

MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

**NOVEMBER 2-3, 2021
SUMMARY MINUTES**

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MEETING PURPOSE

The United States (US) Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC) convened a meeting of the Advisory Committee on Immunization Practices (ACIP) on November 2-3, 2021. The meeting took place remotely via Zoom, teleconference, and live webcast. This document provides a summary of the meeting, which focused COVID-19, hepatitis B, orthopoxvirus, and Ebola vaccines and immunization schedules.

TUESDAY: NOVEMBER 2, 2021

WELCOME AND INTRODUCTIONS

Call to Order/Roll Call

Dr. Grace Lee (ACIP Chair) called to order and presided over the first day of the November 2-3, 2021 ACIP meeting. She conducted a roll call, which established that a quorum was present. Dr. Chen reported that his employer, the University of Maryland Baltimore, has a grant from Emergent BioSolutions that supports research he conducts on developing a *Shigella* vaccine. No other potential or perceived conflicts of interest (COIs) were identified or declared. A list of Members, *Ex Officios*, and Liaison Representatives is included in the appendixes at the end of this summary document.

Announcements

Dr. Melinda Wharton (ACIP Executive Secretary, ACIP/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 12:10 PM Eastern Time (ET) on the first day and approximately 3:45 PM ET on the second day. 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-2021-0112. Further information on the written public comment process can be found on the ACIP website.

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

CDC Update

Dr. Rochelle Walensky (CDC Director) thanked Drs. Lee and Wharton for giving her the opportunity to speak with ACIP during this meeting, emphasizing that this was a monumental day in the course of this pandemic and one that many have been very eager to see. Ever since ACIP's vote on December 12, 2020 recommending COVID-19 vaccination for those ≥ 16 years of age, everyone has been asking when it will be possible to expand this protection to younger children. In the nearly 12 months that have passed since that vote, a tremendous amount has been learned about COVID-19 disease and the vaccines to combat it. During this meeting, ACIP would have the opportunity to review those data, discuss the benefits of expanded vaccinations and consider the risks, and make a recommendation that likely would have tremendous impact. She pointed out that as ACIP reviewed the data throughout the day, it would be key to keep in mind the specific risk to children from this virus and this pandemic and to put that risk into the context of other vaccine-preventable diseases, such as varicella. In the 5 years prior to recommendation of varicella vaccination for children, each year there were between 4 to 31 hospitalizations per 100,000 children less than 20 years of age. In those 5 years, 16 children 5-9 years of age died from the virus. In the most recent Delta wave, pediatric admissions peaked higher than they had in any previous wave of a pandemic, reaching a rate of 25 hospitalizations per 100,000 per year in children between the ages of 5 to 11 years. There have been 745 deaths in children less than 18 years of age and 94 deaths in children 5-11 years of age since the start of this pandemic. Fortunately these most severe outcomes are generally rare.

The chance that a child will have severe COVID, require hospitalization, or develop a long-term complication like multisystem inflammatory syndrome in children (MIS-C) remains low. But still, the risk is too high and too devastating to children and far higher than for many other diseases for which children are vaccinated. There are now over 5200 children diagnosed with MIS-C and living with the complications of that disease. It is also known that beyond the clinical impact of COVID-19 on children, there have been detrimental social and mental health impacts that are just beginning to be fully understood. For almost 2 full years, school has been fundamentally changed. There are children in 2nd grade who have never experienced a normal school year. There are students in middle school who missed out on school sports and extracurricular activities. There are missed proms and homecoming dances and too many missed graduations. The education gaps that exists in this country have widened as this virus has disproportionately impacted racial and ethnic minority communities. Pediatric vaccinations have the power to help change all of that, move toward school as it was once known, and offer hope that it can be a safe and enriching environment for all children. Pediatric vaccination is just one important piece to this puzzle. It is important that as many adults as possible continue to be vaccinated to provide protection to children in the community, including those younger than 5 years of age who may not be eligible yet for vaccination.

Looking at data from August-October 2021, Delta cases increased sharply across the country. There were stark differences in pediatric cases based on community vaccination level. In a stepwise fashion, as the percent of eligible populations fully vaccinated increased, the number of pediatric hospitalizations decreased. It is an ongoing responsibility to make sure as many people as possible are vaccinated and protected from COVID-19. Dr. Walensky recognized that ACIP had much to discuss throughout the day and emphasized that she looked forward to listening to the deliberations. As always, she said she was most interested in hearing how ACIP would interpret what is known and acknowledge areas of uncertainty. She stressed that she greatly appreciates ACIP's dedication to getting this right, making sure that efforts continue to move forward to end this pandemic with science leading the charge, and for all that they are doing for everyone.

Dr. Lee (ACIP Chair) expressed ACIP's appreciation for Dr. Walensky's engagement in their work, and emphasized that ACIP looks forward to providing the advice and guidance that she needs to support decision-making for the country.

CORONAVIRUS DISEASE 2019 (COVID-19) VACCINES

Session Introduction

Dr. Matthew Daley (ACIP, WG Chair) introduced this session on behalf of the ACIP COVID-19 Vaccines' Work Group (WG). In terms of daily trends and number of COVID-19 cases in the US for all ages from January 2020 through October 28, 2021, the US is in the midst of a second wave that is exceeded only by the wave experienced in December 2020. In the US, almost 46 million cases of COVID-19 have been reported.¹ To introduce the topic of the burden of COVID-19 in children 5-11 years of age, 1.9 million cases have been reported in children in this age group. In addition, there have been more than 8000 hospitalizations in this age group. There have been 2316 MIS-C and 94 deaths reported among children 5-11 years of age in the US. It is important to highlight the fact that the burden of COVID-19 in children in this age group extends well beyond these case counts, including school being tremendously interrupted and lives entirely disrupted.

During October 2021, the WG has been reviewing data regarding pediatric COVID-19 vaccines. Topics have included review of data on SARS-CoV-2 seropositivity in children, pediatric COVID-19 epidemiology, ScenarioHub Modeling results of impact of pediatric vaccination on the pandemic, results of the Pfizer BioNTech clinical trial in children 5-11 years of age, GRADEing (Grading of Recommendation Assessment, Development and Evaluation) of the evidence, and the Evidence to Recommendations (EtR) Framework for the decisions before ACIP during this meeting.

The Food and Drug Administration (FDA) expanded the Emergency Use Authorization (EUA) for Pfizer BioNTech COVID-19 vaccine to include children 5-11 years of age.² To highlight a couple features of this, the pediatric formulation is a 10 µg dose given intramuscularly (IM). The vaccine is administered as a 2-dose series given 3 weeks apart. During this session, ACIP would hear extensive evidence on this. To highlight a few points, there were 4600 participants 5-11 years of age in a clinical trial that was randomized 2:1, with 3100 who received vaccine and 1538 who received placebo. In addition, knowledge and experience have been gained from administering more than 247 million doses to individuals 12 years of age and older in the US with Pfizer-BioNTech's 30 µg formulation.³ This vaccine was fully licensed in people 16 years of age and older in August 2021, which was based on longer term follow-up data.

¹ https://covid.cdc.gov/covid-data-tracker/#trends_dailycases. Accessed October 29, 2021.

² <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/comirnaty-and-pfizer-biontech-covid-19-vaccine>

³ https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total Accessed November 1, 2021

Pfizer-BNT162b2 Use in Children Aged 5-11 Years

Dr. Alejandra Gurtman (Pfizer) presented the Pfizer-BioNTech clinical data that received EUA in individuals 5 to <12 years of age, focusing primarily on the clinical data that demonstrate clear and compelling vaccine safety and efficacy that supported EUA in this age group. A lower 10 ug dose was selected as the optimum dose for this age group based to elicit robust immune responses with an acceptable safety profile. The indication is for immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 5 to <12 years of age administered as the primary series of 2 doses of 0.2 mL each 3 weeks apart. The vaccine met all safety data expectations and immunobridging criteria, with 90.7% efficacy observed. Plans have been established for active follow-up under the EUA.

In terms of the clinical data, the goal of Phase 1 with 48 participants 5 to <12 years of age was to identify a preferred dose level based on immune response and a safety profile. As noted, the 10 ug dose was chosen because it had the right balance between the immune response and safety profile. In Phase 2/3, the first group of safety information includes approximately 1500 individuals who received the vaccine versus 750 placebo recipients. At the request of the FDA, an additional 1500 vaccine recipients and 750 placebo recipients were enrolled, most of whom who had at least 2 weeks of safety data after Dose 2. Non-inferior responses have been established to infer vaccine efficacy (VE) in children 5 to <12 years of age compared to individuals 16-25 years of age from the pivotal Phase 3 study. Although not required for EUA approval, COVID-19 surveillance was conducted, permitting evaluation of VE.

Similar to other populations in which the doses are administered 21 days apart, reactogenicity data were captured for 7 days. Non-serious adverse events (AEs) were captured for 1 month and serious AEs (SAEs) were captured for 6 months for participants 5 to <12 years of age. To enhance possible detection of myocarditis in adolescents and young adults should it occur, specific instructions were provided to investigators to be vigilant for symptoms and signs of this condition, including chest pain, and to perform a work-up in the event of suspected myocarditis. Blood draws for immunogenicity were done at Dose 1, 1 month, and 6 months. Surveillance continues to look for the potential to demonstrate efficacy.

There were 2 datasets submitted to support the EUA. The first was the initial cohort of 2268 participants for whom the median follow-up time was 2.3 months. In the latest submission, follow-up of this group was extended for additional follow-up time to 3.3 months. However, those data were not discussed during this presentation. An additional cohort of 2379 participants also were enrolled. In conjunction with the original cohort, this permitted evaluation of a total of approximately 3000 vaccine recipients for at least 2 weeks for most of the 3000 vaccine recipients, and 2 to 3 months for over 1500 vaccine recipients in the submission to the FDA. In terms of the demographics for children 5 to <12 years of age in the Phase 2/3 safety population initial enrollment group (N=2268), demographics for the vaccine and placebo groups were similar. There was good representation in terms of gender, race, and ethnicity and age at vaccination. More than 11% of the population had obesity as an underlying condition. Comorbidities, including obesity, were represented in approximately 20% of the population.

Looking at local reactions by maximum severity within 7 days after each dose in persons 5 to <12 years of age and 16-25 years of age, there was some increase in mild to moderate redness and swelling after Dose 1 and Dose 2 in the 5 to <12 age group. Pain at the injection site was comparable between the two age groups. In general, local reactions met a satisfactory safety profile. In terms of systemic events by maximum severity within 7 days after Dose 2 in children 5 to <12 years of age compared to persons 16-25 years of age, reactions were typically higher in

vaccine recipients. Dose 1 reactions tended to be less frequent and were not shown in this presentation. If anything, the incidence of fever was lower and mostly mild to moderate in individuals 5 to <12 years of age compared to the older age group. This was true for chills and across other systemic event parameters. This represented an acceptable systemic event profile for children 5 to <12 years of age. Moving to system events by maximum severity within 7 days after each dose in individuals 5 to <12 and 16-25 years of age, local reaction rates were very similar regardless of baseline status. There was a slight increase after Dose 1 in participants who were SARS-CoV-2 positive at baseline, which is similar to what has been observed in the adult studies.

There were very few SAEs, no related SAEs, and no deaths after Dose 1 among children 5 to <12 years of age. There was 1 female participant withdrawn from the study due to a fever of 40°C on Day 2 after the first dose, accompanied by neutropenia. The fever resolved in 1 day and she has been followed by a hematologist and recovered uneventfully. In terms of AEs occurring at an incidence of $\geq 1.0\%$ by system organ class (SOC) for children 5 to <12 years of age from Dose 1 to the cutoff date in the safety expansion group (N= 2379), rates were comparable between vaccine recipients and placebo recipients for any AE. Lymphadenopathy has been infrequently observed in other populations after vaccine and was observed in fewer than 9% of recipients in this BNT162b2 enrollment group. For the safety expansion enrollment group of children 5 to <12 years of age, the rates of AEs were very similar between the vaccine and placebo recipients. In terms of overall AEs from Dose 1 to 1 month post-Dose 2 in children 5 to <12 years of age by baseline SARS-CoV-2 status the rates were very similar or a little lower in those who were positive compared to those who were negative prior to vaccination.

Regarding SAEs from Dose 1 to the cutoff date in children 5 to <12 years of age in both safety groups, in the initial enrollment group all SAEs were unrelated to vaccine. One participant in the BNT162b2 group reported an SAE of an upper limb fracture and one participant in the placebo group reported an SAE of abdominal pain and an SAE of pancreatitis related to trauma. In the expansion safety group, one participant reported an infection 15 days after Dose 1 of infective arthritis, one reported an SAE of epiphyseal fracture, and one participant reported an SAE of ingestion of a foreign body.

Participants also were followed for adverse events of special interest (AESI) as designated by either the FDA or the CDC. For the FDA AESIs, no cases were reported of anaphylaxis, myocarditis/pericarditis, Bell's Palsy, or appendicitis. The CDC AESIs (e.g., hypersensitivity, arthritis, and vasculitis) were uncommonly observed in vaccine and placebo recipients and they were short-lived. Rashes tended to be more common after vaccine, but in general they were uncommon and were mild and short-lived overall. The case of arthritis was infective and was the one that already was described. One participant had a case of vasculitis that was reported as a mild case of Henoch-Schönlein Purpura (HSP) that was considered to be unrelated to vaccine that occurred 21 days after Dose 1. Follow-up of this child is ongoing.

In terms of safety conclusions for children 5 to <12 years of age, reactogenicity was mostly mild to moderate and was short-lived. Observed mild to moderate local reactions such as redness and swelling captured by e-diary were more common and systemic reactions, including fever, were less common than those in persons 16-25 years of age. The observed AE profile in this study did not suggest any safety concerns for BNT162b2 vaccination in children 5 to <12 years of age. The database of approximately 3000 active vaccine recipients provides a high degree of confidence that rare AEs after vaccination such as myocarditis or anaphylaxis are unlikely to occur at the rate of 1 in 1000 or higher.

Turning now to the examination of the immune response to the vaccine, immunobridging criteria between persons 5 to <12 and 16-25 years of age were met for both geometric mean ratios (GMRs) and seroresponse. The observed GMR was above the pre-specified criterion of 0.8 and also above the GMR of 1.0 requested by the FDA. In addition, seroresponses were virtually identical in children 5 to <12 years of age compared to persons 16-25 years of age at 99.2% a piece. This criterion also met the lower end of the confidence interval of -2.0%, with immunobridging declared since the lower bound of the 95% confidence interval for the percentage difference was greater than the -10 required.

Looking at geometric mean titers (GMTs) by baseline SARS-CoV-2 status among subjects 5 to <12 years of age, it is important to keep in mind that the number of positive participants in this analysis was relatively small. When looking at GMTs by age subgroup, titers were virtually identical across all ages. It was also important and requested by the FDA to assess the response to the Delta variant given its prominence as a cause of COVID -19. In an analysis of 34 individuals at 1 month following receipt of the reference strain (USA-WA1/2020) or Delta strain (B.1.617.2), the comparable response predicts efficacy for children 5 to <12 years of age during the time that the Delta variant is prominent. High efficacy against COVID-19 was observed in children 5 to <12 years of age in a descriptive analysis of first COVID-19 occurrence from 7 days after Dose 2. Remembering that this study had a 2:1 vaccine versus placebo randomization, the case split of 3 in the vaccine group versus 16 in the placebo group results in an efficacy of 90.7% (67.7, 98.3), with a high degree of confidence shown as well. No severe cases of COVID-19 or cases of MIS-C were reported in either group. Notably, the cases occurred in July to September when Delta was the most prominent variant in circulation. At this time, 14 of the 19 samples had been successfully sequenced and were all found to be the Delta variant, confirming high efficacy against this highly transmissible strain of SARS-CoV-2. In terms of the cumulative incidence of COVID-19 after Dose 1 among children 5 to <12 years of age, the mean length of follow-up time after Dose 2 was 3.3 months. Efficacy was suitable for this period of follow-up to date and surveillance is continuing.

To summarize immunogenicity and efficacy, immunobridging success criteria were met for children 5 to <12 years of age compared to persons 16-25 years of age at the 10 µg dose level. BNT162b2-immune sera effectively neutralized both USA-WA1/2020 (reference strain) and the highly transmissible B.1.617.2 (Delta) variant of concern. BNT162b2 as a 2-dose series was highly protective against COVID-19 in children 5 to <12 years of age when the Delta variant was prominent. Pharmacovigilance activities are a critical component of activities to detect unexpected safety events rapidly. Pfizer continues to conduct robust pharmacovigilance activities, which include spontaneous report collection, active follow-up, and frequent signal detection and evaluation. Proactive risk mitigation activities (e.g., labeling, educational materials, and vial differentiation) will continue. In terms of pharmacoepidemiology studies, 5 studies will include children ≥5 years of age to detect myocarditis occurrence and sequelae and other possible rare AEs. These include one study that will follow up identified US post-vaccination myocarditis cases for 5 years within the Pediatric Heart Network (PHN).

Discussion Summary

- Referring to Slide 25 on GMTs for immunogenicity, Dr. Lee pointed out that a parallel slide on safety would be helpful for clinicians as well.
- Dr. Caine pointed out that because there is such a high rate of obesity among African Americans, probably greater than 30%, people are asking if they should wait to get children who are African American and obese vaccinated at 12 years of age in order to receive the

larger dose. She noted that she would raise the issue again during the clinical considerations session.

- Several members posed questions with regard to what the protocol should be for children who turn 12 years of age between doses.
 - Dr. Gurtman clarified that the children in the trial received the 10 µg formulation even if their age changed from 11 to 12 between doses. This was done knowing that some children would turn 12 during the study because they wanted to ensure that the protocol remained the same.
 - Dr. Fink indicated that the FDA authorized either the 10 µg formulation that is authorized for use in children 5-11 years of age or the 30 µg formulation that is authorized for use in ages 12 years and above can be used for either Dose 1 or Dose 2 in a scenario in which a child will be 11 years of age at the time of Dose 1 and then turns 12 years of age before time to receive Dose 2. The most data-driven approach, the approach for which the data are actually available, would be for a 10 µg dose be given to a child who is 11 years of age at the time the dose is administered and a 30 µg dose to be given to a child who is 12 at the time the dose is administered. However, FDA did recognize that there may be some situations in which there would be a need for flexibility and a totality of data to support this more flexible approach in which there would be a change in age occurring in between the 2 doses. It is up to ACIP and CDC to make whatever they consider to be the most appropriate recommendations for implementation of the doses such as they are authorized.

Public Comment: November 2, 2021

The floor was opened for public comment on November 2, 2021 at 12:31 PM ET. Given that many more individuals registered to make oral public comments than could be accommodated, 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-2021-0112. Visit <http://www.regulations.gov> for access to the docket or to submit comments or read background documents and comments received.

Mrs. Christina Dietrich Delaware MOMs (Moms Oppose Mandates)

I speak on behalf of Delaware MOM, Moms Opposed Mandates. Like most of us, I vaccinated my 4 children right on schedule. We trusted pediatricians, FDA, and the CDC. The response to COVID has shattered the trust that many Americans used to have. We're confused and upset. We see FDA members resign facing political pressure to make approvals. We sounded the alarm on myocarditis long before you acknowledged it. We're told not to trust our lying eyes with a barrage of talking points. There are "lies, damned lies, and statistics." This week, Director Walensky said those unvaccinated with a recent infection were 5 times more likely to have COVID-19 than those recently fully vaccinated without prior infections. Sounds pretty definitive. But actually, among adults hospitalized for COVID-like illness, those with lab-confirmed COVID in the same hospital system within 3 to 6 months were more likely to test positive for COVID 19 than those who had an mRNA vaccine within 3 to 6 months. Can you really extrapolate that to the general public? On the same day, the CDC website was updated to include a systematic

review and meta-analysis which found no significant difference in the level of protection provided by infections as compared to vaccinations. When the agency, politicians, and the press tout the hospital and *MMWR* and ignore the meta-analysis, parents wonder when else they promote or ignore in research in order to advance a narrative. Immunity is a very salient point in your deliberations today. We know that as of June the seroprevalence for these kids is 42%. What is it now in November? Parents are already being forced to vaccinate their children in order for them to participate in certain activities. Their risk is so low and many are immune. They don't do it for the health reasons but for social consequences. I today propose a compromise. Doses are sent out. We know you will approve this. We beg you to say that kids 5 to 11 *may* receive the vaccine not that they *should*. Otherwise, your approval will be used to enact mandates unjustified by an EUA. They will mandate without evidence that it reduces severe disease or death in children when it doesn't prevent transmission, the effectiveness wanes over time, the dosing schedule is sub-optimal, and a new buffer is being used—not the ones in the trial. When 40% of hospitalizations in these kids are incidental and the remaining 70% of kids have a comorbidity, you won't even acknowledge that the risk benefit-ratio is different for healthy children versus those with risk factors. There are enough unknowns that parents should be able to wait for more data without suffering pressure and coercion. Mandela said that "There can be no keener revelation of a society's soul than the way in which it treats its children." Our children have given up so much. The benefits of this vaccine for kids are minimal. There are also risks. Protecting the community is not their job. We do not sacrifice the health of a single child to protect adults. That is counter to our nature. Please say that the children *may* receive the vaccine and not that they *should*. Words matter. Thank you so much for your attention and I appreciate the work you're doing today.

Ms. Patricia Neuenschwander, MSN, RN
None

Thank you for allowing me my public comment today. My name is Patricia Neuenschwander and I have been a nurse for 27 years. I am not sure if there's anything I can say to you today to reach you, but I must try. Pfizer clinical trials did not detect any health benefit at all from their shots. They did not prevent a single hospitalization, ICU (intensive care unit) visit, MIS-C case, asymptomatic infection, nor death in the treatment group. There was a total of 19 mild infections out of 2300 children. The injection has not been shown to stop transmission or infection. In a meta-analysis combining from 11 countries, Stanford researchers found that children 0-19 infected with COVID have a 99.9973 survival rate. This is a mild illness in the vast majority of children. The science being used for this are small studies using immuno-bridging, short follow-up time, vaccinating the control group as soon as possible, and excluding any immunocompromised or significantly ill children. It is estimated that over 40% of children have already been infected, but prior natural immunity is being ignored. We don't know if giving the vaccine after the infection is safe or the consequences to the immune system post-infection. Does it destroy the natural antibodies that you created? Does boosting those antibodies impair the innate immune response to future or other infections? Pfizer's clinical trial in kids was intentionally undersized to [not clear]. If the rate of a particular adverse outcome in kids is the result of the shot is 1 in 5000. The trial only enrolled 1500. Then you are unlikely to spot any particular harm. Supplemental data was obtained from an expansion group of another 1500, but that data was only followed up for 2 weeks. The follow-up period is intentionally too short. Two months of follow up will not provide information on the immediate or long-term safety of this experimental shot. Vaccine effectiveness was inferred by immuno-bridging data from 16-25 year olds, or junk science. You know, this injection will kill and maim some children—some immediately, some in the intermediate, and some in the long-term. You know that if you make this general recommendation for all children, it will be viewed as a mandate for all children ages

5 to 11. You can say “no.” The science does not support this as safe or effective in preventing serious complications or death. Please use your critical thinking, your wisdom, your experience, and be brave. Admit that the status does not support injecting perfectly healthy children. If you listen to the discussion from VRBPAC (Vaccine and Related Blood Products Advisory Committee) meeting last week, you heard several of the committee members had concerns. They were hesitant to recommend the full authorization of this. There is no amount of money, career advancement, or prestige that will make up with a crime against humanity of you recommending this experimental intervention on innocent healthy children. May God have mercy on the souls of the millions of children who receive this based on your recommendation. Please do not recommend this for children. Thank you.

Andrea Kline-Tilford, PhD, CPNP, FAAN
Pediatric Nurse Practitioner
President, National Association of Pediatric Nurse Practitioners

I am Andrea Kline-Tilford and I do not have any conflicts to report. I'm a Pediatric Nurse Practitioner (PNP) and the President of the National Association of Pediatric Nurse Practitioners (NAPNAP), a professional organization representing more than 8000 pediatric-focused nurse practitioners. We support the timely and complete immunization of all infants, children, and adults in an attempt to maximize the health and wellbeing of all people. The last 20 months have brought immense strain to the world, including our nation's more than 20 million 5-11 year old children. Our children have been pivoting in all areas of life. Children can and do suffer acute illness, multi system inflammatory syndrome, and long-haul physical symptoms from SARS-CoV-2. Data shows children of marginalized racial and ethnic groups have suffered greater disparities. The strain has been immense and has resulted in mental health challenges that will undoubtedly have lasting impact on social, emotional, and mental health. In a poll conducted by researchers in Chicago, 71% of parents or caregivers believe the pandemic impacted their child's mental health. Pediatric Nurse Practitioners are on the frontline in primary and acute care settings encountering these challenges in our children each and every day. There has been an alarming increase in child and adolescent anxiety, depression, and suicide. According to the CDC, mental health-related emergency department (ED) visits by adolescents increased 31% in 2020. At one point during the pandemic, emergency department visits for suicide attempts in girls 12-17 years of age was up 51% from 2019. Eating disorders, serious and sometimes deadly, have increased 62%, and more than 140,000 children have lost a parent or caregiver during the pandemic. Children have paid a significant toll associated with COVID-19 and we have the ability to alter this trajectory. Right now we rely on masking, physical distancing, hand hygiene, and surrounding children with adolescents and adults who are vaccinated. Without other options, these strategies were acceptable, but are not a long-term solution and leave a tremendous gap in protection for our children. NAPNAP urges the ACIP to authorize the Pfizer BioNTech COVID-19 vaccine for all children 5-11 years and supports widespread equitable rollout to every eligible child in the US using all possible vaccination sites, including primary care offices, schools, pharmacies, pop-up sites, and mobile units. COVID-19 vaccination is safe and effective. With the adjusted dosing for children 5-11, we can protect our school-aged children immediately to further shield them from short- and long-term physical and mental health consequences and to re-establish more ordinary daily activity. Let's use the newly provided data on the Pfizer BioNTech COVID-19 vaccine to deliver comprehensive, equitable immunization to all children 5-11 years of age. NAPNAP offers provider- and family-focused resources about COVID-19 vaccination at napnap.org.

**Mrs. Tia Severino
Individual**

Yes, this is Tia Severino. I appreciate the opportunity to speak today. I requested to speak after watching the FDA VRBPAC meeting last week. I was heartbroken and outraged at the vote to recommend this vaccine despite legitimate concerns raised by voting members about unknown adverse events and known events such as myocarditis, which has already been observed in 12-17-year-olds at startlingly high rates, especially for boys. One member even said, "We won't know the rare events until we start giving the vaccine." This is not okay. The adverse events which are under-reported are very disturbing. VAERS (Vaccine Adverse Event Reporting System) data as of October 22nd shows 17,619 deaths; 86,542 hospitalizations; 8,656 heart attacks; 2,712 miscarriages; 27,277 permanent disabilities; and 10,956 cases of myocarditis/pericarditis, and this is just scratching the surface. By recommending these vaccines, which are still under Emergency Use Authorization, you are paving the way for mandates in workplaces across the country and in schools. This is an illegal Emergency Use Authorization because there are effective alternative treatments for this virus, which has a greater than 99% recovery rate. I'm begging you to do something you've never done before. Vote "no" today. There is no reason to give this vaccine to children who are not at risk for severe COVID. We have already seen severe adverse events in the vaccine in the 12-17 age group. I will share one with you now. Maddie de Garay, a 12-year-old girl, was a participant in the Pfizer COVID trial. Previously healthy, energetic, and full of life—now she is confined to a wheelchair and has to be fed through a tube in her nose. She has been hospitalized numerous times. Maddie and her family have been ignored and dismissed by Pfizer and the CDC. Her voice matters. As the vaccine mandates roll out and people are losing their jobs over a personal medical choice that is their right, it appears you have found a way to get rid of the shaky front line of health care practitioners and soon there will only be compliant first responders, law enforcement, and military. At the same time, you are galvanizing those of us who are against the vaccines and creating greater vaccine hesitancy, including among those who previously believed in the vaccine program. Please, please, vote "no." I cannot stress this enough. It is wrong to use our children as lab rats and it is equally wrong to use children as a shield with a failing vaccine. This vaccine is not preventing infection no matter how many you vaccinate or how many boosters you give. If you do vote "yes," be prepared to face more distraught parents.

**Ms. Claire Hannan, MPH
Executive Director, Association of Immunization Managers**

Good afternoon. I'm Claire Hannon, Executive Director of the Association of Immunization Managers (AIM). Thank you for the opportunity to provide comments on behalf of the state, territorial, and local public health immunization program managers. I'd like to take this opportunity to express the critical importance of vaccinating children against COVID, as well as draw attention to implementation challenges that continue to test public health's response. First, I express strong support for universal recommendation for children aged 5-11 years old to receive COVID vaccination as authorized by the FDA. As of October 21, there have been 6.3 million children who have tested positive for COVID-19 and of those, greater than 1.9 million aged 5-11. 8,300 cases have resulted in hospitalization and 745 children have died. I want to repeat that. There have been 745 deaths in children under 18 from COVID. Some say this illness is mild, but there is no acceptable number of deaths in children. Death is preventable with the vaccine, which is effective and safe. I look forward to the opportunity for children aged 5-11 to receive protection through vaccination. Vaccinating kids minimizes disease spread in school settings and it's the best way to keep our schools safe and open. Next, I want to draw attention to 2 ongoing implementation challenges. First, the logistical and IT challenges involved

with giving a half dose of Moderna vaccine as a booster. Jurisdictions and providers have been working diligently over the course of this pandemic, and previously through 27 years of the Vaccines for Children (VFC) program, to manage vaccine inventory and avoid waste. But now, a 14-dose vial can yield up to 20 booster doses, or 14 regular doses, or anywhere in between and providers must manually track how many times they've drawn from the same vial. With the addition of the half dose Moderna booster and no change to the technology and coding tied to the 14-dose vials, there is no way to accurately track inventory and waste. A second implementation challenge is the need to provide electronic verification of vaccination and the lack of national standards to do so. There is no standard way for consumers to show digital proof of vaccination. Many states already provide consumer access to vaccination records through immunization information systems (IISs), but the lack of a nationally approved standard for QR codes and electronic verification has limited the ability of states to provide an electronic COVID vaccine record to consumers. I draw attention to these challenges so that efforts can continue to develop solutions and improve future pandemic response. Thank you.

Martha Nolan, JD
HealthyWomen

Good afternoon. My name is Martha Nolan and I am speaking today on behalf of HealthyWomen, the nation's leading nonprofit health information organization for women, providing consumers and healthcare providers accurate evidence-based information about diseases, conditions, and innovations and research changes in policy that impact the treatment and care women receive. HealthyWomen is also a convener of the COVID-19 Vaccine Education and Equity Project where we are joined by over 220 organizations representing patients, caregivers, families, diverse communities, health care workers, older Americans, veterans, frontline workers, and scientists—all who believe we have a responsibility to come together to provide information about the clinical trials process, regulatory review, and distribution and access to COVID-19 vaccines in a way that promotes equity and trust. Since the start of the COVID 19 pandemic, HealthyWomen has been diligent in working to understand the facts of COVID-19 and its related vaccines. COVID-19 vaccines have saved a significant number of lives. A National Institute on Aging-funded study published on August 18 in *Health Affairs* found that COVID-19 vaccines prevented more than 139,000 deaths during the first 5 months they were available saving 2,285 lives per day. And the estimated economic value of preventing these deaths is close to a trillion dollars. But the value to families is priceless. Women are the predominant caretakers in our society and are often called upon to make critical decisions for the health and wellbeing of their families and communities. Since COVID-19 vaccines were approved by the FDA for adults, women have led in the vaccination rates, with 60% being fully vaccinated compared to men at 55%. But everyone eligible should be encouraged to get vaccinated as soon as possible if we're going to stop the spread of the current COVID 19 Delta variant and more importantly, the development of new variants not covered by the COVID-19 current vaccines. We need to protect ourselves and more importantly, our kids and grandkids. Vaccinating our children is the best protection against serious infection, hospitalizations, and deaths from COVID-19. Rates of COVID-19 hospitalization among children and adolescents rose to the highest levels in August and September of 2021. Over 8,300 children in the 5-11 age group have been hospitalized since the beginning of the pandemic. And sadly, the pandemic has taken a serious toll on our children's emotional and mental wellbeing. Children need access to safe and effective COVID-19 vaccines to reestablish that safe environment where they can once again learn, play, and socialize without fear of serious illness. We adults started to feel that relief almost a year ago and finally, it's our kids' turn. The COVID-19 Vaccine Education and Equity Project supports the robust regulatory review of the vaccines for children ages 5-11 and urgency to provide the American people with clear guidance on their

use. Thank you for the important work you are doing on behalf of Americans of all ages. We remain committed to partnering with you to ensure everyone understands the facts about this critical tool for protection. Thank you.

Julie Boom, MD
Baylor College of Medicine
Director, Texas Children's Hospital Immunization Project

On behalf of Texas Children's Hospital, I would like to thank the CDC staff and ACIP members who have so diligently analyzed COVID-19 disease burden, vaccine safety, and efficacy data and then provided risk-benefit assessments based on this information. Using your in-depth analyses, my colleagues and I have been able to assure families about the safety and efficacy of COVID-19 vaccines in adolescents and adults. As a general pediatrician with 26 years of experience and Director of the Immunization Project at Texas Children's Hospital, I know that vaccines are the best way to protect children from COVID-19. As you continue your discussion today, I urge you not to minimize the disease burden and risk of COVID-19 in children. To date, COVID-19 has proven to be more contagious and deadly than influenza, having killed almost 800 children ages 0-17 years, with 172 deaths in children 5-11 years. Even though the number of pediatric deaths pales in comparison to number of deaths among adults, especially the elderly, the risk to children shouldn't be minimized. To frame the number of pediatric deaths, let me offer the following comparison. COVID-19 has killed more children than would fill 2 packed 747 airplanes. COVID-19 has killed more children than would fill 26 full classrooms or 16 full school buses sitting 2 children per seat. During any other years, these deaths would have made national headlines and created an outcry to mitigate the risks to these young persons. Unfortunately, pediatric deaths have been largely overshadowed and as a result, many have questioned the risk-benefit ratio of COVID-19 vaccination for children. In addition to the risk of death, we know that many children have experienced the long-term effects of COVID-19. Similar to adults, children are experiencing symptoms such as persistent chest pain, fatigue, and cognitive difficulties long after their acute COVID-19 infection. These debilitating symptoms have prevented their return to normal activity. In addition, over 5,000 children have been diagnosed in the US with MIS-C, multi-system inflammatory syndrome in children. Most often these children present with symptoms severe enough to require hospitalization in an intensive care unit. Unfortunately, 46 children have died from the severe post-COVID inflammatory process. As mask requirements in schools and public places have been lifted in many parts of the country, recommendations for vaccinating children 5-11 years of age with COVID-19 vaccine cannot come soon enough. Children younger than 12 remain a vulnerable population among which COVID-19 can spread. Please give these factors your strongest consideration as you weigh the benefits and risks of COVID-19 vaccine. Thank you.

Joan Edelstein, MS, MPH, DrPH
Professor of Nursing, School Nurse Credential Program
California State University, Sacramento

Thank you. I'm Joan Edelstein, professor in both nursing and faculty in the School Nurse Credential program at California State University Sacramento. As a pediatric nurse for over a half century, I've seen the devastating long-term effects of infectious diseases. I've personally cared for infants and children with rubella syndrome, polio, tuberculosis, and measles inclusion-body encephalitis (MIBE). We all know people who've had months of painful shingles due to having had chickenpox, and I have several friends who've had polio and now suffer the effects of post-polio syndrome decades later. As we try to address the highly unlikely long-term effects

of clearly safe and effective COVID vaccines, we do not yet know the long-term damage of having COVID in childhood. We do know that children suffer from long COVID as has been well-demonstrated by long COVID kids in the UK. We do know that COVID causes organ damage that may lead to long-term health problems. We do know organ damage can affect children with COVID as reflected in multi system inflammatory syndrome. We don't know if organ damage will affect them weeks, months, years, or decades after having been infected with COVID-19 and we should not wait to find out. We ask that you provide Emergency Use Authorization for this clearly safe and effective vaccine now for children ages 5-11. Implementation purposes. As a credentialed school nurse, I'd also like to make a statement about the need for the CDC to support school nurses in vaccination administration that will impact the success of pediatric vaccine programs. Our pediatric public health population is right here in our schools, the ideal place to implement primary prevention measures such as vaccine. School nurses are responsible for the entire school health program and are the health experts in this non-healthcare setting. Nonetheless, school nurses have been disregarded. We've been specifically excluded in planning for safe schools in my own state in spite of repeated requests to be at the table. In order to advocate for students and have effective mitigation programs and successful vaccine programs, school nurses nationwide are the public health experts in partnering for successful school-located vaccine clinics, in educating families, staff, and the community on the importance of vaccine. The CDC should include in all school-related recommendations that school nurses be actively included in assessment planning, policy, program development, implementation, and evaluation of both vaccine programs and mitigation efforts. Funding should be targeted to school nurse positions as they now have twice the work, uncompensated in time or money for inadequate pay. Rather than eliminating or ignoring school nurse positions in districts, the CDC should take the lead in recognizing the importance of including school nurses in all recommendations, and [inaudible] state, county, and city health departments to partner with school nurses at the district and school level to carry out this most critical task of getting our pediatric public health population vaccinated. Thank you.

