B® group, with a lower proportion adjudicated as definite or probable AMI. An additional strength of this study is the large and diverse study population in contrast to the demographics of the licensure trials. In conclusion, there is no evidence of an increased risk of AMI associated with vaccination with HEPLISAV-B® compared to ENGERIX-B®.

EtR Framework for Universal Adult HepB

Dr. Mona Doshani (CDC/NCHHSTP) presented the EtR Framework for the question pertaining to whether all HepB-unvaccinated adults should receive hepatitis B vaccinations. In terms of the PICO question, the population under consideration is previously HepB-unvaccinated adults ≥18 years of age. The intervention is a universal vaccination strategy using the 2-dose and 3-dose schedules. The comparison group is a current risk-based HepB vaccination strategy using the 2-dose and 3-dose schedules. The WG identified the outcomes of incidence of hepatitis B, morbidity related hepatitis B, mortality related to hepatitis B, and SAEs associated with the 2-dose vaccine. The last outcome was fully aimed at assessing the 2-dose vaccine HEPLISAV-B® vaccine that was approved by FDA in 2017 and recommended by ACIP in 2018. The 3-dose vaccines already have been extensively evaluated for their safety. The WG felt that the first set

of outcomes (e.g., incidence, morbidity, and mortality) were important, while the second outcome (e.g., SAEs associated with the 2-dose vaccine) was critical.

Beginning with the first EtR Framework domain of public health problems, the WG first sought to describe the burden of hepatitis B in the US. Several studies were found that showed that in spite of existing resources for vaccinations, screening and treatment, and reduction in incidence over the years, the burden of chronic hepatitis B disease is still substantial. People with chronic hepatitis B serve as a continued source of potential infection. Chronic hepatitis B estimates vary by data source and study methodology. During 2013-2018, an estimated 880,000 people were living with chronic hepatitis B infection in the US.[40] Other modeling studies yielded higher estimates of prevalence of 1.89 million persons (range 1.49-2.40 million).[41] In 2019, data from death certificates from the Vital Records Offices of the 50 states and DC demonstrated that the hepatitis age-adjusted death rate was 0.42 deaths per 100,000, which equated to about 1,662 deaths each year.[42]

Looking at acute hepatitis B infections in the US, over half of the acute hepatitis B cases reported in 2019 occurred among people aged 30 to 49 years.[43] In 2019, there were 3,192 acute hepatitis B cases reported to the CDC National Notifiable Disease Surveillance System (NNDSS) leading to an estimated 20,700 infections in the US in one year. This was obtained after adjusting for case under-ascertainment and under-reporting. In terms of the rate of reported acute hepatitis B infections from 2004 to 2019 broken down by age group, 2 age groups (40-49 years and 50-59 years) seemed to have a slight upward deflection since 2017 that likely was driven by the ongoing opioid epidemic.[44]

Regarding the available information on the 3,192 case reports of acute hepatitis B received by CDC for 2019 with risk behavior or exposure identified, it is important to note that information on risk behaviors and exposures are missing for 37% of the cases and more than one risk was reported for each case. Among the risk behaviors and exposures identified, it was observed that injection drug use (IDU) was most commonly reported risk behavior/exposure, followed by multiple sex partners.[45]

The goals of the HHS and CDC Division of Viral Hepatitis elimination plans are similar. One of the goals of the HHS Viral Hepatitis National Strategic Plan is to reduce acute hepatitis B infections by 2030. The national HHS Target Measures is to reduce acute hepatitis B infections 20% by 2025 and 90% by 2030.[46] However, over 95% of acute hepatitis B infections reported to CDC in 2019 were in adults ≥18 years.[47] Having a universal vaccination recommendation in adults could have averted approximately 20,000 cases of acute hepatitis B infection.

[40] Roberts H et al. Hepatology. 2021
[41] Lim et al. Am J Gastroenterol. 2020
[42] Wong et al. Am J Med. 2021
[43] https://www.cdc.gov/hepatitis/statistics/2019surveillance/HepB.htm
[44] 2019 CDC Hepatitis Surveillance Report
[45] CDC, Nationally Notifiable Diseases Surveillance System
[46] https://www.hhs.gov/sites/default/files/Viral-Hepatitis-National-Strategic-Plan-2021-2025.pdf
[47] 2019 CDC Hepatitis Surveillance Report. https://www.cdc.gov/hepatitis/statistics/2019surveillance/HepB.htm

Hepatitis B complications lead to higher healthcare demands.[48] The population previously diagnosed with chronic hepatitis B infection has continued to age and if untreated, their chronic hepatitis B infection may progress to more advanced liver disease, such as decompensated cirrhosis, hepatocellular carcinoma (HCC), or liver transplant resulting in higher healthcare resource demand. US cancer data from the Data from Surveillance, Epidemiology and End Results (SEER) Program stated that by 2030, there will be 56,000 HCC cases and that nearly 10%-15% of people with HCC are infected with hepatitis B. Looking at the burden of hepatitis B hospitalization each year, more than $1 billion are spent in the US on hepatitis B-related hospitalizations. That does not include indirect costs, such as poor quality of life, reduced economic productivity, long-term disability, and premature death.

The WG found several studies that looked at missed opportunities in HepB vaccination coverage among unvaccinated adults ≥19 years. These studies showed that despite the universal vaccine recommendation in children and adults and in groups with risk factors, the vaccination coverage among adults was low and rising very slowly. The results from the 2018 NHIS[49] survey indicated that only 40% of adults aged 19-49 years and approximately 19% of adults aged 50 years and older had received 3 doses of hepatitis B vaccine. Data from a National Health and Nutrition Examination Survey (NHANES)[50] for 2013-2018 estimated that 21.4% of the US non-institutionalized population age 25 years of age and older had vaccine-induced immunity to hepatitis B. In particular, high-risk groups represent a substantial portion of the adult population, but have low vaccination coverage.[51] One study reported that 87% of individuals who are greater than 60 years of age with diabetes mellitus were unvaccinated.[52] And another study reported that more than half of the women with more than one risk factor who visited or talked to a health professional in the past year were unvaccinated.[53]

Looking at the timeline of hepatitis B recommendations in the US overlaid on hepatitis B virus incidence from 1980-2019, all US infants were recommended for hepatitis B vaccination in 1991. That means that presently, all people through age 30 should have been vaccinated against hepatitis B. In 1999, all US children and adults through 18 years of age were added to the hepatitis B recommendations. This means that currently, all people through age 40 should have been vaccinated against hepatitis B.[54] The WG's interpretation was that hepatitis B is a problem of public health importance.

In terms of the domain of benefits and harms, the benefits of hepatitis B vaccine have been reviewed previously by ACIP and have been well-established in terms of safety, immunogenicity, and efficacy. The vaccine offers over 90% protection among healthy adults who complete the 3-dose series, with rare adverse reactions.[55] Immunogenicity is estimated to last for 3 decades after vaccination.[56] More than 90% of people have evidence of protection 30 years after receiving the primary series.[57] Studies have shown that immunocompetent people are protected even if their titers decline to less than 10 IU/L.

[48] Nelson et al. Clinics in Liver Disease. 2016; Aly et al. Hepat Oncol. 2020; Bennett et al. Medscape.2021; and Corte et al. J Gastroenterol Hepatol. 2014
[49] Vaccination Coverage Among US Adults, NHIS, 2018 | CDC
[50] Roberts H et al. Hepatology. 2021
[51] Ladak et al. Infection. 2012
[52] Hyer et al. Vaccine. 2019
[53] Miller et al. Conference abstract. 2016
[54] Source: National Notifiable Diseases Surveillance System (NNDSS)
[55] Assad et al. Vaccine. 1999; Venters et al. Expert Rev Vaccines. 2004; Andre et al. Am J Med. 1989; Schillie et al. MMWR. 2018
[56] Schillie et al. MMWR. 2018
[57] Bruce et al. J Infect Dis. 2016

Several studies have shown that in the last 3 decades, incidence of new hepatitis B infection has declined due to VE. There has been a dramatic decrease of 68% in hepatitis B infection prevalence among children, which was observed within 10 years of initiation of a universal hepatitis B vaccination in 1991.[58] The WG found no studies for universal vaccination among adults and found weak evidence[59] related to vaccination among high-risk adults. The WG also looked at a few studies among pregnant people under the harms criterion. One was a Vaccine Safety Datalink (VSD) study that looked at hepatitis B vaccines administered in approximately 1,400 pregnant people, most commonly administered in the first trimester. This study showed no increased risk of AEs among pregnant people or their infants.[60] Insufficient data were available on HepB-CpG (HEPLISAV-B) administered to pregnant people.[61] An ongoing pregnancy registry is collecting information from 250-300 pregnant people on outcomes following pregnancy exposure to HEPLISAV-B®, which has an expected completion date of August 9, 2023).[62] It was advised that until safety data in pregnancy are available for HEPLISAV-B®, providers should continue to vaccinate pregnant people needing hepatitis B vaccination with a vaccine from a different manufacturer. In addition, the WG assessed studies looking at Hepatitis B vaccines co-administered with other vaccines and found no increased safety concerns.[63]

Also under the benefits criterion, the WG found several studies that discussed the importance of vaccinating the general population before they develop chronic liver disease (CLD) and other comorbidities, stating that people with CLD are known to have a decreased immunogenicity with a 3-dose vaccine.[64] Only 64% of patients with CLD developed immunity with the new vaccine, in contrast to 90% reported in healthy volunteers in their registration trial. Studies also were found that showed lower seroprotection rates of 45% in persons with cirrhosis and CLD.

