MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

JUNE 24-25, 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 an emergency meeting of the Advisory Committee on Immunization Practices (ACIP) on June 24-25, 2021. The meeting took place remotely via Zoom, teleconference, and webinar. This document provides a summary of the meeting, which focused on a variety of topics, including dengue, influenza, rabies, zoster, and pneumococcal vaccines. The ACIP voted on dengue, influenza, and rabies vaccines.

THURSDAY: JUNE 24, 2021

WELCOME AND INTRODUCTIONS

Call to Order/Roll Call

Dr. José R. Romero (ACIP Chair) called to order and presided over the meeting. He conducted a roll call during which no 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.

Procedural Overview

Dr. Amanda Cohn (ACIP Executive Secretary) indicated that copies of the slides for the day were available on the ACIP website and were made available through a ShareLink™ file for ACIP Voting Members, *Ex Officios*, and Liaison Representatives. She indicated that there would be an oral public comment session at approximately 3:45 PM Eastern Time (ET). Given that more individuals registered to make oral public comments than could be accommodated, selection was made randomly via a lottery. Those individuals who were not selected and any other individuals wishing to make written public comments may submit them through https://www.regulations.gov using Docket Number CDC-2021-0034. 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 stated COIs at the beginning of the meeting.

ACIP is accepting applications and nominations for new members to fill upcoming vacancies. Applications should be submitted by August 1, 2021 for the 4-year term beginning July 1, 2022. The application and additional information can be found on the ACIP website.[1]

[1] https://www.cdc.gov/vaccines/acip/apply-for-membership/index.html

ACIP Membership Updates

Dr. Amanda Cohn (ACIP Executive Secretary) took a few moments to bid farewell and expressed appreciation and gratitude to 3 members who would be departing over the next couple of months whose terms end July 1, 2021: Dr. Sharon Frey, Dr. Hank Bernstein, and Dr. Jose Romero. Although the new slate of members had not yet received final approved, they were invited to attend meetings in the interim. Dr. Cohn emphasized that the departing members joined ACIP during a very challenging time when there was a focus on live attenuated influenza vaccine (LAIV) and whether to preferentially recommend inactivated influenza vaccine (IIV) over LAIV or return to recommending it. They are leaving in an even more challenging time. It is usually possible to see ACIP Members, *Ex Officios*, and Liaisons in person and everyone really does become somewhat of a family. Obviously, that has been much harder over the last year and a half. Nevertheless, the dedication of all of these members, in particular the departing members, overwhelms Dr. Cohn and the CDC staff on a daily basis. She then offered a few remarks about each of these members.

Dr. Henry or "Hank" Bernstein has been the Chair of the Child and Adolescent Schedule Work Group (WG), and the Pertussis Vaccines WG and served as a longstanding and critically important member of the Influenza Vaccines WG before he was an ACIP member. He also was on the Meningococcal Vaccines WG during his tenure with ACIP. Dr. Cohn said she was particularly appreciative of Dr. Bernstein as he was one of the first people she encountered during her first year of residency as a pediatrician. Dr. Bernstein was a true primary care pediatrician, who started talking to her about vaccines many years ago and was one of the people who mentored her through her career. He also has been a major advocate and supporter of not only ensuring all children are vaccinated, but also talking to parents and working through questions with them to understand how to improve vaccination rates. When Dr. Cohn asked Dr. Bernstein what he would say to those who are hesitant to get an influenza vaccine, his words were, "It's extremely important to be sympathetic to individual concerns, which are likely to be different for different people." While the understanding of the challenges in vaccine confidence now gets down to individual questions and everyone understands this mantra, Dr. Bernstein was there well ahead of her and many others. He has always thought about public health on a personal level, but also on a population level. She expressed hope that Dr. Bernstein would continue to participate in ACIP WGs, at least the Influenza WG. Everyone will miss his amazing questions, wisdom, and input and his ability to stick to his perspective at the right times, in the right way, and in such a collaborative manner on the ACIP.

Over her tenure with ACIP, Dr. Sharon Frey has served as Chair for the Ebola Vaccines WG, the Hepatitis Vaccines WG, the Rabies Vaccines WG. She also has been a member of the Anthrax Vaccines WG. While everyone thought that she would be chairing all of the issues on the table, COVID-19 overwhelmed that. Dr. Cohn noted that while she did not know Dr. Frey before she began her tenure at ACIP, she is always excited to be introduced to amazing, wonderful people who join the committee. Dr. Frey is not only an amazing researcher in vaccinology, but also she has lived life to its every moment. One of the first things everyone learned about Dr. Frey is that in addition to working around the clock on vaccine clinical trials, she also is a vintage sportscar driver. One thing they learned is that while vintage sportscars do not go more than 130 miles per hour, the turns are really challenging. Over the last year, not only did Dr. Frey participate in some of the busiest WGs of the past couple of years, but also she helped the Vintage Sports Car Drivers Association (VSCDA) back to driving with her epidemiologic expertise and her public health guidance to them.[2] Something that Dr. Frey does