**Dr. David Wiseman
Synchion, Inc.**

Good morning. Thank you, Dr. Lee. Please refer to our previous submissions for disclosures. Former FDA medical officer, Dr. David Gardner, just wrote that FDA failed in its duty to ensure vaccine safety for children. After criticizing the UK for rushing to approve Pfizer's vaccine, Dr. Fauci called FDA the "gold standard" of regulation. With extensive medical industry experience, I say this is the "gold standard" of regulatory dereliction. FDA touted its children's vaccine review as thorough and transparent. Far from it. For safety, 1,500 patients were followed less than 3 months and another 1,500 only two and a half weeks. A small immuno-bridging study against Wuhan, still with no immune correlation of protection. A similar study against Delta was marked, "Assay not validated. Analysis not verified by FDA." Where is FDA? The efficacy study yielded only 16 placebo and pre-vaccine outcome events, with a large imbalance of mysteriously excluded vaccinated subjects, bias in this observer-blinded but not double-blinded study could drop the 90% efficacy to zero. See today's BMJ for allegations of trial unblinding. Where is FDA? Why was the efficacy analysis not verified by FDA? Where were FDA? Where is Pfizer's sub-study on troponin levels in subclinical myocarditis? Where is FDA? FDA's risk-benefit analysis failed to consider a 42% serum prevalence. Non-myocarditis serious AE reports as many as for myocarditis, an improperly model wave and waning efficacy. When properly accounted for, we find risks outweigh benefits by nearly 2:1 before under-reporting. The one thing FDA got right was revealing an almost 5-fold rate of under-reporting at least and a database more reliable than theirs that CDC didn't know about. Pfizer has changed to a buffer that could change the particle charge, but there has been no assessment of particle distribution

in animals. No safety. No efficacy studies. Where was FDA? With no cancer or immunogenicity studies, especially in young animals, FDA has not assuaged the concern for radiation-like toxicity of this gene therapy product. With CDC's study on all-cause mortality and vaccination, we find correlations between vaccine coverage and mortality. Adults benefit from 4 to 26 weeks outside of which there are detriments. In non-vaccinated children, all-cause deaths correlate with adult vaccine coverage. Vaccination already appears to harm non-vaccinated children. Will ACIP request our analysis? No emergency, unblinding, unverified efficacy data, missing, unlimited safety data, faulty risk benefit analysis—you have nothing to work with and FDA has shunted the work of defining risk groups onto you. We're never going to learn how safe this vaccine is until we start giving it. FDA has abandoned their responsibility to our children. Will you?

SARS-CoV-2 Epidemiology in Children

Dr. Jefferson Jones (CDC/NCIRD) presented an overview of the epidemiology of COVID-19 in children 5-11 years of age covering incidence and seroprevalence estimates, COVID-19-associated hospitalization rates and mortality, MIS-C, additional post-COVID conditions, and transmission.

In terms of incidence and seroprevalence, over 45 million cases of COVID-19 have been reported in the US as of October 22, 2021. The majority of these have been in adults, who have experienced the most hospitalizations and deaths due to COVID-19 illness. However, children have been greatly impacted by the pandemic. In total, there have been over 1.9 million cases of COVID-19 reported among children 5-11 years of age. Starting in July and August of 2021, there was a sharp increase in cases in this age group. Over the past few months, children 5-11 years of age have been making up a greater proportion of total cases. This age group has represented 10.6% of all cases reported to CDC as of the week of October 10, 2021, while making up 8.7% of the total US population in the 2020 Census. These data are for cases reported to CDC; however, many infections are asymptomatic or result in mild illness and are not tested and reported.⁴

To estimate all infections, CDC conducts an ongoing nationwide seroprevalence study in collaboration with commercial laboratories. Every 2 weeks, approximately 50,000 de-identified residual sera specimens collected by commercial laboratories or preventive or acute clinical care for routine screening and are tested for SARS-CoV-2 antibodies. However, many jurisdictions have limited availability of pediatric specimens. People presenting for acute clinical care or screening and having their blood drawn by commercial laboratories might not represent the general population, particularly in children who do not frequently require blood tests. The most common reasons for the clinical visits among children, as documented by International Classification of Diseases (ICD)-10 codes, include general examination (e.g., cholesterol as all children are recommended to have cholesterol screens between 9-11 years of age), obesity, long-term drug monitoring, and fatigue.⁵

⁴ <https://covid.cdc.gov/covid-data-tracker/#demographicvertime>

⁵ <https://covid.cdc.gov/covid-data-tracker/#national-lab>; <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/geographic-seroprevalence-surveys.html>; Couture et al. Methods for Estimation of SARS-CoV-2 Seroprevalence and Reported COVID-19 Cases in U.S. Children, August 2020—May 2021. medRxiv. <https://doi.org/10.1101/2021.09.26.2126375>; Bajema et al. Estimated SARS-CoV-2 Seroprevalence in the US as of September 2020. JAMA Intern Med. 2021;181(4):450–460.

Looking at weighted infection-induced antibody seroprevalence estimates by age groups for September 2021 for 47 US jurisdictions, seroprevalence in children 5-11 years of age was estimated to be 38%. This is higher than seroprevalence estimates among adults and similar to estimates in children 12-17 years of age. Notably, these results are preliminary and are subject to change. Seroprevalence varies greatly by state and jurisdiction. Among 23 jurisdictions with at least 75 specimens collected from this age group during September, the state or jurisdiction-level estimates ranged from 11% to 61%. This seroprevalence estimate is different than the estimates presented at the FDA VRBPAC meeting, as it includes 47 jurisdictions for September as opposed to 15 jurisdictions from May to June. Using seroprevalence to estimate the cumulative number of infections, the number of infections per reported case by age was calculated. For the general population, including adults, the jurisdiction-level infection-to-case ratio had a median of 2.4 with a range of 2.0 to 3.9. For children, the infection-to-case ratio was substantially higher with a median of 6.2 and a range of 4.7 to 8.9.

Numerous children 5-11 years of age have previously been infected, but what does this mean for vaccination? Based on data in adults, infected individuals have a low risk of infection for at least 6 months, but protection is not 100% and is likely lower against the Delta variant. Of note, the antibody response after infection is lower and less consistent, meaning there is a wide range of antibody titers in response to infection compared with mRNA vaccine-induced antibody response, which produces higher and more consistent antibody titers. Additionally, antibody titers generated after infection are lower in people with mild or no symptoms. Infections resulting in mild or no symptoms appeared to be much more common in children with SARS-CoV-2 infection than in adults. Data among children are lacking and data in adults might not apply to children. Substantial immunologic evidence and a growing body of epidemiologic evidence indicate that vaccine after infection significantly enhances protection and further reduces risk of reinfection. Among those eligible, CDC recommends vaccination regardless of a history of infection, and serologic testing to assess for prior infection is not recommended for the purpose of vaccine decision-making.⁶

Seroprevalence data suggest that infections in children are less likely to be reported compared with adults. Seroprevalence estimates in children 5-11 years of age were approximately 38% in September 2021. Seroprevalence indicates that children are at least as likely as adults to be infected with SARS-CoV-2. Note that residual sera specimens collect by commercial laboratories may not be representative of the general pediatric population. Antibody tests cannot determine whether a person is protected from infection. The assay used for the analysis, a total antibody test that maintains a high sensitivity for at least 6 months after infection, is good for detecting previous infection but is unlikely to correlate with protection from infection.

Now to review pediatric hospitalization data from the COVID-19-Associated Hospitalization Surveillance Network (COVID-NET). COVID-NET is a population-based surveillance system that collects data on laboratory-confirmed COVID-19-associated hospitalizations among children and adults through a network of over 250 acute care hospitals in 14 states. Data are preliminary and subject to change. Cases are identified in COVID-NET if they test positive for SARS-CoV-2 through a test ordered by a health care provider (HCP) and are hospitalized within 14 days of the positive test. In terms of weekly rates of COVID-19-associated hospitalizations by age group, the cumulative hospitalization rate was 32.3 per 100,000 population for children 5-11

⁶ CDC. Science Brief: SARS-CoV-2 Infection-induced and Vaccine-induced Immunity. <https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/vaccine-induced-immunity.html>; CDC. Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States: <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.htm>

years of age as of October 23, 2021. Rates for this age group have been consistently lower than other age groups. However, population-based hospitalization rates for children 5-11 years of age were higher in September 2021 than in any other previous point during the pandemic. Variations in hospitalization rates by race and ethnicity are seen with American Indian and Alaskan Native (AI/AN), Hispanic, and non-Hispanic Black children having cumulative hospitalization rates that were 3 times as high as the hospitalization rates in non-Hispanic White or non-Hispanic Asian children. This disparate impact of the pandemic, including high rates of hospitalizations on these groups, is similar to disparities seen in other age groups.⁷

To further put the burden of COVID-19 illness in context, COVID-19 and influenza-associated hospitalization rates were compared among children aged 5 to 11 years using data from COVID-NET and data from the Influenza Hospitalization Surveillance Network (FluSurv-NET). FluSurv-NET, a longstanding platform that was leveraged to create COVID-NET, conducts population-based surveillance from October 1 through April 30 each year. This is roughly *Morbidity and Mortality Weekly Report (MMWR)* Weeks 40 to 18. This timeframe is the typical US influenza season. Influenza-associated hospitalizations occur seasonally, with very low influenza detection during May through September, suggesting that few influenza-associated hospitalizations are missed outside the October through April surveillance window. Therefore, FluSurv-NET rates from October through April were used to approximate the annual influenza hospitalization rate. FluSurv-NET has a similar catchment area to that of COVID-NET and uses similar methods for case ascertainment and data abstraction.

The influenza 2020-2021 rate was added to influenza seasons 2017-2018, 2018-2019, and 2019-2020. The hospitalization rate was extremely low with only 9 influenza hospitalizations being reported across all pediatric age groups. This is likely because during 2020-2021 influenza season, mitigation measures (e.g., school closures, mask wearing, et cetera) were in place and decreased influenza transmission. During the same time frame, the COVID-19-associated hospitalization rate was added. It was calculated for a 1-year period from October 1-September 30, 2021 because COVID-19 transmission has been occurring throughout the year. The 2020-2021 annual COVID-19-associated hospitalization rate was similar to influenza-associated hospitalization rates for the 2017-2018 and 2018-2019 seasons, and the COVID-19 rate was lower than the rate for the 2019-2020 season for influenza. The low influenza hospitalization rate for the 2020-2021 season suggests that the annual rate of COVID-19 hospitalizations might have been much higher, including higher than influenza hospitalization rates during typical influenza seasons had these COVID-19 mitigation measures not been in place.

Outcomes and interventions in children 5-11 years of age hospitalized with COVID-19 were compared with influenza, combining three pre-pandemic influenza seasons from 2017 to 2020. The median length of stay among children hospitalized with influenza was 2 days versus 3 days for children with COVID-19. Twenty-one percent of children with influenza versus 32% of children with COVID-19 required ICU admission, and 4.6% of children with influenza versus 7.2% of children with COVID-19 required invasive mechanical ventilation. A similar proportion of children with influenza versus COVID-19 died in the hospital at approximately 0.6%. Of 562 children 5-11 years of age who were hospitalized with COVID-19 during March 2020 to August 2021, 68% were Hispanic or non-Hispanic Black, which make up one-third of the general population. Thirty-two percent of hospitalized children had no underlying conditions, and the most common underlying conditions were chronic lung disease, primarily asthma, and obesity.

⁷ <https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covid-net/purpose-methods.html>

As of October 22, 2021, over 730,000 COVID-19 deaths have been reported in the US—the vast majority of whom were adults. However, deaths in children have been reported. Between January 1, 2020 and October 16, 2021, there were 94 COVID-19 deaths reported among children 5-11 years of age. Among deaths in this age group, COVID-19-associated deaths account for 1.7% of all deaths during the same time period. Notably, there was a lag in death reporting. To put this into context, the top 10 causes of death for children 5-11 years of age for the year 2019, the most recent year with complete National Center of Health Statistics (NCHS) mortality data, were accidents (unintentional injuries); malignant neoplasms; congenital malformations, deformations, and chromosomal abnormalities; assault (homicide); diseases of the heart; chronic lower respiratory diseases; influenza and pneumonia; intentional self-harm (suicide); cerebrovascular diseases; and septicemia.⁸

Restricting this to the 12-month period of October 3, 2020 through October 2, 2021, there were 66 COVID-19-associated deaths reported for this age group. This would be equal to the 8th leading cause of death for 2019. In contrast to COVID-19, during the 2020-2021 influenza season, only 1 death from influenza was reported in all age groups for children. This is likely because of reduced transmission due to COVID-19 mitigation measures. During 2019, 84 influenza pneumonia-associated deaths occurred among children 5-11 years of age—the 7th most common cause of death. This suggests that similar to COVID-19 hospitalizations, more COVID-19-associated deaths would likely have occurred had these mitigation measures not been implemented.

Now to discuss MIS-C followed by additional post-COVID conditions, MIS-C is a severe hyperinflammatory syndrome typically occurring 2 to 6 weeks after acute SARS-CoV-2 infection resulting in a wide range of clinical manifestations and complications. Incidence is estimated as 1 MIS-C case in approximately 3200 SARS-CoV-2 infections. This varies by race, ethnicity, age, and region. Approximately 60% to 70% of patients with MIS-C are admitted to intensive care and 1 to 2% die.⁹ Nationally, 5217 MIS-C cases have been reported with date of onset between February 19, 2020 through September 23, 2021. Children 5-11 years of age are most frequently affected by MIS-C. The median age of cases is 9 years and 2,316 (44%) of all reported MIS-C cases have occurred in children in this age group. A disproportionate 61% of children with MIS-C are Hispanic/Latino or non-Hispanic black. Again, these populations comprise only one-third of the overall population of persons 0-20 years of age. Among children 5-11 years of age, 9 MIS-C associated deaths have been reported, which is 20% of all MIS-C deaths.¹⁰

Beyond MIS-C, additional post-COVID conditions occur in children. These encompass a wide range of new, returning, or ongoing health problems, including physical and mental health consequences, experienced by patients 4 or more weeks after initial infection with SARS-CoV-2. Few data exist on post-COVID conditions in children. It appears that post-COVID conditions in children is less common than among adults. In published reports, frequencies of occurrence

⁸ CDC NCHS WONDER Online Database. Accessed at <http://wonder.cdc.gov/ucd-icd10.html> on May 6, 2021

⁹ Bowen, et al. Demographic and Clinical Factors Associated With Death Among Persons <21 Years Old With Multisystem Inflammatory Syndrome in Children—United States, February 2020–March 2021, *Open Forum Infectious Diseases*, Volume 8, Issue 8, August 2021, <https://doi.org/10.1093/ofid/ofab388>; • Payne AB, et al. Incidence of Multisystem Inflammatory Syndrome in Children Among US Persons Infected With SARS-CoV-2. *JAMA Netw Open*. 2021;4(6):e2116420. Published 2021 Jun 1. doi:10.1001/jamanetworkopen.2021.16420; • Feldstein LR, et al. Characteristics and Outcomes of US Children and Adolescents With Multisystem Inflammatory Syndrome in Children (MIS-C) Compared With Severe Acute COVID-19. *JAMA*. 2021;325(11):1074-1087. doi:10.1001/jama.2021.2091; • Belay ED, et al. Trends in Geographic and Temporal Distribution of US Children With Multisystem Inflammatory Syndrome During the COVID-19 Pandemic [published online ahead of print, 2021 Apr 6]. *JAMA Pediatr*. 2021;e210630. doi:10.1001/jamapediatrics.2021.0630; • <https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance>.

¹⁰ Bowen, et al. Demographic and Clinical Factors Associated With Death Among Persons <21 Years Old With Multisystem Inflammatory Syndrome in Children—United States, February 2020–March 2021, *Open Forum Infectious Diseases*, Volume 8, Issue 8, August 2021, <https://doi.org/10.1093/ofid/ofab388> <https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance>

have varied depending on the characteristics of the children studied and other factors. Further investigation is needed to better characterize post-COVID conditions in children. However, a national survey in the United Kingdom (UK) found that 7% to 8% of children with COVID-19 reported continued symptoms >12 weeks after their initial diagnosis.¹¹ Post-COVID conditions in children may appear after mild or severe infections or after MIS-C. Symptoms are similar to those seen in adults and include fatigue, cough, muscle and joint pain, headache, insomnia, and trouble concentrating.¹²

Now to review SARS-CoV-2 transmission among children. Multiple factors impact the transmission of SARS-CoV-2 virus, including presence and type of symptoms of the index case, type and timing of the exposure, viral load, and variant. Some studies have reported similar rates of transmission from infected children as from infected adults, while others have found lower rates of transmission from infected children compared with rates from infected adults.^{13,14,15} Some data from earlier studies likely underestimated infections in children; however, it is clear that secondary transmission from children both to other children and to adults can and does occur and has been reported in both household and school settings.¹⁶ Studies have shown that vaccination decreases transmission.¹⁷

Multiple household studies and outbreak and contact tracing investigations have demonstrated efficient transmission among children and adults in multiple settings. A recent *MMWR* article describing Delta variant transmission within a classroom setting in an elementary school showed an attack rate of 50% among students too young to be vaccinated. Some students were linked to transmission to other students, siblings, and their parents.¹⁸

In summary, children 5-11 years of age are at least as likely to be infected with SARS-CoV-2 as adults, with over 1.9 million cases reported. Seroprevalence is estimated to be approximately 38% through September 2021 using the dataset previously described. Seroprevalence data suggest that infections in children are less likely to be reported as cases than infection in adults. Children 5-11 years of age are at risk of severe illness from COVID-19. Over 8300 hospitalizations have occurred to date. Hospitalization rates were 3 times higher for non-Hispanic Black, non-Hispanic AI/AN, and Hispanic children compared with non-Hispanic white children. Hospitalization rates are similar to pre-pandemic influenza-associated hospitalization rates. Severity was comparable among children hospitalized with influenza and COVID-19.

¹¹ Office for National Statistics United Kingdom. (2021) Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK. Retrieved on September 17, 2021 from Office for National Statistics' website.

<https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronavirus> covid19infectionintheuk/1april2021

¹² Buonsenso D, Munblit D, De Rose C, et al. Preliminary evidence on long COVID in children. *Acta Paediatr.* 2021;110(7):2208-2211. doi:10.1111/apa.15870. 3Molteni E, Sudre CH, Canas LS, et al. Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2. *Lancet Child Adolesc Health* 2021; 5: 708–18.

<https://www.thelancet.com/action/showPdf?pii=S2352-4642%2821%2900198-X>

¹³ Bi Q et al. *Lancet Infect Dis.* 2020;20(8):911-919

¹⁴ CDC Science Brief: Transmission of SARS-CoV-2 in K-12 schools. https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/transmission_k_12_schools.htm

¹⁵ McLean, et al. Household Transmission and Clinical Features of SARS-CoV-2 Infections by Age in 2 US Communities. *medRxiv.* <https://doi.org/10.1101/2021.08.16.21262121>

¹⁶ CDC Science Brief: Transmission of SARS-CoV-2 in K-12 schools. https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/transmission_k_12_schools.html; McLean, et al. Household Transmission and Clinical Features of SARS-CoV-2 Infections by Age in 2 US Communities. *medRxiv.* <https://doi.org/10.1101/2021.08.16.21262121>; Chu VT, Yousaf AR, Chang K, et al. Household Transmission of SARS-CoV-2 from Children and Adolescents. *N Engl J Med.* 2021;NEJMc2031915; Goldstein E et al. On the Effect of Age on the Transmission of SARS-CoV-2 in Households, Schools, and the Community. *J Infect Dis.* 2021 Feb 13;223(3):362-369; and Larosa E et al. Secondary transmission of COVID-19 in preschool and school settings in northern Italy after their reopening in September 2020. *Euro Surveill.* 2020;25(49):2001911.

¹⁷ CDC Science Brief. COVID-19 Vaccines and Vaccination. <https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html>

¹⁸ Lam-Hine et al. *MMWR* Morb Mortal Wkly Rep ePub: 27 August 2021.

Approximately one-third of hospitalized children 5-11 years of age require ICU admission. At least 94 COVID-19-associated deaths occurred in children 5-11 years of age. MIS-C was most frequent among children 5-11 years of age. Post-COVID conditions have been reported in children. All of these adverse outcomes likely would have been more numerous had pandemic mitigation measures not been implemented. Finally, secondary transmission from school-aged children occurs in household and school settings.

Discussion Summary

- Dr. Poehling asked whether there are any data on MIS-C in children 12-17 years of age in terms of how the frequency has changed since vaccine has been approved for children in that age group.
 - Dr. Campbell indicated that these data are not available yet, noting that there is a lag to the MIS-C national surveillance system reporting. The cases were low through the summer. Now that vaccination has become more common in children 12 years of age and older, that may make a difference in the current wave of cases being reported to CDC. In a few weeks, they hope to have enough cases to look specifically at vaccine effectiveness (VE) against MIS-C in hospitalized children.
- Dr. Daley observed that based on the numbers, COVID-19 severity in children appeared to be at least as great, or perhaps more severe, than influenza in children.
- Regarding seroprevalence, it seemed to Dr. Daley that children who have blood drawn may differ from children who do not. For example, a child having blood drawn due to fatigue would suggest that an asymptomatic case of COVID may have led to that blood draw. Perhaps there is more likely an overestimate of seroprevalence in the general population. Ms. Bahta asked how the infection-to-case ratio was determined.
 - Dr. Jones confirmed that the seroprevalence comes from a unique group of children having their blood drawn. Serum samples for children having blood drawn specifically for COVID-19 are excluded from the study. There could be other reasons for a blood draw without an ICD-10 code mentioned for COVID-19. However, there are not many randomized household-based studies to which a comparison can be made. These results are somewhat similar to other seroprevalence studies in children, but most of those studies used a similar approach of using a convenience sample from laboratory-sampled children.
 - In terms of the infection-to-case ratio, Dr. Jones explained that for the 6 or 7 jurisdictions that had complete age data (e.g., >90%), the cumulative number of reported cases in children were compared to the projected number of cumulative infections in children using the seroprevalence data. If 5% of the population reported cases and 20% would be projected to be infected for seroprevalence, that would be a 4:1 ratio.
- Dr. Sanchez inquired as to whether children in COVID-NET who were identified as having an infection, but perhaps presented for a trauma and then tested positive for COVID-19 as opposed to being hospitalized for COVID-19, were included or excluded from the analysis.

- Dr. Jones indicated that the COVID-19 team reviews medical records for all children. Approximately 79% to 80% of children were confirmed to be hospitalized for COVID-19, with other cases being somewhat more difficult to determine. He did not believe they were excluded from the analysis.
- Dr. Garg added that among the 79% to 80% of children 5-11 years of age who were admitted specifically related to COVID-19, about 87% had at least 1 of the symptoms on which data are collected. These children were not excluded from either the rates or from the analysis comparing severity among those with COVID-19 versus those with influenza.
- Dr. Poehling asked whether any disparities were observed among children who died from COVID-19. Dr. Lee remarked on the stark disparities that continue to exist in adult and pediatric population in terms of severe disease and hospitalization. It is recognized that disparities in health are a consequence of decades of compounding inequities that impact both the health and education of these children. There is much to do not only through ACIP recommendations, but also through implementation to address those disparities. Thus far in the pandemic, data continue to show disparities in the outcomes for children and adults.
 - Dr. Jones indicated that he was unaware of any analyses of COVID 19 deaths by race and ethnicity that were available at this time. Since infections, hospitalizations, and MIS-C have all followed similar patterns as those occurring among adults, disparities would be expected to follow similar patterns among children as well.
 - Dr. Campbell added that in terms of deaths associated with MIS-C, a paper led by Bowen published in *Open Forum Infectious Diseases (OFID)* showed an increased odds ratio in Blacks, Black non-Hispanics, and Hispanics relative to Whites. While the numbers were not large enough for adjusted analyses for AI/AN and Native Hawaiians or Pacific Islanders, the crude ratios for those populations were very elevated relative to the white population.

Myocarditis in Adolescents and Young Adults

Dr. Matthew Oster (CDC/NCBDDD) presented on mRNA COVID-19 vaccine-associated myocarditis following COVID-19 vaccination, primarily in adolescents and young adults, comparing types of myocarditis and 3- to 6-month outcomes. As a reminder, the reporting rates of myocarditis within 7 days after vaccination exceeded background incidence¹⁹ for males 12-24 years of age after the first dose and males 12-49 years of age after the second dose. Among females, an increased risk or reporting rates was not seen after Dose 1. A slight increase was observed among females 12-24 years of age after Dose 2, with a peak in females 16-17 years of age.

¹⁹ An estimated 1–10 cases of myocarditis per 100,000 person years occurs among people in the United States, regardless of vaccination status; adjusted for the 7-day risk period, this estimated background is 0.2 to 1.9 per 1 million person 7-day risk period.

Of the cases reported to VAERS, further investigation was performed to obtain more clinical information and to verify cases. Of the total 1640 reports, 877 met the case definition of myocarditis and 637 reports are still under review and need more information. Of the 877 meeting the case definition,²⁰ 829 were known to have been hospitalized. At the time of the report, 789 patients had been discharged. Of those, 607 (77%) were known to have recovered from their symptoms at the time of the report. A small number (34) were not hospitalized (e.g., were seen in the ED, urgent care, outpatient clinic, not specified). About 312 of the 877 received cardiac MRIs, with 223 of the 312 (72%) having an abnormal MRI.

Now to address deaths reported to VAERS with concern for myocarditis in persons <30 years of age among about 86 million doses from about 47 million individuals. When CDC receives reports of deaths through VAERS or other means, an extensive process is undertaken that includes reading reports submitted to CDC, reaching out to the reporter to acquire additional information, obtaining extensive medical records and autopsy reports if available, having discussions/meetings with the state health departments and the Medical Examiner (ME) for each death, and offering to review pathology samples at CDC to try to answer any questions that may be pertaining to the case in terms of diagnosis or potential causes. CDC is aware of 9 cases with concern for myocarditis for which information was available for 8 cases. The case for which there was no information available was in an adult 27 years of age with Trisomy-21. This case has been published in the literature and is available online. This case was reported as fulminant myocarditis, but it was not possible to confirm this as a myocarditis case because the individual did not have an MRI and an autopsy was not available. Therefore, a full investigation to look for other potential causes could not be undertaken by CDC.

Among the 8 individuals for whom information was available, 2 have an ongoing evaluation. Of the 6 individuals for whom evaluations have been completed, 3 were determined to have myocarditis and 3 were found not to have myocarditis on the review of pathology samples. These are felt to be other cardiac causes of sudden death for which there is a background rate as well, with no evidence of being due to myocarditis. For the cases with myocarditis, further investigation was completed looking for other potential infectious causes with classic myocarditis. There are bacterial, infectious, and other causes that can lead to myocarditis. A potential infectious cause of myocarditis was identified in each of the 3 cases found not to be COVID-19 vaccine-related myocarditis.

The term “myocarditis” technically means inflammation of the heart muscle, but types of myocarditis can differ in how it presents, is treated, and what the short- and long-term outcomes are. “Classic myocarditis” refers to myocarditis in a pre-COVID era. Within the COVID-19 era, 3 types of myocarditis have been observed: myocarditis related to COVID-19 infection, myocarditis related MIS-C, and COVID-19 vaccine-related myocarditis. Classic myocarditis could have a number of infectious etiologies (e.g., common viral, parasitic, bacterial, fungal, and protozoal agents), as well as non-infectious etiologies (e.g., toxins, hypersensitivity to medications, and immunologic syndromes). The incidence of classic myocarditis among children and infants is about 0.8 per 100,000 per year. Incidence among persons 15-18 years of age was 1.8 per 100,000 in 2015-2016. There is an early peak before 1 year of age, which is thought to be due primarily to genetic causes, but that rises again in adolescents. About 66% of cases are male and there has been significant mortality (4% to 7%) and morbidity (e.g., 4% to

²⁰ Definition available from Gargano JW, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices — United States, June 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:977–982. <https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7027e2-H.pdf>

9% transplant), especially in the pre-COVID era.²¹ There is a peak seen in adolescents and young adults, especially amongst males, that generally decreases over time. The percentage for females was static over time, with a slight peak in adults 50-60 years of age.²²

For MIS-C myocarditis, a paper was published earlier in 2021 regarding the first 1700 symptoms or cases of MIS-C reported to CDC. Myocarditis was listed on the case report form in about 300 cases (17%).²³ Data from COVID-NET showed that more than just myocarditis pertains to heart involvement in MIS-C. Of the first reported cases, 80% had cardiovascular involvement. Approximately 50% had elevated troponin, 73% had elevated brain natriuretic peptide (BNP), and 40% had decreased ejection fraction.²⁴ There have been some reports of myocarditis due to COVID-19 infection, which seems to be more of a problem in adults than in children. Based on aggregate data from Epic Cosmos™ and from the Children's Hospital Association Pediatric Health Information System® (PHIS®) database, most clinical myocarditis seen in pediatric patients is due to MIS-C. However, subclinical myocarditis would not be captured by clinical databases.²⁵

A medRxiv study published online²⁶ compared MIS-C-related myocarditis, classic viral myocarditis, and COVID-19 vaccine-related myocarditis. It did not include COVID-19 myocarditis, because there were insufficient cases defined that way. This study found that at least on presentation, cases of vaccine-related myocarditis looked very similar to classic myocarditis or pre-COVID myocarditis in terms of troponin, BNP, lymphocytes, white blood cells, C-reactive protein, and platelets. Looking at their cardiac function as measured by ejection fraction by echocardiogram, the picture was different. On initial presentation, about two-thirds each of the classic myocarditis group and MIS-C myocarditis group had a decrease in their ejection fraction. Just over 30% had a normal ejection fraction at presentation. In the vaccine-related myocarditis group, 7 of the 9 had a normal ejection fraction at presentation. It took a while for a number of the individuals in the classic myocarditis group to reach normal function, with about a third of them not reaching normal function by 2 weeks. Contrast that with the MIS-C myocarditis group in which almost all individuals regained normal function by 10 days after presentation. All individuals in the vaccine-related myocarditis group regained normal function. The 2 who had decreased function both regained normal function within a couple of days.

Regarding long-term outcomes, a study published early in 2021²⁷ looked at the outcomes in pre-COVID myocarditis and identified the characteristic variables that could be associated with good or poor long-term outcomes. Like the pre-COVID myocarditis group, the classic myocarditis with vaccine-related myocarditis tend to have chest pain at clinical presentation with little to no heart failure symptoms identified in the New York Heart Association (NYHA) Functional Classification. Patients tend to have a good outcome if their electrocardiogram (ECG or EKG) shows abnormalities that tend to be ST-elevation with a pericarditis pattern, their biomarkers show early rise and fast decline in troponin, and they have preserved ejection fraction at onset with early improvement or normalization. One variable associated with poor outcomes is that 72% of those who had an MRI had abnormalities and the presence of late

²¹ Vasudeva et al. *American J Cardiology*. 2021; Kyto et al. *Heart*. 2013; Ghelani et al. *Circ Cardiovasc Qual Outcomes*. 2012; Butts et al. *Pediatric Cardiology*. 2017; Sachdeva et al. *Am J Cardiol*. 2015.

²² Kyto et al. *Heart*. 2013.

²³ Belay et al. 2021, Trends in Geographic and Temporal distribution of US Children With Multisystem Inflammatory Syndrome During the COVID-19 Pandemic. *JAMA Pediatrics*.

²⁴ Feldstein et al. 2020, Multisystem Inflammatory Syndrome in US Children and Adolescents. *NEJM*.

²⁵ <https://www.epic.com/software#Cosmos> and <https://www.childrenshospitals.org/phish>

²⁶ Patel et al. 2021

²⁷ Piccirillo F, Watanabe M, Di Sciascio G. Diagnosis, treatment and predictors of prognosis of myocarditis. A narrative review. *Cardiovasc Pathol*. 2021 Sep-Oct;54:107362. doi: 10.1016/j.carpath.2021.107362. Epub 2021 Jun 27. PMID: 34192559.

gadolinium enhancement (LGE). What exactly this means for this particular group remains unclear.

Because of pre-COVID classic myocarditis and some of the long-term outcomes, the concern has been sudden cardiac event. The American Heart Association (AHA) and the American College of Cardiology (ACC) published guidelines²⁸ in 2015 recommending that before persons diagnosed with myocarditis return to competitive sports, they should undergo extensive cardiac testing including 24-hour Holter monitoring and exercise ECG no less than 3 to 6 months after the initial illness. The 2015 guidelines left the issue of whether resolution of myocarditis-related LGE should be required for return to competitive sports. Importantly, the recommendation at the time was independent of age, gender, and function. Given the lack of data in the current era while still learning about vaccine-related myocarditis, these guidelines often have been applied to those with vaccine-related myocarditis as well.

A 3-month follow-up review of cases with at least 1 follow-up visit since the initial episode was conducted using data from Vaccine Safety Datalink (VSD), which includes medical records data from a large network of health systems. The 3-month chart review assessed the status of cases in 4 areas: 1) recovered, no medication, without exercise restrictions or symptoms; 2) still symptomatic; 3) still on medication (primarily NSAIDs, colchicine); and 4) still on exercise and/or physical activity restrictions. About 30% of persons 12-17 years of age and about 40% to 50% of persons 18-39 years of age were recovered with no medication, exercise restrictions, or symptoms. About 25% of persons 12-17 years of age were still symptomatic according to their charts, 13% were still on medications, and 44% were still on exercise/physical activity restrictions.

In addition to the chart reviews, CDC launched an investigation of patients reported to VAERS to assess the long-term effects of myocarditis that involves conducting surveys of the patients (or their parents or guardians) and their HCPs to obtain information about myocarditis after mRNA COVID-19 vaccination.²⁹ CDC has reached just under 250 patients thus far and has asked for a self-report of whether the patients had particular symptoms (e.g., fatigue, palpitations, shortness of breath, chest pain) within the prior 2 weeks of the phone calls. The calls were made approximately 3 months after their initial myocarditis diagnosis. Each of the 4 symptoms was reported in about a quarter of patients at any point in the prior 2 weeks—not just at the time of the call. About half of patients reported no symptoms and about half reported at least 1 symptom within the prior 2 weeks. To date, the data are limited on cardiac testing. About 83% of electrocardiograms that were performed were normal and about 14% were borderline. About 88 of echocardiograms were normal. Only 15 cardiac MRIs were done among the study patients, with about 67% normal and 33% abnormal. When checked (N=25 cases), troponin was normal at 96%. Among cardiologists and other HCPs, 91% indicated that the patient was fully or probably recovered. Of the 91%, 74% said the patient had fully recovered and 17% said the patient was probably recovered, but they were awaiting additional information from further testing/MRI.

²⁸ Maron et al. JACC. 2015; Burns et al. J Peds X. 2020

²⁹ Vaccination <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myo-outcomes.html>

Discussion Summary

- Dr. Lee asked whether any differences in severity have been observed in distinguishing features in terms of the phenotype and outcomes between males and females and, if not, whether that might be worth studying moving forward.
 - Dr. Oster indicated that while they have not noticed a big difference, it certainly would be worth assessing moving forward for males and females. Overall, the epidemiology is classic myocarditis. What has been seen in vaccine-related myocarditis thus far is that it seems vary in terms of peaking in adolescents, though not as high in the older population. The post-vaccine side effects follow what has been seen for classic myocarditis in the younger age group, which is not expected to be as prevalent in adolescents.
- Dr. Poehling asked whether any disparities have been observed by race and ethnicity in hospitalizations or in COVID-related myocarditis.
 - Dr. Oster responded that at least in the younger population, little hospitalization is seen with COVID infection-related myocarditis. With MIS-C myocarditis, as is seen with MIS-C in general, hospitalization is definitely higher in African Americans. That is not fully explainable by their baseline COVID infection rates. It is higher in Hispanics, which is partially explained by the baseline COVID infection rates in the population. For other populations, there are not enough data to make strong determinations. For most of the cases for which race and ethnicity are known, myocarditis after vaccination tends to occur more often in whites, but with 2 caveats. First, race and ethnicity are not always listed on the VAERS report form. Second, it has not been possible to assess the percentages compared to the underlying vaccination rates. There are disparities in who is getting vaccinated, making it difficult to interpret the disparities in who is experiencing vaccine AEs.
- Dr. Brooks inquired as to whether there was increased incidence of myocarditis in VAERS reporting among persons under 30 years of age with underlying cardiac disease.
 - Dr. Oster indicated that for those on whom full investigations have been done, no strong patterns or major upticks have been seen so far in terms of co-morbidities and underlying diseases. Among the 877 cases reported to VAERS of persons ≤ 30 years of age, there were 9 or 10 deaths out of 86 million doses. Vaccine-related myocarditis could not be identified as the cause of death in any of those cases.
 - Along the same lines, Dr. Hogue asked whether there were any data about the risks among individuals with congenital cardiac defects/abnormalities of experiencing myocarditis resulting from receipt of Pfizer vaccine.
 - Dr. Oster reported that an increased risk for myocarditis has not been observed in those with congenital heart disease, either through his work with CDC or through his work as a pediatric cardiologist taking care of these patients. One study has been published and another was going through channels to be published that focus on children with congenital heart disease who have had severe COVID-19 that required hospitalization. These studies showed that once children were hospitalized, they were more likely to have critical outcomes requiring ICU-level support or more. His advice to families is that he is much more worried about what would happen to a

patient with congenital heart disease if they got COVID-19 versus getting the vaccine.