Lastly, under benefits, the WG looked at the cost-effective modeling study presented in the previous ACIP meeting that compared the current vaccination recommendations and coverage with either a 3-dose or a 2-dose universal hepatitis B vaccination series. The analytic horizon was 35 years, which is the average life expectancy in the cohort. Universal adult vaccination against hepatitis B infection with either a 2-dose or a 3-dose vaccine series may increase the percent of people protected, moving from a 23.7% in the current strategy to 44.9% in the 3-dose universal strategy and 45.7% in a 2-dose universal strategy. Some of the outcomes examined included acute and chronic infections, hepatitis B-related deaths, and hepatocellular carcinoma.[65]

Considering that vaccination is already recommended for adults at increased risk, the primary analysis included conservative base-case data that did not vary vaccination coverage among persons at increased risk. However, the actual implementation of the universal adult vaccination recommendation would likely result in an increase in vaccination among adults at an increased risk, in addition to the intended effects among general population. The similarity of the model impact between 3-dose and 2-dose strategies was driven by the fact that a higher proportion of adults complete the full series in a 2-dose strategy. But based on a smaller proportion of adults receiving protection from an incomplete series, the overall proportion of adults is similar. The purpose of this economic analysis was to show that regardless of which hepatitis B vaccine

[58] Nelson et al. Clinics in Liver Disease. 2016
[59] Tressler et al. Preventive Medicine. 2020
[60] Groom et al. Vaccines. 2018
[61] Schillie et al. MMWR. 2018
[62] HEPLISAV-B -fda.gov. FDA approval letter. November 9, 2017
[63] Haber et al. Vaccine. 2018; Alberer et al. Travel Medicine. 2015
[64] Roni, D.A. et al. Advances in Virology. 2013; Moreno-Fernandez et al. Primary Care Diabetes. 2020
[65] Hall et al. ACIP Feb. 2021

option was chosen for this particular question, hepatitis B vaccination provides a benefit to the US population.[66]

Under harms, the 3-dose schedule vaccines have been extensively evaluated for safety. Overall, these hepatitis B vaccines have very mild side effects and adverse reactions.[67] The estimated incidence of anaphylaxis following hepatitis B vaccine recipients is 1.1 per million vaccine doses. Over a 7-year study period in a VSD study, no deaths were reported in the 0-30 Day window after vaccination following administration of 876,209 HepA and HepB vaccines.[68] In a VAERS (2005-2015) study there were 2,365 reports in adults, 15 deaths, and 139 serious reports including general disorders/administration site conditions, musculoskeletal conditions and connective tissue disorders, and central nervous system (CNS) disorders.[69]

In summary of the evidence for harms, the WG looked at HEPLISAV-B® vaccine especially closely for reasons previously described. HEPLISAV-B® vaccine was recommended by ACIP in 2018, after which a few mild AEs, SAEs, and cardiovascular events were reported. To summarize the GRADE assessment for the cardiovascular and SAE outcomes only, the WG did not find any studies comparing the two strategies, universal and risk-based for adult hepatitis B vaccination and had no data on hepatitis B incidence, morbidity, and mortality. Hence only these two outcomes were assessed. For cardiovascular events, 5 studies were included of which 4 were RCTs and 1 was observational. In the pooled analysis of the 4 Phase 3 RCTs, there were 41 cardiovascular events in the intervention arm and 16 events in the comparator arm. The risk ratio was 1.33, which was not statistically significant. In terms of the certainty assessment, the risk of bias was judged as not serious, inconsistency was rated as serious, and indirectness was rated as not serious. Given that there were relatively few events and the 95% confidence interval could not exclude the possibility of no meaningful harm, imprecisions was assessed as serious. The overall certainty was assessed as Type 3, or low, due to imprecision and inconsistency. The importance of this outcome was rated as critical.

The observational study for cardiovascular events was presented earlier by Dr. Bruxvoort. In that study, there were 52 events in the intervention group and 71 events in the comparison group for a ratio of 0.92, which was not statistically significant. For the certainty assessment, the risk of bias was judged as not serious, inconsistency and indirectness were rated as not serious. For imprecision, there were relatively few events and the 95% confidence interval could not exclude the possibility of no meaningful harm. Therefore, imprecision was assessed as serious. The overall certainty was assessed to be Type 4, or very low, due to imprecision. The importance of this outcome was rated as critical.

There were 6 studies included for SAEs, 1 Phase 2 RCT and 5 Phase 3 trials. Overall, there were 528 events in the intervention group and 277 events in the comparator group, for a risk ratio of 0.96, which was not statistically significant. For the certainty assessment, risk of bias, inconsistency, indirectness, and imprecision were judged to be not serious. The overall certainty was assessed as Type 1, or high, and the importance of this outcome was rated as critical.

[66] Hall et al. ACIP Feb. 2021
[67] Assad et al. Vaccine. 1999; Schillie et al. MMWR. 2018
[68] McCarthy et al. Pediatrics. 2016
[69] Haber et al. Vaccine. 2018

In conclusion, cardiovascular events were more common in the HEPLISAV-B® arm of the RCTs compared to the ENGERIX-B® arm. This difference was not statistically significant in the estimates for heterogeneity across trials or imprecision. In the observational study, a lower rate of cardiovascular events was observed in the HEPLISAV-B® group compared to the ENGERIX-B® group. The estimates were imprecise and the risk of SAEs was not significantly lower in the HEPLISAV-B® arm of the RCT. The WG's interpretation was that the desirable anticipated effects are large, the undesirable anticipated effects are minimal, and the desirable effects outweigh the undesirable effects and favor the intervention. For the overall certainty of evidence for the critical outcomes, the WG found that there probably is not important uncertainty.

Moving to the values and preferences domain, the WG did not find much information on values and preferences with respect to universal hepatitis B vaccinations in adults. The information they did find suggests that values and preferences vary by risk factors. Among adult patients in high-risk settings, 47% of participants did not respond to the questions about risk factors.[70] Very limited information was available on people with risk factors, and most of this was from refugees and immigrants born in highly endemic countries. A systematic review showed that 54% to 98% of participants knew that hepatitis B was a vaccine-preventable disease.[71] There was wide variation across attitudes and confusion around benefits and side effects of vaccinations. In a convenience sample study of Chinese American immigrant adults surveyed in Southern California, 60% reported "feeling well/having no health problems" as a barrier for vaccination.[72] Another convenience sample of Vietnamese American immigrant adults surveyed were not worried about getting hepatitis B or liver cancer, but the participants expressed awareness of the benefits of vaccinations and were not worried about getting liver disease after getting vaccinated.[73] The WG concluded that the population probably feels that the desirable effects are large relative to the undesirable effects, and that there is probably not important uncertainty or variability in terms of how much people value the main outcome.

Under the acceptability domain, the WG found a few articles related to stakeholder support for a universal adult hepatitis vaccination recommendation and improving adult immunization rates.[74] Achieving high hepatitis B vaccination coverage in the US among adults is a complex undertaking that requires active participation and coordination by a range of immunization stakeholders. In an expert meeting sponsored by a vaccine manufacturer, specialist in primary care, GI/hepatology, infectious disease, travel medicine, and public health concluded that that hepatitis B vaccination should be universally recommended for adults and that this strategy is the most practical approach to control hepatitis B in adults. Similarly, in a round table discussion at an America's Health Insurance Plan (AHIP) meeting, stakeholders discussed the importance of increasing vaccination rates and reducing ethnic and racial disparities. These stakeholders also expressed willingness to invest in hepatitis B vaccination programs for adults at increased risk.

[70] Bridges et al. Vaccine. 2019
[71] Owiti et al. BMC Pub Hlth. 2015
[72] Zhao et al. JAANP. 2015
[73] Ma et al. J Im Min Hlth. 2007
[74] Schiff et al. J Appl Res. 2007.
2. Time for a bold advance to defeat hepatitis B | The Hill; https://www.ahip.org/wp-content/uploads/2016/04/Vaccine_Report_8.26.15-1.pdf; Harris et al. MMWR. 2016; https://www.nfid.org/wp-content/uploads/2019/08/cta-hep-b-at-risk-adults.pdf

The WG also found a national provider survey that assessed adult hepatitis B vaccination practices among 433 family medicine physicians and 420 internists in the US. In this survey, 68% of providers felt that patients were not willing to disclose high risk behaviors and nearly 45% of providers reported that they were feeling too pressed for time to routinely assess patients for risk factors. Nearly 65% of providers said that the lack of adequate reimbursement vaccination and up-front costs of purchasing the vaccine was not a barrier. The survey also showed that patient and provider concerns about vaccine safety was definitely not a barrier to vaccinate. The survey also addressed providers' perceived barriers on using standing orders given to nurses and medical assistants for identifying and vaccinating adults with risk factors. Around half the providers stated that nurses and medical assistants had questions about who should be immunized and around half felt that the assessment of risk factors required a higher level of medical knowledge than what some nurses and medical assistants had. Of the providers, 66% felt that nurses and medical assistants are too pressed for time to assess patients for risk factors.[75] The WG felt there was some uncertainty due to indirect evidence and the acceptability domain, with the members split 50/50 as "probably yes" and "yes" to the question regarding whether a universal strategy is acceptable to stakeholders.