[2] VSCDA moves from plans to action for June 19-21 Blackhawk Classic | RACER

not talk about as much is that she has spent many weeks of her career extremely war-torn, challenging countries providing health care, including Kosovo and other places. She is an incredible woman and has been an incredible person to have on the ACIP. She has an incredible ability to bring basic science and vaccinology to the forefront of ACIP discussions about disease impact and policy decisions, and she has contributed to discussions in ways that Dr. Cohn did not anticipate. She expressed gratitude to Dr. Frey for her service over the last 4 years, emphasized that she would be incredibly missed, and expressed hope that she would continue to participate on ACIP WG over the coming years and work with CDC and the vaccine world in many different ways.

Dr. Cohn indicated that Dr. Romero began his tenure as an ACIP member in 2014. He was the last ACIP member who was present on the ACIP before she and Ms. MacNeil began their roles on ACIP. Over the course of time, Dr. Romero has served as the Chair of the Child/Adolescent Schedules WG, the HPV Vaccines WG, the Hepatitis Vaccines WG, the Mumps Vaccine WG, the Rabies Vaccine WG, and the COVID-19 Vaccines WG. He has chaired ACIP with such enormous leadership, kindness, and brilliance, which is just an incredible combination of skills that he brought to the table. Dr. Cohn pointed out that she and Dr. Romero had a few differences they had to work through over the last couple of years. When Dr. Bennett was leaving as Chair, the first thing Dr. Romero said to Dr. Cohn was, “You have to make these meetings start later.” Before every single meeting they would go back and forth about whether to start earlier or later to let him sleep in a little bit so that he would be more refreshed. He finally won when ACIP had to shift to virtual meetings and they recognized the importance of making sure that they were not starting at 5:00 in the morning for our West Coast colleagues. The second difference Drs. Cohn and Dr. Romero had pertained to the breaks in the ACIP agendas. He wanted to have breaks at all times during the meeting, and CDC was just trying to get through the enormous amount of work on the agenda. Dr. Cohn came to appreciate his pushing to give people breaks as they realized that the more exhausted they got, the more they really needed time in between sessions to refresh and regenerate. They will definitely take that with them going forward and will not have ACIP meetings go as extensively long as they used to without breaks. The third issue they had between them was Dr. Romero’s desire to let everyone speak for as long as they wanted to and not try to stop or hinder any discussion. Dr. Cohn was always trying to balance this with knowing that prior to COVID, ACIP would get kicked out of the room at 5:30. As they learned during the last virtual ACIP meeting, their feed also ends at 5:30. Unfortunately, when they moved over to ZOOM, the “last question” looks she would give him became text messages. Dr. Cohn expressed her appreciation to Dr. Romero for the last year of flying in to attend the ACIP meeting in-person in the same socially distanced room with her so that she could give him those looks. Still, he would stick to his guns and would not listen to her most of the time. She said she could not say enough about how much Dr. Romero’s leadership has been appreciated from the beginning and especially over the last year and a half. He has brought his incredible scientific expertise along with his focus on health equity and balance, and his understanding of vaccinology from a researcher academic perspective and his more recent experience as the State Health Officer of the Arkansas Department of Health (ADH). CDC and ACIP have been incredibly lucky to have Dr. Romero and will miss him greatly. Everyone will miss the fun they had with him outside of ACIP meetings and as Dr. Bernstein referred to it, his “unflappable” leadership during ACIP meetings. Dr. Cohn called upon Dr. Grace Lee to say a few words to Dr. Romero on behalf of the ACIP members.

Dr. Lee thanked Dr. Cohn for the opportunity to say a few words about her good friend and colleague, Dr. Romero. When he started ACIP nearly 7 seven years ago, Dr. Romero was already a national leader in pediatric infectious diseases with a passion to improve knowledge about viral infections and a passion to improve health care delivery among underrepresented minority communities as a young professor of pediatrics in the University of Arkansas School for Medical Sciences (UAMS). As the years went by, he decided that was not enough. During his tenure on ACIP, he decided to take on the role of Chief Medical Officer at the Arkansas Department of Health (ADH). Then he was appointed Secretary of Health for the State of Arkansas. All the while, he was leading the ACIP. His gray hair reflects his years of wisdom and courage to serve both his own community and his nation simultaneously during a raging pandemic. As Chair of the ACIP, he has reflected the type of leadership that is really needed in this world. He trusts the work of his team, both the ACIP members as they lead various working groups, and the CDC staff, while also quietly guiding the direction of the ACIP. He demonstrates patience in the sense of calm during innumerable meetings and deliberations, particularly over the past year and a half where having the ability to have these transparent and full discussions has been extremely helpful as they have navigated together through COVID. Dr. Romero also is inclusive of all opinions and all viewpoints. He respectfully listens to everyone, provides thoughtful responses, and ensures that the ACIP members are being their best selves. As Dr. Romero has said, “Public health touches the lives of everyone. It has a key role in protecting and improving the health of our nation.” Dr. Romero personally has done both. He has touched their lives and he continues to serve tirelessly as a leader, protecting and improving the health of the country. Dr. Lee expressed her extreme gratitude to Dr. Romero and thanked him personally and on behalf the entire ACIP membership.