- Dr. Duchin requested further comment on myocarditis with COVID-19 being approximately 3 times more common than that associated with vaccination found in the Israeli study, and about vaccine-related myocarditis among children 5 to 11 years of age.
 - Dr. Oster pointed out that so far, the epidemiology for vaccine-related myocarditis by age and sex appears to be following the pattern that has been seen with classic myocarditis. There is no reason to suspect that this would differ in children under 12 years of age. There are a number of pathophysiological mechanisms and rationales for why that is. One of the most common thoughts is that testosterone plays a role, which fits the profile over time by sex and age.
 - Dr. Long added that she has managed a couple of manuscripts on patients who had myocarditis for other reasons. One was a typical viral-type myocarditis who was recovering who got the vaccine, 2 days later had chest pain, and had a recurrence of their myocarditis with vaccine-associated pericarditis. The other was a young man who 20 days after his first dose of vaccine had typical vaccine-associated myopericarditis. Then 2 to 3 weeks later after Dose 2, he had typical 2-day myopericarditis. Therefore, one could be thought to have had typical myocarditis who still could have vaccine-associated myopericarditis. Therefore, it is possible someone could have underlying typical viral myopericarditis that was exacerbated by the vaccine.
 - Dr. Oster acknowledged that people can be walking around for weeks or months with myocarditis and then have something push them over the edge, such as an infectious stressor or something else. It is possible that vaccine could be the stressor. While this will be a difficult question to answer without knowing someone's baseline, it is certainly worth considering and trying to capture when possible.
 - To help parents better weigh the risk of vaccinating their children 5-11 years of age in terms of myocarditis, Dr. Shah suggested further quantifying the relative risk reduction or the differences in risk from vaccine-associated myocarditis versus COVID-19-associated. In effect, this would translate the information on Slide 10 into a rate and incident and have that on a bar graph alongside what is shown on Slide 4 on the risk of vaccine-associated myocarditis to demonstrate the risk for each of those. This would be extremely helpful from a communications perspective.
- Ms. McNally requested that Dr. Oster discuss the current management approach for myocarditis in the adolescent age group and whether imaging is part of the work-up for these patients and asked whether it is less likely that children 5-11 years of age will have vaccine-related myocarditis than adolescents based on the epidemiology, and if the benefits of vaccination in children 5-11 years of age outweigh the potential risk of vaccine-related myocarditis in his professional opinion and to a reasonable degree of medical certainty with the information currently available.
 - Dr. Oster indicated that primary management is symptom-based in terms of assessing how the person is presenting. For instance, chest pain is a prominent feature so treating with pain medicine is going to be a first-line treatment. Many children with vaccine-related myocarditis have received non-steroidal anti-

inflammatory drugs (NSAIDs) like ibuprofen. If there are cardiac problems, such as poor heart function or other cardiac manifestations, cardiac medications are considered (e.g., diuretics, rhythm-monitoring agents). For those who are critically ill, critical measures are instituted as needed. While cardiac manifestations or critical illness are common features of classic myocarditis, this has not been seen much in vaccine-related myocarditis in children. In terms of imaging, the first step is to look at cardiac manifestations. EKG and ECG are very common, along with looking for biomarkers such as troponin and BNP. MRIs can be institution-dependent. Some institutions will do an MRI if the diagnosis is unclear or for monitoring purposes in the acute or long-term phase to look for evidence of inflammation in the heart.

- In terms of whether it is less likely that children 5-11 years of age will have vaccine-related myocarditis than adolescents, Dr. Oster did not think the pediatric trials were sufficiently powered to determine this.
- Dr. Oster indicated that in his professional opinion, the benefits of vaccination in children 5-11 years of age outweigh the risk of vaccine-related myocarditis.

Vaccine Safety Surveillance in Children

Dr. Tom Shimabukuro (CDC/NCEZID) discussed surveillance systems and processes for monitoring vaccine safety among children, emphasizing that COVID-19 vaccines are being administered under the most intensive vaccine safety monitoring effort in history. CDC's strong and complementary systems include v-safesm, VAERS, VSD, and the Clinical Immunization Safety Assessment (CISA) Project. A full list of US COVID-19 vaccine safety monitoring systems is available on the CDC website.³⁰

v-safesm is CDC's smartphone-based active safety monitoring system that was developed for COVID-19.³¹ It uses text messaging and secure web-based surveys. It is now available to enroll children and for third-dose reporting. Participants can register themselves and their dependents through a voluntary self-registration process after Dose 1, 2, or 3. Dependents can be added even if the primary smartphone account is not a v-safesm participant. The parent or guardian must create a profile and then add the dependent. The text messaging is directed to the parent or guardian. The v-safesm check-in schedule is the same for all ages: Once a day (days 0–7), once a week (weeks 2–6), and once a month (months 3, 6, and 12). The schedule restarts after each dose received. v-safesm will aggregate data from health surveys completed on Days 0-7 after vaccination for children 5-11 years of age. The analytic plan for this age group will be to describe the data based on demographics (e.g., sex, median age, race/ethnicity), local and systemic reactions, and health impacts by dose received. The reactogenicity profile for children 5-11 years of age will be compared to adolescents 12-17 years of age. Reports to VAERS solicited by active telephone follow-up of v-safesm participants are included in VAERS analyses.

VAERS is a jointly operated spontaneous reporting or passive surveillance system operated by CDC and FDA.³² VAERS accepts reports from anyone regardless of the plausibility of the vaccine causing the event or the clinical seriousness of the event. Its key strengths are that it can rapidly detect potential safety problems and can detect rare AEs. The key limitations of VAERS are that it is a passive surveillance system that has inconsistent quality and completeness of information, reporting biases, and generally cannot be utilized alone to

³⁰ <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety.html>

³¹ <http://cdc.gov/vsafe>

³² <http://vaers.hhs.gov>

determine cause and effect. The VAERS pre-specified AESIs as of October 27th include: death; acute myocardial infarction; anaphylaxis; coagulopathy (e.g., thrombocytopenia, deep venous thrombosis or pulmonary embolism, or disseminated intravascular coagulopathy); Guillain-Barré Syndrome (GBS); Kawasaki disease; MIS-C; myocarditis, myopericarditis, and pericarditis; narcolepsy/cataplexy; seizure; stroke; thrombosis with thrombocytopenia syndrome (TTS); and transverse myelitis. The assessment of these AESIs includes a clinician review of the VAERS report, follow-up to obtain/review medical records, application of case definitions, and adjudication to classify the report with respect to the case definition.

There will be a specific focus on myocarditis/pericarditis reports in children 5-11 years of age. Potential reports are identified by Medical Dictionary for Regulatory Activities (MedDRA) standardized codes assigned to reports that could indicate a potential myocarditis or pericarditis case. Clinical abstraction includes a review of the initial report, outreach to the healthcare provider involved in the report of a patient's care, request and review of medical records, and comparison of abstracted data elements against the CDC case definitions for myocarditis and pericarditis. CDC will conduct periodic analyses of case counts and reporting rates and comparison of reporting rates to background.

The VSD is an electronic health record (EHR)-based system that includes 9 participating integrated health care organizations with data on over 12 million persons per year. The VSD conducts rapid cycle analyses (RCA). The aims are to monitor the safety of COVID-19 vaccines weekly using pre-specified outcomes of interest and to describe the uptake of COVID-19 vaccines over time. Surveillance in the VSD began in December 2020. The VSD analytics strategy statistical analysis will be similar to what has been done for other age groups but will include stratified analysis on children 5-11 years of age. For the primary analysis, the number of outcomes observed in a risk interval after vaccination will be compared to the number expected. The risk intervals are 0-7 days for myocarditis/pericarditis and seizures and 1-21 days for other outcomes. The expected is derived from "vaccinated concurrent comparators" who are in a comparison interval of 22-42 days after COVID-19 vaccination. On each day that an outcome occurs, vaccinees who were in their risk interval are compared with similar vaccinees who were concurrently in their comparison interval. Comparisons will be adjusted for by single year of age, sex, race/ethnicity, VSD site, and calendar date.

For children 5-11 years of age, VSD will continue to review medical records and adjudicate any potential cases of myocarditis/pericarditis identified within 1-98 days following any COVID-19 vaccination. In addition, VSD will conduct chart review of all identified cases of GBS, Acute disseminated encephalomyelitis (ADEM), transverse myelitis, anaphylaxis, and cerebral venous sinus thrombosis (CVST) within 1-98 days following any COVID-19 vaccination. VSD is able to capture information on simultaneous vaccinations.

The CISA Project is a collaboration between CDC and 7 participating medical research centers. CISA COVID-19 vaccine core activities include clinical case reviews and clinical consults on complex cases of vaccine AEs; technical consultation on clinical guidance and clinical considerations for use of COVID-19 vaccines; contributions to enhance surveillance for AEs; and clinical research, including in pediatric populations. More information about clinical consults is available on the CDC website.³³

³³ <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html>

In terms of other federal programs, FDA's COVID-19 surveillance programs include the Center for Biologics Evaluation and Research (CBER) active surveillance program and the Biologics Effectiveness and Safety (BEST) system and collaborations with federal partners. The Indian Health Service (IHS) vaccine safety monitoring systems include passive surveillance with VAERS through a collaboration with CDC and the IHS Safety Tracking and Response System. IHS also conducts active surveillance through the IHS Sentinel Survey. The Department of Defense (DoD) also monitors DoD VAERS reports through a collaboration with CDC. They have a system known as the Vaccine Adverse Event Clinical System (VAECS), the DoD Electronic Health Record and Defense Medical Surveillance System (AHLTA/MHS GENESIS), and the Joint Trauma System/COVID 19 Vaccine Breakthrough Metrics. The DoD detected the initial safety signal for myocarditis through monitoring in their active duty population, and they are a key partner in safety monitoring.

The COVID-19 Vaccine Safety Technical (VaST) WG serves as the central hub for technical subject matter expertise from federal agencies conducting post-authorization and post-approval safety monitoring. They meet weekly or biweekly to review data on AESIs. They share learning, including all members, federal partners, and subject matter experts (SMEs). They review, evaluate, and interpret post-authorization safety data and advise the federal agencies on monitoring, analyses, and interpretation of data. There also is independent discussion of findings by the VaST WG members. The VaST WG's plans for children 5-11 years of age are to review safety in this age group as soon as available, continue close review of myocarditis data, and provide updates to the ACIP COVID-19 Vaccines WG and ACIP on COVID-19 vaccine safety.

In closing, Dr. Shimabukuro made a plea to health care and public health partners and to the public, especially parents/guardians of children and those getting booster doses, to participate in vaccine safety. Participation matters. Everyone can help CDC by getting involved in terms of reporting AEs following vaccination to VAERS, even if not sure whether the vaccination caused the AE, and by enrolling in v-safesm. HCP can encourage their patients to enroll in v-safesm and parents/guardians can enroll their children in v-safesm.

Discussion Summary

- ACIP members emphasized that since December 2020, these multiple surveillance systems have demonstrated the ability to detect rare AEs following vaccination. They are designed to assess the situation rapidly and the findings are communicated transparently to the public and policymakers at FDA and CDC. There have been instances of the data from these systems being deliberately misrepresented, which can cause concern/confusion among the public. However, these large and distinct systems are reassuring and are constantly evaluating the safety of COVID-19 vaccines, including for new groups. With over 420 million doses administered in the US, there is an extensive amount of data to date.

Implementation of COVID-19 Vaccine Pediatric Program

Dr. Kevin Chatham-Stevens (CDC/NCIRD) described some of CDC's work in preparation for vaccination among children 5-11 years of age. High-level implementation goals are to: 1) enable access to and availability of vaccine providers where populations are most likely to seek vaccination in order to reach the most families and children possible; 2) establish programming to ensure vaccine access for vulnerable, underserved, and hard-to-reach pediatric populations; 3) minimize delays between FDA authorization of pediatric vaccines and initial rollout of pediatric administration; and 4) disseminate timely clinical guidance to jurisdictions and

providers. To achieve each of these goals, CDC is harnessing the existing robust pediatric vaccination network in the US, complementing that network with additional sites and building on successes and lessons learned from the adult and adolescent vaccine programs.

Regarding the approach to reaching children through a variety of settings, utilization of providers serving children 5-11 years of age is the optimal location for many children to be vaccinated. This includes clinical settings such as primary care clinics, Federally Qualified Health Centers (FQHCs), rural health clinics (RHCs), health departments, IHS clinics, and others who can help ensure vaccine equity and broad coverage. Given that not every child 5-11 years of age has a medical home, the medical home will be complemented by other vaccine providers. For instance, pharmacies will be leveraged to administer a vaccine to children who may not seek or have access to care in a pediatric practice. In addition, schools can partner with vaccine providers such as health departments, pediatric clinics, FQHCs, and pharmacies to host school-located vaccination clinics. School-located vaccination clinics can provide a convenient option for parents and caregivers who may experience challenges taking their child to a clinic. As announced by the White House recently as part of several key initiatives, more than 100 children's hospitals will set up vaccination sites. This will be a critical part of efforts to provide vaccine access for children, especially those with underlying medical conditions.

Jurisdictions also may use temporary community clinics, leveraging the experience with these clinics from the adult and adolescent vaccine programs. To assess jurisdictions' plans to use various COVID-19 vaccination providers for children 5-11 years of age, CDC surveyed 64 state and local health departments in late September. Of the 64 jurisdictions, 58 responded to the question regarding which providers they plan to use to deliver the vaccine. It is important to note that these options were not mutually exclusive. Jurisdictions seem to be using an "all of the above" approach, with most jurisdictions planning to use large pediatric providers, VFC providers, pharmacies, temporary community vaccine clinics, and temporary school-located vaccine clinics. In a follow-up survey, jurisdictions were asked to rank the settings in which they anticipated that most children 5-11 years of age would be vaccinated. Pediatric providers were the most highly ranked, followed by FQHCs/RHCs, health departments, and pharmacists.

A parental survey was conducted by CDC, RAND, and the University in late September/early October among just over 1000 parents of children 5-11 years of age. Almost two-thirds of parents felt comfortable having their child vaccinated in their regular doctor's office or clinic, followed by the pharmacy or in another doctor's office or clinic. Approximately a quarter of parents felt comfortable having their child vaccinated at school with the parent present and about 15% felt comfortable without the parent present. Thus, surveys of both jurisdictions and parents indicate that children 5-11 years of age likely will be vaccinated across a variety of settings.

Data from the 2 jurisdictional surveys have helped to guide CDC's outreach and planning and identify key issues. In addition, the agency has disseminated an Operational Planning Guide³⁴ and preliminary information about the Pfizer BioNTech vaccine.³⁵ The Operational Planning Guide includes key information about the vaccine, assumptions to inform planning, and strategies for jurisdictions to consider implementing. For example, a checklist in the document includes various tasks such as jurisdictions routinely evaluating the adequacy of the provider network, identifying gaps, and determining whether additional vaccination locations (e.g., FQHCs, pharmacies, school-located vaccination clinics, or RHCs) may be needed to further

³⁴ <https://www.cdc.gov/vaccines/covid-19/downloads/Pediatric-Planning-Guide.pdf>; <https://www.cdc.gov/vaccines/covid-19/planning/children.html>

³⁵ <https://www.cdc.gov/vaccines/covid-19/downloads/Pfizer-Pediatric-Reference-Planning.pdf>

increase equitable access and ensure vaccine equity. The document about the Pfizer BioNTech vaccine includes a side-by-side comparison of the adult/adolescent formulation and the formulation for children 5-11 years of age. CDC also is working to provide guidance on, and support of, school districts partnering with pharmacies to conduct school-located vaccine clinics. Resources for schools are available on the CDC website.³⁶ CDC also has conducted numerous listening sessions with a variety of public health, clinical, and other partners to hear about potential challenges in the rollout of the vaccine and what resources CDC or others could provide to help facilitate the rollout.

Discussion Summary

- Dr. Daley requested information about communication plans for providers and the public, given that considerations pertaining to myocarditis may be the focal point of many parents' decision to vaccinate.
- Dr. Chatham-Stevens indicated that CDC's communications experts have done a fantastic job of laying out a plan to make sure the agency is communicating to key populations such as parents, providers, and partners (e.g., health departments and academic professional societies) so that they can amplify the messages. This includes the key points that have been eloquently laid out previously that COVID-19 presents a risk to children and that the risk must be balanced with the potential side effects. Communications materials will be disseminated in the coming days on this topic.
- Dr. Poehling inquired about the extent to which input was acquired from historically marginalized populations to inform the implementation planning process.
- Dr. Chatham-Stevens stressed that vaccine equity is definitely top of mind for CDC and state, territorial, local, and tribal health departments. This is an opportunity to build on the lessons learned and successes from the adult and adolescent rollout. The agency has numerous resources online, including various toolkits, that are aimed at various partners to help ensure that equity work is being incorporated across the vaccine program. Each of the settings he described can contribute to this. For instance, the VFC program has done a great job historically of providing vaccine to children whose families may not be able to afford the vaccine otherwise. FQHCs, RHCs, school-located vaccine clinics, and travel health care partner providers also can help to ensure that vaccine is available for their particular populations. Due to transportation and other challenges, some families cannot make it to a clinic during regular business hours. Vaccine availability at pharmacies and school-located vaccine clinics can help to ensure that the vaccine is widely available to various populations.

Clinical Considerations for COVID-19 Vaccination in Children

Dr. Kate Woodworth (CDC/NCEZID) explained that the interim clinical considerations provide additional information to healthcare professionals and public health officials on the use of COVID-19 vaccines and are informed by ACIP/CDC recommendations; data submitted to the FDA; and other data sources, such as general best practice guidelines for immunization and expert opinion. This presentation included a review of the Pfizer-BioNTech COVID-19 vaccine formulation and dosing for children 5-11 years of age; proposed considerations for vaccine recipients (e.g., those with underlying medical conditions, prior SARS-CoV-2 infection, and/or a

³⁶ <https://www.cdc.gov/vaccines/covid-19/planning/school-located-clinics/how-schools-can-support.html>

history of MIS-C); patient and parent/guardian counseling; and vaccine administration, including co-administration and administration errors.

The Pfizer-BioNTech COVID-19 vaccine for children 5-11 years of age is a new and different formulation from the current formulation for persons 12 years of age and older. The formulation for children 5-11 years of age comes in an orange capped vial as opposed to the purple vial for those 12 years of age and older. The dose will be 10 µg, a third of the concentration of the mRNA vaccines in the purple capped and older formulation for those 12 years of age and older. The formulation for children 5-11 years of age requires a different injection volume and amount of diluent, will contain 10 doses per vial, is stable at ultra-low temperatures (-90°C to -60°C) for up to 6 months, and can be stored at routine refrigerator temperatures (2°C to 8°C) for 10 weeks.

Similar to the formulation for those 12 years of age and older, children 5-11 years of age would receive 2 doses spaced 3 weeks apart. Currently, children 5-11 years of age with moderate and severe immunocompromise are not recommended to receive an additional, or third, primary dose. ACIP and CDC will continue to evaluate the data to update these recommendations if needed. Booster doses are not recommended for anyone under 18 years of age. Children should receive the age-appropriate vaccine formulation regardless of their size or weight. As opposed to many medications, vaccine dosages are based on age, not weight or body size. In general, the formulation and dosage should be based on the child's age on the day of vaccination. However, if a child turns 11 to 12 years of age in between their first and second doses and receives the 5–11 years 10 µg (orange cap) for their second dose, they do not need to repeat the dose and this is not considered an error per the EUA.

Children with underlying medical conditions may be at increased risk for severe illness from COVID-19.³⁷ However, severe COVID-19 can occur in children with and without underlying medical conditions. As the policy question for ACIP currently stands, COVID-19 vaccination would be recommended for everyone 5 years of age and older regardless of underlying medical conditions. People with known current SARS-CoV-2 infection should defer vaccination, at least until the person has recovered from their acute illness, if the person has symptoms and they have met criteria for discontinuing isolation.³⁸ Serologic testing to assess for prior infection is not recommended for the purpose of vaccine decision-making.³⁹ As the policy question for ACIP currently stands, COVID-19 vaccination would be recommended for everyone 5 years of age and older, regardless of a history of symptomatic or asymptomatic SARS-CoV-2 infection or seropositivity. More than 7 million adolescents 12-15 years of age have been fully vaccinated with a Pfizer-BioNTech COVID-19 vaccine in the US.⁴⁰

In the general population, there have been no safety concerns associated with vaccination of those who have had prior infection. Additionally, data from clinical trials in children 5-11 years of age indicate that the Pfizer-BioNTech COVID-19 vaccine can be safely given to those of evidence of prior SARS-CoV-2 infection. Current evidence suggests that protection from reinfection is high after initial infection but decreases with time due to waning immunity. Substantial heterogeneity exists in the individual immune responses to infection. In adults, asymptomatic infection leads to lower antibody levels. Growing epidemiologic evidence from adults and adolescents indicates that vaccination following infection increases protection from

³⁷ <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html#ChildrenAndTeens>

³⁸ <https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html>

³⁹ <https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html>

⁴⁰ <https://covid.cdc.gov/covid-data-tracker/#vaccination-demographic>

subsequent infection, including in the setting of more infectious variants.⁴¹ There are numerous limitations to antibody testing. Antibody tests cannot determine when a person was infected. Antibody tests vary greatly in their sensitivity, particularly more than 3 months after infection. People can test positive on commercial antibody tests even after other markers of immunologic response, such as neutralizing antibodies, have waned. At this time, there is no FDA-authorized or approved test that providers or the public can use to reliably determine whether a person is protected from infection.

For children with a history MIS-C, the benefits of COVID-19 vaccination are likely to outweigh any theoretical risk of a MIS-like illness or the known risks of COVID-19 vaccination if they meet all the following criteria: 1) clinical recovery has been achieved, including return to normal cardiac function; 2) it has been ≥ 90 days since their diagnosis of MIS-C; 3) they are in an area of high or substantial community transmission of SARS-CoV-2, or otherwise have an increased risk for SARS-CoV-2 exposure and transmission; and 4) onset of MIS-C occurred before any COVID-19 vaccination. COVID-19 vaccination may also be considered for children with a history of MIS-C who do not meet all the prior criteria. However, experts view clinical recovery, including return to normal cardiac function, as an important factor when considering COVID-19 vaccination. Additional factors when considering individual benefits and risks may include an increased personal risk of severe COVID-19 (e.g., age, underlying conditions) and timing of immunomodulatory therapies. If a child develops MIS-C or a similar clinical illness after receiving a COVID-19 vaccine, referrals to a specialist should be considered. Because MIS-C is a condition known to occur with SARS-CoV-2 infection, these individual should be assessed for laboratory evidence of current or prior SARS-CoV-2 infection. Any cases should be reported VAERS.⁴² Consultation is available to healthcare providers and health departments from the CISA Project.⁴³

With respect to counseling patients and parents/guardians on expected side effects from Pfizer-BioNTech COVID-19 vaccine, children may experience fewer side effects than adolescents or young adults based on the clinical trial data presented earlier in the day. Children with evidence of prior infection may have fewer side effects than those without evidence of prior infection.⁴⁴ The expected side effects are similar to those seen in adolescents and include local reactions (e.g., pain, swelling, erythema at the injection site) and/or systemic reactions (e.g., fever, fatigue, headache, chills, myalgias, arthralgia, lymphadenopathy). While preemptive medication prior to vaccination is not routinely recommended, routine antipyretic or analgesic medications can be taken for the treatment of post-vaccination local or systemic reactions if medically appropriate. In general, aspirin is not recommended for use in children and adolescents ≤ 18 years due to risk of Reye's syndrome.

Myocarditis and/pericarditis have occurred rarely in some people following receipt of mRNA COVID-19 vaccines, typically within a few days following receipt of the second dose. What is known about this risk comes from post-marketing data available from adolescents and adults. The highest risk observed has been in males 12-29 years of age.⁴⁵ The risk of myocarditis or

⁴¹ Dan 2021, Science: <https://doi.org/10.1126/science.abf4063>; Cavanaugh 2021, MMWR; 70(32):1081-3. Lumley 2021; Clin Infect Dis; doi: 10.1093/cid/ciab608. Gazit 2021, medRxiv; <https://doi.org/10.1101/2021.08.24.21262415>. Shenai 2021, medRxiv; <https://doi.org/10.1101/2021.09.12.21263461>.

⁴² <https://vaers.hhs.gov/reportevent.html>

⁴³ <http://www.cdc.gov/vaccinesafety/Activities/CISA.html>

⁴⁴ <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/comirnaty-and-pfizer-biontech-covid-19-vaccine>

⁴⁵ Gargano JW, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices — United States, June 2021. MMWR Morb Mortal Wkly Rep 2021;70:977–982. DOI: <http://dx.doi.org/10.15585/mmwr.mm7027e2>

pericarditis after receipt of an mRNA COVID-19 vaccine in adolescents and adults is lower than the risk of myocarditis associated with SARS-CoV-2 infection in adolescents and adults.⁴⁶ No cases of myocarditis or pericarditis were reported in the clinical trial for children 5-11 years of age, which included 3,082 children followed for at least 1 week after Dose 2. However, the study was not powered to assess the risk of myocarditis.⁴⁷ As discussed earlier, the baseline risk of myocarditis prior to the COVID-19 pandemic was much higher in adolescents 12-17 years of age compared to children 5-11 years of age.

The FDA has authorized the Pfizer-BioNTech COVID-19 vaccine in children 5-11 based on the determination that the benefits of COVID-19 vaccination outweigh the risk in this population. People receiving mRNA COVID-19 vaccine, especially males less than 30 years of age, should be made aware of the possibility of myocarditis or pericarditis following receipt of mRNA COVID-19 vaccines and informed to seek care for symptoms of chest pain; shortness of breath; or feelings of having a fast beating, fluttering, or pounding heart. Any cases of myocarditis or pericarditis after vaccination should be reported to VAERS.⁴⁸

COVID-19 vaccines may be administered without regard to timing of other vaccines. This includes simultaneous administration of COVID-19 vaccine and other vaccines on the same day. This is all the more important as influenza season begins in order to ensure that children are protected against both influenza and COVID-19. If multiple vaccines are administered at a single visit, they should be administered at different injection sites separated by 1 inch or more and according to recommendations by age.⁴⁹ If more than 2 vaccines are injected into a single limb in younger children 5-10 years of age, the vastus lateralis muscle of the anterolateral thigh is preferred site because of greater muscle mass. For children ≥ 11 years of age, the deltoid muscle can be used. In terms of vaccinating before someone's eligible birthday, the 4-day grace period that is in place for other vaccines would apply to this population as well.

With a new formulation for children 5-11 years of age, it is important to highlight a couple possible administration errors. Importantly, the formulation of the Pfizer-BioNTech COVID-19 vaccines are not interchangeable. If a child 5-11 years of age inadvertently receives a Pfizer-BioNTech purple capped 30 μg dose for their first dose, they should receive a single age-appropriate 10 μg dose for their second dose 21 days later and should be considered as having completed a primary series. If a child 5-11 years of age inadvertently receives a 30 μg dose for their second dose, they should be considered as having a completed primary series. Administration errors should be reported to VAERS. The Clinical Considerations website provides a much longer table with additional possible administration errors, as well as actions to take after an error has occurred.⁵⁰ CDC is updating many current tools to help providers with the information they need to provide these vaccines safely. All of the information discussed during this presentation be found on the CDC website page with the Interim Clinical Consideration for Use of COVID-19 Vaccines, which will be updated to include information on children 5-11 years of age in the coming days.

⁴⁶ Boehmer TK, Kompaniyets L, Lavery AM, et al. Association Between COVID-19 and Myocarditis Using Hospital-Based Administrative Data — United States, March 2020–January 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:1228–1232. DOI: <http://dx.doi.org/10.15585/mmwr.mm7035e5>

⁴⁷ <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/comirnaty-and-pfizer-biontech-covid-19-vaccine>

⁴⁸ <https://vaers.hhs.gov/reportevent.html>

⁴⁹ <https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html>

⁵⁰ <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html>; Updates will be posted at: <https://www.cdc.gov/vaccines/covid-19/info-by-product/index.html>

Discussion Summary

- Dr. Amanda Cohn (CDC) noted that this presentation was given prior to the EtR Framework presentation because there are so many clinical considerations, which ACIP members already raised throughout the day. She emphasized that the clinical considerations would be predicated on ACIP voting to recommend vaccination for children 5-11 years of age.
- Questions were raised regarding whether parents or guardians would be given an EUA Fact Sheet or Vaccine Information Statement (VIS), what information would be included regarding myocarditis in this age group, what information would be provided about the protocol in a scenario in which someone experiences myocarditis/pericarditis after their first dose, and whether vaccine injuries among children 5-11 years of age would go through the Countermeasures Injury Compensation Program (CICP).
 - Dr. Cohn indicated that CDC is working on other parent education materials that distill the provider fact sheet into the key messages that would be important for parents to understand prior to vaccination. CDC will ensure that its communication materials include information about the potential AE of myocarditis for parents of children 5-11 years of age and adolescents 12-17 years of age.
 - Dr. Fink (FDA) added that the EUA Fact Sheet for Vaccination Providers and the EUA Fact Sheet for Vaccine Recipients/Caregivers for the new lower dose formulation for use in children 5-11 years of age includes the same language regarding the risk of myocarditis as currently appears in the Fact Sheet for the 30 µg formulation that is authorized for use in persons 12 years of age and above. To summarize, the Warning Statement notes that a risk of myocarditis in the week following Dose 2 has been observed and appears to be greatest in males under 40 years of age. It also states that in most cases, symptoms have resolved with conservative management but that longer-term follow-up is needed.
 - Dr. Woodworth indicated that the existing Clinical Considerations address a scenario in which a vaccine recipient experiences myocarditis after their first dose of an mRNA vaccine. While this will be updated somewhat, the same scenario would apply for adults as well as children who develop myocarditis after their first dose. It is possible that the preference would be to defer the second dose, but this would be discussed with a clinical team to decide whether a second dose should be administered and under what scenario.
 - It was confirmed that vaccine injuries among children 5-11 years of age would go through the CICP.

EtR Framework: Pfizer-BioNTech COVID-19 Vaccine in Children Aged 5-11 Years

Dr. Sara Oliver (CDC/NCBDDD) presented the EtR Framework for the policy question, “Should vaccination with Pfizer-BioNTech COVID-19 vaccine (2-doses, 10µg, IM) be recommended for children 5-11 years of age, under an Emergency Use Authorization?” For the PICO question, the population is children aged 5-11 years; the intervention is Pfizer-BioNTech COVID-19 vaccine (BNT162b2, 2-doses, 10µg, IM); the comparison is no vaccine; and the outcomes are: symptomatic laboratory-confirmed COVID-19, hospitalization due to COVID-19, MIS-C, asymptomatic SARS-CoV-2 infection, SAEs, and reactogenicity of Grade ≥3. As a reminder, the

EtR domains include the Public Health Problem, Benefits and Harms, Values, Acceptability, Feasibility, Resource Use, and Equity.

Regarding the public health problem, over 45 million COVID-19 cases were reported in the US between January 22, 2020 and October 29, 2021. The current 7-day moving average is approximately 70,000 cases per day.⁵¹ To summarize the epidemiology of SARS-CoV-2, over 1.9 million cases have been reported in children 5-11 years of age. Infections in children are less likely to be reported as cases than infections in adults. Children 5-11 years of age are at risk for severe illness from COVID. The cumulative hospitalization rate for COVID is similar to pre-pandemic influenza seasons. Severity is comparable among children hospitalized with influenza and COVID-19, with approximately 1/3 of hospitalized children 5-11 years of age requiring ICU admission. In addition, MIS-C is most frequently reported among children in this age group. Post-COVID conditions have been reported in children. Secondary transmission from these young school-aged children can and does occur in household and in school settings.

To put this epidemiology into other contexts, additional hospitalizations per year prior to the recommended pediatric vaccines varied by disease. COVID-19 just in children 5-11 years of age is in line with many of the diseases for which vaccination is routinely recommended.⁵² Average deaths per year prior to recommended pediatric vaccines also varied by disease. In just children 5-11 years of age, COVID-19 is among the highest deaths across these now vaccine-preventable diseases.⁵³ Through collaborations with the CDC Modeling Team and the COVID-19 Scenario Modeling Hub Consortium, multi-model projections were created to evaluate the impact of vaccination of children 5-11 years of age on COVID-19 cases and hospitalizations in this population.⁵⁴ They assumed vaccination started November 1, 2021 and would have similar uptake rates as adolescents 12-17 years of age. Scenarios projected cases prevented in the presence or absence of pediatric vaccination and in the presence or absence of a new, more transmissible variant. Their pooled projections showed that vaccination among children 5-11 years of age is expected to accelerate the decline in cases currently being experienced, reducing the cumulative incidence nationally by an expected 8% (~600,000 cases) from November of 2021 through March of 2022. The emergence of a more transmissible variant could impact future COVID-19 epidemiology and projected impact. The models estimate that vaccination of children 5-11 years of age would dampen but not prevent a resulting resurgence.

In addition to the severe outcomes of hospitalization, ICU admission, and death, missed school is another potential adverse outcome of COVID-19 illness and exposure among children. Numerous reports have described the negative impact on the social, emotional, and physical health of children, with disproportionate impacts on children of color. The School Dismissal Monitoring System performs daily systematic searches of Google, Google News, and Google Alerts to assess information on unplanned school closures, including the number of districts, individual schools, students, and teachers impacted. In this school year to date, over 2,000 schools had unplanned closures impacting nearly 1.2 million students. For the 2020-2021

⁵¹ https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases

⁵² <https://www.cdc.gov/mmwr/preview/mmwrhtml/ss5603a1.htm> (Hepatitis A); Meyer PA, Seward JF, Jumaan AO, Wharton M. Varicella mortality: trends before vaccine licensure in the United States, 1970-1994. *J Infect Dis.* 2000;182(2):383-390 (Varicella) doi:10.1086/315714; and <https://www.cdc.gov/flu/weekly/weeklyarchives2007-2008/07-08summary.htm> (Influenza)

⁵³ Vogt TM, Wise ME, Bell BP, Finelli L. Declining hepatitis A mortality in the United States during the era of hepatitis A vaccination. *J Infect Dis* 2008; 197:1282-8; National Notifiable Diseases Surveillance System with additional serogroup and outcome data from Enhanced Meningococcal Disease Surveillance for 2015-2019; Meyer PA, Seward JF, Jumaan AO, Wharton M. Varicella mortality: trends before vaccine licensure in the United States, 1970-1994. *J Infect Dis.* 2000;182(2):383-390. doi:10.1086/315714; Roush SW, Murphy TV; Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. *JAMA* 2007; 298:2155-63; and Glass RI, Kilgore PE, Holman RC, et al. The epidemiology of rotavirus diarrhea in the United States: surveillance and estimates of disease burden. *J Infect Dis.* 1996 Sep;174 Suppl 1:S5-1

⁵⁴ <https://covid19scenariomodelinghub.org/>

school year, at least 19,000 school closures occurred in all 50 US states affecting at least 12 million students.⁵⁵ A larger and growing body of literature describes the numeric indirect impacts from the COVID-19 pandemic on children. A few of these include worsening of mental or emotional health, widening of existing education gaps, decreasing physical activity and increasing body mass index (BMI), decreasing healthcare utilization, decreasing routine immunizations, increasing Adverse Childhood Experiences (ACEs), and/or loss of caregivers. An estimated 140,000 children have lost a caregiver to COVID-19. This is by no means an exhaustive list. For all of the indirect impacts, children of color have been disproportionately impacted.

To summarize the public health problem, children 5-11 years of age are at increased risk of severe illness from COVID. This includes hospitalization as well as MIS-C. Other post-COVID conditions have been seen in children. COVID in children leads to missed school for themselves and their communities. Wide use of an effective vaccine would reduce the public health burden of COVID in children 5-11 years of age. The WG felt that COVID-19 disease among children in this age group is an important public health problem.

For the domain of benefits and harms, Dr. Oliver provided an overview of GRADE outcomes, potential benefits and harms in seropositive children, and potential risk of myocarditis. A systematic review was conducted to identify evidence related to the policy question, which identified 1 clinical trial for inclusion. There also were data from the trial described earlier for the critical outcome of the prevention of laboratory-confirmed symptomatic COVID-19. There was a 2:1 randomization of vaccine to placebo and a median follow-up time of 3.3 months. The primary efficacy endpoint selected was the estimate among children with or without prior evidence of SARS-CoV-2 infection as it best reflects what may be seen as a real-world estimate. There were 3 COVID cases occurring at least 7 days post-Dose 2 among approximately 1,400 children in the vaccine arm and 16 cases among approximately 700 children in the placebo arm, which resulted in a VE estimate of 90.9%. The Phase 2/3 trial was designed and powered to use immunobridging to evaluate efficacy. Immunobridging studies compare immunogenicity in a group of interest (e.g., children 5-11 years of age) with a comparison group in which efficacy has been demonstrated in clinical trials (e.g., persons 16-through 25 years of age). The immune response to vaccine in children 5-11 years of age was at least as strong as the immune response in young adults 16-25 years of age based on SARS-CoV-2 neutralization titers measured one month after Dose 2 in participants without prior evidence of SARS-CoV-2 infection.

In terms of the GRADE evidence table for the outcome of symptomatic laboratory-confirmed COVID-19, indirectness was noted due to the short duration of observation. The VE observed with a 3-month follow-up may differ from efficacy with ongoing follow-up. However, for GRADE specifically under an EUA, this was deemed not serious. This resulted in a final certainty of Type 1.

Data on SAEs from the initial enrollment group were reviewed for all randomized participants who received at least one dose of vaccine. SAEs on a safety expansion group also was included with an additional 1,500 children in the vaccine arm and 700 children in the placebo arm. The median follow-up time for the safety expansion group was 2.4 weeks. Due to the short follow-up time in the safety expansion group, SAEs in this population were noted and described

⁵⁵ Data from the Unplanned School Closure Monitoring Project (DGMQ/CDC), ongoing research that uses systematic daily media searches (methods explained in <https://doi.org/10.1371/journal.pone.0248925>).

but not pooled for GRADE purposes. In the initial enrollment group, there was 1 SAE of limb fracture in 1 child in the vaccine arm and 2 SAEs of pancreatitis and abdominal pain related to injury in 1 child in the placebo arm. In the safety expansion group, there were 3 SAEs of infective arthritis, foreign body ingestion of a penny, and an epiphyseal fracture in 3 children in the vaccine arm. There were no SAEs in the placebo arm within the safety expansion group. No SAEs were assessed by the investigator to be related to the study intervention, and no deaths were reported in any trial participants. Regarding the GRADE table for SAEs, the relative risk for SAEs between the vaccinated and placebo groups was 0.49. Serious concern for indirectness was noted due to short follow-up time and sample size. There also was very serious concern for imprecision due to the wide confidence intervals, resulting in a final certainty of Type 4.