Now moving to the domain of resource use. As a reminder, results from the sensitivity analyses from the economic evaluation were presented to ACIP during the February 2021 meeting. Two scenarios were modeled: 1) Sensitivity analysis 1: 50% vaccination coverage in general population; +20% additional coverage among people with risk factors; and 2) Sensitivity analysis 2: 70% vaccination coverage in general population; +60% additional coverage among people with risk factors. While there is not a specific source for the numerical value of these increased coverage assumptions, feedback received during the February ACIP meeting and during the Hepatitis Vaccine WG discussions indicates that additional vaccinations would be plausible. Comparing the base-case column and moving to Scenarios 1 and 2, as vaccination increases among people with greater risk, the intervention becomes more cost-effective. The WG noted somewhat balanced estimates between the 2-dose and 3-dose strategies. All models have uncertainties. The particular uncertainty of this model mainly hinges on the differences in adherence likelihood and cost between the 2-dose and 3-dose vaccines, as well variance of risk across age groups as Dr. Hall presented in February 2021.[76]

The findings from this analysis indicate that a universal adult hepatitis B vaccination strategy result in additional costs, but also additional QALYs compared to the current strategy. The purpose of this economic analysis was to show that regardless of which hepatitis B vaccine option was chosen for this particular question, hepatitis B vaccination provides a benefit to the US population. Dr. Hall's study results indicated the cost and health benefits are very similar for universal vaccination strategy that utilizes a 3-dose vaccination regimen and a strategy that utilizes a 2-dose vaccination regimen. Furthermore, results hold true across the range of vaccination coverage scenarios and are robust against the influence of any single model assumption or input. Vaccination coverage in the intervention strategies resulted in better health outcomes. The average QALYs gained, life years gained, number of acute hepatitis B infections averted, and number of hepatitis B related deaths averted all increased as vaccination coverage in the intervention strategy increased. The WG judgement was that the universal vaccination strategy is a reasonable and efficient allocation of resources.

[75] Daley et al. Am J Prev Med. 2009
[76] Hall et al. ACIP Feb 2021

For the domain of equity, the WG sought to answer the question regarding what the impact of a universal vaccine strategy would be on health equity. Racial disparities in hepatitis B infection rate showed slow improvement under the risk-based hepatitis B vaccination strategy. After 24 years of a risk-based policy first recommended in 1982, among non-Hispanic Blacks, hepatitis B infection rates did decline but remained over twice as high as among other racial ethnic populations.[77] Most new hepatitis B infections were among adults aged 19 years and older. The rates among Black Americans are up to 3 times those of other racial ethnic minority groups. Furthermore, data from the 2019 surveillance report also showed that hepatitis B infection rates have increased among non-Hispanic whites due to outbreaks among people aged 30-39 years and who use injection drugs.[78] After a universal hepatitis B vaccination strategy for children and adults was implemented, the rates of hepatitis B disease for children and adults in all ages did converge to a lower rate.[79]

There are some differences in hepatitis B vaccination coverage across race and ethnicity, which is reflected in the most recent 2018 NHIS survey. There is disproportionate coverage in white versus the other racial and ethnic minority groups. It should be recognized that risk factors assessed include socio-structural factors that may criminalize and stigmatize.[80] For example, in the ongoing opioid crisis,[81] stigma associated with drug use may keep people from reporting risk factors to the clinicians.[82] Healthcare providers may rely on self-reported vaccine history to determine need for vaccinations, but self-reported vaccination history does not predict immunity well.[83] A universal vaccination recommendation could eliminate the need for risk factor assessment prior to vaccination and reduce stigma among people who have been marginalized And at increased risk, and among immigrants with concerns about stigma associated with hepatitis B-related care.[84] The WG concluded that the impact of the universal vaccination strategy on health equity would be increased.

For the domain of feasibility, the WG sought to answer whether a universal vaccination strategy would be feasible to implement. Evidence supports the successfully implementing the current risk-based strategy can be challenging. One CDC-funded pilot study showed lower vaccine acceptance than anticipated and lower series completion rates.[85] Several studies noted that physicians administer hepatitis B vaccination to adults at increased risk at suboptimal rates.[86] In an urban HIV clinic, 30% of patients who were eligible were not offered the hepatitis B vaccine.[87] During a meeting sponsored by a vaccine manufacturer, experts suggested that standing orders and consistent recommendations from professional societies and government agencies may address some implementation obstacles.[88] A study on electronic provider reminders in California demonstrated an increase in the hepatitis B initiation rate among adults with diabetes by 70-fold compared to a control site.[89] The series completion improved by 20-fold, demonstrating that electronic provider reminders can be a good tool to achieve serious completion of hepatitis B vaccination.

[77] Wasley et al. MMWR. 2008
[78] Harris et al. MMWR. 2016; https://www.cdc.gov/hepatitis/statistics/2019surveillance/HepB.htm; Schiff et al. Journal of Applied Research. 2007
[79] https://www.cdc.gov/hepatitis/statistics/2019surveillance/HepB.htm
[80] Taylor J, et al. BMC Infect Dis. 2019
[81] Harris A, et al. MMWR. 2016
[82] Taylor J, et al. BMC Infect Dis. 2019
[83] Figgatt M, et al. Public Health Rep. 2020; Collier, MG et al. Vaccine. 2015; Topp, L et al. Drug Alcohol Rev. 2009
[84] Kim, MJ et al. Asia-Pacific J Onc Nurs. 2015; Mokaya j et al. Wellcome Open Research. 2018; Owiti, JA et al. BMJ Public Health. 2015
[85] Bridges et al. Vaccine. 2019
[86] Miller et al. Conference abstract. 2016; Bailey et al. IJID. 2008
[87] Bailey et al. IJID. 2008
[88] Schiff et al. J Appl Res. 2007
[89] Hechter et al. Vaccine. 2019

Another aspect brought about by ACIP during the February meeting was that opportunities to vaccinate in the older adult groups are being missed, given that they might be going into see their physicians more often. Among adults with no risk factors and one or more risk factors, lower hepatitis B vaccination coverage is seen among adults aged 50 years and older compared to those aged 19-49 years, which is likely due to the universal hepatitis B vaccine recommendation for children and adolescents.[90] National influenza vaccine coverage over time was higher in the 50 years and older age group, which suggests that vaccine coverage among older adults can be increased.[91] The biggest gain will be in creating access when adults are seeing their physicians.

Evidence supports that either a 2-dose or a 3-dose vaccine schedule is effective, but the 2-dose vaccine may be of higher value in the populations with certain risk factors[92] whereby the 2-dose vaccine could lead to higher series completion rates. In regard to insurance coverage, the ACA Act requires coverage of routinely recommended vaccines with no cost-sharing with some caveats. Finally, the Hepatitis Vaccine WG recognizes its mandate to primarily address the role of vaccination policy without rolling testing guidelines into a policy decision for an ACIP vote. Meanwhile, the Hepatitis Vaccine WG understands that hepatitis B testing guidelines, such as the universal testing approach, and practical considerations are concurrently being developed by a parallel process, with a goal to release new testing guidelines around the same time with robust clinical guidance to accompany that. The WG understands that the screening piece is important, but knows that they do not want screening and testing to be a barrier to access to vaccination. The WG concluded that the universal vaccination strategy is feasible to implement.

In terms of the EtR Framework, the WG concluded that the desirable consequences clearly outweigh the undesirable consequences in most settings. The draft Policy Option for ACIP consideration is that “All adults previously unvaccinated for hepatitis B should receive hepatitis B vaccinations.”

Key Discussion Points

- Following Dr. Bruxvoort’s presentation on the HepB-CpG post-marketing surveillance study:
    - It would be beneficial to have a sense of the percent of coverage across the sites of this population in terms of assessing who is at risk of hepatitis B and what the uptake is among high-risk individuals.
- Following Dr. Doshoni’s presentation on the EtR Framework for universal adult hepatitis B vaccination:
    - Some members found the EtR Framework to be extraordinarily optimistic and the benefits probably overemphasized, and had concerns about some of the data and interpretations. This decision would result in recommending vaccines for hundreds of millions of people, many of whom do not have any disease or risks of exposure. While it is likely to work, it would be very expensive. Perhaps the WG could break it down into age cohorts.