Departing Member Comments

Dr. Bernstein thanked Dr. Cohn for her kind words. He said that for him, the phrase “time flies” captured his 4-year term on ACIP well. This has been truly an amazing opportunity and memorable experience—often challenging, but always rewarding. COVID-19 has added to the intellectual challenge. It is incredibly impressive to him how ACIP balances science, implementation, and equity in transparently making its policy recommendations. One of his personal mantras always has been team, T-E-A-M. Together, everyone achieves more. During these past 4 years, he learned firsthand and how ACIP is a team effort. Of course, numerous CDC folks always provide their remarkable intelligence, expertise, commitment, leadership, and service. In addition, led by ACIP’s unflappable chairs, Dr. Nancy Bennett followed the past 3 years by Dr. José Romero, and previous and current fellow ACIP members have inspired critical thinking, deciphered complex details, created thoughtful ideas, and fostered lifelong learning—all in the name of public health. Many liaisons also have shared their brilliant minds and passions and the public voices have shared their valued perspectives. ACIP discussions are stimulating, lively, and vital. Dr. Bernstein said that he listens closely to everyone and often reflecting to himself, “Why didn’t I think of that?” On a personal level, he said he also want to recognize and warmly thank 3 individuals, Drs. Cohn, Lee, and Long. As Dr. Cohn mentioned, he first met this bold ACIP leader and Dr. Grace Lee, the splendid incoming ACIP Chair, years ago when they were pediatric residents and he was a faculty member at Boston Children’s Hospital. It was obvious that they were destined for vaccinology greatness, educating him back then and still educating him now all these many years later. Dr. Sarah Long, a recent addition to ACIP, was one of his own mentors when he was a pediatric resident in Philadelphia. She helped ignite his love of vaccines, infectious diseases, and medical education. He ended by sincerely thanking everyone for all that they do as a team in making public health for the entire country a top priority. This experience on ACIP has been an exceptional honor for him and he said that he was deeply indebted to all of them.

Dr. Frey thanked Dr. Cohn for a pretty amazing introduction. She stressed that she learned an incredible amount of information and gained an incredible amount of knowledge by participating on the ACIP. First, she thanked the CDC ACIP leadership for the invitation to be part of this committee, on which it has been an enormous honor and a true pleasure to serve during the past 4 years. As she was sure her colleagues would agree, being a voting member of the ACIP is a truly remarkable experience, wonderful opportunity, and a major highlight of their careers. Second, she thanked her past and present ACIP colleagues for their service, emphasized what an incredible honor it had been to serve with them during the past 4 years, and expressed her deep admiration and respect for them. Next, she acknowledged ACIP leadership, Dr. Nancy Messonnier, *ex officio* members, CDC WG leads, liaison representatives, consultants, subject matter experts (SMEs), and anyone else she was forgetting for the incredible and tireless hard work and the dedication they have provided and continue to provide on behalf of this country and the world at large. She stressed that they are all amazing in terms of being earnest and persistent in the public health mission and in their ability to scrutinize the latest evidence-based data to make the best possible decisions given the current science. The time of COVID has been extremely challenging for all, and the demands everyone has placed upon themselves were and remain enormous—they are her heroes. The ACIP engine is a beautiful and multifaceted jewel embedded in one of the national treasures, the CDC. She said, "That my friends was my elaborate way for me to say to you, you rock." Dr. Frey expressed her gratitude for being allowed to be a small part of this amazing force and wished everyone the best and happy trails until they meet again.