Local and systemic events were solicited from participants or their parent or legal guardian via an electronic diary for 7 days following each dose. Grade 3 or higher local reactions or systemic events were reported in 2.7% of children in the vaccine arm and 1.1% of children in the placebo arm. Most of these events were Grade 3, with 1 Grade 4 event of pyrexia reported in a vaccine recipient. Events were more common after Dose 2. Pain at the injection site, fatigue, and headache were the most common events. The relative risk for any Grade 3 or 4 event was 2.5. There was serious concern for imprecision given the wide 95% confidence interval, which cannot exclude the possibility of no difference between vaccine and placebo. The final certainty was Type 2.

The conclusion for GRADE is the Phase 2/3 randomized controlled trial (RCT) for the Pfizer COVID-19 vaccine was conducted among persons 5-11 years of age. Over 3,000 children were vaccinated with BNT162B2. The efficacy estimate against symptomatic laboratory-confirmed COVID-19 for children with and without prior infection with SARS-CoV-2 was 90.9%. The certainty for this critical benefit was high. SAEs were rare, but the certainty estimate was low for this evidence. No SAEs were judged to be related to vaccination and there were no deaths. Grade 3 or 4 local or systemic reactions were reported by 2.7% of children who were vaccinated. The certainty estimate for this important harm was moderate.

Moving to potential benefits and harms in seropositive children in the trial, geometric mean titers (GMTs) were higher in those with prior infection. Although, the GMTs pre-vaccination among seropositive individual were substantially lower than GMTs seen post-vaccination in either population. The fold rise was less in the seropositive population, which is likely due to the slightly higher GMTs initially. To summarize what is known about COVID-19 vaccines and seropositivity with the focus on children, data from the Phase 3 three clinical trial show that about 9% of children in the trial were baseline SARS-CoV-2 seropositive. Post-vaccination antibodies were higher in children who were seropositive. Rates of local and systemic reactions and AEs were lower in children who were seropositive. Based on broader US studies, approximately 38% of children 5-11 years of age have evidence of prior infection based on seroprevalence estimates from residual commercial laboratory sera. Prior infection can result in some protection against infection, but not 100% and likely decreases over time. Children have a greater proportion of asymptomatic infection relative to adults, and asymptomatic infection can result in lower antibody levels compared to severe disease.⁵⁶

⁵⁶ Viner RM, Ward JL, Hudson LD, et al. [published online ahead of print, 2020 Dec 17]. *Arch Dis Child*. 2020;archdischild-2020-320972; Irfan O, Muttalib F, Tang K, Jiang L, Lassi ZS, Bhutta Z. [published online ahead of print, 2021 Feb 16]. *Arch Dis Child*. 2021;106(5):440-448; Dawood FS, Porucznik CA, Veguilla V, et al. [published online ahead of print, 2021 Oct 8]. *JAMA Pediatr*. 2021;10.1001/jamapediatrics.2021.4217. doi:10.1001/jamapediatrics.2021.4217; and Poline J, Gaschnignard J, Leblanc C, et al. *Clin Infect Dis*. 2021;72(12):2215-2217. doi:10.1093/cid/ciaa1044.

Considering the balance of benefits and risks by seropositive status, Delta wave surges of pediatric COVID hospitalizations occurred even with the known seroprevalence, suggesting that this alone is not sufficient to provide broad protection for children. There are limited data on rates of reinfection in children. Protection against asymptomatic or mild infection is still an important outcome in children. MIS-C typically occurs after asymptomatic or mild infection. Additional post-COVID conditions also can occur after mild infection. Over 400 million doses of COVID-19 vaccines have been administered to persons 12 years of age and over. No concerns have been identified in post-authorization safety surveillance with seropositive adolescents and adults. Individuals 12-64 years have seropositivity of over 30%. Vaccine recommendations that require serologic testing place unnecessary barriers to vaccination and would be difficult to implement. While there may be limited data to estimate the direct impact of vaccination on seropositive children, the risks are minimal. Based on that, the balance of benefits and risks is favorable for vaccination of all children 5-11 years of age.

Concerning vaccine-associated myocarditis, identified rates of myocarditis are based on data from adolescents and adults receiving a 30 µg dose of Pfizer-BioNTech COVID-19 vaccine, which is different from the dose proposed for this age group. Myocarditis is a rare event that is most common in males 12-29 years of age. No cases of myocarditis occurred during the clinical trials in this pediatric population of children 5-11 years of age. A formal benefit-risk assessment was conducted in this population. In terms of the estimated benefits for every million Pfizer vaccinations given in children 5-11 years of age using recent incidence projecting out over 6 months and using epidemiologic data from mid-September, over 50,000 cases, hundreds of hospitalizations, and 130 MIS-C cases, and 60 ICU cases would be prevented in children. Given that recent epidemiology estimates were from close to the peak of the recent Delta surge, other epidemiology estimates were made for context. Looking back at the pandemic average and smoothing out all the previous peaks and troughs to determine a pandemic average, the prediction would be that nearly 20,000 cases of COVID-19, 80 hospitalizations, and 40 MIS-C cases would be prevented.

The rates of myocarditis after vaccination among children 5-11 years of age are unknown. No cases occurred during clinical trials. While the underlying epidemiology of viral myocarditis varies greatly between children 5-11 years of age and adolescents 12-17 years of age, myocarditis after vaccination is substantially lower in children 5-11 years of age than adolescents 12-15 years of age. The dose used in children 5-11 years of age is a third of the one used in adolescents. A formal risk-benefit assessment cannot be conducted in those 5-11 years of age due to these factors. However, estimated rates of myocarditis after vaccination in adolescents 12-15 years of age per million second doses total 21.5 in VAERS and 60.2 in VSD. The outcomes for vaccine-associated myocarditis are reassuring, making it possible to think through the benefit-risk balance. The benefits include prevention of COVID-19 cases, hospitalizations, MIS-C, deaths, and additional post-COVID conditions. There also could be possible prevention of transmission and a greater confidence in safer return to school and social interactions. Risks include possible myocarditis or other rare AEs after mRNA vaccination; however, short-term reactogenicity data are reassuring in terms of the possible risk of myocarditis or other rare events after receipt of mRNA vaccines.

Regarding the number of children 5-11 years of age needed to vaccinate to prevent a case of COVID-19, COVID-associated hospitalization, or an MIS-C case, the absolute numbers depend on the epidemiology. Using the current epidemiology, less than 10 children 5-11 years of age would need to be vaccinated to prevent a case of COVID-19.

To summarize benefits and harms, the clinical trial demonstrated that the Pfizer-BioNTech COVID-19 vaccine is safe, immunogenic, and efficacious in children 5-11 years of age. The trial was not powered to assess the rate of rare AEs, but no cases of myocarditis were identified in over 3,000 vaccinated children. The balance of benefits and risks varies by COVID incidence as with all previous analyses, with the largest benefits in higher incidence settings. The balance of benefits and risks is favorable regardless of seropositivity rates. While many children 5-11 years may be seropositive, duration of protection is unknown for asymptomatic infection in children. Safety data are reassuring in the seropositive population. The WG felt that the desirable anticipated effects are large and the undesirable anticipated effects are small. Therefore, the balance favors the intervention.

Moving to the values domain, there have been several parental surveys to assess intent to have children vaccinated. Among parents surveyed 34% to 57% plan to get their children vaccinated. Parental intent varies by several factors, with 90% of parents who are very worried their child would get COVID-19 reporting an intent to vaccinate their child compared to 7% of parents who are not worried at all. In addition, 82% of fully vaccinated parents report an intent to vaccinate their child compared to 1% of parents who are unvaccinated and do not plan to get vaccinated. Recommendations from a child's healthcare provider is important. Among parents of teens who discussed vaccination with their pediatrician, 3/4 of those whose pediatrician recommended vaccination say their child received at least one dose.⁵⁷ Those intending to vaccinate their child vary by age of the child as well as by race and ethnicity.⁵⁸ Based on data from a survey of 1,000 US parents of children 5-11 years of age in September 2021, 57% of parents stated that they definitely or probably would get their child vaccinated. Parents frequently reported concerns for long- or short-term side effects (e.g., fever, anaphylaxis, or myocarditis), lack of trust for the vaccine, or that their child does not need the vaccine as reasons not to get the vaccine. Among the parents surveyed, 37% reported side effects as a reason for not wanting a COVID-19 vaccine for their child. The WG determined that the target population felt that the desirable effects are moderate compared to the undesirable effects and that there is probably important uncertainty or variability in how people value these outcomes.

Moving to the acceptability domain, over 70% of VFC providers were enrolled as COVID-19 vaccine providers as of October 15, 2021. These providers represent over 80% of VFC vaccines distributed in 2019 for influenza and MMR. As an American Academy of Pediatrics (AAP) survey demonstrated, 75% of primary care pediatricians reported that their main work setting is enrolled as a COVID-19 vaccine provider and 70% are already giving vaccine to those 12 years of age and older in their practice. To summarize acceptability, most jurisdictions plan to utilize a variety of implementation strategies to vaccinate children 5-11 years of age. Parents report the greatest comfort with receiving a COVID vaccine at their primary care provider's office. Jurisdictions anticipate that most children will be vaccinated at these providers. Over 70% of VFC providers are already enrolled as COVID providers. The WG group felt that the Pfizer vaccine is acceptable to key stakeholders for children.

⁵⁷ Szilagyi PG, et al. Parents' Intentions and Perceptions About COVID-19 Vaccination for Their Children: Results From a National Survey [published online ahead of print, 2021 Aug 3]. *Pediatrics*. 2021;e2021052335; Ruggiero KM, et al. Parents' Intentions to Vaccinate Their Children Against COVID-19 [published online ahead of print, 2021 Jun 30]. *J Pediatr Health Care*; Brennan M. In U.S., 55% Would Get COVID-19 Vaccine for Young Child. Gallup. September 28, 2021. Available at: <https://news.gallup.com/poll/354998/covid-vaccine-young-child.aspx>. Accessed October 1, 2021; Unpublished data from the CDC, the University of Iowa, and RAND Corporation Survey of Parents, September 2021; Gallup Panel Poll. Available at <https://news.gallup.com/poll/354998/covid-vaccine-young-child.aspx>. Accessed September 29, 2021; and Lopes L, et al. KFF COVID-19 Vaccine Monitor: Available at: <https://www.kff.org/coronavirus-covid-19/poll-finding/kff-covid-19-vaccine-monitor-trends-among-children-school/> Accessed: October 1, 2021.

⁵⁸ Szilagyi PG, et al. Parents' Intentions and Perceptions About COVID-19 Vaccination for Their Children: Results From a National Survey [published online ahead of print, 2021 Aug 3]. *Pediatrics*. 2021;e2021052335

Regarding the feasibility domain, implementation goals were described earlier to reach the most children, including those who are hard-to-reach. There are approximately 28 million children 5-11 years of age in the US.⁵⁹ There are some feasibility concerns with regard to the formulation for the vaccine for children 5-11 years of age, given that it may lead to administration errors. Provider education regarding this must be ongoing. In addition, this new formulation can be stored at refrigerator temperatures for up to 10 weeks prior to use and has a 100-dose minimum order size. The WG felt that the vaccine is feasible to implement among children 5-11 years of age.

For the resource use domain, the US government has purchased enough vaccine to support vaccination of the pediatric population. The vaccine will be available at no cost. Cost-effectiveness may not be a driver in the pandemic, but will be reassessed in the future. The use of COVID-19 vaccines in as many populations as possible likely will have a positive economic impact in terms of returning to pre-pandemic activities. The WG felt that the vaccine is a reasonable and efficient allocation of resources.

With respect to the equity domain, some children may be disproportionately affected by COVID-19 and/or access to healthcare due to place of residence, race/ethnic, gender/sexual identity, socioeconomic status, personal characteristics associated with discrimination, and/or features of relationships such as family stability or not being enrolled in school. There are disparities among adolescents in terms of COVID-19 vaccine coverage based on the National Immunization Survey (NIS)-Teen survey conducted in September 2021. The proportion of those who are vaccinated already or who definitely/probably will get vaccinated varies by sex, age, and race. This unrealized intent is also quite high for those living below poverty and those living in rural areas. While there are no data on inequities with the vaccine in children 5-11 years of age, lessons learned from the adolescent population can be considered. Nearly 5 months after the adolescent vaccine rollout, there remains unrealized intent for adolescent COVID-19 vaccine. This is largest for adolescents living in poverty and rural areas. It is critical for CDC and public health partners to redouble efforts for equitable access to COVID-19 vaccines. This can include novel strategies, such as school-located vaccinations. There are a variety of other opportunities to increase the equitable access, including utilizing trusted providers in the medical home, partnering with school-located clinics to reach those without a medical home, and utilizing the broad reach of pharmacies. As with previous EtR Framework presentations, the WG struggled with the impact of a Pfizer vaccine among children on equity. Broad prevention of disease, especially disease that has disproportionately impacted communities of color and lower income communities, can provide equity only if every effort is made to ensure that the intervention is accessible to all.

To summarize the conclusions for each of the WG judgements, the WG discussed that vaccine policy decisions are made on the balance of known benefits and risks to the individual. Other benefits (e.g., prevention of transmission, greater confidence in return to school or social interactions, and risks such as extrapolation of myocarditis risks from other ages) are part of a broader picture. There is experience with over 400 million doses of mRNA vaccines administered to people 12 years of age and over with a reassuring safety profile. Overall, the benefits outweigh the risk regardless of seropositivity rates. Thinking about the direct impact of vaccination of children 5-11 years of age, there is over 90% efficacy in the prevention of COVID-19 cases. There also is likely prevention of COVID-19-related post-COVID conditions, MIS-C, hospitalizations, ICU admissions, and deaths and the possibility for more social interactions and uninterrupted school. Children are also part of a family. Vaccination of children possibly could

⁵⁹ US Census Bureau, Population Division, 2020 Demographic Analysis

prevent transmission to vulnerable family members. If a family's children are not getting sick, parental participation in a workforce may be more stable and predictable. Children also live within a community. Vaccination of children could result in lower transmission within schools in a community and could result in a more confident return to in-person learning.

As with all ages and vaccines, next steps would include ongoing close monitoring and post-authorization safety surveillance. As was done for Pfizer vaccine recommendations in those 16 years of age and over, the vaccine recommendations made under EUA are interim and will be reviewed at the time of Biologics License Application (BLA) submission. At that time, there will be longer-term follow-up data for children enrolled in the clinical trials. The benefit-risk analysis can be updated with additional data from the clinical trials, as well as post-authorization safety surveillance. Evaluation will continue of ways to mitigate risk of rare events after vaccination. Plans are already in place for post-authorization monitoring VE, so it is possible that estimates will be available as early as 90 days after authorization. As always, this will depend upon vaccine coverage and rates of disease.

Since the beginning of the COVID-19 pandemic, there have been 1.9 million cases of COVID-19 disease among US children 5-11 years of age. There also have been 8,300 hospitalizations, over 2,000 MIS-C cases, and at least 94 deaths in this age group. COVID-19 is vaccine-preventable, meaning that there is now an ability to prevent the burden of disease, future hospitalizations, and deaths from COVID-19 in children 5-11 years of age. Considering the totality of the data, the WG felt that the desirable consequences clearly outweigh the undesirable consequences in most settings and proposed to recommend the intervention.

Liaison Organization Statements

Dr. Bonnie Maldonado American Academy of Pediatrics

I'd like to read a statement on behalf of the American Academy of Pediatrics in my role as Chair and representing the Committee on Infectious Diseases for the Academy. This is our stand on COVID-19 vaccines in children and adolescents. Vaccines are safe and effective in protecting individuals in populations against infectious diseases. New vaccines are evaluated by a longstanding, rigorous, and transparent process through the US Food and Drug Administration and the Centers for Disease Control and Prevention, by which safety and efficacy data are reviewed before authorization recommendations. The American Academy of Pediatrics recommends the following related coronavirus disease 2019 or COVID-19 vaccine in children and adolescents. The AAP recommends COVID-19 vaccinations for all children and adolescents 5 years of age and older who do not have contraindications using a COVID-19 vaccine authorized for use for their age. Any COVID-19 vaccine authorized through Emergency Use Authorization or approved through a Biologic License Application by the US Food and Drug Administration, recommended by the CDC, and appropriate by age and health status can be used for COVID-19 vaccination primary series, additional doses, or booster doses according to CDC guidelines for children and adolescents. Children with prior infection or disease with SARS-CoV-2 should receive COVID-19 vaccination according to CDC guidelines. Given the importance of routine vaccination and the need for rapid uptake of COVID-19 vaccines, the AAP supports co-administration of routine childhood and adolescent immunizations of COVID-19 vaccines or vaccination the day before or after for children and adolescents who are behind on or due for immunizations based on the CDC/AAP recommended children and adolescent immunization schedule and/or at increased risk for vaccine-preventable diseases. Pediatricians are encouraged to promote vaccinations through ongoing proactive messaging. For example,

reminder recall, vaccine appointments, and clinics as well as to use existing patient visits as an opportunity to promote and provide COVID-19 vaccines. Pediatricians' role in promoting vaccination among their patient population and in their community is critical, especially among those of highest risk for severe illness, hospitalization, and death from COVID-19, as well as their household contacts. Parents, caregivers, and patients might have questions that need to be addressed related to the vaccine. Pediatricians play an essential role in helping answer these questions, as well as in reducing existing disparities in addressing any barriers to accessing COVID-19 vaccine in the community. For additional guidance on the administration of COVID-19 vaccine, storage, handling, reporting, and patient education for each specific visit, please visit the appropriate CDC and AAP websites at AAP.org.

Pamela Rockwell
American Academy of Family Physicians

Hi, this is Pamela Rockwell, liaison to the American Academy of Family Physicians. The AAFP strongly supports COVID-19 vaccination in all eligible children 5-11 years of age as authorized by the FDA. Vaccination will provide children protection from the very real and significant harms of COVID-19 infection. In speaking as a family physician with 30 years of clinical experience treating both children and adults in my practice, I have seen the devastating effects of COVID-19 infection, not only in my patients who have died from the disease, but also in those who have survived and now suffer from long-term effects of COVID-19. They suffer physical, mental, and emotional effects of long-haul COVID. And as we have seen in the presentations today, long-haul COVID also occurs in children and data are still emerging. Vaccination of children ages 5-11 years will not only help prevent COVID-19 infection and serious consequences of infection in this age group, but it will also help children emotionally and socially to improve their development. It will help reduce inequities in the impact of COVID-19 on our population, reduce the need for future school closures, disruptions, and obligatory times of quarantine, allowing sports after school and other school-based and social activities to occur without risk and anxiety, and help improve our children's quality of life, not just prevent COVID-19 illness and death in children and all the adults around them.

Ms. Patsy Stinchfield
National Association of Pediatric Nurse Practitioners

As the ACIP liaison representative for America's Pediatric Nurse Practitioners, I want to offer our strong support of the use of Pfizer-BioNTech pediatric formulation equitably distributed to all children 5-11 years of age, as you heard during our public comment from our NAPNAP president. We cannot reliably predict which child will have severe disease, with 1/3 of those children admitted to hospitals not having any underlying condition. We have heard the national data today, which includes the nearly 800 deaths of children, which is 4 times that of the annual influenza deaths, 94 children in the 5-11-year-old age group. For parents and clinicians, there is an urgency to act. To look at this at a local level, at just one of the United States' 250 children's hospitals, last week alone, as an example, Children's Minnesota tested 107 children positive for COVID. Eighteen of those children were admitted to the hospital. Half of them went to the ICU. None of them were vaccinated and half of them were not age eligible for vaccines. We must protect our kids directly, which, in turn, protects families and the community at large against both direct and indirect harms from COVID disease. Having been called to the PICU over my 34 years as a pediatric nurse practitioner in infectious disease to talk to parents of children on life support for vaccine-preventable diseases, such as HIB, measles, and influenza, the common sentiment parents in that situation expressed is regret. Their question is, "Why didn't we vaccinate? We didn't know that children could get this sick." While hospitalization and death in

children from COVID-19 is rare, even one child and family loss is one too many when we have a safe and efficacious vaccine. We urge the committee to vote to recommend COVID vaccine for all children and encourage all families to enroll your child in the v-safesm program. We must remove all barriers and not put up more new ones. We encourage all clinicians to report anything unusual to VAERS. All things considered, this is ultimately a risk-benefit decision for ACIP, parents, and clinicians. And we agree, all measures point to COVID vaccine in 5-11-year-olds is a greater benefit than the real risk of children being unvaccinated. Pediatric nurse practitioners will be strongly recommending vaccination to our patients. Thank you for your commitment.

Dr. Shawn O’Leary
Pediatric Infectious Diseases Society

Thank you, Dr. Lee, and thanks to all of the great presenters today. This is on behalf of the Pediatric Infectious Diseases Society. The Pediatric Infectious Diseases Society, the world’s largest organization of pediatric infectious diseases specialists, strongly supports a universal recommendation for COVID-19 vaccination of children 5-11 years of age as authorized by the FDA. PIDS also strongly encourages efforts to ensure equitable access to pediatric COVID-19 vaccine. More than 28 million children will be eligible for vaccination against COVID-19 with this recommendation. To date, over 6 million children have been diagnosed with COVID-19. Vaccination will provide children with critical protection against serious disease and long-term complications of COVID-19 and will help bolster overall immunity in the community. Vaccinating school-aged children has other benefits, such as limiting disruptions in school attendance, which allows children to participate in learning and other activities that are crucial to mental health and development. PIDS is encouraged that the federal government has developed a vaccine implementation plan that includes pre-purchasing vaccine dosage for children and outlining a multi-pronged distribution strategy. The federal government and state and local partners should collaborate with trusted community-based organizations to ensure equitable vaccine access and uptake. This is a good time for parents to ensure that children are also up-to-date on all of the other recommended vaccines of childhood, including seasonal influenza. Don’t procrastinate. Vaccinate. Thank you.

Dr. Michael Hogue
American Pharmacists Association

The American Pharmacists Association is very supportive of routine immunization of children 5-11 with COVID-19 vaccine. We strongly believe that the benefits outweigh the risks. There were great presentations that we saw today. I do want to remind consumers who may be listening to this presentation that vaccinations are a part of a child’s well-development. There are many things that pediatricians want to visit with you as a parent and your children about when you have a healthcare encounter. We would encourage you to have conversations with your pediatricians, to follow-up on well-child visits that may have been missed during the pandemic, and to catch up on the vaccines that you need by working with your pediatric office. That said, community pharmacies are accessible in local communities and rural areas and sometimes in places where it may be inconvenient and not possible to get to your primary care provider’s office. Pharmacists are more than willing to help ensure that vaccine is available and to administer those vaccine doses. We do want to advise parents, however, that you should expect to have to make an appointment at a pharmacy to get vaccinated and you should expect that there may be a longer than normal waiting time. We are experiencing staffing shortages in pharmacies, much like the rest of the workforce is experiencing shortages of personnel. We just want to set an expectation with consumers on being able to get vaccinated.

Dr. Patricia Whitley-Williams
National Medical Association

Thank you for this great presentation. While equitable access to this vaccine was mentioned, and particularly at appropriate facilities (e.g., pharmacies, community health centers, and children's hospitals, physician's offices), there are lessons that we learned through our experience with the rollout of the adult COVID-19 immunizations. It taught us valuable lessons and if we really look at our experience, community health centers and community-based vaccination sites made access more equitable, particularly in communities of color. Not all communities of color have the larger pharmacies based right in their community. At the top 10 children's hospitals, most of which are located in major cities and serve diverse populations of children, if they were to be a major player and successful in outreach, that would be extremely supported. I think what is not taken into account, and that is that parents or guardians of children, especially in communities of color, may be working and having a necessity to work. We do not have the buy-in from all employers to protect the employment of those individuals or loss of wages of those parents to take time off and to take their child or children to get vaccinated. I think it is critical for us to continue to monitor the equitable access issue. I think the other consideration is the need for children to be in school because some of the children who are at highest risk depend on their schools as a safe haven as well as a source of 2 meals a day, 5 days a week. To get the 5-11-year-old school-age children vaccinated will provide protection, especially when they are in school. And hopefully, they will continue to stay in school. The National Medical Association will continue to provide education to its membership, many of whom practice in communities of color and continue to conduct educational outreach programs to persons and communities of color. We certainly support the vaccination and rollout to continue to protect the public, particularly those who are most vulnerable. Thank you.

Discussion Summary

- While it is impressive that the new formulation can be stored at refrigerator temperatures for up to 10 weeks, it is important to emphasize to pediatric offices and pharmacies that the vaccine must be used within 6 hours once opened. CDC noted that they have communicated this message to health departments and clinical partners to ensure that this aspect of the vaccine is being incorporated into implementation plans.
- For future meetings, it would be beneficial to have the number needed to vaccinate (NNV) to prevent 1 case of COVID-19 among adults.
- Sentiment was expressed that this recommendation needs to stand on its own merit, meaning that the benefits of vaccinating an individual child strongly outweigh the vaccination risks for that very same child. Children in this age group in the US are dying from COVID-19. This includes children who were healthy and did not have any underlying chronic medical conditions. Real-world in adults demonstrates that deaths from COVID-19 are vaccine-preventable. In any context, it should be considered a tremendous medical breakthrough that death can be prevented through vaccination. The available safety evidence comes not only from the clinical trial in this age group, but also from the safety knowledge that has been gained from vaccinating several hundred million adults and adolescents with this vaccine.

- Regarding an inquiry about whether the vaccine rollout for the formulation for children 5-11 years of age would be similar to the Pfizer adult formulation, Dr. Chatham-Stevens indicated that the approach to this vaccine rollout would be somewhat different in that a large initial bolus of vaccine will be distributed to jurisdictions, pharmacies, and some federal entities. After that initial bolus, there will be a more titrated approach with weekly doses going out as well. CDC has been encouraging jurisdictions, pharmacies, and providers who are getting vaccine to take into account how they will manage their second doses to ensure that everyone is aware and planning for that contingency.
- It was observed that one of the most dramatic numbers in the presentations during this session was that the number of deaths per year prevented with COVID-19 vaccine was 3 times the number of those prevented with other standard childhood vaccines routinely given to children. Vaccinating children also helps prevent spread to other children and to adults in the community, especially those who would be less well-protected by vaccination. Too many children have either lost a parent or become orphaned in this pandemic, which is incredibly tragic.
- Regarding an inquiry about whether the majority of the WG supported the proposed recommendation for this age group, Dr. Oliver indicated that the WG reviewed and discussed the data and felt strongly that the vaccine should be recommended for this population.
- For members of the public listening to the meeting, it was emphasized that the WG is comprised of several ACIP liaison members and additional consultants from the healthcare setting. As seen earlier with their public statements, many organizations (AAP, AAFP, PIDS, APhA) emphasized the importance of this vaccine to their members and their patients.
- Numerous ACIP members stressed that in addition to being practicing professionals (e.g., pediatricians, adult practitioners, infectious disease specialists, immunologists, pharmacists, et cetera) they are parents and grandparents who fully support recommendation of Pfizer COVID-19 vaccine use in children 5-11 years of age—including in their own children and grandchildren.
- With regard to an inquiry about COVID-19 vaccine and fertility, Dr. Reddy (ACOG) indicated that a lot of data have been reviewed regarding COVID-19 vaccine safety in pregnant women, women who want to get pregnant, and women who were recently pregnant and are now breastfeeding. All of the evidence supports the recommendation to vaccinate women in all of those categories.
- ACIP members recognized the importance of dissenting voices, emphasized that they heard loud and clear that some parents remain concerned about COVID-19 vaccination, and stressed that it is understandable to have questions and concerns. Given that there seems to be a deliberate campaign of disinformation, parents were encouraged to talk to their child's pediatrician or family physician to express concerns and ask questions. Pediatricians and family physicians know the family, child, and medical history and can help to walk through the information with them.

Vote: Pfizer COVID-19 Vaccine Use in Children 5-11 Years of Age

Dr. Oliver (CDC/NCBDDD) reminded everyone that based on the available data, the WG interpreted that the desirable consequences clearly outweigh the undesirable consequences in most settings and that they proposed to recommend the intervention. The proposed vote language read as follows:

The Pfizer-BioNTech COVID-19 vaccine (2-doses, 10µg, IM) is recommended for children 5-11 years of age under the FDA's Emergency Use Authorization.

Motion/Vote: Pfizer COVID-19 Vaccine Use in Children 5-11 Years of Age

Dr. Kotton made a motion for ACIP to adopt an interim recommendation stating that "The Pfizer-BioNTech COVID-19 vaccine (2-doses, 10µg, IM) is recommended for children 5-11 years of age under the FDA's Emergency Use Authorization." Ms. Bahta seconded the motion. Dr. Chen reminded everyone that his employer, the University of Maryland Baltimore, has a grant from Emergent BioSolutions that supports research he conducts on developing a *Shigella* vaccine. With 14 affirmative votes, 0 negative votes, and 0 abstentions, the motion carried. The disposition of the vote was as follows:

14 Favored: Bahta, Bell, Brooks, Chen, Cineas, Daley, Kotton, Lee, Loehr, Long, McNally, Poehling, Sanchez, Talbot

0 Opposed: N/A

0 Abstained: N/A

Member Statements

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

Dr. Daley indicated that the reason he voted for this individual protection was because he values preventing infection in children and thought it could have a huge positive impact on their health, social and emotional well-being, educational outcomes, and long-term trajectory. While other ways are available to prevent infection such as masking, it is known that there is substantial variability in the use of masks in school settings, transmission can occur, and vaccines are the only consistent and reliable way that protection can be provided to these children other than cocooning them at home to minimize their risk. This deprives them of many other important aspects of their childhood. He also emphasized the importance of continuing to invest resources and effort in understanding the broader health and non-health impacts of COVID-19 infections in the pediatric population and in children in general. He expressed his hope that this recommendation would take them one step further along in that journey. He also highlighted what Dr. Whitley-Williams mentioned about disparities continuing to exist and the need to make additional efforts, in partnership with communities, where the need is the greatest. This seems to him to be an incredibly important investment in their efforts, in addition to making sure that children are able to seek care in their medical homes.

Dr. Talbot stressed that while there seemed to be an impression that ACIP members are not parents or people, many of them spoke up as parents throughout the day. She has reviewed the data and has vaccinated her children because she feels like it is safe. She would not recommend something if she did not feel that way. Therefore, she thought it was very important to reiterate what many of them said, "We are parents and we have given this to our children because we have seen the devastation of this disease and the destruction in our kids' lives and are looking forward to moving forward."

Ms. McNally indicated that she also has a child in this age group and was going to take that child to get this vaccine. She has gotten her other children vaccinated as they are in the older age group. She is doing this to prevent the 95th death. Some 94 parents have had to bury their child, 8300 children have been hospitalized, 1.9 million lives have been disrupted by cases, and 2300 families have experienced a child with multiple organ failure. To say that this disease is not impacting children is not an accurate statement. She expressed hope that people would understand that. She also took a moment to talk to providers caring for children in this age group to emphasize the importance of recommending this vaccine and the significance on families if not. She expressed her confidence in the US's vaccine safety monitoring system and stressed that she felt very comfortable as a parent and as the consumer representative recommending that children 5-11 years of age be vaccinated.

Dr. Brooks emphasized to the public at large that the vote ACIP took was based on the data that brought them to this conclusion and recommendation. For those who may be conflicted due to misinformation, he clarified that ACIP members have nothing to do with employment termination regarding mandates or what happens once this recommendation is made.

Dr. Bell stated that all of the ACIP members have a lot of enthusiasm for this vaccine in this age group, but also understand that parents have legitimate concerns and legitimate questions. ACIP's vote is a way of telling the American public that, based on their expertise and the information that they have, they are very enthusiastic. Many members talked about getting their children and grandchildren vaccinated. Another point to be made to the American public is that ACIP members do understand that people have legitimate concerns and a lot of questions and encourage them to ask their providers, visit the CDC website, talk their friends, talk to other parents, and do what they need to do to feel comfortable with their decision.

Dr. Loehr said that like his colleagues, he feels that this is a safe and effective vaccine with more benefits than risks.

Dr. Lee thanked the committee members for their incredible and ongoing service to the country. She also expressed gratitude to all of the speakers of the day for their outstanding presentations and all of their federal colleagues and liaisons for supporting ACIP with the robust discussion throughout the day.

WEDNESDAY: NOVEMBER 3, 2021

WELCOME AND INTRODUCTIONS

Call to Order / Roll Call

Dr. Grace Lee (ACIP Chair) called to order and presided over the meeting. She conducted the roll call during which no new COIs were identified or declared. A list of Members, *Ex Officios*, and Liaison Representatives is included in the appendixes at the end of this summary document.

HEPATITIS VACCINES

Session Introduction

Dr. Kevin Ault (ACIP, WG Chair) provided the session introduction on behalf of the Hepatitis Vaccines WG. He indicated that Dr. Wang would present the WG's considerations for universal adult hepatitis B vaccination recommendations and would review how the risk-based strategy has been given over a decade to prove itself. The risk-based strategy has not panned out because of the complex list of risk factors, many of which do not lend themselves to well-defined identifiable populations who regularly access care in dedicated locations or the structure of current clinical practice. The guiding principles for these considerations are to decrease new hepatitis B infections, prevent ongoing transmission, and reduce health disparities. HHS has called for the elimination of viral hepatitis as a public health threat by 2030.⁶⁰ The National Academies of Science, Engineering, and Medicine (NASEM) has provided a roadmap to achieve viral hepatitis elimination. Their report emphasized the role of vaccination and called for expansion and simplification of adult hepatitis B immunization recommendations.⁶¹

Looking at the rates of reported hepatitis B in the US over the past 15 years stratified by age group, the success achieved over the past 20 to 30 years in the US is a result of the implementation of universal adult and infant hepatitis B vaccination. The rate of new infections among persons 20-29 years of age dropped from 3.5 in 2014 to 0.5 in 2019. There also have been extremely low infection rates among persons 0-19 years of age over the past decade. Unfortunately, the level of success achieved among children, adolescents, and young adults less than 29 years of age has not been achieved among adults 30 years of age and older. There has been a slow rate of decline among adults 30-39 years of age and increasing rates among adults 40 years of age and older. It is important to note that this is about half of all people with acute hepatitis B when the available risk factor data do not report any identifiable risks.⁶²

⁶⁰ <https://www.hhs.gov/sites/default/files/Viral-Hepatitis-National-Strategic-Plan-2021-2025.pdf>

⁶¹ <https://www.nationalacademies.org/our-work/a-national-strategy-for-the-elimination-of-hepatitis-b-and-c>

⁶² <https://www.cdc.gov/hepatitis/statistics/2019surveillance/index.htm>

The current risk-based hepatitis B vaccination strategy has taken public health as far as it can and falls short of the goal of elimination. In the past 10 years, the total number of hepatitis B cases has plateaued at more than 20,000 estimated new infections every year. Furthermore, rates of new cases are highest among adults 30 years of age and older and have been increasing among adults 40 years of age and older. Despite 16 different categories of risk (e.g., blood and sexual exposure, diabetes, household contact, living with someone with hepatitis B, et cetera), determining risk for vaccination across all those categories is not easily incorporated into clinical practice/provider screening. The risk-based strategy also assumes patient recognition and disclosure of risk and exacerbates health disparities, favoring patients with a higher degree of health literacy and engagement in care.

The Hepatitis Vaccine WG has been deliberating universal hepatitis B vaccinations for several years and is unanimous in proposing the universal hepatitis B vaccination recommendation. During the fall 2016 ACIP meeting, the topic of universal hepatitis B adult vaccination was initially suggested to the ACIP as the next step toward hepatitis B elimination. In 2016, 2017, and 2018, the WG focused on evaluation of HEPLISAV-B vaccine and updates to the hepatitis A policy. Since 2019, the WG has focused its review and discussion in 15 WG calls on a universal hepatitis B protocol. This brought them to the in-depth presentation and economic model during the February 2021 ACIP meeting, during which ACIP members advised the WG to move forward with a universal hepatitis B immunization recommendation. Based on that advice, the WG presented the EtR Framework and GRADE analysis during the September 2021 ACIP meeting.

In the context of all evidence presented and considered over the past 2 years with the SMEs comprising ACIP's Hepatitis Vaccines WG, the WG unanimously agreed that the current risk-based recommendations need revision, with the majority preferring a universal adult hepatitis B strategy with no upper age limit. There was no WG support for retaining the current risk-based recommendations. Two scenarios were presented for ACIP consideration:

<u>WG Preferred</u>	<u>WG Alternative</u>
All adults previously unvaccinated for hepatitis B should receive hepatitis B vaccination.	Adults aged ≤59 years and previously unvaccinated for hepatitis B should receive hepatitis B vaccination. Note: Adults >59 years would continue to follow existing risk-based recommendations.