[90] Yue et al. Vaccine. 2018
[91] Flu Vaccination Coverage. United States. 2019–20 Influenza
[92] Bruxvoort et al. JAMA Netw Open. 2020; Rosenthal et al. Vaccine. 2020

- Many older adults are still sexually active, many are looking at new sexual partners, and some of them use IV drugs. While including them may or may not be cost-effective, it is critically important to prevent disease spread in this age group.
- It would be beneficial to hear data on other vaccines or other situations in which making a universal recommendation actually increased coverage among a risk group. Some members were uncomfortable without any evidence to suggest that the intended goal (e.g., universal hepatitis B vaccination to increase vaccination coverage among people in risk groups in a roundabout way because that is where disease is occurring) would be achieved with a universal strategy.
- Consider performing a more technical analysis of NNV.

ORTHOPOXVIRUSES VACCINES

Introduction

Dr. Pablo Sanchez (ACIP, WG Chair) reminded everyone that during the February 2021 ACIP meeting, the WG discussed background information, presented the 4 PICO questions that were drafted by the WG, and planned the consolidation of the previous ACIP recommendations into a single updated document about ACAM2000 and JYNNEOS vaccines in persons at risk for occupational exposure to orthopoxviruses. Since that time, the WG has convened several meetings during which they discussed and added an additional PICO question, set the GRADE tables and the EtR Framework, and drafted the wording for proposed recommendations. During this session, background information important to understanding GRADE and EtR was provided and the EtR Framework was presented. In terms of the anticipated timeline, the WG plans to review the clinical guidance and entertain a vote during the October 2021 ACIP meeting, with a subsequent *MMWR* publication anticipated in early 2022.

Background

Dr. Agam Rao (CDC/NCEZID) presented background information to interpret the GRADE tables and EtR framework about JYNNEOS®. The populations in the US who are currently at risk for orthopox infections are much smaller than previously such that by 1972, routine smallpox vaccinations for children ended in the US. Vaccinations to prevent smallpox have continued for some populations, such as members of the military, designated health care workers and response personnel, and laboratorians with occupational risk. However, the risk for orthopoxvirus infections other than smallpox exist. Monkeypox infections are re-emerging in parts of Africa, and there was an imported case into the US a few months ago. Vaccinia virus is increasingly used in research laboratories to study orthopoxviruses but also, as a functional vector for development of vaccines against unrelated agents.

It is difficult to specify the exact number of persons at risk, but it is certainly much smaller than for the pathogens that were discussed during the talks earlier in the day. The reason it is challenging to settle on a specific number is that some people are not vaccinated, such as those who are dealing with the less virulent orthopoxviruses. There is not very good surveillance on this issue. Even though CDC is the one to send out shipments of the vaccines, it is unclear how many people are vaccinated with a given shipment because these are multiuse vials. It is important to point out that members of the military are a critical component and make up the largest proportion of people who are vaccinated. Given that the US military rather than ACIP develops vaccine recommendations for military personnel, so the remainder of this presentation

did not take military personnel into consideration. However, the military may be able to adapt recommendations based on what is said about other groups.

The morbidity for the populations at risk is well-known. Inadvertent needlesticks and eye splashes have occurred among laboratorians, and several persons have been hospitalized for assessment for medical and surgical interventions. Nearly all of those have been unvaccinated people. Because of this known morbidity, there have been multiple CDC guidelines about vaccination for persons at occupational risk for orthopoxviruses over the last several decades (e.g., 2003, 2008, 2015). These have been focused on Dryvax, which is no longer available, and ACAM2000, which is a clonal derivative and is available currently. In 2019, JYNNEOS® joined ACAM2000 as an FDA-approved vaccine to prevent orthopoxvirus infections. That is the reason that this ACIP WG was formed. The WG's goals have been to: 1) develop recommendations for the newly licensed live, replication-deficient modified vaccinia virus vaccine, JYNNEOS®; and 2) merge all previous CDC recommendations about pre-exposure use of Dryvax/ACAM2000 so that these recommendations are consolidated with those for JYNNEOS®.

When the recommendations for Dryvax and ACAM2000 were made, there were two major considerations. The first pertained to which populations should be recommended to receive the vaccine and the second regarded what should be said about booster doses. The populations at high risk were determined to be select laboratorians who routinely work with orthopoxviruses, HCP, and response team members who could be at risk if there were a smallpox or monkeypox event. Populations whose contact with those viruses is limited. When it occurs, it is primarily through contaminated materials like dressings. These groups typically follow appropriate infection control measures and are at a much lower risk for inadvertent infection. These groups were offered vaccinations in previous ACIP recommendations due to the theoretical risk of exposure, but there were no firm recommendations.

When recommendations for booster doses were being considered, the factor that weighed the most into recommendations was the virulence of the orthopoxvirus. Since there would be serious implications to the affected individual and also to public health if infections from more virulent othropoxviruses, such as smallpox or monkeypox, occurred. For this reason, booster doses were recommended historically in ACIP recommendations much more frequently for persons working with the more virulent orthopoxviruses than for those at risk from the less virulent ones. Only those with continuous risk receive booster doses at specific intervals, such as the response teams who are vaccinated for preparedness purposes. The CDC guidance has been no booster doses until there is an event, at which time they would be vaccinated out-the-door and not at specific intervals before that.

With that background in mind, that the ACIP recommendations for ACAM2000 can be framed in terms of these considerations:

	ACAM2000
Populations recommended	Persons at occupational risk for orthopoxviruses (i.e., diagnostic laboratorians, healthcare response teams)
Populations offered	Persons who administer ACAM2000 or care for patients after vaccination with replication competent virus (e.g., dressing changes)
Populations for whom booster is recommended at specific intervals	Persons who are at continued or sustained risk for orthopoxviruses [Note: Response teams are not at continued risk and will receive boosters only at the time of a smallpox/monkeypox event]
Frequency of boosters: Those working with smallpox and monkeypox	Every 3 years (had previously been every year)
Frequency of boosters: Those working with less virulent orthopoxviruses	At least every 10 years

For JYNNEOS®, the WG thought about the considerations that went into the ACAM2000 recommendations. ACAM2000 is clonal derivative of Dryvax and there are extensive data about Dryvax that helped inform ACAM2000 recommendations. However, JYNNEOS® is different from ACAM2000 and the recommendations for JYNNEOS® will need to rely on data specifically about JYNNEOS®. The WG cannot utilize a lot of the data from ACAM2000 to make decisions. When JYNNEOS® was introduced into the above table, the WG felt that the populations the JYNNEOS® recommendations probably should address the same populations and provide the same recommendations. That is how the WG came to the first two PICO questions:

PICO Questions 1 & 2

1. Should JYNNEOS® be recommended for research and clinical laboratory personnel performing diagnostic testing for orthopoxviruses and for designated response teams at risk for occupational exposure to orthopoxviruses?

2. Should JYNNEOS® be recommended, for healthcare personnel who administer ACAM2000 or care for patients vaccinated with replicating orthopoxviruses (e.g., clinical trials).

Moving to the second half of the ACAM2000 table, the WG determined that regarding booster doses, similar to ACAM2000 only persons with continued or sustained risk for orthopoxviruses should receive boosters at specific time intervals. The WG felt that an increased frequency for more virulent orthopoxviruses still made sense, and that the frequency for those working with smallpox and monkeypox for that reason should be more frequent than for those working with less virulent pathogens. The preferred time interval was 2 years. The WG felt that the frequency of boosters for those working with the less virulent pathogens should be specifically delineated at a specific time point. If there is simply clinical guidance that a booster needs to be given, the concern was that this would fall off people's radar and they would not know to get a booster. For that reason, 10 years was somewhat arbitrarily chosen. That is how the WG came to the third and fourth PICO questions:

PICO Questions 3 & 4

3. Should persons who are at continued risk for occupational exposure to more virulent orthopoxviruses such as variola virus or monkeypox virus receive a booster dose of JYNNEOS® every 2 years after the primary JYNNEOS® series?

4. Should persons who are at continued risk for occupational exposure to replication-competent orthopoxviruses like vaccinia virus or cowpox virus receive a booster dose of JYNNEOS® at least every 10 years after the primary JYNNEOS® series?

There are some important distinctions between JYNNEOS® and ACAM2000 that explain why the WG decided to develop an additional PICO question since the February 2021 ACIP meeting. These distinctions also explain some of the EtR answers that the WG came up with. While effectiveness is believed to be about the same for these two vaccines, nearly everything else is different. To highlight some of those differences, JYNNEOS® is a replication-deficient modified vaccinia Ankara, whereas ACAM2000 is replication-competent vaccinia virus. Because JYNNEOS® is replication-deficient, there is not a concern for unchecked replication or the SAEs from that and auto-inoculation and spread to others. Myocarditis is known to occur at a rate of 5.7 per 1,000 primary vaccinees for ACAM2000 according to the package insert, while the rate for JYNNEOS® is believed to be lower. The two vaccines also are administered differently. There is a special way that the single dose of ACAM2000 is administered that involves a bifurcated needle and multiple puncture wounds, whereas JYNNEOS® is administered subcutaneously in 2 doses about 28 days apart.
A number of AEs can occur after live replication-competent orthopoxvirus vaccines. Following ACAM2000, a “take” occurs that is infectious. Improper handling of dressings it can result in spread of vaccinia to oneself to other parts of the body. For JYNNEOS® there is no “take.” Inadvertent inoculation to others such as family members can occur with ACAM2000. Other potential AEs with ACAM2000 include postvaccinal encephalitis and encephalomyelitis, eczema vaccinatum, generalized vaccinia, erythema multiforme major (Stevens-Johnson syndrome), and fetal vaccinia and fetal death.