Dr. Romero tanked Dr. Cohn and Dr. Lee for their very touching words. He began by thanking Dr. Jean Smith, the ACIP Medical Officer, and Dr. Larry Pickering, the ACIP Executive Secretary, at the time he was appointed to the ACIP. These two former senior administrative members allowed him to serve as ACIP's Vice Chair, a roll that ultimately led to him chairing the committee. In addition, he extended a heartfelt thanks to Dr. Cohn and Ms. McNeil, the senior leadership of the ACIP who were extremely patient with him and who kept him on the right track. In addition, he expressed gratitude to Stephanie Thomas for all of the work she does in the background to keep ACIP going, Natalie Green who got him to and from the CDC without a hitch every time and could modify travel plans at the drop of a dime, and to Chris Caraway who has been managing the web-based transmissions and who he has become very fond of as they sat socially distanced in a room together. Dr. Romero also expressed his gratitude to his public health colleagues in Arkansas and the Arkansas Governor who understood the significance of the work being carried out by the ACIP and provided him the time to be absent from regular duties to dedicate time to this important effort. Lastly, Dr. Romero said he would be remiss if he did not acknowledge his understanding wife, who during his increased level of commitment to the ACIP over the last 18 months was so patient and supportive. He emphasized that his term as an ACIP member and in particular as Chair has been possibly the most rewarding period of his professional career to date. The last 7 years have allowed him to work with the extremely talented and dedicated staff of the CDC as well as experts in the field that form part of the committee. It also provided him a unique vantage point offered to only a few to observe, participate, and understand how vaccine policy is developed and implemented in its finest form. ACIP's voting members are true experts in their respective fields. The bring with them their unique experiences and points of view that, coupled with sound data analysis provided by the women and men of the world's premier public health agency, the CDC, and supplemented by real-world perspectives offered by the ACIP liaison members, allow this committee to create, craft, and modify evidence-based vaccine policies that affect the lives of millions in this country and at times extend well beyond this country's borders. The preceding 18 months have been filled with uncertainty, apprehension, sadness, frustration, disbelief, and at times anger as they

have confronted the worst pandemic in modern history. Throughout it all, the voting members of the ACIP, CDC personnel, *ex officio* members, and liaison representatives have dedicated countless hours to dispassionately developed evidence-based vaccine policy initially for the prioritization of scarce vaccine resources and the use of truly novel vaccines for the prevention and mitigation of COVID-19. In addition, they all have evaluated rare adverse events (AEs) associated with these vaccines in order to be certain that they are recommending them appropriately. All the while, multiple non-COVID vaccine WGs continued their work uninterrupted on multiple other vaccines and vaccine issues. Participation on the ACIP has allowed Dr. Romero the opportunity to contribute to the improvement of the health and lives of millions of persons. He only hopes that he has made a small contribution to the policies and recommendations that have come from this committee during his tenure on the ACIP. He is truly grateful for this opportunity. He has made strong friendships while on the ACIP, ones that will last well into the future. He expressed his regret that the pandemic had taken the opportunity from him to interact with ACIP's newest members and liaisons and to say "goodbye" in person to those he has worked with so closely. He stressed that he would miss them all and underscored what a privilege and an honor it had been to serve as a member of the ACIP.

DENGUE VACCINES

Introduction

Dr. Wilbur Chen (ACIP, WG Co-Chair) first noted that all of the tributes he was hearing for ACIP's departing voting members were truly inspirational to him and that their presence had been terrific. To avoid the tone of a funeral, he said he was looking forward to crossing paths with and potentially working with each of them in the future. He then introduced the dengue vaccines session, reminding everyone that the pivotal data for DENGVAXIA® was created in 2015 with the efficacy studies that were performed. In May 2016, the World Health Organization's (WHO's) Strategic Advisory Group of Experts (SAGE) provided their recommendations for DENGVAXIA®, which was for originally for persons 9 to 45 years of age living in high seroprevalence areas. In November 2017, new data on DENGVAXIA® were made available to SAGE from a case-cohort study showing increased risk of severe dengue among persons who were seronegative prior to their dengue infection. Therefore, SAGE published revised recommendations in April 2018 that included the mention of a pre-vaccination screening strategy under which only dengue seropositive persons would be vaccinated. In May 2019, the US FDA licensed DENGVAXIA® and the Dengue Vaccines WG began working toward the recommendations for DENGVAXIA® with an eye toward a vote in 2021.

In terms of the Dengue Vaccines WG timeline, there was initially a Flavivirus Vaccines WG in 2016 and 2017 that presented to the ACIP in February and June of 2017. The Flavivirus Vaccines WG was put on hold in 2018 and the Dengue Vaccines WG was formed. In 2019, the Dengue Vaccines WG discussed the cumulative Phase 3 safety and pharmacovigilance, a GRADE (Grading of Recommendation Assessment, Development and Evaluation) analysis, a cost-effectiveness analysis, dengue diagnostic options and commercial assays, partially effective vaccines, and dengue vaccine in Philippines. Following review by the Vaccine and Related Blood Products Advisory Committee (VRBPAC) review and recommendation, the Food and Drug Administration (FDA) approved DENGVAXIA® in 2019. Between February and October of 2020, the ACIP heard presentations of the possible phased implementation of DENGVAXIA® in Puerto Rico, cost-effectiveness analyses, economic analyses, a survey of the results of the acceptability from stakeholders (e.g., pediatricians, school officials, and other interviewees in the community), feasibility, and health equity. During the February 2021 ACIP

meeting, the results of an independent evaluation of the dengue serologic tests and the Dengue Vaccines WG's interpretation were presented to the ACIP. In the meantime, the Dengue Vaccines WG also had been working closely with the American Academy of Pediatrics (AAP) Committee on Infectious Diseases (COID) to try to ensure that the concerns of the AAP, which represents the pediatric population and where the vaccine is targeted, are addressed. During the May 5, 2021 ACIP meeting, the WG presented the Evidence to Recommendations (EtR) Framework.