Considerations for a Universal Adult HepB Recommendation

LCDR Mark Weng, MD, MSc, FAAP (CDC/NCHHSTP) presented considerations for universal adult hepatitis B vaccinations on behalf of the Hepatitis Vaccines WG. There are 20,700 estimated acute hepatitis B infections annually in the US.⁶³ Over \$1 billion is spent on hepatitis B-related hospitalizations each year, not including indirect costs. Almost 2 million people are estimated to be living with chronic hepatitis B in the US,⁶⁴ among whom there is a 15% to 25% risk of premature death from sclerosis or liver cancer.⁶⁵ The WG's goal is to examine hepatitis B vaccine policy and propose strategies that are most effective at preventing new infections

⁶³ <https://www.cdc.gov/hepatitis/statistics/2019surveillance/HepB.htm>

⁶⁴ Wong et al. Am J Med. 2021

⁶⁵ <https://www.cdc.gov/std/treatment-guidelines/hbv.htm>

and hepatitis B-related cancer and death. It is in this context that the WG was proposing that the existing risk-based hepatitis B vaccination strategy be expanded among adults and simplified to a universal recommendation. As noted by Dr. Ault, the risk-based recommendations among adults are complex and include 15 specific behavioral and non-behavioral risks in 3 categories (e.g., sexual exposure, percutaneous or mucosal exposure to blood, and others such as travel or having chronic liver disease). Moving through a universal vaccine recommendation among adults would serve as a natural extension of existing routine childhood vaccination redocumentations. It also would serve to collapse the numerous existing adult risk groups into a single recommendation in that all adults previously unvaccinated for hepatitis B would be recommended to receive hepatitis B vaccination. Dr. Weng distilled prior WG discussions on the evidence and experience of patient, provider, and practice factors underpinning this universal proposal.

The hepatitis B immunization strategy has evolved over the last 4 decades. Risk-based strategies were first introduced among adults and prenatally exposed infants in the early 1980s. Then universal infant vaccination was introduced in 1991, with catch-up vaccination recommendations for all adolescence in 1999, followed by the introduction of a universal birth dose among all newborns in 2005. All of these steps toward routine hepatitis B vaccination resulted in large declines in new hepatitis B infections among children and adolescents. However, hepatitis B incidence has plateaued over the past 10 years with more than 20,000 new infections estimated to occur each year. The past decade has illustrated that risk-based screening among adults has achieved as much as it can. Initial decreases in new infections have stagnated. Rates of acute infections are now high among adults 30-59 years of age and rates have increased among adults 40 years of age and older, indicating that ground is being lost. It will not be possible to eliminate hepatitis B in the US without a new approach.

There was limited hepatitis B vaccine coverage among adults in 2018. Overall, coverage was 30% for adults 19 years of age and older. Reported vaccine coverage rates were likewise low across risk groups, including travelers, people with chronic liver conditions, and people with diabetes. Rates were particularly low among older people with diabetes. Surprisingly, hepatitis B vaccination coverage was only about 67% among HCP—far short of this group's Healthy People 2020 target of 90%.⁶⁶ Hepatitis B vaccination coverage in adults with identified risk factors is suboptimal across all age groups and is lower among older adults. The youngest adult age groups might have received protection under the universal childhood hepatitis B recommendations in 1991, with a catch-up recommendation in 1999. However, as the age groups get older, coverage rates steadily drop. Less than 20% of older adults with identified risk report having been vaccinated.⁶⁷

It is important to recall that only one-third of people with reported acute hepatitis B reported any risk factors. For the remaining two-thirds of reported acute infections, the current risk-based vaccination strategy among adults provides no advantages in identifying and vaccinating people who were missing risk data or reported no identified risk.⁶⁸ Multiple health disparities could be improved with a universal hepatitis B recommendation. Among children and adolescents, acute hepatitis B infection rates in all races and ethnicities converged to a lower rate when a universal vaccination strategy was implemented for children \leq 18 years of age.⁶⁹ Current acute infection

⁶⁶ National Health Interview Survey (NHIS) – US, 2018; Lu et al. Vaccination Coverage Among Adults in the United States, National Health Interview Survey, 2018. 2021 May 14;70(3):1-26. Surveillance of Vaccination; Coverage Among Adult Populations -United States, 2018 - PubMed (nih.gov)

⁶⁷ Lu et al. National Health Interview Survey, 2018. Unpublished 2021.

⁶⁸ <https://www.cdc.gov/hepatitis/statistics/2019surveillance/index.htm>

⁶⁹ <https://www.cdc.gov/hepatitis/statistics/2019surveillance/HepB.htm>; Wasley et al. MMWR. 2008

rates among black American adults are up to 3 times the rates of Asian/Pacific Islanders and Hispanic groups.⁷⁰ Racial and ethnic disparities remain in terms of who gets infected with hepatitis B virus. The WG recognizes that the risk for acquiring hepatitis B is dynamic throughout one's lifetime, meaning that a person might move in and out of risk categories. Exposure, whether recognized or not, might change over time. The current risk-based hepatitis B vaccination recommendations favor patients with access to healthcare over their lifetime, trust to disclose potentially stigmatizing risk factors to the provider, awareness of risk, and a high degree of health literacy.

Hepatitis B vaccination provides lifelong protection whether someone develops diabetes, enters an assisted living facility, shares a home with a person with hepatitis B, and/or chooses to travel. The WG reasoned that it would be better to be vaccinated before people get exposed and that the universal adult vaccination recommendation would promote health equity. The WG distilled ACIP feedback from the February and September 2021 sessions into 3 overarching questions to help drive the decision-making during this session: 1) Can universal recommendations increase vaccine uptake among people with risk factors?; 2) Is a universal hepatitis B vaccination recommendation an effective use of resources?; and 3) Should the proposed hepatitis B recommendation include adults of all ages or revisit adding an upper age limit of 59 years, compared with adding an upper age limit at ≤ 59 years and resuming the existing risk-based recommendation for persons >59 years? Notably, the cutoff of 59 years of age was selected to align with the hepatitis B diabetes recommendations.

To address the first question regarding whether universal recommendations increase vaccine uptake among people with risk factors, the WG recognized that while there is no perfect parallel, several vaccine-preventable diseases provide useful comparison points, common themes, and rationales that ACIP has discussed in the past. In 2010, influenza vaccine coverage of adults with high-risk conditions was 28.6%. Universal influenza recommendations were then promulgated that year. By the 2020-2021 season, influenza vaccine coverage has nearly doubled to 51% for people with high-risk conditions.⁷¹ Pneumococcal vaccines provided a different type of example where in 2018 there was a risk-based cohort among persons 19-64 years of age at the same time as a universal cohort among adults 65 years and older. Under risk-based recommendations, just under a quarter of persons 19-64 years of age who had increased risks were vaccinated, while adults 65 years of age and older under the universal recommendation were vaccinated at nearly triple the vaccination coverage.⁷² To bring it back to hepatitis B, the WG looked at birth dose recommendations. Shifting from a risk-based to a universal vaccine in 1991 resulted in increased coverage among all newborns. Birth dose coverage went from half of newborns in 2005⁷³ to almost 80% in 2018—just shy of the Healthy People 2020 target of 85%.⁷⁴ The WG felt strongly that these and other examples provide compelling examples of how universal recommendations increased vaccine uptake among people with risk factors and therefore answered “yes” to this question.

⁷⁰ Harris et al. *MMWR*. 2016

⁷¹ CDC FluVaxView

⁷² NHIS 2018. NHIS captures “any” pneumococcal vaccination; risk-based recommendation includes groups with different pneumococcal recommendations

⁷³ Allred, NJ et al *CDC MMWR* 2008. Birth Dose, to 3 days from birth

⁷⁴ CDC ChildVaxView, HepB Birth Dose by Age 0-3 Days

The WG summarized limitations and advantages of universal recommendations to increase hepatitis B vaccine uptake. The limitation is that future increased vaccine uptake is unknown. However, that magnitude can be inferred from public health experience with other vaccine-preventable diseases. The advantages for patient groups with high-risk behaviors might be concerned with stigma, which reduces the motivation to get hepatitis B vaccines. A universal recommendation would facilitate patients' access to routine standard of care by not requiring patients to recognize and disclose risk. Even though current indications allow for vaccination among anyone who requests it, it already has been demonstrated that only one-third of people who reported acute hepatitis B in the US report any risk factors. About two-thirds of the people in the US with chronic hepatitis B infection are estimated to be unaware of their own infection, precluding them getting treatment for their own health or informing their contacts of possible transmission risk. For providers, a simplified recommendation facilitates implementation and empowers clinicians to offer vaccination. It shifts the onus to vaccinate from patients to providers and at the same time, makes it easier for providers to help their patients.

The WG drew parallels with opt out public health policies that have shown success in lowering barriers to care, such as universal hepatitis C and HIV screening among adults and routine HIV, hepatitis B, hepatitis C, and syphilis screening during pregnancy. Simpler clinical implementation likely would result in increased vaccinations for healthy adults and adults with the risk factors who have not yet been vaccinated. The WG showed data during the September 2021 ACIP meeting published by Dr. Daley and colleagues suggesting that even providers have trouble processing that long list of risk factors during a busy clinical session. For public health and clinical practice, universal hepatitis B recommendations would contribute to larger efforts to eliminate hepatitis B nationally and globally. Underlying all these advantages is that it facilitates health equity goals in terms of reducing disparities and inequities in accessing hepatitis B vaccination. Based on all of the points just discussed and the EtR Framework provided in September 2021, in a straw poll, 100% of WG members said that universal hepatitis B recommendations would increase vaccine uptake among people with risk factors.

In terms of the second question regarding whether a universal hepatitis B vaccination recommendation is an effective use of resources, the incremental cost-effectiveness ratio (ICER) was calculated at \$153,000 per quality-adjusted life-year (QALY) gained.⁷⁵ The ICER decreases as coverage improves in groups at higher risk. For example, with 20% additional coverage in people with increased risks, the cost per QALY decreases to \$135,000, illustrating the benefits of an increased access. The economic model presented to ACIP in February 2021 was used to estimate the health improvements of a universal adult hepatitis B vaccination, which would reduce acute infections by 24% and deaths by 23%. The WG had selected a conservative base-case in the economic model. After the February presentation, several committee members considered the model assumptions to be too conservative because the base-case did not assume any increase in additional vaccination among people with risk factors. The WG agreed with the committee that higher hepatitis B coverage likely could be assumed in this population, which then would lead to a lower cost estimate than the conservative base-case cost and would increase access at the same time. The results of the analysis presented in February are available for these assumptions of increased coverage. In a straw poll, 70% of the WG agreed that universal hepatitis B vaccination is an effective use of resources. The remaining 30% said that it probably would be an effective use of resources.

⁷⁵ Hall et al, ACIP Presentation, Feb 2021. Assumptions: 3-dose vaccine; base case summary input of ~30% coverage (based on 35.8% protected, with varying age-group specific coverages among people with risk factors; 50% vaccination coverage in general population)

With regard to the third question pertaining to whether the recommendation should include all ages or if it should include an upper age limit of 59 years of age, a sub-analysis of the Hall economic model included the upper age limit. The ICER, NNV, and dose are lower for the upper age limit. There is a similar reduction in infections. Despite the cost, the WG saw many advantages of the universal recommendation for all ages. The upper age limit did initially receive some support of the WG, but when presented to ACIP as an option in February, the committee discussion seemed to support universal recommendation without an upper age limit. Based on the committee's subsequent September feedback, the WG revived the age limit scenario for consideration for this meeting. In terms of the limitations on including adults of all ages as discussed by the WG, there is a relatively lower incidence among persons over 59 years of age that yielded a higher ICER to protect older populations.⁷⁶ With an upper age limit, specificity would be improved by clearly defining an age group of interest. The WG also reasoned that the trade-off is that a complex risk-based recommendation still would be required for adults over 59 years of age with all of its inherent flaws as just discussed. A key unknown is the exact impact on vaccine uptake. The WG believes that based on the supporting evidence just shown, it is likely that uptake would increase though it is hard to say exactly how much. As a committee member observed in February, opportunities would be missed to vaccinate older adults by maintaining barriers to access at a time in their lives when older adults might otherwise be going in to see their providers.

Regarding the main advantages of a recommendation to include adults of all ages, hepatitis B still causes significant disease in older adults, so individuals over the age of 59 still deserve protection. Many adults will age into one of the risk groups like diabetes, kidney disease, or certain lifestyle changes. Therefore, it is better to vaccinate them early. If a large portion of adults already have or will eventually develop one or more risk factors, why wait until they become sick with comorbidities—comorbidities that might actually lower their response to vaccines just when they need it most? Implementation will be less complicated without the additional age cutoff, so the WG preferred a recommendation that is more likely to be followed by patients and providers. Again, improved health equity is sought across the ages in this case. In a WG straw poll, 56% favored a universal adult recommendation to include adults of all ages. They felt that a one-time completion of a hepatitis B vaccination would provide lifetime protection. For many adults, the absence of a risk factor now does not mean that they will be without risk for the rest of their lives and that people respond better to vaccination at younger ages before comorbidities or risk factors develop. Therefore, why not vaccinate people before they acquire that risk factor and can transmit the virus if infected?

To recap, no one on the WG supported staying with the current risk-based recommendations and 100% of the WG preferred a universal adult hepatitis B recommendation, with the majority supporting inclusion of all ages. To summarize in the context of the calls from HHS and NASEM to eliminate viral hepatitis, there are multiple examples and evidence supporting where universal recommendations are preferred over risk-based vaccination approaches. This is in line with public health principles and practice. The WG reviewed these examples along with the previously shown hepatitis B infection rates, dynamic risks of hepatitis B over everyone's lifetime, and health equity observations. The WG concluded that by relying on the current risk-based recommendations focusing only on the slow bottom-up approach of vaccinating all children who will then take their immunity with them when they reach adulthood would be a disservice to a large portion of the US population. Plus, the current risk-based policy creates obstacles for the provider to identify risk and for the patient to self-advocate, which is a

⁷⁶ Assumptions: 3-dose vaccine, base case: 50% vaccination coverage in general population; ~30% coverage (summary input based on 35.8% protected, with varying age-group specific coverages) among people with risk factors

particularly challenging barrier for people in vulnerable and medically underserved communities. In terms of what else is different this time compared to 1982 when risk-based hepatitis B recommendations were first introduced, there is now a growing toolbox and new access points for vaccination to eliminate this potentially fatal virus. There are now 2 single antigen 3-dose vaccines available that are safe, effective, and with long-term immunogenicity. There is one 2-dose vaccine that is safe and effective. There also is 1 combination vaccine and 1 vaccine in the pipeline. The WG concluded that the universal recommendation would allow the US to leverage this growing toolbox for public health and equity goals. With an eye toward implementation, this universal recommendation dovetails with recent developments—the ongoing expansion of viral hepatitis surveillance, a renewed focus on vaccination delivery, improved integration of services, and expanded immunization venues. By late 2022, CDC recommendations are anticipated for 1-time hepatitis B screening guidelines for all adults. Hepatitis B is vaccine-preventable. Safe, effective, cancer-preventing vaccines have been available for over 40 years. However, the current risk-based hepatitis B vaccine policy has clearly become a barrier to public health objectives. For these reasons, the WG believes a universal hepatitis B vaccination recommendation among adults would provide the best chance of achieving hepatitis B elimination goals in the US. This is the language of the proposed recommendation for the ACIP consideration:

All adults previously unvaccinated for hepatitis B should receive hepatitis B vaccination.

Discussion Summary

Key discussion points from ACIP voting members:

- Dr. Chen inquired as to how the screening mentioned would dovetail with the vaccination program and the frequency of testing.
 - Dr. Nelson indicated that CDC testing/screening recommendations have been drafted. This is a separate process following the CDC evidence review. The draft will go to peer review and public comment. What has been proposed in the draft is 1-time testing/screening using hepatitis B surface antibody (HBsAb), hepatitis B surface antigen (HBsAg), and hepatitis B core antibody (HBcAb) tests for all adults over 18 years of age. This is anticipated to be recommended later in 2022. Additional intermittent testing may be warranted for persons with ongoing risk, though that may be based on provider guidance and frequency has not been determined.
 - It was noted that additional screening was not incorporated as part of the universal vaccination recommendation. Dr. Nelson indicated that cost analyses were performed for the screening, but they were not prepared to present these data in the ACIP forum at this time.
- Dr. Long observed that the NNV seemed low among persons over 60 years of age, pointing out that they probably will not live long enough to get sclerosis and cancer from hepatitis B. She requested clarification about why the NNV to avert an acute infection was relatively similar and low for the age group that seems to have such a low incidence.
 - Dr. Weng indicated that in that age group, the WG was focused on the concept of dynamic risk and the heterogeneity of the nature of behavioral and non-behavioral risk factors in this group rather than being able to predict how long someone might live.

- Dr. Hall added that in terms of how the NNV was calculated within this model involved a couple of key elements. The first was that the analytic horizon of this model was the lifetime of the initial cohort of individuals vaccinated. The NNV also applied to a static cohort of adults in time moving forward, which was discussed previously. Second, the NNV within this current cohort of adults was calculated going forward in order to prevent an acute infection. This is simply the difference in the number of people protected by vaccination divided by the difference in number of infections between the 2 strategies. In this setting, it pretty much has a direct tie to the incidence of acute infection within the different age groups. That is slightly different from other types of vaccination modeling studies that incorporate a dynamic risk of infection so there are herd immunity type effects, such that the NNV can change as a higher proportion of people are vaccinated and prevalence of disease goes down in the population.
- While Dr. Loehr agreed that the risk-based strategy had achieved as much as possible and that the proposed universal strategy was appropriate, he had concerns about a recommendation for adults over 60 years of age for several reasons. There is diminishing return in that vaccinating only people under 59 years of age would result in giving 298 million doses versus 352 million doses if given to all adults. That is an additional 54 million doses. Although this would increase the percent of people who are protected by 28%, it would reduce acute infections by only 1%. The \$153,000 base-case for all adults is reasonable, the ICER would be over \$500,000 if persons over 60 years of age are included. He was not comfortable supporting that. The reason the past recommendation for hepatitis B vaccination for diabetics over 60 years of age was not a routine recommendation in 2011 was because it did not appear to be cost-effective. He agreed with Dr. Long that if an adult 70 to 80 years of age got an acute infection, only about a 5% to 10% of them would have a chronic infection and it would take 20 years before that chronic infection would affect their health with cirrhosis or cancer. Therefore, a recommendation for all adults would not be a good use of resources.
- Conversely, Dr. Talbot emphasized that this is a disease with a lot of disability and mortality, adults 60 years of age and older are very good vectors. One example is that people who need hemodialysis are very unlikely to respond by the time they are identified. If they could be identified prior to renal failure and vaccinated as adults, this would reduce the risk of outbreaks occurring in these facilities. Another example occurs in facilities such as hospitals and nursing homes where there are many documented outbreaks of hepatitis B due to sharing of glucometers. In addition to the potential for spread, the public health cost in time, money, and human resources to investigate outbreaks must be considered.
- Dr. Bell expressed concern about the potential for vaccinating a lot of people who are not at risk and do not need it, with the possibility of still not seeing an impact on disease incidence due to not vaccinating the right people. The success of this program may hinge on implementation to the right populations.
- Dr. Kotton emphasized how shocked she was at the number of at-risk people who are not vaccinated against hepatitis B.

- As a busy PCP, Dr. Cineas emphasized that simplification of the recommendations would help reach more individuals at risk and would offer a great opportunity to promote health equity among disproportionately affected groups. In addition, adults 60 years of age represent a very heterogeneous group. Some may have more risks than others, with some older adults engaging in higher risk activities. For these reasons, she supported a universal hepatitis B recommendation without an age cutoff.
 - Ms. McNally indicated that she was leaning in favor of a universal recommendation due to concerns about health literacy. This is a complicated disease to understand and for which to self-identify risk factors. It can present without symptoms and develop into chronic and debilitating diseases. In addition, this disease disproportionately impacts minority populations.
- Dr. Poehling pointed out that one of the reasons behind the success of childhood vaccination was due to having a universal registry. She wondered what the plans were for a universal registry for adults.
 - Dr. Posner pointed out that considerable progress had been made in the ability to document adult vaccinations in the context of the COVID-19 pandemic. CDC is working to increase the ability to document other adult vaccines as well and to have a more comprehensive adult immunization program, which also will support reporting to the registries.
 - Dr. Coyle (AIRA) added that the same IISs that are capturing childhood and COVID-19 vaccines are lifetime registries that are capturing all vaccines being administered birth to death. Prior to 2020 when adults were starting to be vaccinated with COVID-19 vaccine, 60% of all adult vaccinations were captured in an IIS. It is anticipated that that has increased dramatically and that a lot of the adults who potentially would receive hepatitis B vaccines already would be in the system. Not all providers who are vaccinating adults are reporting to an IIS, but there have been significant strides in closing that gap over the past year—particularly with COVID vaccines. Pharmacies are great reporters of vaccination data to immunization registries, and more adult providers are now aware of and reporting to these registries.
 - Dr. Bell pointed out that in order to achieve the elimination for which everyone is clamoring, there also needs to be funding. This has not occurred for hepatitis in general or hepatitis B in particular.
 - Dr. Nelson agreed with the importance of making sure that efforts are not detracted away from making sure that outreach is made to specific risk-based groups, and that it was important for ACIP to recognize that they were seeing this recommendation as one part of a many pronged strategy to try to address hepatitis B incidence rates. It is sometimes easier to revert to a universal recommendation as the default and not always have the funding or effort to continue to make sure that outreach is enhanced to difficult-to-reach communities. While the way to tackle this has not yet been figured out, it is important to ensure that funding and effort are being allocated to outreach in areas where implementation will be the most impactful even though they are the most difficult to reach. CDC recognizes the benefit of a complementary program that also would enhance the ability to capture these populations.

- Ms. McNally asked whether there are any other countries with a universal recommendation for hepatitis B vaccination.
 - Dr. Weng indicated that this was of interest to the WG as well. When the GRADE and EtR Framework were presented in September, no evidence was found of other countries pursuing this universal policy. Short of having evidence from other countries, they relied on assessment of a subset of well-defined patient groups such as those in the dialysis setting, which is a well-defined group that regularly accesses care in designated locations. They also drew from other vaccine-preventable diseases.

Key discussion points from ACIP liaison members:

- Dr. Schaffner (NFID) pointed out that the US began a strategy to eliminate hepatitis B virus transmission through immunization in 1991. Since then, hepatitis B infections have declined substantially. However, infections have persisted and even increased in parts of the adult population due to low adult vaccination rates and the opioid crisis. While most of the discussion has focused on individuals, universal coverage also would eliminate complicated discussions that doctors have to have with patients. Retiring the risk-based approach would eliminate cost barriers and increase equity. He urged everyone to think big in the use of these safe and effective vaccines in a universal manner, which has the potential to achieve the goal to eliminate hepatitis B virus transmission in the entire population. This aspirational goal is why the NFID supports universal hepatitis B vaccination.
- Dr. Hogue (APhA) observed that there seemed to be a strong case for persons less than 59 years of age and strongly supported a universal recommendation in that group. However, he was not convinced of the marginal benefits among persons 60 years of age and older. Arguably the risk in persons over 85 years of age seemed to be very small. For many years, the Centers for Medicare and Medicaid (CMS) have covered hepatitis B vaccine under Part B for patients on dialysis. Subsequently, that was expanded to some extent. He requested input regarding coverage if a universal recommendation was adopted by ACIP for people over 65 years of age who are Medicare-eligible, and on whether private insurance providers would be required to provide first-dollar coverage under the Affordable Care Act (ACA). Given that a large segment of people at highest risk are uninsured and there is not a program in the US that provides free vaccines to uninsured adults like the VFC program does for uninsured children, he wondered if there are any plans to ensure that vaccine is available for uninsured adults.
 - Ms. Hance (CMS) indicated that Medicare Part B currently covers hepatitis B vaccines for those who are at medium or high risk. Instances are identified that place individuals at increased risk (e.g., hemophilia, end stage renal disease, diabetes, hepatitis B, HCP with frequent contact with blood or bodily fluids, and others). Being a specialist on the Medicaid side, she did not feel comfortable speaking definitively for CMS regarding whether a universal recommendation would be covered under part B. Therefore, she reached out to Medicare colleagues to get a response to address that question.
 - Dr. Wharton added that CDC concurs regarding the importance of vaccine coverage for the uninsured, which will be a policy decision in the future.

- Dr. Zahn (NACCHO) indicated that NACCHO supports the recommendation for universal vaccination of all adults based on local public experience. When jurisdictions follow-up on cases of acute hepatitis B, they often find that the field person had no previously identified risk factors and had not previously been offered hepatitis B vaccine despite contact with the healthcare system months or years previously. Follow-up with cases also has confirmed that there is reluctance to report risk factors due to the associated social stigma. Cases certainly are identified in persons 60 years of age and older, long-term care facilities (LTCF), and dialysis clinics. Even a single case in a facility requires a large facility and public health response, so it is not a trivial issue. NACCHO strongly supports the need for continued and increased support for outreach to at-risk populations, and believes that local public health should continue to play a role in leading outreach efforts to high-risk populations on multiple fronts.
- Dr. Goldman (ACP) said that as a practicing physician, he strongly favored a universal recommendation. He teaches colleagues nationally how to implement vaccine programs and has heard from them that the biggest barrier to implementation is how confusing and detailed the current hepatitis B recommendations are. Making a simple universal recommendation is key to increasing uptake. PCPs must manage chronic illnesses, blood pressure, diabetes, hypertension, recommending screening for colonoscopies and mammograms, et cetera in addition to learning vaccine schedules. He emphasized that the presumption of risk decreasing after 60-65 years of age is not necessarily accurate. There are many areas in Florida where sexually transmitted disease (STD) outbreaks are increasing persons over 65 years of age. A database of Florida's reportable diseases showed that over 25% of the acute hepatitis B reported cases were in persons over 60 years of age in 2021 alone. A universal vaccine recommendation would help to decrease the incidence of hepatitis B. Dr. Goldman suggested a revision to the proposed language to state, "all previously unvaccinated adults without evidence of immunity."
- Ms. Howell (AIM) pointed out that one gap in having adult immunizations in IISs is not receiving reporting from federal systems such as IHS, VA, and DoD, which will be critical for compiling complete adult immunization records. Another gap is due to adults being highly mobile, so interstate data exchange between IISs is critical to ensure that adults have a single central record of their immunizations to inform future vaccines needed. Many awardees use Section 317 vaccines that provide access to vaccines to uninsured adults. Section 317 vaccine funding is limited such that state awardees may or may not be able to include hepatitis B vaccines in their formulary for all uninsured adults unless there is an increase in that funding.
- Dr. Schmader (AGS) indicated for the record that AGS supports universal hepatitis B vaccination with no upper age limit for all of the advantages presented on Slide 19. He pointed out that what will happen in practice is that very old persons or those with limited life expectancy and their caregivers and clinicians will make their own common sense decisions.
- Dr. Fryhofer (AMA) said that speaking as a practicing internal medicine physician, she supported universal recommendation of hepatitis B vaccinations. When she was a third year medical student, she rotated through a hepatitis unit. These were some of the sickest and most miserable patients she had ever seen and she knew she never wanted to feel that way. That was before a hepatitis vaccine was available. As soon as a vaccine was available, she signed up for it. No one should endure the suffering she witnessed before vaccine was

available from something that is now totally vaccine-preventable, so she hoped that ACIP would recommend universal vaccination for all adults—including older adults.

- Dr. Baker (IDSA) said that speaking as a former member and Chair of ACIP, it is the mandate of the ACIP to make good evidenced-based health policy. A lot of the comments made throughout the day were very true and she personally strongly support the comments that funding is needed for all vaccine programs. As the representative for the IDSA, which is comprised of leaders in a variety of areas (e.g., public health, vaccine research, clinical practice, advising, community education, policy-making, et cetera), she conveyed that the IDSA supports universal hepatitis B vaccination for many of the reasons mentioned. This includes improving health equity. The evidence is overwhelming that a risk-based recommendation is a failed policy.
- Dr. Zimmerman (APTR) indicated that he actively treats hepatitis B in his clinical practice. He works in an FQHC that reports adult immunization to the state registry. A universal non-risk-based recommendation would be very helpful in his inner-city practice, particularly for those less than 60 years of age due to the number of persons who have been infected with hepatitis B who have risk factors such as diabetes. Many of his patients do not have risk factors to his knowledge or have been vaccinated because they have been in a dialysis program. There is notably a diminishing return in adults 60 years of age and older. He could see some advantages to phasing in a universal recommendation starting with the younger age group and then perhaps extending that in a number of years.

Vote: Hepatitis Vaccines

Dr. Mark Weng (CDC/NCHHSTP) indicated that based on the discussions and in order to allow for deliberation of screening considerations separately, the WG revised the proposed recommendation language to read:

All adults are recommended to receive hepatitis B vaccination.

Discussion Summary

- Dr. Talbot made a motion for ACIP to adopt an interim recommendation stating that “All adults are recommended to receive hepatitis B vaccination.” Ms. Bahta seconded the motion.
- Dr. Loehr made a motion for ACIP to adopt an amended interim recommendation stating that “All adults ≤59 years of age are recommended to receive hepatitis B vaccination. Adults >60 years of age would continue to follow existing risk-based recommendations.” Dr. Long seconded the motion.
- Dr. Lee indicated that per *Roberts Rules of Order*, they would need to vote on the amendment proposed by Dr. Loehr first. If the amendment passed, the initial motion would be amended and voted on accordingly. If the amendment failed, they would vote on the initial motion made by Dr. Talbot.

Motion/Vote to Amend the Proposed Recommendation Language: Hepatitis B Vaccines

Dr. Loehr made a motion for ACIP to adopt an amended interim recommendation stating that “All adults ≤59 years of age are recommended to receive hepatitis B vaccination. Adults >60 years of age would continue to follow existing risk-based recommendations.” Dr. Long seconded the motion. No COIs were declared. The motion carried with 8 affirmative votes, 7 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

As the amendment motion passed, the initial motion was amended to include the following language:

Vote: Hepatitis B Vaccines

The Advisory Committee on Immunization Practices (ACIP) recommends the following groups **should** receive hepatitis B vaccines:

- Adults 19 through 59 years
- Adults 60 years and older with risk factors for hepatitis B infection

The ACIP recommends the following groups **may** receive hepatitis B vaccines:

- Adults 60 years and older without known risk factors for hepatitis B infection

The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Member Statements

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

- Regarding hepatitis vaccine and ages, Dr. Talbot pointed out that for so long, the focus of the immunization programs has been on the pediatric population. That is rightly so as this work has led to a strong infrastructure to implement widespread and efficient vaccination processes integrated into the routine care at pediatricians' offices. This has dramatically reduced the morbidity from vaccine-preventable diseases among children, which is a blessing because one of her favorite sayings is that "vaccines cause adults." The discussion throughout the day and other discussions that ACIP recently has had illustrate that there needs to be re-examination of the approach to adult and older adult immunizations. Now that there are more immunization options for adults, especially older adults, ACIP needs to re-examine the approach to immunizations in this population in a way that takes into account the unique aspects of adult primary care practices, the presence of multiple comorbidities, and immune senescence. As a reminder, adults are not big kids. To this end, she would like to advocate for and will personally commit to work with ACIP leadership to strategically assess how the goal to improve the adult immunization program can be achieved. Even if it was half as successful as the child and pediatric program, she would be ecstatic.
- Dr. Chen emphasized that they must acknowledge that the projection is 300 million chronic hepatitis B cases all throughout the world and 1.5 million new or acute infections per year. This is a global health problem. ACIP is being asked to address global health, about which he is passionate.
- Dr. Loehr said he would have been content if the hepatitis B recommendation had not had an age restriction, but felt that it was better policy to have an age restriction. The discussion regarding this recommended showed that the ACIP can be a very transparent and open body on which he looked forward to working over the next 4 years.
- Dr. Lee said she was swayed by the resource use domain in particular, realizing that immunization efforts are underfunded in many ways. She felt like it came down to values to a certain extent at the end of the day, which was the value of preventing an acute infection versus the value of preventing chronic liver disease or death due to hepatitis B infection. For her, the older age population was tougher. However, she also was reassured by the fact that anyone who wishes to get a vaccine can receive that vaccine. She expressed her hope that they would continue to focus efforts on this and believes expansion may be possible. She absolutely believes that ACIP's decision-making is dynamic and not fixed in time, so they always need to reevaluate what makes sense for the US population.
- Dr. Long pointed out that because of the way the "may" and "should" accompanied the age recommendations for hepatitis B, it certainly would be within the purview of the practitioner who has a patient population above 60 years of age with risks that are out of proportion to others to be strong advocates for their patients. That certainly would be within the spirit of the recommendation. She inquired as to whether anyone disagreed with that interpretation of the recommendation, which no one did.

IMMUNIZATION SCHEDULES

Session Introduction: Combined Immunization Schedule WG

Dr. Kevin Ault (ACIP, WG Chair) provided the session introduction. He acknowledged Dr. Henry Bernstein, who Co-Chaired the committee until he rotated off the ACIP earlier in the year, and welcomed new member, Dr. Sybil Cineas, who joined the WG in July 2021.

As a reminder, the Combined Immunization WG updates the Child and Adolescent and Adult Immunization Schedules annually. The Child and Adolescent Immunization Schedule summarize ACIP's vaccination recommendations for persons 18 years of age or younger, while the Adult Immunization Schedule summarizes ACIP's vaccination recommendations for persons 19 years of age or older. The goal of the Combined Immunizations Schedule WG is to better harmonize the Child and Adolescent and Adult Immunization Schedules. It is important to note that the use of vaccine trade names is for identification purposes only and does not imply endorsement by the CDC. The 2022 schedules presented during this session are drafts and are therefore subject to change based on ACIP's discussion and vote. New policies are not established in the proposed schedules. Annual schedules reflect recommendations already approved by ACIP.

The Child and Adolescent and Adult Immunization Schedules are presented to ACIP for votes every fall. The ACIP's approval is necessary prior to publication of the schedule in the *Morbidity and Mortality Weekly Report (MMWR)* in January of the following year. In addition, ACIP approval is necessary before partners from the following professional societies review and approve the schedules prior to publications:

- American Academy of Pediatrics (AAP): only child/adolescent schedule
- American College of Physicians (ACP): only adult schedule
- American Academy of Family Physicians (AAFP)
- American College of Obstetricians and Gynecologists (ACOG)
- American College of Nurse-Midwives (ACNM)
- National Association of Pediatric Nurse Practitioners (NAPNAP): only child/adolescent schedule
- American Academy of Physician Assistants (AAPA)
- Society for Healthcare Epidemiology of America (SHEA): only adult schedule

This session included presentations on harmonization between the Child and Adolescent and Adult Schedules; edits to all tables that have occurred since October 2020; content changes of the notes; the new appendix listing contraindications and precautions; and discussion and votes for each schedule.

Proposed Changes to 2022 Child and Adolescent Schedule

Dr. Patricia Wodi (CDC/NCIRD) presented the proposed edits for the 2022 Child and Adolescent Immunization Schedule. ACIP votes since October 2020 have included a vote in June 2021 on the use of dengue vaccination in children and adolescents 9-16 years of age in endemic areas. Influenza vaccination votes in June 2021 included 2021-2022 influenza vaccine recommendations, minimum age for cell culture-based inactivated influenza vaccine (IIV), and contraindications and precautions for influenza vaccines. In addition, edits were made to

sections of the tables and notes of other vaccines to improve readability of the schedule. An appendix was added listing contraindications and precautions for each vaccine type.

Changes to the tables included the cover page and Tables 1, 2, and 3. To harmonize with the cover page of the adult schedule, a section was included with information on how vaccine providers can contact CDC with questions and comments about the schedule. In addition, a link was included to the webpage for vaccine information. A QR code was placed on the right lower corner of the cover page that when scanned will take providers directly to the online version of the Child and Adolescent Schedule. In the box describing how to use the schedule, a fifth step was added instructing providers to review the newly added appendix of contraindications and precautions for each vaccine type. A row was added to the cover page to identify vaccine abbreviations and trade names.

The proposed edits to Table 1, which is the graphical representation of the immunization schedule, now includes a row for dengue vaccine with a column for persons 9-16 years of age shaded in yellow to indicate the recommended age for vaccinations. In addition, overlying text was included stating, "Seropositive in endemic areas only (See Notes)." In the human papillomavirus (HPV) row, the WG made a change to the column for children 9-10 years of age because the descriptive text in the blue box within the table signifies "recommended based on shared clinical decision-making." Some providers found this confusing, so the WG decided to replace the blue color to a new checkered yellow color that signifies, "Recommended vaccination can begin in this age group." The blue box within the legend was revised. The Tdap row for children 11-12 years of age was changed to "1 dose." The emphasis on the color was removed for ages 4-6 years, 11-12 years, and 16 years by changing the color from green to black to match the other columns in this table. Emphasizing these columns was not a part of an ACIP recommendation and providers should review vaccination status at every encounter. However, some WG members indicated a preference for continuing emphasizing this age column as a way for providers to check vaccination status.

Table 2 outlines the catch-up immunization schedule for children and adolescents who started immunizations late or are more than one month behind. A row has been added to Table 2 for dengue vaccine showing the minimum age for Dose 1 and the minimum intervals between Dose 1 to Dose 2 and Dose 2 to Dose 3. In the *Haemophilus influenzae (HIB)* row, the text in the minimum interval between Dose 2 to Dose 3 was updated to include a 4-week interval and to delete COMVAX® from the 8-week interval as COMVAX® was discontinued in 2014.

Table 3 is the graphical representation of the recommended child and adolescent schedule by medical indication. The sub-header for HIV infection CD4+ count was changed to <15% or total CD4 cell count of </mm. This change was made to be consistent with *ACIP's General Best Practice Guidelines for Immunization*. For clarity, the descriptive text in the red box within the legend was changed from "not recommended/contraindicated" to "contraindicated or not recommended." In addition, the checked yellow box was revised to read, "Vaccination is recommended, and additional doses may be necessary based on medical condition or vaccine. See notes." A row was added for dengue vaccine indicating that the vaccine is contraindicated in persons with an immunocompromising condition, including those with severe immunosuppression due to human immunodeficiency virus (HIV) infection. In the columns for pregnancy and persons with HIV infection who do not have immunosuppression, the orange color was used to point out that the vaccine might be indicated if the benefits of protection outweighs the risk of adverse reaction.