The ACAM2000 package insert acknowledges that there are many warnings and precautions. The following is taken directly from the wording on the package insert:[93]

- Contraindicated for individuals with severe immunodeficiency who are not expected to benefit from the vaccine

- Some individuals experience serious adverse events
  - Risk for serious adverse events is increased in the following populations: Pregnant persons, infants <12 months of age, persons treated with topical steroids for eye disease, and those with a history of cardiac disease or presence of eczema and other skin conditions

  - Serious adverse events may result in severe disability, permanent neurological sequelae and/or death

- Contact spread can lead to inadvertent inoculation and infection to household members and close contacts

[93] https://www.fda.gov/media/75792/download

The JYNNEOS® package insert warnings and precautions follow:[94]

- Immunocompromised persons may have a diminished immune response to the vaccine
- Insufficient data to inform JYNNEOS® vaccine-associated risks in pregnancy and during lactation

Given all of this, there have been many requests to CDC for JYNNEOS®. Like ACAM2000, JYNNEOS® would be available from the US government stockpiles and there would be no vaccine cost to recipients because of that. This factors into the EtR Framework answers. JYNNEOS® has a familiar administration technique (i.e., subcutaneous rather than multiple punctures with bifurcated needle). Because JYNNEOS® involves a non-replicating virus, there is a lower risk for SAEs, there is concern for inadvertent infection or spread to others, and there are fewer relative contraindications. In addition to requests for JYNNEOS® for those who have not been vaccinated with ACAM2000, there have been requests for boosters for those who were vaccinated with ACAM2000 and are interested in getting their booster doses with JYNNEOS® going forward. Because of all of those requests, the WG developed a fifth PICO question:

PICO Question #5

5. Should persons who are at continued risk for occupational exposure to orthopoxviruses, and who received an ACAM2000 primary vaccination, receive a booster dose of JYNNEOS® as an option to a booster dose of ACAM2000?

The reverse of switching from JYNNEOS® to ACAM2000 is not a PICO question, given that the WG expects that this would be a rare request. Clinical guidance will be discussed during the ACIP meeting in October 2021.

EtR Framework

Dr. Rao (CDC/NCEZID) next presented the EtR Framework. The WG conducted a very thorough GRADE assessment and those evidence tables were shared with the ACIP through the ShareFile® and also be posted online at a later date. In addition, much of the GRADE information was included in this presentation in the extra slides section. Given that the GRADE information was shared with ACIP members beforehand, Dr. Rao went over a lot of the GRADE information relatively quickly. However, the WG made every effort to ensure that a lot of footnotes were included to explain why elements were downgraded. As a reminder, the WG developed 5 PICO questions. The first 2 are related to primary vaccination with JYNNEOS® in at-risk populations, the third and fourth pertain to the frequency of the booster dose in persons with continued risk, and the fifth regards a change from a booster with ACAM2000 to a booster with JYNNEOS®.

Beginning with EtR Questions 1 and 2 regarding primary vaccination, it is known that orthopoxvirus infections cause morbidity and mortality. There are several populations at occupational risk. The ones to whom the ACIP recommendations would apply include: 1) research and clinical laboratory personnel performing diagnostic testing for orthopoxviruses; 2) designated response teams approved by public health authorities; and 3) select healthcare personnel who might choose to be vaccinated even if their risk is low, such as healthcare

[94] https://www.fda.gov/media/131078/download

personnel who administer ACAM2000 or care for patients after vaccination with replication-competent orthopoxviruses (e.g., persons enrolled in clinical trials). ACAM2000 is currently recommended by the ACIP, which would not be changing. There are benefits to having more than one recommended vaccine available. Vaccinations are effective. Breakthrough infection despite adherence to ACIP recommendations has been reported only once.[95]

Policy Question #1 is, "Should JYNNEOS® be recommended for research and clinical laboratory personnel performing diagnostic testing for orthopoxviruses and for designated response teams at risk for occupational exposure to orthopoxviruses?" The footnotes explain more about what is meant by these populations. The intervention is vaccination with JYNNEOS® and the comparison is ACAM2000 because it is currently recommended for these population groups. When this question was first shown to ACIP, 4 outcomes were thought to be critical: prevention of disease, severity of disease, SAEs, and myo-/peri-carditis. On further review, the WG felt that severity of disease is important rather than critical. Though all of the GRADE tables were completed, including for severity of disease, those are posted in the ShareDrive® presentation by Dr. Whitehill and was not included in this presentation.

Moving to the first domain of benefits and harms, the WG concluded that the desirable anticipated effects are small in terms of benefits. This is because the evidence table for Outcome A, prevention of disease, suggests that there is a small benefit of JYNNEOS® compared to ACAM2000. FDA also found JYNNEOS® to be non-inferior to ACAM2000 for immunogenicity. JYNNEOS® is a non-replicating virus, so there is no potential to spread to others. Looking at the GRADE Evidence Table for this question, GMTs and seroconversion rates are two different indirect measures of prevention of disease. The mean difference in titer units between those who received JYNNEOS® versus those who received a live, replicating vaccinia vaccine (ACAM2000 or Dryvax) was 1.62 titer units higher, with a 95% confidence interval from 1.32 to 1.99 titer units higher. Those who received JYNNEOS® were 1.02 times more likely to seroconvert versus those who received Dryvax or ACAM2000, and the 95 percent confidence interval ranged from 0.99 to 1.05. It was these values that led to the WG to determine that there seems to be a small benefit of JYNNEOS® compared to ACAM2000.

For harms, the WG determined the undesirable anticipated effects to be minimal based on the GRADE Evidence Tables. Again, JYNNEOS® is a non-replicating vaccinia virus, so there are fewer relative contraindications for JYNNEOS® compared to ACAM2000. The GRADE tables evaluating SAEs and myopericarditis were used to answer this question. As a reminder, the WG included only RCTs that compared JYNNEOS® to ACAM2000. Looking at the Evidence Table, suggested SAEs were less likely with JYNNEOS®. However, too few subjects enrolled to assess for this rare event. Observational data were included because the WG was not satisfied with the RCTs and the few subjects enrolled. The WG was reassured to find that the observational data also showed fewer SAEs and myopericarditis, and that there were many more people enrolled in those studies.

For the benefit/harm ratio, the WG determined that because the benefits were small but the harms were minimal, the desirable effects outweigh the undesirable effects and intervention is favored. Regarding the certainty of the evidence, the certainty level was moderate for prevention of disease and was low for SAEs and myopericarditis. Prevention of disease was the only critical outcome that assessed effectiveness of the intervention. After considering the GMT and seroconversion rate data together, the WG had moderate certainty, Type 2, that there

[95] Hsu CH et al. Laboratory-acquired vaccinia virus infection in a recently immunized person--Massachusetts, 2013. MMWR Morb Mortal Wkly Rep. 2015 May 1;64(16):435-8.

would be a small increase in disease prevention provided by JYNNEOS® compared to ACAM2000. The WG estimated that there are fewer SAEs and myopericarditis cases after a JYNNEOS® primary series compared to ACAM2000 vaccination, but had low certainty in this estimate, Type 3. RCT data were downgraded due to the sample size being small and therefore not meeting the optimal size to assess these outcomes suggesting fragility of the estimate. Also, the 95% confidence interval includes the potential for meaningful harm. Observational data contributed data about a larger sample size but were downgraded from Level 3 to Level 4 because of concerns for selection bias and data were indirect comparison of naively pooled single-arm studies compared to a historical control.

For the values domain, the WG thought that the target population probably feels that that the desirable effects are large relative to the undesirable effects. CDC conducted a survey in 2015 of 275 health care workers in the Democratic Republic of Congo (DRC) to evaluate the target populations' values and found that 99% of those people had reported having seen a monkeypox case there. Most of them had said that it was in their line of duty. Greater than 75% of those respondents were not interested in ACAM2000 after it was explained to them. Many of them cited AEs, the potential for autoinoculation, and not wanting a vaccine scar as their rationale. When JYNNEOS® was explained to these individuals, 98% were interested in JYNNEOS®. While this was an unpublished survey performed in another country, the WG thought that these data were somewhat telling about what the target population in the US might feel in general. The target population has made multiple requests about when this vaccine might be available to them. Another question under the values domain regards whether there is important uncertainty about or variability in how much people value the main outcomes. No research was identified, but stakeholders are expected to value the immunity. A 2-dose JYNNEOS® vaccine was found to be non-inferior to ACAM2000 for immunogenicity by FDA. Only 1 dose of vaccination is needed for ACAM2000. Given that 2 doses of JYNNEOS® are administered over 28 days, it likely will take longer for someone to have appropriate immunity after the 2-dose JYNNEOS® series. However, the WG still felt that the answer was probably there is no important uncertainty or variability.