During the February 2021 ACIP meeting, the Dengue WG discussed that this vaccine requires a pre-vaccination serological test for screening. The screening test needs to be both sensitive to maximize the ability to identify eligible children for vaccination and specific to reduce the risk of vaccinating seronegative children. The CDC independently evaluated a number of commercially available assays and identified one enzyme-linked immunosorbent assay (ELISA) and two rapid tests that met the WG's criteria for high sensitivity and specificity. Test performance characteristics will be published in the *Morbidity and Mortality Weekly Report* (*MMWR*), included in the ACIP recommendations, and posted on the CDC website.

During the May 5, 2021 ACIP meeting, the WG discussed the EtR Framework analyses. The WG's findings from this analysis were that dengue is an important public health problem, DENGVAXIA® is an effective vaccine for seropositive children 9-16 years of age, cumulative information suggests that the benefits outweighs the risks, the vaccine is likely to be acceptable to the target population and stakeholders, vaccination with DENGVAXIA® is likely to be a cost-effective public health strategy under the expected seroprevalence scenarios, will increase health equity, and is feasible to implement. It will require a lot of work by local public health departments working very closely with providers and parents in planned educational programs

The WG believes that DENGVAXIA® should be implemented as a routine vaccination for children 9-16 years of age in endemic areas. The plan for this meeting was to vote on the DENGVAXIA® recommendations. Presentations during this session focused on acceptability of dengue vaccine in Puerto Rico, implementation of dengue vaccine in Puerto Rico, and dengue vaccine draft recommendations using the EtR Framework.

Acceptability of Dengue Vaccine in Puerto Rico

Dr. Ines Esquilin (University of Puerto Rico, School of Medicine) presented the dengue vaccine knowledge and attitudes data from Puerto Rico. This information was obtained from 3 sources: the general population, physicians (mostly pediatricians), and parents of children between 9-16 years of age. The general population data were obtained from a community-based cohort study implemented in 2018 known as Communities Organized to Prevent Arboviruses (COPA). This presentation includes data from the third year of the study from November 2020 through June 2021. Participants were recruited from 38 cluster areas. Enrollment was offered to all household members between 1-50 years of age. Questions on interest in a free or low cost (≤$10) dengue vaccine if approved and available in Puerto Rico were ask to all those participants. A total of 1,082 adults participated. When asked if they would receive the dengue vaccine, 84% said they would receive it for themselves, 83% said they would administer it to their children, 6% said they were not sure for themselves, 8% said they were not sure whether they would administer it to their children, and 11% they would not receive the vaccine themselves, and 8% said they would not administer it to their children. When asked the reasons they would not or were unsure that they would vaccinate their children, 50% said they were concern about safety and side effects. This was followed by a lack of information about how the vaccine works (17%) and not believing in vaccines in general (14%). Dengue and

general vaccine perceptions were assessed among participants who would be willing to vaccinate their children and those who would not. Most participants acknowledged that dengue can be severe and cause death irrespective of their willingness to get vaccinated for dengue. The dengue vaccine intention appears to be more closely tied to general perceptions of vaccines and vaccine safety rather than perception of risk of dengue. For those who are unsure or not willing to vaccinate their children, 77% believed that the vaccines are important to prevent certain diseases and 61% believed that FDA-approved vaccines are safe.

The knowledge and attitudes survey in Puerto Rico physicians was supported by the Puerto Rico Academy of Pediatrics, the Puerto Rico College of Physicians, the Science and Technology Trust, and the University of Georgia (UGA). A pediatrician from the CDC Dengue Branch gave 3 presentations to local pediatric associations during the 2019 and 2020 Fall and Winter continuing education meetings. Physicians were asked to complete the survey after the presentation. The survey included information on the risk of hospitalization and severe illness in vaccinated seronegatives and on the implications for pre-vaccination test specificity. Additional surveys were obtained from pediatricians in the San Juan metropolitan area and from the University of Puerto Rico School of Medicine Department of Pediatrics and provided with a copy of the CDC presentation published later showing the vaccine and availability of laboratory tests or pre-vaccination screening. There were a total of 114 respondents. Only 31% of the physicians administer vaccines in their offices. Most vaccines are administered in public and private immunization clinics in Puerto Rico. Of the physician participants, 98% acknowledged that dengue is a significant public health problem in Puerto Rico. Only 57% of physicians knew that there was an FDA-approved dengue vaccine. Assuming a laboratory test with acceptable specificity was available, 73% of physicians would recommend the vaccine and 21% did not know at the time of the survey. Of those who would recommend the vaccine, 92% think that dengue is an important public health problem in Puerto Rico and 38% think the laboratory testing reduces the risk sufficiently. Of those unsure of recommending the vaccine to their pediatric patients, 75% needed more information, 71% had concerns about the risk of vaccinating patients with false positive dengue laboratory results, and 39% would wait until a better vaccine comes along. When asked for documentation in the medical record of a dengue diagnosis, 43% of physicians have documentation of a positive dengue laboratory test in the medical record for some of their patients and only 5% for all of their patients. Most pediatricians would favor a phased implementation of vaccine to sort out the logistics before implementing a large-scale program in Puerto Rico.