Now moving to changes made to the notes sections. For COVID-19 vaccination, additions were made to Additional Information as highlighted here, “COVID-19 vaccines are recommended for use within the scope of the Emergency Use Authorization or Biologics License Application for the particular vaccine, **or as otherwise recommended by ACIP and adopted by the CDC director.** ACIP recommendations for the use of COVID-19 vaccines can be found at www.cdc.gov/vaccines/hcp/acip-recs/index.html. **CDC’s interim clinical considerations for use of COVID-19 vaccines can be found at www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html.**

Dengue vaccination was added to the notes section to summarize the recommendations for routine vaccinations and provide guidance on geographical areas where Dengue is endemic. This reads as follows:

Routine vaccination

- Age 9–16 years living in dengue endemic areas **AND** have laboratory confirmation of previous dengue infection
 - 3-dose series administered at 0, 6, and 12 months
- Endemic areas include Puerto Rico, American Samoa, US Virgin Islands, Federated States of Micronesia, Republic of Marshall Islands, and the Republic of Palau. For updated guidance on dengue endemic areas and pre-vaccination laboratory testing see [weblink pending].

The routine catch-up vaccinations section has been updated to include a revised bullet in which a notation was added about Vaxelis as highlighted in yellow, “For other catch-up guidance, see Table 2. **Vaxelis can be used for catch -up vaccination in children less than age 5 years. Follow the catch -up schedule even if Vaxelis is used for one or more doses. For detailed information on use of Vaxelis see www.cdc.gov/mmwr/volumes/69/wr/mm6905a5.htm**

A minor edit was made for clarity within the hepatitis A vaccination routine recommendations to read, “2-dose series (minimum interval: 6 months) at age 12-23 months.” Within the Hepatitis B notes, the introductory sentence in the Special Situation section regarding recommendations for the vaccination was updated to include post-vaccination serology such that it now begins with, “Post-vaccination serology testing and re-vaccination (if anti-HBs < 10mIU/mL) . . .”

Within the HPV notes, the final bullet in the routine vaccination section was edited for clarity to read as follows, with changes highlighted:

Routine and catch-up vaccination

Revised bullet: **No additional dose recommended when any HPV vaccine series has been completed using the recommended dosing intervals.**

Special situations

- Revised bullet: Immunocompromising conditions, including HIV infection: **3-dose series regardless of age at initial vaccination**
- Revised bullet: Pregnancy: **Pregnancy testing not needed before vaccination; HPV vaccination not recommended until after pregnancy; no intervention needed if vaccinated while pregnant**

For influenza vaccine, the Special Situation section included revised and deleted bullets as shown here:

Special situations

Revised bullets:

- Egg allergy with symptoms other than hives (e.g., angioedema, respiratory distress) or required epinephrine or another emergency medical intervention: [see Appendix listing contraindications and precautions](#)
- Severe allergic reaction (e.g., anaphylaxis) to a vaccine component or a previous dose of any influenza vaccine: [see Appendix listing contraindications and precautions](#)

Deleted bullets:

- Severe allergic reactions to vaccines can occur even in the absence of a history of previous allergic reaction. All vaccination providers should be familiar with the office emergency plan and certified in cardiopulmonary resuscitation.
- LAIV4 should not be used in persons with the following conditions or situations:

Within the MMR section, the Routine Vaccinations section was updated to include the use of MMRV. In addition, language was included stating, “*Note: For dose 1 in children aged 12-47 months, it is recommended to administer MMR and varicella vaccines separately. MMRV may be used if parents or caregivers express a preference.” Under the Catch-Up Vaccination section, a bullet was added reading, “Minimum interval between MMRV doses: 3 months.”

Under the Special Situations section for meningococcal serogroup A,C,W,Y vaccination, the Menactra note was revised to read, “Menactra should be administered either before or at the same time as DTaP. *MenACWY vaccines may be administered simultaneously with MenB vaccines if indicated, but at a different anatomic site, if feasible.*”

For the varicella vaccine section, the following additions or revisions were made to various bullets:

Routine vaccination

- Added bullet: VAR or MMRV may be administered*
- Added: *Note: For dose 1 in children aged 12-47 months, it is recommended to administer MMR and varicella vaccines separately. MMRV may be used if parents or caregivers express a preference.
- Revised bullet: Dose 2 may be administered as early as 3 months after dose 1 (a dose inadvertently administered after at least 4 weeks may be counted as valid)

Catch -up vaccination

- Revised bullet: Age 7-12 years: routine interval: 3 months (a dose inadvertently administered after at least 4 weeks may be counted as valid)

Changes to the appendix include the addition of the following to the top of the page:

Guide to Contraindications and Precautions to Commonly Used Vaccines

Adapted from Table 4 in Advisory Committee on Immunization Practice (ACIP) General Best Practice Guidelines for Immunization: Contraindication and Precautions available at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html and ACIP’s Recommendations for the Prevention and Control of 2021-22 seasonal influenza with Vaccines available at www.cdc.gov/mmwr/volumes/70/rr/rr7005a1.html

Interim clinical considerations for use of COVID-19 vaccines including contraindications and precautions can be found at www.cdc.gov/vaccines/covid-19/clinicalconsiderations/covid-19-vaccines-us.html

Discussion Summary

- The schedule may become so complex with so many colors, it may become difficult to display visually. Every time a new color is added, it becomes harder to interpret. This is especially true for those who are colorblind.
 - Dr. Wodi indicated that the schedule can be accessed online and printed. There is a color version and a grayscale version. They are working with the graphics team to ensure that it can be used by people who have colorblindness.
- The link to download the CDC Vaccine Schedules app for providers included on the cover pages of the schedules was observed to be extremely beneficial.
- An inquiry was posed regarding approval of the immunization schedule recommendations by the societies listed earlier in terms of whether this always has been the case, the protocol/timeframe for their approval, and what occurs should any of the societies disagree with the recommendations (e.g., would the recommendations go back to ACIP?).
 - Dr. Ault indicated that as part of the ACOG committee that reviews these recommendations, after the ACIP votes, ACOG distributes them to others in the organization and then ACOG endorses the recommendations. He did not recall a society not endorsing a schedule in the past, likely because liaisons spend so much time attending committee meetings.
 - Dr. Goldman reported that the way that ACP handles this is that once a vaccine schedule is approved by CDC, he takes it back to ACP's vaccine committee, which then votes and brings it up to the Board of Regents. When the Board of Regents approves the policy, it is published in the *Annals of Internal Medicine*. ACP is usually in concert with and supports ACIP/CDC guidelines, but sometimes does not agree. When that happens, ACP would publish the policy differently in the *Annals of Internal Medicine*.
 - Dr. Wharton pointed out that because of the involvement of the listed groups in the WG, the schedule is developed collaboratively. If there are late changes, they are worked through by the group as a whole. Although there are formal processes for approval, they tend to work seamlessly.
- A key feature of IISs is that they can evaluate what vaccines/doses someone has received in the past and compare these to the ACIP recommendations to forecast what that person is likely recommended to receive, which can aid the provider and patient in decision-making.
- Concern was expressed about inclusion of the process language "or as otherwise recommended by ACIP and adopted by the CDC director" for COVID-19 vaccination when it is not included for other vaccines and given that the process does not always flow in that direction.

- Dr. Wodi indicated that they worked with CDC's Office of General Counsel (OGC) to help write the language.
- Dr. Lee requested that a representative from CDC confer with the CDC team to clarify this. This is part of the charter and should not be included in every recommendation, nor is it unique to this particular recommendation.

Proposed Changes to 2022 Adult Immunization Schedule

LCDR Neil Murthy (CDC/NCIRD) presented proposed substantive changes to the 2022 Adult Immunization Schedule, noting that minor grammatical or formatting edits meant to improve clarity of the language would not be presented. He discussed proposed edits to the tables, proposed vaccine-specific changes in the notes section, and the addition of a new appendix with contraindications and precautions for each vaccine.

There were 4 main changes on the cover page. The first was in the how to use the adult immunization schedule box, where a Step 4 was included instructing providers to review the newly added appendix that lists the contraindications and precautions for all the vaccines listed in the adult immunization schedule. The second edit was in the box in the upper right-hand corner of the cover page, where SHEA was added as a partner organization approving the adult schedule. The third edit was the list of adult vaccines, where PCV13 was removed and the 2 new pneumococcal conjugate vaccines, PCV15 and PCV-20, were added to the list. The final edit was the addition of a QR code at the bottom right-hand corner of the cover page that when scanned takes the user to a CDC website with the adult immunization schedule, which can be viewed from a mobile device if preferred.

Table 1 had 4 proposed edits. The first edit was to the Zoster vaccine row, where 2 doses of recombinant zoster vaccine (RZV) are now recommended for adults 19-49 years of age who have immunocompromising conditions. This change reflects the new ACIP recommendations. The second edit was to the pneumococcal vaccine row. To reflect the new ACIP recommendations, the new pneumococcal conjugate vaccine and the polysaccharide vaccine were collapsed into one row. Guidance for which vaccines are indicated for certain age groups was displayed by the corresponding colors and overlying text. The final edit to Table 1 was to the hepatitis B row, which was changed to yellow in anticipation of ACIP's recommendation for universal Hepatitis B vaccination for adults up to and including 59 years of age. Those 60 years of age and older will continue to have risk-based recommendations, which is indicated by the purple bar.

There were 5 changes proposed for Table 2, the medical indications table. The first change was to the CD4 percentages and counts header to harmonize with the way this information is presented in the Child and Adolescent Schedule. The second edit was to the legend at the bottom of the table where the description was reworded for the color red in the legends. Red now indicates the vaccine is contraindicated or not recommended. The third edit was to the zoster vaccine row, where 2 doses of RZV are now recommended to adults ≥ 19 years of age who have immunocompromising conditions, including HIV infection. This change reflects the new ACIP recommendation. The fourth edit was to the pneumococcal vaccine row. As in Table 1, all the pneumococcal vaccines were collapsed into one row with colors and overlying text indicating which groups need which vaccines. The fifth edit was to the Hepatitis B row, which was changed entirely to yellow indicating that the vaccine is recommended for various risk-based groups.

Now turning to the changes proposed in the notes section of the adult schedule, beginning with the COVID-19 vaccination box on the first page of the notes section. In addition to stating that COVID-19 vaccines are recommended within the scope of the Emergency Use Authorization or Biologic License Application for this particular vaccine, a phrase was added reading, “or as otherwise recommended by ACIP and adopted by the CDC director.” Because it was felt that clinicians would benefit from having this information readily available, the hyperlink to *CDC’s Interim Clinical Considerations for the use of COVID-19 Vaccines* was added.

Moving to the hepatitis B section, In this section, clarification was added for the 2-, 3-, and 4-dose hepatitis B vaccine series. Based on the hepatitis B discussions from earlier in the day, language will be included about risk-based recommendations for adults 60 years of age and older.

In terms of the HPV vaccine, the wording was changed in the final bullet of the Routine Vaccination section to increase clarity. This bullet now reads, “No additional dose recommended when any HPV vaccine series has been completed using the recommended dosing intervals.” In the Special Situation section, wording was added to the immunocompromising conditions bullet for clarity, which now reads, “**Immunocompromising conditions, including HIV infection:** 3-dose series as above, when initiating vaccination at age 9-45 years. Recommendations for routine and shared clinical decision-making similar to those for persons without immunocompromising conditions.” Finally, the wording was rearranged for the pregnancy bullets in the Special Situations section, which now reads, “Pregnancy testing is not needed before vaccination; HPV vaccination is not recommended until after pregnancy; no intervention needed if inadvertently vaccinated while pregnant.”

On the first page of the influenza section, the language in the first bullet under routine vaccination was changed to read, “Age 19 years or older: 1 dose any influenza vaccine appropriate for age and health status annually.” The hyperlink to the *2021-2022 Influenza Vaccine Recommendations* was added, along with a bullet for the 2022-23 influenza season recommendations. On the second page of the notes section, much of the special situations with different influenza vaccinations has been condensed and refers HCP to the Appendix to learn about contraindications and precautions.

Under the Special situations Section for MMR vaccination, CD4 percentages were added in addition to CD4 counts for HIV infection to harmonize the language with child/adolescent schedule for the HIV infection bullets.

For meningococcal vaccination, a note was added at the end that states, “Meningococcal B vaccines may be administered simultaneously with MenACWY vaccines if indicated, but a different anatomic site, if feasible.”

The pneumococcal vaccination section was modified substantially to reflect the new ACIP recommendations. The first bullet now states that adults, “Age 65 years or older who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown: 1 dose PCV15 or 1 dose PCV20. If PCV15 is used, this should be followed by a dose of PPSV23.” Once details about the dosing intervals between PCV15 and PPSV23 are finalized, a link will be added to that guidance. A link also will be included for providers to reference the guidance for patients who previously received PCV13 or PPSV23 in the past. The Special Situation section was changed and now has a bullet stating, “Age 19-64 years with certain underlying medical conditions or other risk factors who have not previously received a

pneumococcal conjugate vaccine or whose previous vaccination history is unknown: 1 dose PCV15 or 1 dose PCV20. If PCV15 is used, this should be followed by a dose of PPSV23.” Again, once details about the dosing intervals between PCV15 and PPSV23 are finalized, a link to that guidance would be added here. Similarly, a link would be included for providers to reference the guidance for patients who have previously received PCV13 or PPSV23. A note was added at the end of the pneumococcal section stating, “Underlying medical conditions or other risk factors include alcoholism, chronic heart/liver/lung disease, cigarette smoking, diabetes mellitus, chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, HIV, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplants, congenital or acquired asplenia, sickle cell disease or other hemoglobinopathies, CSF leak, or cochlear implant.”

For the varicella section, CD4 percentages have been added in addition to CD4 counts in the HIV infection bullet to harmonize the language with the child and adolescent schedule. In the Special Situation section, the language was revised for the pregnancy bullet. This now reads, “There is currently no ACIP recommendation for RZV use in pregnancy. Consider delaying RZV until after pregnancy.” To reflect the new ACIP recommendations for persons with immunocompromising conditions, this bullet now states, “**Immunocompromising conditions (including HIV):** RZV recommended for use in persons aged 19 years or older who are or will be immunodeficient or immunosuppressed due to disease or therapy.”

The newest addition to the adult immunization schedule is the appendix that lists all of the contraindications and precautions to each of the adult vaccines. At the top of the appendix, the same items were added that were added to the child/adolescent schedule:

Guide to Contraindications and Precautions to Commonly Used Vaccines

Adapted from Table 4-1 in Advisory Committee on Immunization Practice (ACIP) General Best Practice Guidelines for Immunization: Contraindication and Precautions available at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html and ACIP’s Recommendations for the Prevention and Control of 2021-22 seasonal influenza with Vaccines available at www.cdc.gov/mmwr/volumes/70/rr/rr7005a1.html

Interim clinical considerations for use of COVID-19 vaccines including contraindications and precautions can be found at www.cdc.gov/vaccines/covid-19/clinicalconsiderations/covid-19-vaccines-us.html

The first page of the appendix lists the contraindications and precautions for all of influenza vaccines approved for adults. The second page of the appendix lists the contraindications and precautions for all of the other non-influenza vaccines.

Discussion Summary

- Concern was expressed that cochlear implants were included on Table 2 in the child/adolescent schedule but not on the adult schedule. Physicians want to be alerted to cochlear implants being an indication for a special situation if it impacts their vaccination schedule, which is not captured by this schedule.

- Dr. Murthy indicated that because there were so many nuances with the contraindications and precautions to the influenza vaccination recommendations, the WG decided to have a separate section for the contraindications and precautions in the appendix. The cochlear implant is listed as a contraindication for the live attenuated influenza vaccine (LAIV). The goal is to direct HCP to glean this information from the new appendix. In the pneumococcal vaccination section, there is a special note that mentions that persons 19-54 years of age with cochlear implants should receive vaccinations. However, an analogous appendix is not included per se based on those very specific risk factors. Table 2 does not have cochlear implant, but does have other risk factors that would indicate certain vaccines.
- There was support for including a few words in the pneumococcal statement in addition to referring people to information located elsewhere. For instance, it could read, "PCV15 or PCV20 may be administered. If PCV15 is used, it should be followed by PPSV23." Then 2 weeks to 12 months and the URL could be included. Perhaps a few more words could express the urgency of attaining full coverage as quickly as possible rather than waiting 12 months in persons with a cochlear implant or who just had their spleen removed for instance.
- Dr. Murthy indicated that the team would work closely with pneumococcal vaccine colleagues to consider how this could be presented succinctly in the final version that will be published in February 2022.
- The HPV recommendation in the Special Situation section that references routine and shared clinical decision-making in the context of immunocompromising conditions is confusing. Though the goal was to add clarity, it was not clear what this was trying to convey. Part of the confusion may be due to the sentence prior to this stating 9-45 years of age. Perhaps adding clarifying information about the age-based recommendations for persons 9-45 years of age would make this clearer. This needs to be very direct about needing a 3-dose series even if the first dose is given before 15 years of age.
 - Dr. Murthy said that because people were misinterpreting last year's schedule, the proposed language was developed with input from their HPV colleagues, who pointed out that the recommendations for routine and shared clinical decision-making are similar for persons with or without immunocompromising conditions. Essentially, the point was to state that people still would need to fall within the recommended timeframe and age range. They will work with the HPV SMEs to further clarify this.
- The red box in Table 2 is "contraindicated or not recommended." All of the red boxes have overlaying text of "not recommended," but sometimes a vaccine is contraindicated as distinct from not being recommended. Providers may find this confusing, so it was suggested that either all of the overlaying text be removed or "contraindicated" be placed where appropriate.

Vote: Immunization Schedules

Dr. Wharton (ACIP, Executive Secretary) indicated that the ACIP procedural language that was included in the schedules was removed and other comments throughout the discussion from the committee were incorporated and revised schedules were developed. The language for the vote read as follows:

The ACIP approves the recommended *Child and Adolescent Immunization Schedule, United States, 2022* and the recommended *Adult Immunization Schedule, United States 2022*.

Vote: Child and Adolescent and Adult Immunization Schedules

Dr. Ault made a motion to accept the language stating that, "The ACIP approves the recommended *Child and Adolescent Immunization Schedule, United States, 2022* and the recommended *Adult Immunization Schedule, United States 2022*." Ms. Bahta second the motion. No COIs were declared. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Ault, Bahta, Bell, Brooks, Chen, Cineas, Daley, Kotton, Lee, Loehr, Long, McNally, Poehling, Sanchez, Talbot

0 Opposed: N/A

0 Abstained: N/A

0 Absent: N/A

Member Statements

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

- Dr. Chen recognized that the orchestration of the vaccination schedules and development of these tools in a way that makes sense for providers to be able to use clearly takes a tremendous amount of work, for which he expressed gratitude to the WG.
- Dr. Poehling emphasized that the immunization schedule for adults is complicated, which is good in that it signifies that there are a lot of adult vaccines available. Now is the time to create a universal vaccine registry for adults because this will be an essential component of determining which vaccines people have had. She strongly encouraged the development of a universal vaccine registry for adults, combined across states. Consideration must be given to how to move forward on this.

ORTHOPOXVIRUSES VACCINES

Session Introduction

Dr. Pablo Sanchez (ACIP Chair) provide an introduction and overview of the orthopoxviruses vaccines session. As a reminder, the WG provided background information important to understanding the EtR Framework and presented EtRs for 5 policy questions for JYNNEOS® during the ACIP meeting on September 29, 2021. WG discussions since that ACIP meeting have focused on clinical guidance for the use of JYNNEOS®, including contraindications and precautions/warnings, and wording of proposed recommendations. Topics during this session included presentations on clinical guidance for the use of JYNNEOS®, a summary of WG considerations and proposed policy options, and orthopoxviruses vaccine votes. Publication of the recommendations in the *MMWR* is anticipated in early to mid-2022.

Clinical Guidance for Use of JYNNEOS®

Dr. Brett Petersen (NCEZID/ CDC) presented clinical guidance for the use of JYNNEOS® vaccine in terms of contraindications and precautions/warnings, guidance for minimizing the risk of occupational exposure, and titers and starting work in laboratories. The vaccines under discussion during this session were ACAM2000 and JYNNEOS®. The major difference between these vaccines is that ACAM2000 is a replication-competent vaccinia virus vaccine while JYNNEOS® is replication deficient. With ACAM2000, a vaccine site lesion or a “take” occurs that is not seen with JYNNEOS®. Consequently, there is a risk of an inadvertent inoculation and autoinoculation with ACAM2000 that does not exist with JYNNEOS®. Other SAEs occur with ACAM2000, which are expected to appear less frequently with JYNNEOS®.

Both of these vaccines are licensed by the FDA, and their effectiveness was evaluated by comparing the immunologic responses of these vaccines with their predecessor previously licensed vaccines. The proposed recommendations for these vaccines are for persons at occupation risk of exposure to orthopoxviruses. This includes research laboratory personnel, diagnostic laboratorians, and response team members. This vaccine also would be offered under shared clinical decision-making to persons who administer ACAM2000 or care for patients with infections or after vaccination with replication-competent virus vaccines. The vaccines would also be recommended as a booster for persons who are at continued or sustained risk for exposures to orthopoxviruses. For those working with smallpox and monkeypox, booster doses would be every 3 years for ACAM2000 and every 2 years for JYNNEOS®. Booster doses would be every 10 years for either vaccine for those working with less virulent orthopoxviruses.

Severe vaccinia virus complications can occur following vaccination with replication-competent vaccinia virus vaccines or after occupational exposures and infections with orthopoxviruses, such as progressive vaccinia or eczema vaccinatum, which can occur in individuals with immunocompromise or atopic dermatitis, respectively. These complications are due to uncontrolled viral replication. There also can be severe vaccinia virus complications related to inadvertent transmission. For example, fetal vaccinia can occur following vertical transmission to the fetus or autoinoculation and inadvertent inoculation can occur as well. These can be serious when they affect anatomic areas of particular sensitivity like the eyes. Severe vaccinia virus complications of uncertain etiology can occur as well, such as post-vaccinal encephalitis and myopericarditis. No confirmed cases of any of these severe vaccinia virus complications

have been reported in any of the clinical trials with JYNNEOS® to date. There does remain a theoretical risk that severe vaccinia virus complications of uncertain etiology could occur based on the hypothesis that there may be an immune-mediated phenomenon rather than direct viral infection, which is dependent on the replication status of the vaccine.

Regarding the proposed ACIP contraindications for ACAM2000 and JYNNEOS®, the contraindications for ACAM2000 are unchanged from previous ACIP recommendations as there are no significant new safety data to suggest a need for a change. For JYNNEOS®, the WG recommended a contraindication for persons who have a serious vaccine component allergy. This recommendation was made in recognition of the currently available safety data and the population that is the subject of these recommendations. Precautions and warnings are provided in the footnotes for household contacts, atopic dermatitis/eczema and other active exfoliative skin conditions, conditions associated with immunosuppression, pregnancy, children <1 year of age, breastfeeding, and three or more known major cardiac risk factors.

For household contacts, a bullet was added to note that “JYNNEOS® is a replication-deficient vaccine and therefore should not present a risk of transmission to household contacts.” For persons with atopic dermatitis/eczema and other active exfoliative skin conditions, a bullet was added to indicate that “Studies evaluating JYNNEOS® in persons with atopic dermatitis have demonstrated immunogenicity in eliciting a neutralizing antibody response and did not reveal any significant safety concerns.” Individuals with immunosuppression are contraindicated for receipt of ACAM2000, but a bullet was added to indicate that “Immunocompromised persons, including those receiving immunosuppressive therapy, may have a diminished immune response to JYNNEOS® because of their immunocompromised status.” While pregnant women are contraindicated to receive ACAM2000, bullets were added to indicate that “Available human data on JYNNEOS® administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy. However, animal models, including rats and rabbits, have shown no evidence of harm to a developing fetus.”

Infants aged less than one year are contraindicated for receipt of ACAM2000. Notes have been added that “That JYNNEOS® is not licensed for persons <18 years and has not been rigorously evaluated in this population” and that for that reason “Caution should be used when considering the administration of ACAM2000 or JYNNEOS® to children and adolescents aged <18 years.” Breastfeeding women are contraindicated for receipt of ACAM2000. Information was added to the footnote to indicate that “The safety and efficacy of JYNNEOS® has not been evaluated in breastfeeding women.” Therefore, “It is not known whether JYNNEOS® is excreted in human milk and data are not available to assess the impact of JYNNEOS® on milk production or the safety of JYNNEOS® in breastfed infants.” “However, JYNNEOS® vaccine is replication deficient and therefore should not present a risk of transmission to breastfeeding infants.” Nevertheless, “Caution should be used when considering the administration of JYNNEOS® to breastfeeding women.” Individuals who have an underlying cardiac disease or three or more known major cardiac risk factors are contraindicated for primary vaccination with ACAM2000. However, bullets were added to indicate that “Clinical studies have not detected an increased risk of myopericarditis in recipients of JYNNEOS®” and that “Persons with underlying heart disease or ≥3 major cardiac risk factors should be counseled on the theoretical risk of myopericarditis given the uncertain etiology of myopericarditis associated with replication-competent smallpox vaccines.”

The WG also proposed to include guidance on minimizing risk of occupational exposure, titer testing, and starting work in laboratories as follows:

Guidance for Minimizing the Risk of Occupational Exposure

- Many persons with contraindications to vaccination with ACAM2000 (e.g., atopic dermatitis, immunocompromising conditions, breastfeeding, or pregnancy) may receive vaccination with JYNNEOS®.
- However, such persons may be at increased risk for severe disease if an occupational infection occurs despite vaccination.
- Persons with immunocompromising conditions may be less likely to mount an effective response after any vaccination, including after JYNNEOS® even though JYNNEOS® can be safely administered to such persons.
- Persons who are pregnant, immunocompromised, with atopic dermatitis, or breastfeeding may receive JYNNEOS® when it is considered imperative to provide protection against orthopoxvirus infections and after careful consideration of the risk/benefit ratio.
- To find more information about the risk for severe outcomes if orthopoxvirus infections are acquired, please see [Smallpox Vaccination and Adverse Reactions: Guidance for Clinicians, 2003. *MMWR* 2003, 52(RR04);1-28].

Titer Testing

- As a replication-deficient vaccine, JYNNEOS® does not produce a vaccine site lesion (also known as a “take”) that can be used as a marker of successful vaccination.
- Routine titer testing is not recommended following vaccination with JYNNEOS® to confirm successful administration of vaccine given that high rates of seroconversion were demonstrated in clinical trials.
- However, titer testing could be considered on a case-by-case basis after consultation with public health authorities for select persons with immunocompromising conditions or those working with more virulent orthopoxviruses (e.g., variola virus and monkeypox virus) to confirm an immune response has been achieved.
- A correlate of protection has not been established and there is no known antibody titer level that will ensure protection.
- Titer results should be interpreted with caution in such cases to avoid providing a false sense of security.

Starting Work in Laboratories

- A person can be considered fully immunized 2 weeks following administration of the second dose of JYNNEOS® when clinical studies have demonstrated maximal antibody titers.

Summary of WG Considerations and Proposed Policy Options

Dr. Agam Rao (NCEZID / CDC) reminded everyone that there are 5 PICO questions. The first and the second pertain to primary vaccination with JYNNEOS® for 2 at-risk populations. The third and fourth questions regard the frequency of booster doses after the primary vaccination series with JYNNEOS® and persons with continued occupational risk. The fifth relates to one of the most frequent questions received, which concerns changing from boosters with ACAM2000 to boosters with JYNNEOS® for those who received the ACAM2000 primary series. Because there are 5 PICOs, there are 5 EtR frameworks. Dr. Rao noted that she would go over the first one in detail, but would move quickly through the other 4 because many of the WG sentiments were the same.

Beginning with the EtR for the first 2 PICO questions pertaining to primary vaccination with JYNNEOS[®], orthopoxvirus infections cause morbidity and mortality. Several populations are at occupational risk. The first are research laboratory personnel, who are defined as those who directly handle 1) cultures or 2) animals contaminated or infected with replication-competent vaccinia virus, recombinant vaccinia viruses derived from replication-competent vaccinia strains (i.e., those that are capable of causing clinical infection and producing infectious virus in humans), or other orthopoxviruses that infect humans (e.g., monkeypox, cowpox, and variola). The second are clinical laboratory personnel performing diagnostic testing for orthopoxviruses. The third are response team members designated by public health authorities to receive the vaccine for preparedness purposes. The fourth population are select HCP who administer ACAM2000 or care for patients infected with replication-competent orthopoxviruses, such patients enrolled in clinical trials.

ACAM2000 is currently recommended by the ACIP for persons at occupational risk. If JYNNEOS[®] were to also be recommended, there would be benefits to having more than one effective vaccine available. Additionally, having more than one vaccine provides options. Some people may prefer receiving one of these vaccines over the other. The first PICO question is, "Should JYNNEOS[®] be recommended for research laboratory personnel, clinical laboratory personnel performing diagnostic testing for orthopoxviruses, and designated response team members at risk for occupational exposure to orthopoxviruses?" The intervention is vaccination with JYNNEOS[®] and the comparison is ACAM2000, which is the standard of care for persons at risk for occupational exposure. The outcomes listed for this question are the same as for the other 4 PICOs to be presented: prevention of disease, severity of disease, SAEs, myo-/pericarditis. The outcomes of prevention of disease, SAEs, and myo-/pericarditis were deemed critical by the WG. These are the outcomes that will be evaluated in the Evidence Tables.

Regarding the first EtR domain of benefits and harms, JYNNEOS[®] is not a replicating virus so there is not potential spread to others. FDA found JYNNEOS[®] to be non-inferior to ACAM2000 for immunogenicity. Most importantly, the evidence table for outcome A suggests that there is as small benefit of JYNNEOS[®] compared to ACAM2000 for prevention of disease. For this reason, the WG concluded that the desirable anticipated effects are small. Looking at the evidence table, GMTs and seroconversion rates are the 2 indirect measures of prevention of disease evaluated. Regarding prevention of disease assessed with GMT, the mean difference in titer units between those who received JYNNEOS[®] compared to those who received a live replicating vaccinia vaccine with either ACAM2000 or Dryvax[®], was 1.62 titer units higher. The 95% confidence interval ranged from 1.32 to 1.99 titer units higher.

In terms of harms and how substantial the undesirable anticipated effects are, JYNNEOS[®] is a non-replicating vaccinia virus, so there were fewer contraindications to JYNNEOS[®] compared to ACAM2000. The RCTs and pooled observational data and the evidence tables indicate fewer AEs with JYNNEOS[®]. The WG decided that the answer to this question was "minimal" based on the data considered for this question. The absolute effect from the RCT data was 3 fewer SAEs per 1000 with JYNNEOS[®] compared to ACAM2000. The observational data support the RCT data. Because it is relevant to later aspects of the EtR, many more people were included in the observational data than the RCT data. Similarly, there were fewer myocarditis events associated with JYNNEOS[®] compared to ACAM2000. The observational data supported the same conclusion, offered a lot more data, and showed that there are minimal harms from JYNNEOS[®].

The benefits were determined to be small and harms minimal, so the desirable effects were determined to outweigh the undesirable effects. Therefore, the WG favored the intervention. The overall certainty in the benefits was moderate based on the evidence table for prevention of disease. After considering GMT and SCR data together, there is moderate certainty that there was a small increase in disease prevention provided by JYNNEOS[®] compared to ACAM2000. The certainty level was determined by an assessment of the RCTs for study design, risk of bias, inconsistency, indirectness, and imprecision. GMT is an indirect measure of prevention of disease, which is what has led to a Level 2 or moderate-level certainty for the effect estimate.

The WG estimated that there were fewer SAEs in myocarditis cases after a JYNNEOS[®] primary series compared to ACAM2000 vaccination, but there was low certainty in these conclusions. For SAEs, RCT data were downgraded due to the sample size being small and therefore not meeting the optimal size to assess this rare outcome. Also, the 95% confidence interval includes the potential for meaningful harm. The observational data included many more subjects (over 5000) in the JYNNEOS[®] arm and showed no harm. This was reassuring for the WG and is the reason that both the RCT data and observational data were presented. Similarly, for myo/pericarditis, there were too few subjects enrolled in the RCTs to assess for this rare event. Therefore, there was very serious concern for imprecision. While the observational data included many more subjects, the certainty level for observation studies is low to start with at Level 3. It was downgraded here because of serious concerns for risk of bias because of selection bias and for indirectness because this was an indirect comparison of pooled single-arm studies compared to a historical control.

Moving to the values domain, the WG concluded that the target population probably feels that the desirable effects are large relative to the undesirable effects. In 2015, CDC surveyed 275 HCP in the Democratic Republic of Congo (DRC) to evaluate the target population's values. Among the respondents, 99% reported having seen a monkeypox case, over 75% were not interested in ACAM2000 after they heard what it was, and 98% were interested in JYNNEOS[®]. The US target population has made multiple requests for JYNNEOS[®] vaccine, although the US does not have similar data. The WG determined that while no research has been identified, stakeholders are expected to value immunity. FDA deemed the JYNNEOS[®] primary vaccination series to be non-inferior to that for ACAM2000. It will take longer from the first vaccination before a person given JYNNEOS[®] is considered fully vaccinated compared to a person given ACAM2000, given that 2-doses of JYNNEOS[®] administered over 28 days are required compared to 1 vaccination for ACAM2000. The WG concluded that there is probably no important uncertainty or variability.

For the acceptability domain, there is ease in finding a provider and it is known that some vaccinees have difficulty finding an ACAM2000 provider because it is administered by a technique with which many physicians may not be familiar. It involves the bifurcated needle and multiple punctures. Because JYNNEOS[®] is a non-replicating virus vaccine, there is no risk of transmission to others, particularly to those who are immunocompromised or who have skin conditions like eczema. AEs also are expected to be rarer with JYNNEOS[®] compared to ACAM2000. For all of these reasons, the WG thought that the intervention would be acceptable to key stakeholders.

Now moving to the resource use and equity domains. JYNNEOS[®], like ACAM2000, would be provided from HHS's Strategic National Stockpile (SNS) free of cost. Even in cases where employers do not cover the cost of clinic appointments, there may be similar clinic costs associated with JYNNEOS[®] as with ACAM2000 vaccinations because in some clinics, patients return for in-person clinic appointments on multiple days after ACAM2000 vaccination on Days

3, 7, and sometimes several times after that to perform dressing changes and assess the “take” sites and evaluate for symptoms or complaints consistent with myocarditis. Therefore, the WG felt that JYNNEOS® would be a reasonable and efficient allocation of resources. Because there are fewer costs and challenges associated with identifying a provider, equity would be increased.

For the domain of feasibility, there likely would be the same number of clinic visits or possibly even fewer with JYNNEOS®. Also, there would be less difficulty getting on a vaccine schedule because more providers would be willing to administer subcutaneous injections. People would not necessarily have to go to military sites to receive the vaccine. JYNNEOS®, once thawed and refrigerated, is good for 6 months. According to recent approvals made by FDA, thawed ACAM2000 is good for longer at about 18 months, but the shipping conditions are the same for both. Therefore, the 6-month window allows for ample time for providers to schedule vaccinations. CDC Drug Service would be sending out the vaccine and they foresee no issues with feasibility. Therefore, the WG deemed the intervention feasible to implement.

To summarize the EtR Framework for the first PICO question in terms of the balance of consequences, the WG felt the desirable consequences probably outweigh undesirable consequences in most settings. Therefore, the WG proposed the following language for the first recommendation:

Proposed Recommendation 1

The ACIP recommends JYNNEOS® as an alternative to ACAM2000 for research laboratory personnel*, clinical laboratory personnel performing diagnostic testing for orthopoxviruses†, and for designated response team members at risk for occupational exposure to orthopoxviruses§

*Research laboratory personnel are those who directly handle 1) cultures or 2) animals contaminated or infected with replication-competent vaccinia virus, recombinant vaccinia viruses derived from replication-competent vaccinia strains (i.e., those that are capable of causing clinical infection and producing infectious virus in humans), or other orthopoxviruses that infect humans (e.g., monkeypox, cowpox, and variola). †Clinical laboratory personnel who perform routine chemistry, hematology, and urinalysis testing, including for suspect or confirmed patients with Orthopoxvirus infections, are not included in this recommendation as their risk for exposure is very low §Public health authorities, at their own discretion, may approve a cohort of healthcare and/or public health personnel to receive primary vaccination against Orthopoxviruses for preparedness purposes (e.g., first responders who might participate in a smallpox or monkeypox outbreak).

Moving to the second PICO question regarding whether JYNNEOS® should be recommended for HCP who administer ACAM2000 or care for patients infected with replication-competent orthopoxviruses, many of the responses were the same as for the first PICO question. In terms of benefits and harms, the same evidence tables were used for this PICO. There were differences in the values domain. There is no research data to evaluate whether the target population feels that the desirable effects are large relative to undesirable effects, but it is believed that some members of this population will be interested in vaccination or at least would like the option of being vaccinated, even though it is not indicated for the entire population. In the past, when patients were admitted with AEs from replicating orthopoxvirus vaccines, some HCP were anxious. Allowing for these persons to be vaccinated is consistent with the ACIP recommendations for ACAM2000 and is something that the WG wanted to do. The ACAM2000 language for this particular population is that it “can be offered.” Because of the low risk for such persons who already are wearing personal protective equipment (PPE), many may opt to not get vaccinated. The WG concluded that there is possibly important uncertainty or variability in this recommendation, potentially indicating that it could be recommended by shared clinical decision-making.