For the acceptability domain, the WG sought to answer whether the intervention is acceptable to stakeholders. Even though any provider can give ACAM2000 by using the bifurcated needle, many people do not want to. Therefore, ease of finding a provider has been difficult for some vaccinees. For instance, it can be difficult for someone to get on the schedule for ACAM2000 at a military facility when they work outside in a civilian arena. This issue would be removed from the equation and acceptability would be higher because of the ease in finding a provider, no absences from work to travel to a provider who may give the vaccine, and many more providers would be comfortable administering a subcutaneous injection. JYNNEOS® is a non-replicating virus vaccine, so there is no risk of transmission to others, particularly to immunocompromised persons and those with eczema. In addition, AEs are expected to be rarer with JYNNEOS®. For those reasons, the WG felt that the intervention would be acceptable to key stakeholders.

For the resource use domain, the WG felt that JYNNEOS® would be a reasonable and efficient allocation of resources. Like ACAM2000, JYNNEOS® would be provided from HHS's Strategic National Stockpile (SNS) free of cost to the patient. Even in cases where an employer might not cover the cost of clinic appointments, there may actually be similar clinic costs associated with JYNNEOS® and ACAM2000 even though JYNNEOS® is a 2-dose series. This is because in some clinics, patients return for in-person clinic appointments on multiple days after ACAM2000 administration. Certainly on Day 7, but sometimes on Day 3, and many times afterward for dressing changes, to have the "take" site assessed, and to ask questions about whether the patient is experiencing any symptoms that could be consistent with myopericarditis. Ultimately,

the number of visits that a person receiving JYNNEOS® would have to pay for on their own if their employer is not paying for it would be the same or possibly fewer than with ACAM2000.

Moving to the domain of equity, the WG thought that equity would be increased because for some vaccine recipients, the cost of clinic appointments would be absorbed by the provider and there would be no change in those costs. There would be fewer costs and challenges associated with finding a provider and traveling to see that provider. The WG heard anecdotally from individuals who work in laboratories with nonvirulent orthopoxviruses that the cost is sometimes absorbed by them themselves and that they have to get a hotel and pay the cost of the hotel as well. Not having to deal with all of that would actually increase equity.

In terms of the final domain of feasibility, no research was identified. The subject matter experts (SMEs) on the WG felt that the same number or possibly fewer clinic visits would be needed, but also the amount of providers who could/would administer JYNNEOS® vaccine would be much larger than with ACAM2000 because most providers are comfortable administering a subcutaneous injection. Therefore, the WG thought that the intervention would be feasible to implement. One issue to consider with JYNNEOS® is that once thawed or refrigerated, it is good for only 12 hours, whereas ACAM2000 is good for 18 months. CDC is evaluating whether to distribute JYNNEOS® at -20^{0}C to bypass this issue. The product sponsor is also assessing more lenient cold-chain requirements. That is the only aspect that potentially could impair feasibility, but the WG still felt that JYNNEOS® would be feasible to implement.

To summarize Policy Question #1, part of the reason the overall certainty of the evidence was low is because the WG had to use ACAM2000 as the comparator. A lot of the trials were not set up with ACAM2000 as one of the arms. Observational data automatically begin as Type 3, which is low. That explains why the certainty level for a lot of these questions was low. In addition, there were not always a lot of people enrolled in the RCTs when ACAM2000 was used as a comparator. This left the WG with a balance of consequences in which the desirable consequences probably outweigh the undesirable consequences in most settings. With all of this in mind, the WG drafted the following proposed recommendation:

Proposed Recommendation #1
The ACIP recommends JYNNEOS® as an alternative to ACAM2000 for research and clinical laboratory personnel performing diagnostic testing for Orthopoxviruses* and for designated response teams# at risk for occupational exposure to Orthopoxviruses.

*Clinical laboratory personnel who perform routine chemistry, hematology, and urinalysis testing, including for suspect patients with Orthopoxvirus infections, are not included in this recommendation as their risk for exposure is very low #Public health authorities, at their own discretion, may approve a cohort of healthcare and/or public health personnel to receive primary vaccination against Orthopoxviruses for preparedness purposes (i.e., in the event of a smallpox or monkeypox outbreak)

Moving on to PICO #2, the answers to the EtR questions were mostly identical to that for PICO #1. The population is healthcare personnel who administer ACAM2000 or care for patients after vaccination with replication competent orthopoxviruses. As a reminder, the entire population may not benefit from being vaccinated, but individual members of the population may be interested in being vaccinated because of personal preferences and because the ACIP recommendations indicate that ACAM2000 can be offered. There is clearly an interest from some people. The 3 outcomes included in the GRADE Table for this question include: prevention of disease, SAEs, and myo-/peri-carditis.

For the values domain, the WG sought to answer whether the target population feels that the desirable effects are large relative to the undesirable effects. While no research data were identified to evaluate this, it is believed that some members of the population would be interested in vaccination and would like the option even if it is not indicated for the entire population. In the past when patients were admitted with AEs from replicating orthopoxvirus vaccines, HCP were anxious and appreciated the opportunity. One of the WG specifically remembered this happening. Allowing for these persons to be vaccinated is consistent with the ACIP recommendations for ACAM2000. The WG felt that probably yes the target population would feel that the desirable effects are large relative to the undesirable effects. In terms of the second question in this domain regarding whether there is important uncertainty about or variability in how much people value the main outcomes, many persons within this population may opt to not be vaccinated due to the low risk. Others may wish to be vaccinated due to the factors previously discussed. There is some variability in how much people value this recommendation, potentially indicating that it could be recommended by shared clinical decision-making. For that reason, the WG felt that possibly important uncertainty or variability existed. Everything else in this EtR is identical to what was described for Policy Question #1.

Overall, the WG felt that the desirable consequences probably outweigh the undesirable consequences in most settings and proposed the following draft recommendation language:

Proposed Recommendation #2
The ACIP recommends JYNNEOS®, based on shared clinical decision-making, as an alternative to ACAM2000 for healthcare personnel who administer ACAM2000 or care for patients vaccinated with replication competent orthopoxviruses.*

* For example, patients enrolled in clinical trials

Now moving on the EtRs 3 and 4, which regard the frequency of the booster doses with JYNNEOS after a JYNNEOS® primary series. The problem is that there are virulent orthopoxviruses. For instance, there are increasing numbers of laboratories working with monkeypox virus (e.g., primate laboratories). Work with these typically require personal protective equipment (PPE) and other safeguards. Ensuring long-term immunogenicity through a booster provides an additional level of protection if unintentional breaches occur. In terms of Less virulent orthopoxviruses (e.g., vaccinia virus, cowpox virus, and Alaskapox virus), morbidity may be prevented. For example, a mild case of vaccinia infection occurred in a laboratorian in the US who had not received a booster greater than 10 years after his primary ACAM2000 vaccination. It is possible that this could potentially have been prevented if the individual had received a booster per the ACIP recommendations for every 10 years. The stakes are higher to individual and public health if virulent orthopoxvirus infections are acquired. For that reason, boosters historically have been given more frequently for those working with virulent orthopoxviruses than those working with the less virulent orthopoxviruses.

With that in mind, Policy Question #3 is, “Should persons who are at continued risk for occupational exposure to more virulent orthopoxviruses such as variola virus or monkeypox virus receive a booster dose of JYNNEOS® every 2 years after the primary JYNNEOS® series?”

For the first domain regarding how substantial the desirable anticipated effects would be, the WG felt that there is a small increase in disease prevention after a JYNNEOS® based on the Evidence Tables. After the JYNNEOS® primary series, the booster’s recommended time intervals may provide reassurance of continued protection from inadvertent exposures because smallpox and monkeypox are highly virulent. The observational studies were specific to the 2-

year time point. For this reason, the WG proposed 2 years as the most conservative time point at which JYNNEOS® boosters might be recommended for those interacting with the most virulent orthopoxviruses where the effect of the booster is most important. The footnotes in all of the Evidence Tables explain the WG's reasoning.

For harms, there were no SAEs or myopericarditis cases observed among those persons who received a JYNNEOS® booster dose 2 years after JYNNEOS® primary series. AEs are expected to be minimal because no harmful events were observed. The effect estimate for the randomized controlled trials and observational data were not estimable because there were no recorded events of vaccine-related SAEs after the booster. The denominators were too small to have identified SAEs, including in the observational studies. There were no cases, but that is one of the reasons this ended up very low certainty, Type 4. There also were no cases of myopericarditis, but the number of enrolled subjects was extremely low for both arms. The effect estimate for the RCT was not estimable because there were no recorded events of myopericarditis, and there were no observational data. It was not possible to estimate the effect of JYNNEOS® plus a booster compared to the JYNNEOS® primary series based on the data.