Turning to the data obtained from the focus groups with parents of children 9-16 years of age, the objective was to assess acceptability of the vaccine by parents and physicians. In terms of the methods, there were 5 focus group discussions with parents and 15 in-depth interviews with pediatricians, researchers, and school officials in 2020. In 2021, there were additional group discussions with the goal of validating communication messages. Questions on vaccine acceptability were asked. This included 2 group discussions with physicians and 2 with parents. Parents of children 9-16 years of age were recruited from pediatrician offices, research programs, schools, and the Boys and Girls Club of Puerto Rico. Clinicians were recruited through medical associations and academic institutions. Previous to asking the question, a script was read with information about the vaccine and questions on the script were clarified to participants. Notes were collected, and focus group sessions were recorded.

In terms of opinions about dengue vaccines, most participants have questions on dengue in general and about the vaccine, highlighting the need for education. One participant mentioned that, “Parents should be given support [information] about the types of dengue in order for them to understand that the vaccine is important, they must be clear that there are different types [of dengue] and even if you have already got one, you can get another.” Some will wait to see the effects on other children and others do not find it necessary. Some comments on willingness to vaccinate from parents included: “If he had a previous dengue infection, yes.” and “The blood test gives me peace of mind, and yes, I will consider it.” Comment on unwillingness to vaccinate included, “No, because there is not enough research and data. There needs to be something longitudinal where we can see the effects.” Comments from those who were unsure included, “I will continue to inform myself a little more, for a little while.”

Pediatricians were asked about their opinions about the dengue vaccine. Almost all had a positive opinion about having a dengue vaccine. They said it would be ideal to have a broader age range. One participant thought that if morbidity and the number of hospitalized dengue cases was low among children, parents probably would hesitate to vaccinate. Most pediatrician mentioned that they would participate in a vaccination program with DENGVAXIA®. Pediatricians showed a real support for vaccines and recognized that dengue is a priority and that DENGVAXIA® has shown efficacy against hospitalization. Some potential barriers listed included any payment for vaccines or tests and prolonged time to receive the dengue test results. Almost all participants wanted more information about DENGVAXIA® and about the test to confirm a past dengue infection. Participant questions related to why the vaccine is only for children 9-16 years of age, where clinical trials have taken place and what the results were, what the process of approval involves and how long it takes, what type of vaccine DENGVAXIA® is, what the components are, the dosage and how many times it has to be administered, the percentage of effectiveness, evidence of short- and long-term side effects and how to treat them, whether there are possible interactions with previous medical conditions or medications, what would happen if people get vaccinated and later have dengue again, which countries are using the vaccine, why the vaccine is approved for US territories only, whether the Puerto Rico Health Department will require the vaccine, and what dengue tests are required and how accurate they are. The best sources of information identified included doctors (especially pediatricians), nurses, researchers, and the CDC.

In conclusion, among the general population, adult participants demonstrated interest in the dengue vaccine for themselves or their children. Side effects and possible adverse reactions were the most important reasons for those not wanting to receive the dengue vaccine. From the physicians’ knowledge and attitude survey, it can be concluded that almost all physicians recognized that dengue is a significant public health problem in Puerto Rico and 43% were not aware that there is an FDA-approved dengue vaccine. Further, physician education is needed regarding the vaccine and its schedule, efficacy, and safety. Most physicians would recommend the vaccine if a laboratory test with acceptable specificity were available to document prior dengue infection. Medical record documentation of past positive dengue laboratory diagnostic tests for patients is limited. From the parent and physicians focus groups it can be concluded that most parents will agree to vaccinate their children if they have information on the vaccine. More information was requested on efficacy and side effects, the rationale for its use in Puerto Rico, and current use in other countries. Having the support of the University of Puerto Rico School of Medicine, the Puerto Rico Health Department, and the CDC also was very important to participants. They identified that the main influencers would be pediatricians. Pediatricians showed overall support, recognized that dengue is a priority, and that DENGVAXIA® shown efficacy against hospitalizations.