The WG responses for all of the remaining domains were the same as presented for the first EtR, and they determined that the desirable consequences probably outweigh the undesirable consequences in most settings. With that in mind, the WG proposed the following language for the second recommendation:

Proposed Recommendation #2

The ACIP recommends JYNNEOS[®], based on shared clinical decision-making, as an alternative to ACAM2000 for health care personnel who administer ACAM2000 or care for patients infected with replication-competent orthopoxviruses.*

* For example, those caring for patients enrolled in clinical trials for replication-competent orthopoxvirus vaccines and those caring for persons with suspected or confirmed orthopoxvirus infections (e.g., clinicians and environmental services personnel)

The third and fourth EtRs regard the frequency of JYNNEOS[®] booster doses after the JYNNEOS[®] primary series. The problem here is virulent orthopoxviruses (e.g., variola virus and monkeypox virus). An increasing number of laboratories are working with monkeypox viruses (e.g., primate laboratories). Work with these typically requires PPE and other safeguards, but ensuring long-term immunogenicity through a booster provides an additional level of protection if unintentional breaches occur. For 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 >10 years after his primary ACAM2000 vaccination. These cases could potentially be prevented with the recommended booster. The stakes are higher to individuals and public health if virulent orthopoxvirus infections are acquired. Monkeypox or smallpox in a laboratorian would be a very large problem for public health. An individual getting infected with vaccinia virus is of concern to that individual, but is not a concern on a population level. For this reason, boosters historically have been given more frequently for those working with virulent orthopoxviruses compared to those working with less virulent orthopoxviruses.

The third PICO focuses on whether persons who are at continued risk for occupational exposure to more virulent orthopoxviruses such as variola virus or monkeypox virus should receive a booster dose of JYNNEOS[®] every 2 years after the primary JYNNEOS[®] series, the comparison is no vaccine booster after the JYNNEOS[®] primary series. The fourth PICO question focuses on whether persons who are at continued risk for occupational exposure to less virulent replication-competent orthopoxviruses like vaccinia virus or cowpox virus should receive a booster dose of JYNNEOS[®] at least every 10 years after the primary JYNNEOS series. The outcomes are the same for both (e.g., prevention of disease, SAEs, and myocarditis/pericarditis).

In terms of benefits and harms domain, the WG felt that the desirable anticipated effects are small for the third and fourth policy questions. The evidence tables showed a small increase in disease prevention after the JYNNEOS[®] booster to the JYNNEOS[®] primary series. Nevertheless, boosters may provide reassurance of continued protection from inadvertent exposures. Harms. The WG felt that the undesirable anticipated effects are minimal. No SAEs or myocarditis/pericarditis were reported among those who received a JYNNEOS[®] booster dose 2 years after the primary series. Because of the benefits being small and the harms being minimal, the benefits-to-harm ratio favors the intervention. The overall certainty of the evidence for the critical outcomes was very low for both the fourth and fifth policy questions because of the limited data available about booster doses. This means that the WG estimated that there is a small increase in disease prevention after a JYNNEOS[®] booster following the JYNNEOS[®]

primary series versus the JYNNEOS® primary series with no booster. However, the WG had very low certainty in that estimate.

The reason that the answer was “serious” for PICO #3 and “very serious” for PICO #4 was because there are data for the 2-year timepoint for a booster dose, but there are no data beyond the 2-year time point. Therefore, indirect data inform the 10-year booster recommendation. This was somewhat arbitrarily chosen by the WG, but the WG felt strongly that there had to be a recommendation about when people working with the less virulent orthopoxviruses should get a booster dose or otherwise it would be forgotten. The 10 years was chosen because 2 years clearly was too often and 10 years is the same as what is recommended for ACAM2000. Despite the answer being different for PICO #3 and #4 for indirectness, the certainty level was not impacted and was determined to be Level 4 or very low for both.

For harm, SAEs and myopericarditis were considered. There were no cases of SAEs after the JYNNEOS® booster. The effect estimate for the RCT 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 an SAE known to be a rare occurrence event for ACAM2000, so the certainty in that estimate is very low. There also were no reported cases of myopericarditis, but the number of enrolled subjects was extremely low for both arms. With the available data, the effect of JYNNEOS® plus a booster compared to just the JYNNEOS® primary series cannot be estimated. Therefore, the certainty level was very low for this conclusion. For the remainder of the EtR domains for PICO #3 and #4, all of the WG’s responses were positive.

For the value domain, the WG felt that the target population probably feels that the desirable effects are large. The booster may be desirable to those who want to ensure long-term immunogenicity. The WG thought there probably is not important uncertainty about or variability in values. Stakeholders are expected to value persistent immunity. The WG felt that the intervention is likely to be acceptable to stakeholders because it is easy to find caregivers to administer the vaccine. The WG thought that the intervention would be a reasonable and efficient allocation of resources for PICO #3 and probably would be for PICO #4. There could be costs associated with clinic visits, but the WG thought that this still likely would be acceptable. The WG thought that there probably would be no impact on health equity since many employers absorb the costs. The WG thought that it probably would be feasible to implement the intervention as well. People would need to get a booster dose, but many clinicians can provide that subcutaneous injection. In terms of the balance of consequences, the WG thought that desirable consequences probably outweigh undesirable consequences in most settings. Therefore, the WG proposed the following recommendations for PICO #3 and #4:

Proposed Recommendation #3

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

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

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 at least every 10 years.

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

EtR #5 regards changing from ACAM2000 boosters to JYNNEOS® boosters for those who received the ACAM2000 primary series. In terms of the problem, the 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 receive ACAM2000 boosters would like to change to JYNNEOS® if the ACIP recommendations explicitly allow for this. This is due to the ease of identifying a clinician who can administer JYNNEOS®, no risk for infection spread to others, no dressings to manage, and fewer relative contraindications. The unpublished data from the DRC indicates that JYNNEOS® is preferred to ACAM2000. Therefore, the fifth PICO question regards whether persons who are at continued risk for occupational exposure to orthopoxviruses and who received an ACAM2000 primary vaccination should receive a booster does of JYNNEOS® as an option to a booster dose of ACAM2000. The intervention is a booster with JYNNEOS® and the comparison is a booster with ACAM2000. The outcomes are the same as previously described (e.g., prevention of disease, SAEs, myocarditis/pericarditis).

Regarding the benefits and harms domain, the WG did not know how substantial the desired anticipated effects would be since there are only observational data for this outcome. There were no available comparison data for that, so it is unknown from the evidence table how substantial the desirable anticipated effects would be if a JYNNEOS® booster is given to those individuals who were previously getting ACAM2000 boosters. The WG determined the be undesirable anticipated effects to be minimal. No SAEs or myopericarditis cases were identified. The benefit/harm ratio is unclear because the benefits are unknown in terms of administering JYNNEOS® boosters compared to ACAM2000 boosters. The WG determined the overall certainty of the evidence for the critical outcomes to be very low for effectiveness and safety. For the outcome of prevention of disease, the RCTs showed serious concerns about risk of bias, indirectness, and imprecision. For the outcome of SAEs, serious concerns about risk of bias and very serious concerns about imprecision contributed to the very low rating. There were no myopericarditis events regardless of whether a JYNNEOS® booster or ACAM2000 booster was given to persons previously vaccinated with ACAM2000; however, the WG had very low certainty in this estimate. Because of the very small number of subjects included in the analysis, this was not evaluated.

In terms of the remaining domains, the WG found that the target population feels the desirable effects are large. Target populations have made multiple requests for this vaccine. Unpublished data from the DRC indicates strong interest in JYNNEOS®. The WG thought that there probably was not any important uncertainty about or variability in values. Anecdotally, it is known that some laboratory directors anticipate many of their staff to change to JYNNEOS® boosters if the ACIP explicitly indicates that it is acceptable. The WG thought that the intervention would be acceptable to stakeholders due to ease of finding a provider, no risk of transmission to others, no work absences due to travel to get the vaccine, and fewer contraindications with JYNNEOS® compared to ACAM2000. The WG thought this would be a reasonable and efficient allocation of resources, given that it would be the same as for the ACAM2000 booster. The vaccine is provided free of cost by the SNS. The WG felt that health equity probably would be increased because there is no cost with travel to find a provider. The WG felt that it would be feasible for CDC's Drug Service to ship and for the product to be used within the 6-month time interval after

that. The WG concluded that the desirable consequences probably outweigh the undesirable consequences in most settings. The WG proposed the following language for Recommendation #5:

Proposed Recommendation #5

The ACIP recommends person 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.

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

The 5 proposed recommendations are not preferential for JYNNEOS® and are intended to be an option. In terms of the proposed clinical guidance, the WG felt that if recipients change from ACAM2000 to JYNNEOS®, they should receive subsequent boosters with JYNNEOS® according to the JYNNEOS® vaccination booster schedule. That would be every 2 years instead of every 3 years, which is the ACAM2000 recommendation. The reasons the WG chose this is because there are actual data about 2 years, but there are no data beyond that. While the WG assumed that boosting would be possible, the decision was made to be conservative since there are only data up to the 2-year time period. Given that people changing from JYNNEOS® to ACAM2000 is anticipated to occur much less frequently, the WG thought that these individuals could be handled on a case-by-case basis.

Discussion Summary

- Concern was expressed about the timing of myopericarditis in relation to the vaccine and in terms of concomitant vaccine use, particularly with COVID-19 vaccine.
 - Dr. Petersen indicated that concomitant administration of other vaccines is a concern. Myopericarditis generally occurs within a 10-day timeframe, similar to what is seen with other vaccines. The DoD has raised that as a potential issue since their population receives multiple vaccines simultaneously, including smallpox vaccine. They are planning a separate study to evaluate this to better understand the risk of concomitant administration JYNNEOS® specifically with the other vaccines that they administer.
 - It was noted that the DoD has a waiting period to receive ACAM2000 following COVID-19 vaccine, which should be included in the clarifying statement. CDC will ensure that this is part of the guidance pertaining to this vaccine and will convey the information to the COVID-19 clinical guidance team as well.
 - Some concern was expressed about adding it to the COVID-19 clinical guidance, given that it is so complicated already and likely will just confuse people. Perhaps it should be targeted to the people receiving orthopoxviruses vaccine to inform them that they might want to consider separation until additional information is available.

- Dr. Rao was requested to provide an overview of considerations around a preferential recommendation versus a neutral recommendation between JYNNEOS® and ACAM2000.
 - Dr. Rao explained that there is no preferential recommendation, which means that people can choose either one. Even though several of the PICO questions were set up such that the intervention was JYNNEOS® and the comparison was ACAM2000, the actual recommendations themselves are not saying that people should stop receiving ACAM2000 and only get JYNNEOS® or vice versa. The intent is to allow people to have the option of choosing one or the other. The reason the WG set up the PICO questions this way was because ACAM2000 is currently the standard of care for people at occupational risk for the pox viruses, so the two questions had to have ACAM2000 as the comparator. There is insufficient evidence to make a preferential recommendation.
- A question was raised regarding whether the duration of protection may be shorter for JYNNEOS® since this is a newer vaccine that uses a non-replicating virus instead of the traditional replicating virus, and what the plan would be to follow those who are on a 10-year cycle to ensure that they have adequate protection throughout that timeframe.
 - Dr. Petersen reported that in the clinical trials that have been performed, antibody titers have been observed to drop off with time, so the persistence of antibodies is shorter with JYNNEOS® compared to ACAM2000. However, the memory immune response does persist to the 2-year timepoint for which there are data. Individuals do boost with a robust antibody titer following a booster dose. In terms of how this will be followed, there are some discussions of performing additional vaccine studies to evaluate how far out this immune memory response persists. In particular in the DRC vaccine study, there is a plan to conduct a follow-on booster study at timepoints beyond 5 years to evaluate whether individuals who have received primary vaccination with JYNNEOS® retain the memory immune response at those later timepoints. CDC engages in consultations for exposures that occur in the laboratory as well as infections and tracks those, and would perform routine surveillance to evaluate whether there are any real-world effectiveness data that would be relevant in this population receiving JYNNEOS®.
- It was noted that patient counseling information is particularly important for informing recipients about the potential benefits and risks of vaccination with JYNNEOS® and to emphasize the importance of completing the 2-dose series.
 - Dr. Peterson noted that it is routine practice that individuals receiving ACAM2000 are counseled about risks and benefits prior to beginning the occupational work. Regarding the importance of the 2-dose regimen, it would be reasonable to include information to ensure that individuals are receiving both of those doses so that they do achieve that maximal immune response and the equivalent antibody titers to what was seen with the previous vaccine, ACAM2000.

- Regarding Recommendation #5, an inquiry was posed regarding why the word “option” was used and suggested changing it to “alternative” to a booster dose.
 - Dr. Rao read the following revised version, “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®.

Votes: Orthopoxviruses Vaccines

Dr. Agam Rao (NCEZID / CDC) posted Proposed Recommendations for review before the votes:

Proposed Recommendation #1

The ACIP recommends JYNNEOS® as an alternative to ACAM2000 for research laboratory personnel*, clinical laboratory personnel performing diagnostic testing for orthopoxviruses†, and for designated response team members at risk for occupational exposure to orthopoxviruses§

*Research laboratory personnel are those who directly handle 1) cultures or 2) animals contaminated or infected with replication-competent vaccinia virus, recombinant vaccinia viruses derived from replication-competent vaccinia strains (i.e., those that are capable of causing clinical infection and producing infectious virus in humans), or other orthopoxviruses that infect humans (e.g., monkeypox, cowpox, and variola). †Clinical laboratory personnel who perform routine chemistry, hematology, and urinalysis testing, including for suspect or confirmed patients with Orthopoxvirus infections, are not included in this recommendation as their risk for exposure is very low §Public health authorities, at their own discretion, may approve a cohort of healthcare and/or public health personnel to receive primary vaccination against Orthopoxviruses for preparedness purposes (e.g., first responders who might participate in a smallpox or monkeypox outbreak).

Proposed Recommendation #2

The ACIP recommends JYNNEOS®, based on shared clinical decision-making, as an alternative to ACAM2000 for health care personnel who administer ACAM2000 or care for patients infected with replication-competent orthopoxviruses.*

* For example, those caring for patients enrolled in clinical trials for replication-competent orthopoxvirus vaccines and those caring for persons with suspected or confirmed orthopoxvirus infections (e.g., clinicians and environmental services personnel)

Proposed Recommendation #3

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

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

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® at least every 10 years after the primary JYNNEOS® series.

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

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.

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

Vote #1: Orthopoxviruses Vaccines

Dr. Sanchez made a motion to approve the first recommendation reading, "The ACIP recommends JYNNEOS® as an alternative to ACAM2000 for research laboratory personnel*, clinical laboratory personnel performing diagnostic testing for orthopoxviruses†, and for designated response team members at risk for occupational exposure to orthopoxviruses§."

*Research laboratory personnel are those who directly handle 1) cultures or 2) animals contaminated or infected with replication-competent vaccinia virus, recombinant vaccinia viruses derived from replication-competent vaccinia strains (i.e., those that are capable of causing clinical infection and producing infectious virus in humans), or other orthopoxviruses that infect humans (e.g., monkeypox, cowpox, and variola). †Clinical laboratory personnel who perform routine chemistry, hematology, and urinalysis testing, including for suspect or confirmed patients with Orthopoxvirus infections, are not included in this recommendation as their risk for exposure is very low. §Public health authorities, at their own discretion, may approve a cohort of healthcare and/or public health personnel to receive primary vaccination against Orthopoxviruses for preparedness purposes (e.g., first responders who might participate in a smallpox or monkeypox outbreak)

Dr. Poehling seconded the motion. No COIs were declared. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Vote #2: Orthopoxviruses Vaccines

Ms. Bahta made a motion to approve the second recommendation reading, “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 infected with replication competent orthopoxviruses.”*

* For example, those caring for patients enrolled in clinical trials for replication-competent orthopoxvirus vaccines and those caring for persons with suspected or confirmed orthopoxvirus infections (e.g., clinicians and environmental services personnel)

Dr. Ault seconded the motion. No COIs were declared. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Ault, Bahta, Bell, Brooks, Chen, Cineas, Daley, Kotton, Lee, Loehr, Long, McNally, Poehling, Sanchez, Talbot

0 Opposed: N/A

0 Abstained: N/A

0 Absent: N/A

Vote #3: Orthopoxviruses Vaccines

Dr. Daley made a motion to approve the third recommendation reading, “The ACIP recommends persons who are at continued risk* for occupational exposure to more virulent orthopoxviruses like variola virus or monkeypox virus receive booster doses of JYNNEOS[®] every 2 years after the primary JYNNEOS[®] series.”

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

Dr. Long seconded the motion. No COIs were declared. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Ault, Bahta, Bell, Brooks, Chen, Cineas, Daley, Kotton, Lee, Loehr, Long, McNally, Poehling, Sanchez, Talbot

0 Opposed: N/A

0 Abstained: N/A

0 Absent: N/A

Vote #4: Orthopoxviruses Vaccines

Dr. Kotton made a motion to approve the fourth recommendation reading, “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® at least every 10 years after the primary JYNNEOS® series.”

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

Dr. Sanchez seconded the motion. No COIs were declared. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Vote #5: Orthopoxviruses Vaccines

Dr. Sanchez made a motion to approve the fifth recommendation reading, “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®.”

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

Dr. Chen seconded the motion. No COIs were declared. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

EBOLA VACCINE

Session Introduction

Dr. Wilbur Chen (ACIP WG Chair) reminded everyone that the FDA approved Ervebo® on December 19, 2019. Ervebo® is a replication-competent, live-attenuated recombinant vesicular stomatitis virus (VSV) vaccine in which the glycoprotein of *Ebola Zaire* virus is expressed. The ACIP recommended pre-exposure vaccination with Ervebo® for adults aged ≥18 years in the US population who are at highest risk for potential occupational exposure to Ebola virus species *Zaire ebolavirus* because they are: 1) responding to an outbreak of Ebola Virus Disease (EVD); or 2) work as health care personnel at federally designated Ebola Treatment Centers (ETCs) in the US, or 3) work as laboratorians or other staff at biosafety level-4 (BSL-4) facilities in the US.

During the February 2021 ACIP meeting, 2 additional US populations were described who are at risk for potential occupational exposure to Ebola virus (species *Zaire ebolavirus*). This includes HCP at state designated ETCs involved in the care and transport of confirmed EVD patients and individuals who work as laboratorians and support staff at Laboratory Research Network (LRN) facilities that handle replication competent Ebola virus (species *Zaire ebolavirus*). During that meeting, the WG presented the results of vaccine accessibility surveys for both of these populations.

Although COVID-19 continues to occupy the minds of most of the world, Ebola does continue to be a major global health problem. In February 2021, Ebola broke out in Guinea in West Africa causing 23 cases and 12 deaths (52%). The DRC in Central Africa experienced an outbreak of 12 cases and 6 deaths (50%). Another outbreak was declared on October 8, 2021 that is currently ongoing. An update from the previous day reported that 8 cases have been identified, 6 of which have resulted in deaths.

The WG has continued to solicit input from CSTE to define, enumerate, and better understand state-designated ETCs. The WG also has discussed the risks of exposure to Ebola virus for both of these identified occupational risk groups, and has engaged in ongoing discussions on proposed policy options. Presentations during this session included a review of GRADE and an overview of state-designated ETCs and the LRN, the EtR Framework, and a summary of WG considerations and proposed policy options. As a reminder, HCP have been carefully defined as follows:

Healthcare personnel (HCP) refers to all paid and unpaid persons serving in healthcare settings who have the potential for direct or indirect exposure to patients or infectious materials, including body substances (e.g., blood, tissue, and specific body fluids); contaminated medical supplies, devices, and equipment; contaminated environmental surfaces; or contaminated air. These HCP include, but are not limited to, emergency medical service personnel, nurses, nursing assistants, physicians, technicians, clinical laboratory personnel, autopsy personnel, therapists, phlebotomists, pharmacists, students and trainees, contractual staff not employed by the healthcare facility, and persons not directly involved in patient care, but who could be exposed to infectious agents that can be transmitted in the healthcare setting (e.g., clerical, dietary, environmental services, laundry, security, engineering and facilities management, administrative, billing, and volunteer personnel).⁷⁷

⁷⁷ Adapted from <https://www.cdc.gov/infectioncontrol/guidelines/healthcare-personnel/index.htm>

GRADE Review and Overview of State-Designated ETCs and LRNs

Ms. Amy Whitesell (CDC/NCEZID) presented a review of GRADE and an overview of state-designated ETCs and LRN facilities. For the purpose of this presentation, the rVSVΔG-ZEBOV-GP Ebola vaccine is referred to as rVSV vaccine. As a reminder, these data were presented during a previous ACIP meeting in February 2020.

First, a review of the critical outcomes for the rVSV vaccine evaluated by the GRADE approach. Per the February 2020 ACIP recommendation, the ACIP Ebola Vaccine WG determined the PICO (population, intervention, comparison, and outcome) to be as follows. The population of interest at that time was adults 18 years of age or older in the US population who were at risk of occupational exposure to Ebola virus within 3 subgroups: 1) individuals responding to an outbreak of Ebola virus disease due to Ebola virus (species *Zaire ebolavirus*); 2) HCP involved in the care and transport of confirmed EVD patients at federally-designated ETCs in the US; and 3) laboratorians and support staff working at BSL-4 laboratories that handle a) cultures, or b) animals infected with replication-competent Ebola virus, or c) diagnostic or clinical specimens containing replication-competent Ebola virus.

The intervention of interest was pre-exposure intramuscular immunization with a single licensed dose of the rVSV Ebola vaccine, and the comparison was no vaccine. The outcomes the WG considered to be critical and important included the following:

Critical

- Development of Ebola-related symptomatic illness
- Vaccine-related joint pain or swelling (arthritis or arthralgia)
- Vaccine-related adverse pregnancy outcomes for women inadvertently vaccinated while pregnant and women who become pregnant within in 2 months of vaccination
- Transmissibility of rVSV vaccine virus: Surrogate assessed with viral dissemination/shedding of the rVSV vaccine virus
- Serious adverse events related to the vaccination

Important

- Incidence and severity of oral or skin lesions
- Interaction or cross-reactivity with monoclonal antibody-based therapeutics or other VSV-backed vaccines

Data for the important outcomes have not been analyzed to date and were not included in the GRADE evaluations presented in February 2020. The focus for this session was on the critical outcomes that were subject to analysis. To assess these outcomes, a literature search was executed that resulted in the identification of 18 articles that presented data from 11 unique studies which were included in a qualitative synthesis. Of these articles, 9 were presented and data from 8 studies also were included in a quantitative synthesis or meta-analysis. The outcomes of incidence of arthralgia, severity of arthralgia: events of grade 3 (severe) arthralgia, incidence of arthritis, and vaccine-related adverse pregnancy outcomes for women inadvertently vaccinated while pregnant and women who become pregnant within in 2 months of vaccination were included in a meta-analysis. The outcomes of detection of rVSV vaccine virus in blood or plasma (viremia), saliva (viral shedding), and urine (viral shedding) and SAEs related to vaccination were included for descriptive analyses only.

To summarize an overview of the benefit outcome of Ebola-related symptomatic illness, there was one published study with an unvaccinated comparator that was included in the body of evidence for this outcome from Henao-Restrepo, 2017. This publication was associated with the 2-part Phase III cluster-randomized open-label, ring vaccination trial in the beginning. This initial study involved contacts and contacts of contacts of confirmed EVD, or EVD cases that were randomized to either immediate or delayed vaccination. Delayed vaccination was defined as vaccination that occurred 21 days after randomization. A follow-up study included additional data about clusters who were offered immediate vaccination following cessation of the randomized trial. The primary outcome was the incidence of EVD with an onset of 10 days or more following randomization. The 10 days accounts for the average incubation period of Ebola.

In this study across 51 clusters randomized to receive immediate vaccination, which includes 2108 participants, no cases of EVD occurred 10 days or more after randomization. In contrast, across 47 clusters that were randomized to delayed vaccination, which include 3000 sets of 75 participants, 16 cases within 7 clusters developed EVD 10 days or more after randomization. These randomized cluster data presented in the study equated to a calculated VE of 100% (95% CI: 68.9 – 100, $p=0.0045$), with the confidence interval listed here. The calculated relative risks using participant-level data from the randomized clusters was 0.04 (95% CI: 0.0001 – 0.74), which corresponds to a 96% relative risk reduction. The absolute risk was 5 fewer events of Ebola-related symptomatic illness per 1000 people.

Now to provide a summary of the safety outcomes that were presented during the February 2020 ACIP meeting. The first safety outcome was incidence of arthralgia. Incidence of arthralgia was assessed for the incidence of arthralgia or joint pain that was elicited within 0-42 days. For this outcome, 8 studies with unvaccinated comparators elicited arthralgia within 0-days and were evaluated by GRADE. It is important to note that across these studies, variable definitions for arthralgia were used, including joint pain with or without joint swelling or fusion. In some cases, a definition was not provided. Additionally, length and time of follow-up and dose varied between studies. Across 6 RCTs, arthralgia was reported in 316/1874 (16.9%) of vaccinated participants compared to 42/891 (4.7%) of non-vaccinated participants. Taken together, the calculated risk from the 6 RCTs is 2.55 (95% CI: 0.94-6.91) and the absolute risk is 73 more events of arthralgia per 1000 people.

The next safety outcome is the severity of arthralgia. The severity of arthralgia was assessed with the incidence of severe or Grade 3 arthralgia elicited between 0-42 days and defined as significant, slight pain or discomfort, or prevents daily activity. For background, arthralgia is described on a Grade 1-4 scale, with Grade 1 being mild, no interference with activity; Grade 2 being moderate, some interference with activity; Grade 3 being significant, prevents daily activity; and Grade 4 being potentially life threatening, medical consultation and/or hospitalization. There were no reports of Grade 4 arthralgia across the body of evidence. There were 6 studies in which unvaccinated comparators reported arthralgia severity within 0-42 days. It is important to note that across these studies, variable definitions for arthralgia were used and the time of follow-ups and dose of vaccine used varied between studies. Across 4 RCTs included in the body of evidence, 2/333 (0.6%) of vaccinated participants reported Grade 3 arthralgia compared to 0/264 non-vaccinated participants. The calculated risk ratio from the 4 RCTs included in GRADE was 6.4 (95% CI: 0.0001-27950.69). The absolute risk was 0 more events of severe arthralgia per 1000 people.

The next safety outcome is the incidence of arthritis, which was assessed with an event of arthritis reported within 5-56 days of follow-up. The 6 studies with unvaccinated comparators elicited arthritis within 5-56 days. It is important to note that much like the arthralgia outcome, each of these studies defined and diagnosed arthritis with considerable variability. Additionally, time of follow-up and dose of vaccine used varied between studies. Among the 4 RCTs, arthritis was reported in 39/1776(2.2%) of vaccinated participants compared to 16/858 (1.8%) of non-vaccinated participants. The calculated risk ratio across RCTs was 1.8 (95% CI: 0.21-15.13). The absolute risk was 23 more events of arthritis per 1000 people. Additionally, 3 published studies reported on the detection of vaccine virus in synovial fluid. Across this body of evidence, vaccine virus has been detected by reverse transcriptase polymerase chain reaction (rRT-PCR) in 4/7 vaccinated participants that had synovial fluid tests. Viral isolation was attempted on 1 synovial fluid specimen and was negative.

The next safety outcome was vaccine-related adverse pregnancy outcomes for women inadvertently vaccinated while pregnant, and women who become pregnant within 2 months of vaccination. This was assessed with incidence of pregnancy loss defined as spontaneous abortion and stillbirth. There was 1 study included in the body of evidence for this outcome, which was a non-randomized sub-study of the Sierra Leone Trial to Introduce a Vaccine against Ebola. In this study, 14/31 (45%) of immediately vaccinated pregnant women experienced pregnancy loss compared to 11/33 (33%) of unvaccinated pregnant women. The calculated risk ratio was 1.35 (95% CI 0.73-2.52) and the calculated absolute risk was 117 more events of pregnancy loss per 1000 people. The study concluded that overall, the rate of pregnancy loss among pregnant women who received immediate vaccination is not significantly higher than the rate of pregnancy loss among unvaccinated women. Additionally, among live births, no external congenital anomalies were detected among either group. Further studies with larger sample sizes would be needed to rule out meaningful difference in the percentage of pregnancy loss against pregnancy complications or birth defects.

The next safety outcome is the transmissibility of vaccine virus. There were no available data that reported on transmissibility; therefore, detection of vaccine virus RNA in a vaccine recipient's blood, saliva, and urine by rRT-PCR was used as a surrogate for the theoretical possibility of vaccine virus transmission. Data from 8 studies were included for the body of evidence for detection of rVSV in blood or plasma. Across these 8 studies, the longest recorded rRT-PCR positive blood sample was collected 14 days post-vaccination, and 1/501 samples tested positive. Additionally, 1 study performed viral isolation on solicited blood specimens and all were negative. Data from 4 studies were included for the body of evidence for detection of rVSV in urine and saliva. The longest recorded rRT-PCR positive saliva sample was collected 14 days post-vaccination and 1/98 samples tested positive. The longest recorded rRT-PCR positive urine sample was 7 days post-vaccination when 2/246 samples tested positive. Viral isolation was not attempted on saliva or urine samples.

As previously mentioned, data related to oral and skin lesions, including the detection of rVSV and skin vesicles, was not included in the February 2020 GRADE presentation since the WG termed it to be an important but not critical outcome. The WG limited its assessment of the transmissibility outcomes to detection of vaccine virus in blood, saliva and urine. However, for this presentation, the data were included from the FDA package insert related to skin vesicles for additional background. The longest recorded rRT-PCR positive skin vesicle sample was collected 20 days post-vaccination. In one study among 3 participants with rash, all were positives by rRT-PCR up to 17 days post-vaccination. Virus isolation was positive in 1 specimen with a highest RNA level at 9 days post-vaccination. It is important to note with these data

that the true estimate of duration of shedding is unknown because daily collection was not performed. Additionally, rRT-PCR positivity is not synonymous with infectivity.

The final safety outcome was SAEs. There were 12 clinical trials and 2 additional publications that described vaccine-related SAEs. Across this body of evidence, 3/17,119 (0.02%) people who received the vaccine experienced SAEs judged to be related to or possibly related to the vaccine. Of these, 2 were related to vaccination and included febrile reaction and anaphylaxis, both of which resolved without sequelae. One was judged to be possibly related to the vaccine, an influenza-like illness, which also resolved without sequelae. Additional data that were not included in the initial GRADE analysis included another case of anaphylaxis that was identified in data provided to the FDA and resolved without sequelae. In summary, the majority of studies did not record any vaccine-related SAE.

Now turning to the GRADE summary for the rVSV Ebola vaccine compared to placebo or no vaccine in adults aged 18 and older. The overall evidence type for each outcome is determined by taking the lowest certainty value across RCTs and observational studies for each outcome. As a reminder, this is not measuring how well the individual studies were conducted, but rather how much confidence there is in the estimates of effects in the body of evidence across each outcome. In summary, the WG's findings were that the rVSV Ebola vaccine is effective at preventing EVD. The randomized cluster-level data for this outcome was assessed to be evidence Type 3 (low certainty evidence), while the participant-level data for this outcome was assessed to be evidence Type 2 (moderate certainty evidence). For the safety outcome of incidence of arthralgia, the findings were that arthralgia is more commonly reported among vaccine recipients compared to placebo. This outcome was assessed to be evidence Type 4 (very low certainty evidence).

For the safety outcome of severity of arthralgia, the findings were that severe or Grade 3 arthralgia is more commonly reported among vaccine recipients compared to placebo or unvaccinated, but it is overall uncommon. This outcome was assessed to be evidence Type 4 (very low certainty evidence). For the safety outcome of incidence of arthritis, the findings were that arthritis was more commonly reported among vaccine recipients compared to placebo. This outcome was assessed to be evidence Type 4 (very low certainty evidence). For the safety outcome of pregnancy-related AEs due to vaccination, the findings were that the rate of pregnancy loss among pregnant women who received immediate vaccination was not significantly higher than the rate of pregnancy loss among unvaccinated pregnant women. This outcome was assessed to be evidence Type 4 (very low certainty evidence).

For the safety outcome of transmissibility of vaccine virus, the findings were that the vaccine virus has been detected in blood or plasma up to 14 days, in saliva up to 14 days, and in urine up to 7 days post-vaccination. However, true duration of shedding and potential for transmissibility is uncertain. This outcome was assessed to be evidence Type 4 (very low certainty evidence). For the safety outcome of vaccine-related SAEs, the findings were that the vaccine-related SAEs are an uncommon occurrence with 3 events in 17,119 vaccine recipients across 12 studies. This outcome was assessed to be evidence Type 3 (low certainty evidence).

To provide an overview of the population, the evidence will be discussed in the context of the EtR Framework. After the February 2020 recommendations were made, the ACIP Ebola Vaccine WG identified 2 additional populations at potential risk for occupational exposure to Ebola virus. The first is HCP at state-designated ETCs who are involved in the care and transport of suspect or confirmed EVD patients. Following the importation of Ebola virus

to the US in 2014, certain hospitals were designated by states to serve as state-designated ETCs based on requirements set by the regional Ebola Treatment Network. This group has evolved over time and different terminology has been used to describe them, particularly as a result of the COVID-19 pandemic. This population needs to be described in a way that would be evergreen and not subject to framework changes in the future. Since these facilities are designated by the state, the WG reached out to the CSTE to determine the preferred terminology for these facilities and to define them moving forward. This resulted in CSTE convening a WG who determined that the preferred terminology for these facilities should be changed to Special Pathogen Treatment Centers (SPTCs).

For the purposes of ACIP recommendations for the rVSV Ebola vaccine, these SPTCs have been defined as, "Healthcare facilities that intend to receive and are able to provide care for a suspect or confirmed patient with Ebola virus disease (EVD) for the duration of their illness, as assessed by their state health department. In addition to EVD, these facilities may also be designated by the states to treat other high consequence pathogens."⁷⁸ At this time, 55 SPTCs have been identified and it is estimated that each has a staff of 100 to 150 HCP. Thus, there are approximately 5500 to 8250 individuals at potential risk of occupational exposure to Ebola virus across the SPTCs who potentially could benefit from pre-exposure vaccination with the rVSV Ebola vaccine.

At the time the vaccine acceptability survey was conducted, 51 SPTCs had been identified and an invitation to participate in the survey was sent to 49 of these. A total of 364 survey responses were received. Of these, 56 were incomplete and were excluded. Therefore, a total of 298 responses from SPTC personnel were included in the analysis. Nurses and doctors made up the majority (81%) professional groups among the 298 survey respondents. The response rates were lower from other professional groups of respiratory therapists, emergency medical technicians (EMTs), advanced practice providers (including nurse practitioners and physician assistants), laboratory technicians, managers and safety officers, and environmental services.

When asked if they were eligible for vaccinations and offered the rVSV Ebola vaccine at that time would they choose to be vaccinated, 54% of the survey respondents expressed interest in receiving the vaccine. It is important to note their responses to this question were recorded between October 2020 and January 2021. During this time, the Ebola outbreak in Equateur Province, DRC was declared over in November 2020. Therefore, responses were given as EVD cases were waning or when there was no active EVD outbreak in the world. When survey respondents were given the option of choosing when to get vaccinated, such as when an EVD case was imported into the US or into their state, the interest in receiving the vaccine increased from 54% to 81%, while 19% of respondents would not choose to be vaccinated. When asked if they thought that ACIP should recommend the vaccines to HCP at their facility, 53% thought ACIP should recommend the vaccine, 9% thought ACIP should not recommend the vaccine, and 38% were unsure. Notably, the option of shared clinical decision-making was not included.

The second population that the ACIP Ebola Vaccine WG identified as having potential risks for occupational exposure to Ebola virus was individuals who work as laboratorians and support staff at LRN facilities who handle replication-competent Ebola virus. The LRNs comprise the large network of laboratories that aim to respond quickly to biological and chemical threats and other public health emergencies. The Laboratory Response Network for Biological Threats (LRN-B) has 3 tiers that include thousands of sentinel laboratories that are situated largely in hospitals, clinical institutions, and commercial diagnostic laboratories that perform rule-out

⁷⁸ Definition adapted from: <https://www.cdc.gov/vhf/ebola/healthcare-us/preparing/treatment-centers.htm>

testing. The next tier consists of roughly 130 reference laboratories that are situated in state and local health departments and at various military, veterinary, agricultural, and water-testing facilities that can do additional testing. The top tier is comprised of national laboratories, including those operated by CDC, the US Army Medical Research Institute for Infectious Diseases (USAMRIID), and the Naval Medical Research Center (NMRC). These laboratories are responsible for specialized characterization of organisms, bioforensics, select agent activity, and handling highly infectious biological agents. Thus, a potential recommendation would involve an estimated 580 to 870 individuals.

The structure of the vaccine acceptability survey for LRN facilities was the same as the one administered to the SPTCs. Survey invitations were sent out to facilities that had capacity for Ebola testing, which at the time was 62 possible laboratories. A total of 96 responses were received from these facilities, of which 26 were incomplete and were excluded. Therefore, 70 total responses were included in the analysis. The majority of respondents (64%) self-identified as laboratory scientists, 30% identified as management, and 4 (6%) identified as other occupations of either director or laboratory director.

When asked if eligible for vaccine and offered the rVSV Ebola vaccine that day, 59% of the respondents expressed interest in receiving the vaccine. It should be noted that this survey was administered from December 2020 to January 2021, so there was no active Ebola outbreak at the time of these responses. Similar to the SPTC participants, when LRN survey respondents were given the option about when to get vaccinated either immediately when an EVD case was imported into the US or when the EVD case was imported into their state, interest in receiving the vaccine increased to 86%. Among the LRN population, 59% said that they thought ACIP should recommend the vaccine, 9% thought that ACIP should not recommend the vaccine, and 33% were unsure.