In terms of the benefit/harm ratio, the WG felt that the desirable effects outweigh the undesirable effects and that it favors the intervention. The benefits are small, but the harms are minimal. The desirable effects therefore outweigh the undesirable effects, and the intervention is favored. The certainty of evidence for the benefits and harms outcomes were all very low, Type 4. Again, the GRADE Evidence Table explain in detail why that is the case. Briefly, RCT data were downgraded to very low certainty due to concerns for risk of bias, indirectness, and imprecision. Observational data were downgraded to very low for risk of bias because it was observational data, for inconsistency because there was only one study with intervention data, and imprecision due to the small sample size for the intervention. RCT data for SAEs and myo-/pericarditis were downgraded to very low for multiple reasons including indirectness for the 2-year time point and imprecision because the study population was too small to identify rare events like these. Observational data for the 2-year time point existed to assess SAEs, but the certainty level was downgraded from low certainty to very low certainty because of risk of bias, indirectness, and imprecision.

No research was available pertaining to the target populations' sentiment. However, a booster dose is expected to be interpreted as having large desirable effects relative to undesirable effects, particularly when someone is working with highly virulent pathogens. The desirable effect is protection from inadvertently acquiring these pathogens and there were no undesirable effects. The WG felt that probably yes, the target population would feel that the desirable effects are large relative to the undesirable effects. In terms of whether there is important uncertainty about or variability in how much people value the main outcomes, stakeholders, vaccinees, and employers are expected to value persistent immunity. Employers of persons who work with smallpox currently mandate booster doses and diligently enforce compliance. Therefore, the WG thought that probably there would be no important uncertainty or variability.

For acceptability of the intervention, there are data (albeit limited) to indicate boostability 2 years after the primary series. This is 1 year sooner than the booster frequency for ACAM2000, but it is expected to be acceptable to stakeholders. ACAM2000 booster doses were initially recommended annually. As more data became available, that was pushed back to every 3 years. Clinicians are more willing to administer subcutaneous injections and identifying a provider to administer JYNNEOS® will not be difficult. All of this led to the WG feeling that the intervention would be acceptable to key stakeholders.

In terms of resource use, the WG determined that JYNNEOS® would be a reasonable and efficient allocation of resources JYNNEOS® is provided free of cost from the SNS. For most people, employers will pay the cost of clinic appointments. Those whose employers will not pay these costs are accustomed to booster doses being needed. Because many more clinicians would be willing to administer it, it probably would not be too difficult to find a clinic.

The WG felt that equity probably would not be impacted because many employers will pay the cost of the clinic appointment. Some may not, but because JYNNEOS® is more accessible, the cost would not involve a hotel and travel costs and there are no other costs that are expected for the vaccine.

Although no research was identified for feasibility, the WG felt that JYNNEOS® probably would be feasible to implement. It may take some effort to plan for booster doses, but since nearly every provider would be willing to administer a subcutaneous vaccine, scheduling can be with a wide variety of providers, which likely makes it feasible. As mentioned earlier, there is this issue with the thawed JYNNEOS® product being good for a shorter amount of time. This obviously is important for non-emergency situations when it is not clear when the vaccine might be utilized. Again, CDC is working to determine whether it can be distributed -20^{0}C and the product sponsor is assessing more lenient cold-chain requirements.

In summary, the final balance of consequences by the WG was that the desirable consequences probably outweigh the undesirable consequences in most settings and proposed the following recommendation language:

Proposed Recommendation #3
The ACIP recommends persons who are at continued risk* for occupational exposure to more virulent orthopoxviruses like variola virus or monkeypox receive booster doses of JYNNEOS® every 2 years after the primary JYNNEOS® series.

*Designated public health and healthcare worker response teams approved by public health authorities are not at “continued risk” because they are vaccinated for the purposes of preparedness

Moving to PICO #4, the Policy Question is, “Should persons who are at continued risk for occupational exposure to less virulent replication-competent orthopoxviruses like vaccinia virus or cowpox virus receive a booster dose of JYNNEOS® at least every 10 years after the primary JYNNEOS® series?” There are no data beyond the 2-year time point as shown in the previous GRADE table for boostability. The WG felt strongly that a booster should be given. However, they were concerned that if there is not a specific recommendation and guidance is simply given, boosters will be forgotten and not given to persons who are working with less virulent pathogens. The WG went back-and-forth on what interval would make sense, given that there are no data specifically about this 10-year time point. Ultimately, the WG felt that 10 years is aligned with what is recommended for ACAM2000, realizing that this was somewhat arbitrarily chosen.

All of the information from the GRADE Evidence Tables for the benefits and harms domain for Policy Question #4 are the same as for Policy Question #3, except that for observational data, indirectness was deemed “very serious” instead of “serious” because there were no data about a booster at 10 years. The questions for all of the other domains for Policy Question #4 were the same as for Policy Question #3. The only difference was that for reasonable and efficient allocation of resources, the WG felt the cost of clinic visits would likely be acceptable even though this population works with less virulent pathogens. In terms of the balance of

consequences, the WG felt the desirable consequences probably outweigh undesirable consequences in most settings and proposed the following recommendation language:

Proposed Recommendation #4
The ACIP recommends persons who are at continued risk* for occupational exposure to replication competent orthopoxviruses like vaccinia or cowpox receive booster doses of JYNNEOS® after the primary JYNNEOS® series.

*Continued risk refers to persistent risk due to occupational work performed

Moving on the EtR #5. The problem here is that health authorities and the JYNNEOS® sponsor, are routinely being asked when this vaccine will be available. Some laboratory directors have indicated that many of those who received ACAM2000 boosters would like to change to JYNNEOS® if the ACIP recommendations explicitly allow for this. This is in addition to all of the other reasons discussed that this likely would be preferable (e.g., ease of identifying a clinician who can administer it, no risk for infection spread to others, no dressings to manage, fewer relative contraindications). There also are the unpublished data from the DRC indicating that JYNNEOS® is preferred to ACAM2000. This led the WG to draft PICO #5 with the Policy Question, "Should persons who are at continued risk for occupational exposure to orthopoxviruses, and who received an ACAM2000 primary vaccination, receive a booster dose of JYNNEOS® as an option to a booster dose of ACAM2000?" The population is persons who are at risk for occupational exposure to orthopoxviruses. The intervention is booster with JYNNEOS® and the comparison is booster with ACAM2000. The same 3 outcomes of interest were included (e.g., prevention of disease, SAEs, myo-/pericarditis).

In terms of benefits and how substantial the desirable anticipated effects are, only observational data are available. There were no available comparison data so it is unknown, from the Evidence Table, how substantial the desirable anticipated effects are. For that reason, the WG felt the answer is that it is unknown how substantial the desirable anticipated effects might be.

Moving to harms and how substantial the undesirable anticipated effects are, no SAEs or myo- / pericarditis cases were identified from the Evidence Table. The WG estimated that there were fewer SAEs after a JYNNEOS® booster versus an ACAM2000 booster in people previously vaccinated with ACAM2000. The effect was not estimable for myopericarditis, but no cases were identified in either arm. The GRADE Evidence Tables are indicating that there are minimal undesirable anticipated effects.

Regarding the benefit/harm ratio, it is unknown whether there are benefits to administering JYNNEOS® boosters compared to ACAM2000 boosters. Therefore, the WG settled on unclear for an answer about whether the desirable effects outweigh the undesirable effects. There were no identified harms and there is no reason to suspect that there would be harm from a JYNNEOS® booster, but the answer still would be unclear.

The certainty was very low for all of the outcomes. The overall certainty was very low for benefits and harms because only observational data were available to assess this outcome. These data were downgraded from low to very low due for risk of bias due to lack of comparison data, indirectness because seroconversion rate is an indirect measure of prevention, and imprecision because sample size was small and without a comparison. Regarding the target population' sentiments, target populations have made multiple requests for this vaccine. There are unpublished data from the DRC indicating a strong interest. Therefore, the WG felt that the desirable effects are large relative to the undesirable effects.

In terms of whether there is important uncertainty about or variability in how much people value the main outcomes, no research was identified. However, it is known anecdotally that some laboratory directors anticipate many of their staff changing to JYNNEOS® boosters if the ACIP explicitly indicates that it is acceptable. For that reason, the WG said that there is probably no important uncertainty or variability. The WG determined the intervention to be acceptable to key stakeholders due to the ease of finding a provider to administer the vaccine, no risk of transmission to others, no absences from work to travel to get the vaccine or self-costs associated with getting it, and fewer relative contraindications.

The WG thought that the intervention would be a reasonable and efficient allocation of resources because it would be provided by the SNS free to patients. If the employer does not absorb clinic costs, these may be absorbed by the vaccinee; however, about the same number of visits (or fewer) may be needed for JYNNEOS® as after ACAM2000 booster doses.