Implementation of Dengue Vaccine in Puerto Rico

Dr. Iris Cardona (Department of Health, Puerto Rico) presented on the proposed dengue vaccine implementation in Puerto Rico. Vaccines are administered in Puerto Rico through public and private providers. In 2020, there were about half a million children 7-18 years of age in the population estimates. This is the closest to the proposed recommendation range of 9-16 years of age. Of those children, 55% were covered by a private sector, 45% were under the Vaccines for Children (VFC) program, and 20,000 were uninsured. Puerto Rico has a total of 209 VFC providers and 296 private providers on the island. There are VFC providers and Federally Qualified Health Centers (FQHC) in all health regions. A child is eligible for the VFC program if is younger than 19 years of age and is one of the following: Medicaid Eligible, Uninsured, Underinsured, or American Indian or Alaskan Native (AI/AN). Underinsured or uninsured children in the VFC program are eligible to receive the vaccine only at an FQHC or Rural Health Clinic (RHC). Those are the type of providers that meet certain criteria under the Medicaid program.

Puerto Rico Health Department (PRDoH) has an immunization program. The mission of the PRDoH Immunization Program is to prevent the development of vaccine-preventable diseases through strategic implementation and intervention facilitating services in accordance with the vaccine schedule for children, adolescents, and adults of Puerto Rico. The vision is to maintain a protected population against vaccine preventable diseases thus reducing outbreaks, hospitalizations and deaths. The PRDoH Immunization Program recommends immunization public policy; guarantees immunization quality services; supplies vaccines funded by the federal government to providers serving Medicaid recipients; audits vaccine management, storage, handling, and administration; educates parents, communities, and providers on vaccines; and implements the Puerto Rico Immunization Law #25,[3] which is the immunization mandate law. However, the PRDoH Immunization Program does not offer direct patient care services, except during public health emergencies. The Puerto Rico Immunization Law was enacted in 1983 and established that the Secretary of Health is the one who determines all immunization school requirements adhering to ACIP recommendations and immunization schedules. It covers all educational institutions from day care centers to universities and allows only for medical and religious exemptions. There was good overall immunization coverage for adolescents 13-17 years of age in 2019 for most vaccines, except the second dose of HPV vaccine. Coverage for HPV vaccine has increased in the last 10 years, but remains suboptimal for the second dose of HPV vaccine.[4]

There are some preliminary plans for dengue vaccine implementation in Puerto Rico if there is an ACIP recommendation for DENGVAXIA®. Dengue has been a growing health threat in the Americas over the past 40 years. Transmission is characterized by cyclical epidemics, but overall numbers also show a steady increase in case numbers and disease risk with over 3 million cases in 2019, or the highest number of interaction cases on record.[5] Dengue is also a serious public health problem in Puerto Rico. There was a period of low transmission from 2014 to 2020, but that has not been the case historically and epidemics have occurred every 3 to 5 years. In some parts of Latin American, 2 epidemics occurred at once with COVID-19 and dengue. Dengue transmission started again in Puerto Rico in 2020 and over 1000 cases have been reported.

[3] Puerto Rico Immunization Law: https://adobe.ly/31wTyVv
[4] Fuente: Registro de Inmunización de PR (PRIR), Programa de Vacunación, Departamento de Salud de PR
[5] Source: Pan American Health Organization, PLISA Health Information Platform

The first step for dengue vaccine implementation in Puerto Rico should be education for providers and parent. Training sessions would be conducted with pediatrician and other professional associations. Educational materials for parents need to be developed and a media campaign will be needed to inform the public about the availability of these vaccines and why it can only be administered to seropositive participants. Meetings have been held with Medicaid and insurance companies regarding the vaccine and pre-vaccination screening cost. Vaccine costs will be covered by the VFC and private insurance. The cost of the test will be paid by Medicaid for those under VFC and by private insurance coverers. For children who are uninsured, parents usually cover the cost of testing. Funds to support the test and avoid out-of-pocket expense by parents will have to be identified.

Regarding pre-vaccination screening in Puerto Rico, CDC has evaluated different immunoglobulin G (IgG) tests. There are a few with good performance, but none are FDA-approved. Laboratories can implement non-FDA approved tests under Clinical Laboratory Improvement Amendments (CLIA). After FDA approval, the requirement to perform the test will be simplified. Standing orders for Dengue IgG pre-vaccination screening tests in immunization clinics will be considered. Orders and results can be sent online, which can help reduce the number of visits. Dengue testing in Puerto Rico is currently centralized at the PRDoH laboratory. The arbovirus surveillance system will be updated to receive reports on testing and results from private providers and private laboratories. Test results will be linked to the data from the immunization registry.