In summary, 54% of the SPTC study population was interested in receiving the vaccine at the time survey was administered. When given the option to get vaccinated at a later time, such as when there is an EVD case in the US or in their state, interest in receiving the vaccine increased to 81%. When asked which AE they were most concerned about, concern for a SAEs and transmission of the vaccine virus to others were most common among the study population. Among the LRN study population, 59% of respondents said they would be interested in receiving the vaccine at the time of survey administration. This increased to 86% when they could choose when to be vaccinated. When asked which AEs they would be most concerned about, most responded with an increased risk of arthritis, which differed from the SPTC participants for an increased risk of transmission of the vaccine virus to others.

EtR Framework

Dr. Jason Malenfant (CDC/NCEZID) presented the EtR Framework specifically for expansion of the recommendations for vaccination with rVSV for the categories of SPTC and LRN facilities in the US. The WG developed 2 policy questions for this purpose:

Policy Question 1

Should pre-exposure vaccination with the rVSVΔG-ZEBOV-GP vaccine be recommended for healthcare personnel* involved in the care and transport of suspect or confirmed Ebola virus disease patients at Special Pathogens Treatment Centers?

Policy Question 2

Should pre-exposure vaccination with the rVSVΔG-ZEBOV-GP vaccine be recommended for laboratorians and support staff at Laboratory Response Network (LRN) facilities that handle specimens that may contain replication-competent Ebola virus (species *Zaire ebolavirus*) in the United States?

Notably, the species *Zaire ebolavirus* was selected because it is the most lethal of the 4 viruses that cause Ebola virus disease in humans. It is highly transmissible and is found in all of the body fluids of an infected individual. It causes severe disease, with rapid death usually occurring 7-10 days after symptom onset. In survivors, the virus has been known to persist in immunoprivileged sites and in some instances has resulted in continued disease transmission and disease recrudescence. The virus is known to be a large international public health threat. Ebola Virus (species *Zaire ebolavirus*) is responsible for the majority of reported EVD outbreaks, including the 2014 West Africa outbreak—the largest EVD outbreak in history. This virus has infected over 31,000 persons and resulted in greater than 12,000 deaths. This does not include the ongoing 2018 DRC outbreak. The virus also is a US public health threat, with 11 individuals infected with Ebola virus (species *Zaire ebolavirus*) having been treated in the US. All were associated with the 2014 West Africa outbreak. Of the people infected, 9 were infected in West Africa and 2 were infected in the US while caring for a returned traveler. Additional persons were repatriated to the US following high-risk exposures to confirmed EVD, but none developed EVD. The WG concluded that EVD due to Ebola virus (species *Zaire ebolavirus*) is an important public health problem.

Now turning to the benefits and harms domain. In terms how substantial the desirable anticipated effects of vaccination are, there was 1 study evaluated using GRADE that provided evidence on VE. At the participant level, this study demonstrated a protective effect with 96% risk reduction in vaccinated individuals against acquiring EVD. Given this, the WG felt that the desirable anticipated effects are large. With regard to how substantial the undesirable anticipated effects are, data on AEs showed that arthralgia is more commonly reported among vaccine recipients. Severe arthralgia also is more commonly reported among vaccine recipients, but is overall uncommon. Arthritis is more commonly reported among vaccine recipients as well. Pregnancy loss in vaccinated women was not significantly higher than in non-vaccinated women. rVSV vaccine virus has been detected post-vaccination in blood, saliva, urine, and synovial fluid. Vaccine-related SAEs are uncommon. The WG concluded that the undesirable anticipated effects are moderate.

Regarding whether the desirable effects outweigh the undesirable effects, the WG considered that there is documented protective efficacy of the vaccine; the virus causes high severity of illness; the virus is highly transmissible; Ebola virus has been shown to persist in survivors, with documented instances of continued disease transmission and disease recrudescence; and vaccine-related SAEs are uncommon. Based on these considerations, the WG felt that the desirable effects outweigh the undesirable effects and favor intervention. In terms of the effectiveness of the intervention, the WG again considered the 1 study evaluated using the GRADE process that demonstrated a protective effect from vaccination. At the participant level in that study, the overall certainty in the evidence for effectiveness is moderate (Type 2). At the cluster level, the overall certainty in the evidence for effectiveness is low (Type 3). Taking these into consideration, the WG felt that the overall certainty of evidence for the effectiveness of the intervention is moderate (Type 2). With regard to the safety of the intervention, the majority of the AEs were deemed to be Type 4 (very low certainty), with the exception of SAEs for which was Type 3 (low certainty). The WG determined that the overall certainty of evidence with regard to safety was Type 4 (very low).

The WG next considered whether the target population of HCP at SPTCs think that the desirable effects are large relative to the undesirable effects. Based on the surveys presented earlier, 54% of the study population expressed interest in receiving the vaccine if eligible and offered the vaccine at the time they were surveyed. When people were given the choice to get vaccinated at different time points, such as when there was an EVD case in the US or in their state, interest in the vaccine increased to 81%. Of the surveyed population, 53% thought that ACIP should vote to recommend a vaccine for HCP at SPTCs. Therefore, the WG thought that the target population probably feels that the desirable effects are large relative to the undesirable effects. While there were mixed responses to vaccination among HCP at SPTCs in terms of how much people value the main outcome, interest in the vaccine increased markedly with perceived risk. Given the potential and variability, the WG thought that there is possibly important uncertainty or variability in how much people value the main outcomes. Because 53% of the survey population thought that ACIP should vote to recommend the vaccine to HCP at SPTCs, the WG thought that key stakeholders probably would find the intervention to be acceptable.

Now moving to the second target population, staff at LRN facilities. In terms of whether the target population feels that the desirable effects are large relative to the undesirable effects, the survey responses from staff at LRN facilities were similar to responses received from HCP at SPTCs. Among staff at LRN facilities, 59% of respondents expressed interest in receiving the vaccine if eligible and offered the vaccine at the time of the survey. When people were given the choice to get vaccinated, such as an EVD case in the US or their state, interest in the vaccine increased to 86%. Of the LRN survey population, 59% thought that ACIP should vote to recommend the vaccine to staff in LRN facilities. With that in mind, the WG thought that the target population probably feels that the desirable effects are large relative to undesirable effects.

In terms of whether there is important uncertainty about or variability in how much people value the main outcome, similar to the HCP at SPTCs, there were mixed responses from staff at LRN facilities. When asked if they would get the vaccine at the time of the survey, 59% of LRN staff surveyed expressed interest. When they were given the option of choosing when to get vaccinated, either immediately or when an EVD case was imported to the US or their state, the interest in receiving the vaccine increased to 86%. When the perceived risks seemed to increase and there was flexibility in when to get the vaccine, acceptability also increased. Given the potential and variability seen, the WG thought that there is possibly important uncertainty or variability in how much people value the main outcomes. In terms of whether the intervention is acceptable to key stakeholders, 59% of the LRN survey population thought that ACIP should vote to recommend the vaccine to staff at LRN facilities. Therefore, the WG thought that key stakeholders probably would find the intervention to be acceptable.

Turning to the domain of resource allocation, the WG considered whether the intervention is a reasonable and efficient allocation of resources. A cost-effectiveness analysis was not performed for this vaccine as it is intended for use in preparedness scenarios in limited populations and not as a routine vaccination in the general population. At this time, the vaccine will be stored and made available through the USG. The WG thought that the intervention would be a reasonable and efficient allocation of resources.

Regarding the domain of equity and what the impact of the intervention might be on health equity, the WG did not have a good sense of this since the only demographic characteristics in surveys that were distributed to the facilities included age, sex, and profession of the individual. No race or ethnicity data were collected. Therefore, the WG determined that the impact on health equity is not known. In terms of the feasibility domain and whether the intervention is feasible to implement, licensed doses are currently available through the SNS. Therefore, the WG concluded that the intervention is feasible to implement.

In regard to the balance of consequences, the WG thought that the desirable consequences probably outweigh the undesirable consequences in most settings based on all of the considerations. To make a determination about whether there was sufficient information to move forward with a recommendation, the WG considered that the efficacy data available from outbreak settings show high efficacy. Safety data also are available for the over 17,000 persons who have been vaccinated in the US, Europe, and Africa that the WG evaluated using the GRADE process. Data also are available from the vaccine acceptability surveys for both target populations under consideration. Therefore, the WG concluded that there is sufficient information to move forward with a recommendation.

Discussion Summary

- ACIP members requested clarity regarding why the rVSV vaccine was being discussed rather than the less reactogenic vector vaccine and whether a goal was to encourage the manufacturer to submit this vaccine to the FDA for licensure and then if FDA-approved, the ACIP would make recommendations on it. Or, if the goal was to use the vaccine in outbreaks under an EUA.
 - Dr. Choi indicated that the rVSV Merck vaccine is the only licensed Ebola vaccine. Other vaccines are in development, one of which is the Johnson & Johnson (J&J) vaccine. The J&J vaccine also has been used overseas in the setting of outbreaks, but it should be noted there are several differences between these 2 vaccines. First, the licensed rVSV vaccine under discussion during this session is a 1-dose vaccine after which people are considered to be protected against infection with *Zaire ebolavirus* after a period of time. The J&J MVA adenovirus vaccine is a 2-dose vaccine, with the 2 doses administered 54 days apart. The Merck vaccine is more amenable to outbreak response in that it is a 1-dose vaccine. The approval processes are continuing for the other vaccines.
 - Dr. Fink added that there are regulatory mechanisms that could allow for access to investigational Ebola vaccines, including for pre-exposure vaccination, which include use under an Investigational New Drug (IND) determination, including extended access.
 - Dr. Lee clarified that the purpose of this session was not discussion of outbreak responses, but was instead on pre-exposure use among the 2 additional populations described during the presentations.
 - Commenting from a local public health perspective, Dr. Zahn (NACCHO) pointed out that in 2014-2015, there was a large West African outbreak of Ebola in Orange County in Southern California. There were a few Ebola treatment facilities where patients with symptoms consistent with Ebola or with confirmed disease would be admitted. Because there were so many travelers at the time, some hospitals were

- willing to accept patients with Ebola with symptoms for initial assessment. Patients determined to be at risk would go on to a treatment facility. However, assessment facility conversations were always difficult because nobody wanted to see patients returning from West Africa due to the infection control risk associated with that. If a situation such as this occurred again, there would be difficult conversations about why ETC staff get the vaccine and others do not. This seems important to consider in terms of messaging.
- Dr. Choi indicated that the issue of access to vaccine by assessment hospitals has been raised within the WG. In terms of the priorities for the WG, the focus has been on individuals perceived to have the highest occupational risk, which is why the initial recommendations were for the federally-designated SPTC and LRN facilities. Given that the conversation about assessment hospitals has been raised several times within the WG, it is likely to be the topic of future agendas.
 - Inquiries were posed by ACIP members about why the proposed recommendation did not (but perhaps should) include language about optimal timing and/or shared clinical decision-making, particularly given that when survey respondents intending to care for Ebola-infected patients indicated that they would get the vaccine increased from 54%-59% to 81% in a situation in which there was an EVD case in the US or in their state.
 - Dr. Choi emphasized that when respondents were asked about whether they would be willing to take the vaccine “today,” the word “today” was important because it had to do with perceived risk. At the time the survey was administered, there essentially were no Ebola cases occurring in the world. Short of occupational exposure, they would not get a case. However, they might get arthralgia or other AEs from the vaccine. Therefore, timing and the balance of the consequences tends to swing back and forth. The WG robustly discussed shared clinical decision-making versus recommendation. To her, the gestalt of that discussion was that the WG felt in general that the focus was on the 2 additional populations at risk and whether a vaccine would protect them. The WG felt that the vaccine would protect these populations who are at risk due to their jobs and VE is clear, which compelled the WG to lean toward recommendation.
 - Dr. Chen agreed and added that the WG revisited this question numerous times. There was concern that this could be perceived as a vaccine mandate by the facilities, regardless of whether it was shared decision-making versus a recommendation. Therefore, the WG concentrated on making decisions based on the strength of whether they thought vaccination would be protective to a population who would be at risk because of their occupations versus the general population. The WG fully recognized that this vaccine would be implemented at the local jurisdictional level and would be occupational in nature. Therefore, the employer and employee would be having this conversation. There will be discussion of the precautions and contraindications to help people decide whether a particular person could or perhaps should not be vaccinated.
 - Dr. Lee emphasized that procedurally, regardless of whether this might be a full recommendation or shared clinical decision-making, fear of mandates should not be driving ACIP’s decisions. In addition, she thought it would be beneficial to include timing rationales in the clinical considerations such as when there is an Ebola outbreak, when there are X number of cases, anticipation of an influx of patients who

are traveling in from a location with an outbreak, or some other threshold to give people a sense of risk.

- Regarding shared clinical decision-making, Dr. Poehling expressed concern about the many women working in laboratories who may become pregnant within 2 months of being vaccinated because not all pregnancies are planned.
- Dr. Choi indicated that they reached out to several ETCs and LRNs to get a sense of whether these facilities would be likely to mandate the vaccine, and they said they would not.
- Given that the risk is variable and the definition of HCP is broad and the vaccine is not without side-effects, there was sentiment among some ACIP members that shared clinical decision-making or some other way of conveying “may” rather than “should” ought to be considered.
- It was suggested that perhaps CDC could offer more detailed guidance around thresholds for concern, and perhaps institute a threat level of red, orange, yellow, green as has been done for COVID-19.
- In terms of the potential for vaccine injury, Dr. Rubin (HRSA) confirmed that use of Ebola vaccine would be covered under the CIGP.
- Given the potential for if people have to miss work, just as was done for COVID vaccines, it was suggested that perhaps guidance could be provided to facilities so that they are covering individuals who received the vaccine. This seems particularly important in terms of preventing potential transmission of vaccine virus.

Proposed Policy Options

Dr. Caitlin Cossaboom (CDC/NCEZID) presented the policy options for the use of rVSV Ebola vaccine among personnel working in SPTCs or LRN facilities, noting that the proposed recommendation language could be revised as needed based on the discussion. As noted by Dr. Chen, the ACIP Ebola Vaccines WG had robust discussions on the potential implications of an ACIP recommendation. And as with any other employee health-related vaccine, it is the WG’s expectation that this recommendation will be implemented based on institutional occupational health policy. The majority of voting WG members were in favor of the following proposed recommendation language:

Proposed Vote #1: SPTC HCP

Pre-exposure vaccination with rVSVΔG-ZEBOV-GP vaccine is recommended for healthcare personnel* involved in the care and transport of suspect or confirmed Ebola virus disease patients at Special Pathogens Treatment Centers.

* Healthcare personnel (HCP) refers to all paid and unpaid persons serving in healthcare settings who have the potential for direct or indirect exposure to patients or infectious materials, including body substances (e.g., blood, tissue, and specific body fluids); contaminated medical supplies, devices, and equipment; contaminated environmental surfaces; or contaminated air. These HCP include, but are not limited to, emergency medical service personnel, nurses, nursing assistants, physicians, technicians, clinical laboratory personnel, autopsy personnel, therapists, phlebotomists, pharmacists, students and trainees, contractual staff not employed by the healthcare facility, and persons not directly involved in patient care, but who could be exposed to infectious agents that can be transmitted in the healthcare setting (e.g., clerical, dietary, environmental services, laundry, security, engineering and facilities management, administrative, billing, and volunteer personnel).

Proposed Vote #2: LRN Staff

Pre-exposure vaccination with rVSVΔG-ZEBOV-GP vaccine is recommended for laboratorians and support staff at Laboratory Response Network (LRN) facilities that handle specimens that may contain replication-competent Ebola virus (species *Zaire ebolavirus*) in the United States.

Discussion Summary

- Dr. Poehling proposed an amendment to the language of the two proposed recommendations to include “shared clinical decision-making.”
- Dr. Lee suggested that the two proposed recommendations be taken to a full vote and if the two votes did not pass, the WG could be asked to reconsider the language for a different vote that incorporates “shared clinical decision-making.”

Votes: Ebola Vaccines**Vote #1: Ebola Vaccines for SPTC HCP**

Dr. Loehr made a motion to approve the first Ebola recommendation stating, “The ACIP recommends pre-exposure vaccination with rVSVΔG-ZEBOV-GP vaccine for healthcare personnel* involved in the care and transport of suspect or confirmed Ebola virus disease patients at Special Pathogens Treatment Centers.”

*Healthcare personnel (HCP) refers to all paid and unpaid persons serving in healthcare settings who have the potential for direct or indirect exposure to patients or infectious materials, including body substances (e.g., blood, tissue, and specific body fluids); contaminated medical supplies, devices, and equipment; contaminated environmental surfaces; or contaminated air. These HCP include, but are not limited to, emergency medical service personnel, nurses, nursing assistants, physicians, technicians, clinical laboratory personnel, autopsy personnel, therapists, phlebotomists, pharmacists, students and trainees, contractual staff not employed by the healthcare facility, and persons not directly involved in patient care, but who could be exposed to infectious agents that can be transmitted in the healthcare setting (e.g., clerical, dietary, environmental services, laundry, security, engineering and facilities management, administrative, billing, and volunteer personnel). Adapted from <https://www.cdc.gov/infectioncontrol/guidelines/healthcare-personnel/index.htm>

Dr. Ault seconded the motion. No COIs were declared. The motion carried with 11 affirmative votes, 4 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Vote #2: Ebola Vaccines for HRN Staff

Dr. Loehr made a motion to approve the first Ebola recommendation stating, “The ACIP recommends pre-exposure vaccination with rVSVΔG-ZEBOV-GP vaccine for laboratorians and support staff at Laboratory Response Network (LRN) facilities that handle specimens that may contain replication-competent Ebola virus (species *Zaire ebolavirus*) in the United States.”

Dr. Ault seconded the motion. No COIs were declared. The motion carried with 11 affirmative votes, 4 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Member Statements

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

- Dr. Talbot commented that she felt like people should have the option of receiving the Ebola vaccine. She voted “no” not because she did not feel like they should, but because she felt like it should be shared clinical decision-making.
- Dr. Chen observed that it has become increasingly necessary to address global health pathogens. When Ebola and smallpox are discussed, people do not believe that they are really in the US. However, they are global health pathogens from history to the present that will continue to threaten mankind.
- Dr. Poehling recognized that while Ebola is an important pathogen globally, she voted “no” for the Ebola recommendations because she felt strongly that people should have a choice and that shared clinical decision-making would be the best approach.
- Ms. McNally commented that she agreed with the Ebola vaccination recommendation but hoped it would be under shared clinical-decision making. She thanked the CDC and providers who vaccinate for their continued effort on patient education, given that it is critically important for patients to understand the risks and the benefits.
- Dr. Kotton thanked all of the hardworking people at the CDC who did so much work to get the ACIP to this point. It was a very exciting several weeks of meetings. As a clinician in the field who has seen a tremendous amount of hepatitis B, zoster, pneumococcal disease, et cetera, it was very exciting to see these expanded indications for vaccines. She hopes to see a lot less hepatitis B, pneumococcal disease, and zoster and never to see diseases such as smallpox or Ebola that could be vaccine-prevented. This is a very exciting time, especially for adults.

PUBLIC COMMENT: NOVEMBER 3, 2021

The floor was opened for public comment on November 3, 2021 at 4:47 PM ET. Given that many more individuals registered to make oral public comments than could be accommodated, 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–2021–0112. Visit <http://www.regulations.gov> for access to the docket or to submit comments or read background documents and comments received. The public comment session was conducted prior to the votes. However, the votes were included with their respective sessions for ease of reading.

**Ms. Sarah Barry
Independent Pro-Vaccine Advocate**

Hello, my name is Sarah Berry. I am an independent pro-vaccine advocate. I thank the ACIP members not only for the opportunity to speak today, but also for continuing to have these critical discussions. I would also like to thank ACIP specifically for their vote to recommend the COVID-19 vaccine for children. My main goal as a pro-vaccine advocate has been to educate anybody who will give me their time about the extensive abuse of autistic children at the hands of the anti-vaccine community, and I do this because I truly believe that vaccine hesitancy will not go away until as many people as possible will become aware of the fact. If you don't believe me, then you should at least believe the anti-vaxxers who are afraid of me and my message. As I shared last time I gave public comment, my advocacy has resulted in online harassment from extremists and also what I worry were intentional efforts to intimidate me at my home in the form of multiple protests across the street from where I live. I've also shared how I worked with Angie Nassar from Al Jazeera Plus to expose anti-vax lobbyists who wanted to and tried to censor my testimony at the Ohio State House, and you can find the video evidence of that on the Al Jazeera + YouTube channel. I truly believe that the only reason anti-vaxxers might try to harass and censor me is because they know that what I say is true, and they are terrified of me. When I did my first research on vaccine controversies, I started by reading anti-vaccine articles that were being propped up as evidence that vaccines could cause harm, and anti-vax family members started me on my journey by sending me a PDF of study summaries created by the anti-vax group, Focus for Health, which is run by Brian Hooker. The second study on that PDF was done by Mark Geier, and I believe, as I've shared before, it took me one five-second Google search to discover that he lost his medical license for chemically castrating autistic children. Think of all the times anti-vaxxers accused ACIP of unethical behavior, even to the point of implying that you deserve to go on trial. Where is that same energy for Mark Geier and others like him? Geier literally experimented on autistic children without telling parents the full risks, but Robert F. Kennedy Jr. complained that corrupt medical professionals have systematically disgraced and silenced him. In fact, if you go on the anti-vax nonprofit website run by Robert F. Kennedy Jr., you will find dozens upon dozens upon dozens of examples of Mark Geier's work being propped up as legitimate evidence of vaccine harm. The vaccine hesitancy conversation should be about so much more than just vaccines. To truly win against the misinformation, you have to expose the ridiculous double standards that allow charlatans like Mark Geier to profit off of desperate, anti-vax families. It was not difficult for somebody as average as myself to research this information, and as much as I disagree with them, the anti-vaccine community deserves to know that the leaders they look up to have utterly betrayed them. I again thank the ACIP for continuing to have these important conversations, and if anybody listening has any questions, you can find me on Twitter at @42believer.

**Mrs. Colleen Thomas
Hoosiers Vaccinate**

My name is Colleen Thomas. I work with Hoosiers Vaccinate, a volunteer-led vaccine advocacy group in Indiana. I became a vaccine advocate because my 9-year-old son has a primary immunodeficiency, meaning he was born missing part of his immune system. He also has severe asthma. Since birth, he has suffered from recurrent severe respiratory infections, often taking weeks to recover from multiple rounds of antibiotics, sometimes oral steroids. He depends on herd immunity to avoid exposure to preventable diseases in our community. The more people around him that are vaccinated, the less likely he is to encounter a severe disease that he would struggle to fight off. Having a child with this condition was always a challenge, but the past 20 months, living through a global pandemic has been the biggest challenge we've ever faced. Our family has isolated since March 2020. My son has not been in school. We have missed all holidays. He rarely plays with friends. His education has suffered. The social isolation had a major impact on my son's emotional and mental health. Finally, a vaccine is available and it will allow him to return to school, play sports, and be with friends and family. I'm speaking today to thank you, the ACIP members, who have invested time in reviewing the vaccine studies and recommending this pediatric vaccine. You had an integral part in ending this nightmare for our family. In truth, my son doesn't always mount an immune response to all vaccines. He may not develop as many antibodies as a healthy child once he gets the vaccine. He'll probably wear a mask in school and out in public longer than his peers. But even so, his life is about to improve greatly. I understand there are vaccine-hesitant parents, and they get a lot of press, and I have empathy for all parents through this whole ordeal. But I'm all too keenly aware of risk versus benefit analysis when it comes to my little boy's health. And this vaccine for us is a no-brainer. As I speak, my son is at the health department with his dad. Actually, he's home now because this went long, but he got his first dose of COVID vaccine today. I took the first available appointment and it happened to be right now. I didn't go so I could stay here and make this comment, but I'll for sure be at his second appointment. There are over 300 types of primary immunodeficiencies and they affect thousands of children in the US, many of whom can safely receive the vaccine and who no doubt have parents who have been anxiously waiting for this vaccine just as we have been. Vaccinations have protected children from severe disease for decades and are safe and effective. They protect the most vulnerable in our society. My final comment is I would like to see a better system in place for verifying vaccination status, as the CDC COVID cards have been all too easy for people to falsify. Not all states have electronic verification systems. The US needs a central verification database that's more tamper-proof going forward. I thank you for your time for allowing my comments today and especially for the work you do.

**Susie Olson Corgan
Citizen**

My name is Susie Olson Corrigan. Thank you for the opportunity to speak today. My comments are in direct response to your recommendation to add the Pfizer-BioNTech COVID-19 biological products to the adolescent immunization schedule for 5-11-year-olds. During the Food and Drug Administration's Vaccine and Related Biological Products Advisory Committee meeting last week, Pfizer was asked several questions regarding safety and potential adverse events in children receiving their COVID-19 jab. Answers included the following, "We do not know we don't have that data. We will find out as more children receive them." Hearing, "we do not know" should have been the end of this discussion, yet VRBPAC went ahead and recommended the EUA application to be approved, and the FDA obliged with answers like "we do not know." How could you, ACIP, our public health regulatory agency in good conscience while maintaining your

duty to protect the public add this product to the recommended adolescent schedule? Did you listen to this meeting? Did you ask questions? Did you read all the reports and presentations? Did you do your due diligence before your vote took place yesterday? During these meetings, once again, it was made clear that our children are the safety study. There is nothing definitive showing that children—giving them this jab is justified when looking at the risk-benefit of adverse events from the jab versus potential risk of natural infection. There's no definitive data showing that children are receiving the COVID-19 jab will protect adults. And since when have we as adults been okay with sacrificing our kids and their health to potentially protect us? When did this become a data point we even considered? There is nothing definitive showing that these biological products will stop transmission, hospitalizations, or deaths in adolescents. However, myocarditis, pericarditis, Bell's palsy, death, all adolescent adverse events that have been reported to the Vaccine Adverse Event Reporting System after having received a COVID-19 jab, are these AEs not a concern to you? They surely are to me. As for me and the thousands of parents I've spoken to across the country, we will not give our children any version of the COVID-19 jab no matter how often you participate in, create, or fund social media campaigns trying to convince us otherwise. No matter how many billions of dollars you put into public relations campaigns, we will not give our children this experimental product. No matter how many times you, the ACIP, the FDA, public health officials, politicians, or celebrities tell us that we have to for the greater good. My child is my responsibility and mine alone. I will not give my child this jab despite how many products, services, access to restaurants, bars, or events we are unjustifiably barred from. There's absolutely nothing you can do to convince me that giving this to my child is worth the risk. It is all risk. For any parent listening to this meeting, I beg you please do your own research, read the report submitted to the vaccine manufacturers by the vaccine manufacturers to the FDA for EUA. Make sure that you know the actual risks versus benefit. Public health won't tell you, and after listening to regulatory agency meetings, I will tell you they do not care.

Michaela Jackson
Prevention Policy Manger
Hepatitis B Foundation

Good afternoon. My name is Michaela Jackson. I am the Prevention Policy Manger for the Hepatitis B Foundation. During the September discussion on a recommendation for universal adult hepatitis B vaccination, committee members question the true need for such a recommendation. For the past two years, we have submitted comments filled with statistics and data on the need for all adults to be vaccinated. Today, we would like to answer the question posed during the September meeting with the responses of brave individuals who shared their moving stories with us. So why do we need universal hep B vaccination for all adults? We need universal hep B vaccinations for the daughter who did not know that she should have been vaccinated. Her mother passed away from hepatitis C-related liver cancer, and now she lives in fear that she might develop it too. We need this recommendation for the mother who lost her son to hepatitis C after he was accidentally pricked by a needle in medical school. Hepatitis B vaccination for adults was not common when he was exposed. Just this year, a 56-year-old woman became infected by hep C and she does not know how she was exposed. The woman says, "I want everyone to be vaccinated for hepatitis B. I didn't believe I was at risk." A universal recommendation is needed for the niece who worried about losing her aunt to liver cancer and the emotional toll it took on her family. She asked ACIP to pass the recommendation to help inform the public about the vaccines they need and to prevent others from going through the pain that her family felt. We need universal vaccination for the man who became an advocate after learning he had hepatitis C and hepatitis B co-infection. He now wants everyone to know that this vaccine can prevent two serious severe infections. Another man pays \$2,700 a month

for chronic hepatitis B treatment. Many people are unaware that this vaccine exists. “I have been dealing with hep B for 16 years, and I was never told about the vaccine,” he says. “If I would have known about it, I would have gotten it without question.” We need the universal recommendation for primary care providers who find it burdensome to ask about 18 different risk factors and for people who want to be vaccinated but are afraid to discuss the true risk with their doctor. And finally, we need it for the dozens of people who commented, “I wish I knew about the vaccine before I contracted hep B.” Simply put, the public health community believes as one person wrote that an anti-cancer vaccine should be universally available. The stories told today demonstrate the clear lack of awareness and education from both a patient and provider perspective, in addition to highlighting the need for an inclusive recommendation. They also represent the numerous lives that have been irrevocably changed by a failure to close well-known gaps and access to hepatitis B vaccination. Sadly, stories like the one for today are common, but they do not have to be. The recommendations by ACIP have real-life implications that reach every single American. It is time to eliminate burdensome stigmatizing risk-based guidelines and replace them with effective policies that would help eliminate viral hepatitis. Thank you for this opportunity.

Ms. Beatrice Zovich
Public Health Program Coordinator
Hepatitis B Foundation

Good afternoon. My name is Beatrice Zovich. I am a Public Health Program Coordinator for the Hepatitis B Foundation. While we wait in great anticipation of the vote for universal adult hepatitis B vaccination this afternoon, we must express disappointment with the committee’s decision to exclude adults aged 60 and older in the proposed recommendation. No one should be subjected to the stress and mental anguish of being diagnosed with a preventable illness, and prevention is always more cost-effective than treatment. As a patient advocacy organization, we receive thousands of calls annually from people who have questions or concerns about hepatitis B. And each year, nearly 10% of calls are from people aged 60 and older. We’ve also received countless inquiries from people aged 60 and older who have tried to get vaccinated but were denied by their primary care providers. Many insurance programs provide coverage for ACIP recommended vaccines, but will only cover those who are at high-risk for infection. We cannot claim that everyone has equal access when people are regularly refused the vaccine because of the current guidelines. The reality is that risk-based guidelines for any adult ignore the role of the social determinants of health. Hep B and its risk factors are heavily stigmatized, especially among immigrants who already face health care challenges, including those relating to language and culture. As many as 60% of individuals living with hepatitis B in the United States were born in a different country. The stigma and discrimination faced by those living with hep B and many parts of the world is tremendous. Misperceptions that the disease primarily affects those who engage in certain behaviors run rampant, and it is not uncommon for people to face barriers to obtaining education and employment. Given prevailing cultural attitudes, as well as limited English proficiency and the discomfort and confusion that surround navigation of the health care system in the United States, the burden of requesting hep B vaccination needs to be removed from vulnerable communities. Additionally, the responsibility of questioning each patient about their country of origin in order to determine whether or not they should receive a vaccine, information that is not generally collected by most physicians in standard health surveys, should not be placed on busy physicians either. By making this recommendation universal and creating a standing order for it, all confusion and shame will be removed from the equation, and adults will be able to receive this important vaccine in a way that is as routine as the offering of a flu shot or a blood test for cholesterol. The hep B vaccine prevents not only hepatitis B but also hepatitis Delta, the most severe form

of viral hepatitis that can only occur in people living with hep b. With no treatments approved in the US, people who contract this dangerous co-infection have a nearly 70% chance of developing significant liver damage, including liver cancer. One couple who shared their story with us talked about the heartbreaking ordeal they endured when doctors did not conduct proper monitoring of the husband's infection and did not test for hepatitis Delta until significant liver damage and cancer had developed. No one should have to invest years of their life and countless emotional and financial resources for a vaccine-preventable illness. Vaccinating all adults is a very safe and highly effective way to move swiftly toward the goal of hep B elimination and in as equitable fashion as possible. Thank you for your time.

CERTIFICATION

Upon reviewing the foregoing version of the November 2-3, 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.

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ACRONYMS USED IN THIS DOCUMENT

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
AAPA	American Academy of Physician Assistants
ACA	Affordable Care Act
ACC	American College of Cardiology
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACNM	American College of Nurse-Midwives
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
ADEM	Acute disseminated encephalomyelitis
AE	Adverse Event
AESI	Adverse Events of Special Interest
AGS	American Geriatrics Society
AHA	American Heart Association
AHIP	America's Health Insurance Plans
AI/AN	American Indian/Alaska Native
AIM	Association of Immunization Managers
AIRA	American Immunization Registry Association
AJPM	American Journal of Preventive Medicine
AMA	American Medical Association
AOA	American Osteopathic Association
APhA	American Pharmacists Association
APRN	Advanced Practice Registered Nurse
APTR	Association for Prevention, Teaching, and Research
ASTHO	Association of State and Territorial Health Officers
BLA	Biologics License Application
BNP	Brain Natriuretic Peptide
BSL-4	Biosafety Level-4
CDC	Centers for Disease Control and Prevention
CICP	Countermeasures Injury Compensation Program
CISA Project	Clinical Immunization Safety Assessment Project
CMC	Chronic Medical Condition
CMI	Cell-Mediated Immunity
CMS	Center for Medicare and Medicaid Services
CNS	Central Nervous System
COI	Conflict of Interest
CSTE	Council of State and Territorial Epidemiologists
CVST	Cerebral Venous Sinus Thrombosis
DFO	Designated Federal Official
DIC	Disseminated Intravascular Coagulation
DoD	Department of Defense
DRC	Democratic Republic of Congo
DSMB	Data Safety Monitoring Board
DVA	Department of Veterans Affairs
DVD	Division of Viral Diseases

DVT	Deep Venous Thrombosis
ED	Emergency Department
EHR	Electronic Health Record
ECG or EKG	Electrocardiograms
EMR	Electronic Medical Record
EMTs	Emergency Medical Technicians
ET	Eastern Time
ETC	Ebola Treatment Center
EtR	Evidence to Recommendation
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FluSurv-NET	Influenza Hospitalization Surveillance Network
FP	Family Physician
FQHC	Federally Qualified Health Center
GBS	Guillain-Barré Syndrome
GI	Gastrointestinal
GMR	Geometric Mean Ratios
GMT	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HBcAb	Hepatitis B Core Antibody
HBsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B Surface Antigen
HCP	Healthcare Personnel / Providers
HCW	Healthcare Workers
HepB	Hepatitis B
HHS	(Department of) Health and Human Services
<i>HIB</i>	<i>Haemophilus Influenzae</i>
HIV	Human Immunodeficiency Virus
HM	Hematologic Malignancies
HRSA	Health Resources and Services Administration
HSCT	Hematopoietic Stem Cell Transplant
IBD	Inflammatory Bowel Disease
ICD	International Classification of Diseases
ICD-10-CM	International Classification of Diseases 10 Clinical Modification
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
IDSA	Infectious Disease Society of America
IDU	Injection Drug Use
IHS	Indian Health Service
IIS	Immunization Information System
IIV	Inactivated Influenza Vaccine
IND	Investigational New Drug
IPD	Invasive Pneumococcal Disease
ISD	Immunization Services Division
ISO	Immunization Safety Office
LAIV	Live Attenuated Influenza Vaccine
LGE	Late Gadolinium Enhancement
LRN	Laboratory Research Network

LRN-B	Laboratory Response Network for Biological Threats
LTCF	Long-Term Care Facilities
MIBE	Measles Inclusion-Body Encephalitis
MIS-C	Multisystem Inflammatory Syndrome in Children
<i>MMWR</i>	<i>Morbidity and Mortality Weekly Report</i>
MPH	Masters of Public Health
MRI	Magnetic Resonance Imaging
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization Canada
NAPNAP	National Association of Pediatric Nurse Practitioners
NASEM	National Academies of Science, Engineering, and Medicine
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHHSTP	National Center for HIV, Viral Hepatitis, STD, and TB Prevention
NCHS	National Center of Health Statistics
NCIRD	National Center for Immunization and Respiratory Diseases
<i>NEJM</i>	<i>New England Journal of Medicine</i>
NFID	National Foundation for Infectious Diseases
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
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NYHA	New York Heart Association Functional Classification
NVPO	National Vaccine Program Office
<i>OFID</i>	<i>Open Forum Infectious Diseases</i>
OGC	Office of General Counsel
OID	Office of Infectious Disease
OIDP	Office of Infectious Disease Policy and HIV/AIDS
PCP	Primary Care Practitioner
PE	Pulmonary Embolism
PHAC	Public Health Agency Canada
PHN	Pediatric Heart Network
PhRMA®	Pharmaceutical Research and Manufacturers of America®
PICO	Population, Intervention, Comparison, Outcomes
PIDS	Pediatric Infectious Disease Society
PNP	Pediatric Nurse Practitioner
PPE	Personal Protective Equipment
QALY	Quality-Adjusted Life-Year
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RHCs	Rural Health Clinics
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
RZV	Recombinant Zoster Vaccine
SAE	Serious Adverse Event
SAHM	Society for Adolescent Health and Medicine
SDOH	Social Determinants of Health
SHEA	Society for Healthcare Epidemiology of America
SME	Subject Matter Expert

SNS	Strategic National Stockpile
SOC	System Organ Class
SOT	Solid Organ Transplant
SPTC	Special Pathogen Treatment Centers
ST3	Serotype 3
STD	Sexually Transmitted Disease
STM	Solid Tumor Malignancies
TBE	Tick-Borne Encephalitis
TTS	Thrombosis with Thrombocytopenia Syndrome
UK	United Kingdom
US	United States
USAMRIID	United States Army Medical Research Institute for Infectious Diseases
USG	United States Government
VA	(US Department of) Veteran's Affairs
VAERS	Vaccine Adverse Event Reporting System
VaST WG	Vaccine Safety Technical Work Group
VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VFC	Vaccines for Children
VIS	Vaccine Information Statement
VRBPAC	Vaccine and Related Blood Products Advisory Committee
VSD	Vaccine Safety Datalink
WG	Work Group