The WG felt that equity probably would be increased for those whose employers do not absorb clinic visits because there would be no costs associated with traveling to a provider who is willing to administer ACAM2000 using a bifurcated needle, and there would be increased accessibility to the vaccine because more providers are willing to give JYNNEOS®. In addition, the WG felt that the intervention would be feasible to implement. Again, it is estimated that the same number of clinic visits would be needed and that more providers would be able to provide the JYNNEOS® vaccine booster than ACAM2000. Though once thawed/refrigerated JYNNEOS® is good for only 12 hours, CDC and the sponsor are seeking potential solutions to address this.

In summary of the responses to the domains for PICO #5, the WG felt that the desirable consequences probably outweigh undesirable consequences in most settings and proposed the following recommendation language:

Proposed Recommendation #5
The ACIP recommends persons who are at continued risk* for occupational exposure to orthopoxviruses, and who received an ACAM2000 primary vaccination, receive a booster dose of JYNNEOS® as an option to a booster dose of ACAM2000.

*Public health and healthcare worker response teams approved by public health authorities for the purposes of preparedness are not considered to be at “continued risk”

Key Discussion Points

- Use of the word “contraindications” with regard to the new vaccine is confusing, given that it is a nonreplicating vaccine and should not have any contraindications. Contraindications usually imply risk of harm. Not responding is immune suppressed rather than a contraindication:
    - Dr. Rao indicated this was supposed convey that people with immunosuppression are not going to amount a response, which is probably no different from a lot of vaccines. It would not be a contraindication because it would not be harmful to give to the patient. She will change this.

- Clarify the language for pregnancy and breastfeeding for this vaccine. It probably should be a precaution not contraindication, which is what ACIP typically states when there are no data:

    - The WG will look into this further. The plan is to address populations like pregnant persons and lactating persons who are breastfeeding through the clinical guidance. The package insert for JYNNEOS® specifically says that there are no data in the Warnings and Precautions section.
    - The package insert indicates that there are some favorable animal data for JYNNEOS®.
    - Dr. Fink (FDA) explained that from a regulatory standpoint, when FDA labels use in pregnancy and in lactating individuals, they are required by regulation to list or describe data uncertainties for each of those populations. For JYNNEOS®, as was pointed out correctly, there is no warning or precaution related to use in either pregnancy or lactating individuals.
    - As noted earlier, the WG intends to present clinical guidance during the October 2021 ACIP meeting.

CERTIFICATION

Upon reviewing the foregoing version of the September 29, 2021 ACIP meeting minutes, Dr. Grace Lee, ACIP Chair, certified that to the best of her knowledge, they are accurate and complete. Her original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

ACIP MEMBERSHIP ROSTER

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

EXECUTIVE SECRETARY
COHN, Amanda, MD
Senior Advisor for Vaccines
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, GA

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

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

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

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

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

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

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

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

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

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

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

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

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

EX OFFICIO MEMBERS

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

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

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

Indian Health Service (IHS)
WEISER, Thomas, MD, MPH
Medical Epidemiologist
Portland Area Indian Health Service
Portland, OR

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

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

LIAISON REPRESENTATIVES

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

American Pharmacists Association (APhA)
FOSTER, Stephan L, PharmD CAPT
(Ret) USPHS
Professor, College of Pharmacy
University of Tennessee Health Sciences Center
Memphis, TN

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

Association for Prevention Teaching and Research (APTR)
McKINNEY, W Paul, MD
Professor and Associate Dean
University of Louisville School of Public Health and Information Sciences
Louisville, KY

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

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

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

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

Canadian National Advisory Committee on Immunization (NACI)
QUACH, Caroline, MD, MSc
Pediatric Infectious Disease Specialist and Medical Microbiologist
Medical Lead, Infection Prevention and Control Unit
Medical Co-director – Laboratory Medicine, Optilab
Montreal-CHUM
Montreal, Québec, Canada

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

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

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

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

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

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

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

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

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

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

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

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

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

ACRONYMS USED IN THE DOCUMENT

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ABCs	Active Bacterial Core Surveillance
ACA	Affordable Care Act
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
AE	Adverse Event
AHIP	America's Health Insurance Plans
AIM	Association of Immunization Managers
AIRA	American Immunization Registry Association
AJPM	American Journal of Preventive Medicine
AMA	American Medical Association
AMI	Acute Myocardial Infarction
AOA	American Osteopathic Association
APhA	American Pharmacists Association
APRN	Advanced Practice Registered Nurse
ASTHO	Association of State and Territorial Health Officers
BLA	Biologics License Application
CDC	Centers for Disease Control and Prevention
CER	Cost-Effectiveness Ratio
CMC	Chronic Medical Condition
CMI	Cell-Mediated Immunity
CMS	Center for Medicare and Medicaid Services
CNS	Central Nervous System
COI	Conflict of Interest
CpG-C	Cytosine-Phosphate-Guanine Class C
CSTE	Council of State and Territorial Epidemiologists
DFO	Designated Federal Official
DoD	Department of Defense
DRC	Democratic Republic of Congo
DSMB	Data Safety Monitoring Board
DSTDP	Division of STD Prevention
DVA	Department of Veterans Affairs
DVD	Division of Viral Diseases
ED	Emergency Department
EHR	Electronic Health Record
EIS	Epidemic Intelligence Service
EMA	European Medicines Agency
EMR	Electronic Medical Record
EMTs	Emergency Medical Technicians
ET	Eastern Time
EtR	Evidence to Recommendation
FDA	Food and Drug Administration
FP	Family Physician

GBS	Guillain-Barré Syndrome
GI	Gastrointestinal
GIM	General Internist
GMR	Geometric Mean Ratios
GMT	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HCP	Healthcare Personnel / Providers
HCW	Healthcare Workers
HepB	Hepatitis B
HHS	(Department of) Health and Human Services
HIV	Human Immunodeficiency Virus
HM	Hematologic Malignancies
HRSA	Health Resources and Services Administration
HSCT	Hematopoietic Stem Cell Transplant
HZ	Herpes Zoster
IBD	Inflammatory Bowel Disease
ICD	International Classification of Diseases
ICD-10-CM	International Classification of Diseases 10 Clinical Modification
ICER	Incremental Cost-Effectiveness Ratio
IDSA	Infectious Disease Society of America
IDU	Injection Drug Use
IHS	Indian Health Service
IIS	Immunization Information System
IMD	Immune-Mediated Disease
IPD	Invasive Pneumococcal Disease
ISD	Immunization Services Division
ISO	Immunization Safety Office
JHU	Johns Hopkins University
KAP	Knowledge, Attitudes, and Practices
KPSC	Kaiser Permanente Southern California
MMWR	*Morbidity and Mortality Weekly Report*
MPH	Masters of Public Health
NAC	National Alliance for Caregiving
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization Canada
NANASP	National Association of Nutrition and Aging Services Programs
NAPNAP	National Association of Pediatric Nurse Practitioners
NCBA	National Caucus & Center on Black Aging, Inc.
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCHS	National Center of Health Statistics
NCIRD	National Center for Immunization and Respiratory Diseases
NCOA	National Council on Aging
NEJM	*New England Journal of Medicine*
NFID	National Foundation for Infectious Diseases
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NIH	National Institutes of Health

NMA	National Medical Association
NNDSS	National Notifiable Diseases Surveillance System
NNV	Number Needed to Vaccinate
NVPO	National Vaccine Program Office
OID	Office of Infectious Disease
OIDP	Office of Infectious Disease Policy and HIV/AIDS
PCP	Primary Care Practitioner
PHAC	Public Health Agency Canada
PHN	Postherpetic Neuralgia
PhRMA®	Pharmaceutical Research and Manufacturers of America®
PICO	Population, Intervention, Comparison, Outcomes
PIDS	Pediatric Infectious Disease Society
PPE	Personal Protective Equipment
QALY	Quality-Adjusted Life-Year
RA	Rheumatoid Arthritis
RCT	Randomized Controlled Trial
RSV	Respiratory Syncytial Virus
RZV	Recombinant Zoster Vaccine
SAE	Serious Adverse Event
SAHM	Society for Adolescent Health and Medicine
sBLA	Supplemental Biologics License Application
SDOH	Social Determinants of Health
SHEA	Society for Healthcare Epidemiology of America
SLE	Systemic Lupus Erythematosus
SME	Subject Matter Expert
SNS	Strategic National Stockpile
SOT	Solid Organ Transplant
ST3	Serotype 3
STM	Solid Tumor Malignancies
TBE	Tick-Borne Encephalitis
US	United States
USG	US Government
VA	(US Department of) Veteran’s Affairs
VaST WG	Vaccine Safety Technical Work Group
VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VIS	Vaccine Information Statement
VPCI	Vaccine Policy Collaborative Initiative
VRBPAC	Vaccine and Related Blood Products Advisory Committee
VSD	Vaccine Safety Datalink
VVA	Vietnam Veterans of America
WG	Work Group
WISER	Women’s Institute for a Secure Retirement
ZVL	Zoster Vaccine Live