There are two scenarios for implementation for possible immunization service with dengue vaccine. There are facilities that have laboratory and vaccination services on site, such as the FQHC. In this scenario, during the annual wellness visit, pediatricians can assess eligibility for dengue vaccine, order laboratory tests, and if the results are positive, immunize the child against dengue all in one visit. Results from the laboratory testing will need to be reported to the Puerto Rico arbovirus surveillance database and the vaccine immunization registry, and the child would need to return in 6 and 12 months to complete the recommended 3 doses.
The second scenario is for settings where the medical providers does not have a laboratory on site and does not provide immunization services. In this case, during the annual wellness visit, the provider would assess eligibility for vaccination and order a dengue IgG test. The patient would then visit a laboratory for the sample to be drawn and the test performed. Results of the testing would be reported to the arbovirus surveillance system and returned to the patient who will forward it to provider. The provider would an order for dengue vaccine. Parents would take the child to an immunization clinic where the vaccine is administered. The child would need a pediatrician order for 6 and 12 months to complete the recommended 3-dose schedule. About 25% of all VFC providers in Puerto Rico have laboratory capability in-house, as well as immunization service. Those sites include the FQHC and CDT. The dengue vaccination program in Puerto Rico can have a safe implementation starting vaccination at these sites to help sort out the logistical details and then expand to other areas on the island.

An essential component of dengue vaccination will be to monitor for vaccine safety events after a recommendation, or Phase 4. Events occurring immediately in the hours, days, or weeks after vaccination will be captured to the Vaccine Adverse Event Reporting System (VAERS). Puerto Rico has an experienced VAERS Coordinator. Events are regularly reported to VAERS from the island. Over 800 events have been reported for Puerto Rico this year, showing how the system is in place and ready to identify serious events occurring immediately after vaccination. Other monitoring systems including the Vaccine Safety Datalink (VSD) and the Clinical Immunization Safety Assessment (CISA) Project, which are based on sentinel sites for vaccine safety monitoring. Unfortunately, there are no sites located in Puerto Rico. One of the main concerns

in this group is the seronegative patients who were false positive on the pre-vaccination screening and will be at increased risk for hospitalization and severe dengue.

Because of the case presentation, hospitalization and severe disease among vaccinated children will mostly occur several years after the vaccine was given and will be reported through the existing passive dengue surveillance system in Puerto Rico. All dengue virus testing in Puerto Rico is centralized at the PRDoH laboratory. Specimens from suspected dengue case are submitted with a case investigation form that captures information about clinical signs, symptoms, outcome, including hospitalization and severe dengue. Both the clinical information and laboratory results are entered in the PRDoH arboviral database. This is a passive surveillance system and there is under-reporting of cases. For every case reported, it is estimated that there are 5 or more dengue hospitalizations that were not reported to the health department.

However, there are some steps that will enhance the surveillance for dengue cases after vaccination and improve the reporting. This could happen by conducting outreach to hospitals and educating health care providers about dengue vaccine. Doctors also could receive special training on identifying dengue cases and the need to report the hospitalization. Enhanced surveillance for dengue hospitalization also could be implemented at selected pediatric hospitals in Puerto Rico. When dengue hospitalization or severe cases are reported, the dengue vaccine history will be important new information to collect. This will happen by first adding the dengue vaccine history to the Arboviral case investigation form. A secondary method to verify this information is through the vaccine or immunization registry. This will happen by establishing a link between these two databases to establish the vaccine history for people reported through the arboviral database. With this information, they could monitor the number of reported hospitalizations among vaccinated children to identify any potential safety signals or unexpected events.

In summary, the PRDoH adopts ACIP recommendations for local vaccine schedule and these are reviewed once a year. Immunization registry reporting is mandatory by law. The population of children 9-10 years of age receive limited vaccines because there is no routine vaccine recommended for those ages. Dengue testing can be incorporated into annual wellness visits. About 25% of VFC providers actually have laboratory capability in-house and can start dengue vaccination at these sites. Vaccine series completion in the age cohort is expected to be lower for the second and the third dose, which they will have to work with. VAERS is in place to detect any AEs potentially associated with the dengue vaccine that occur in the days or weeks after vaccination, but the larger challenge for these vaccines will be monitoring for events that occur years after vaccination. These events can still be captured through the existing dengue surveillance system, but this will require vaccine information and improved reporting. Links between the arboviral database and vaccine registry need to be established. With this information, it will be possible to monitor overall numbers of hospitalization and severe disease and assess whether the numbers are higher or lower than expected.

As a pediatrician, Dr. Cardona pointed out that she is aware that dengue in Puerto Rico mainly affects children. If there is an effective vaccine that can help prevent disease among this population, Puerto Rico is willing to work on implementing this program. It will take some effort and some time because of the uniqueness of the vaccine, which require a laboratory test before administration. There are still several logistical details that need to be worked out. However, Puerto Rico acknowledges that this a public health problem and is willing to work on implementing the program if there is an ACIP recommendation.

Dengue Vaccine Draft Recommendations Using the EtR Framework

Dr. Gabriela Paz-Bailey (CDC/NCEZID) reminded everyone that there are 4 dengue types: DENV-1, 2, 3, 4. A person can be infected with dengue 4 times in their lifetime and infection with a serotype provides lifelong type-specific immunity and short-term cross-immunity against other serotypes. To recap the timeline for DENGVAXIA®, trial results in 2015 showed increased risk of severe disease among children 2-5 years of age. Because of this, the WHO published a position paper in 2016 recommending the vaccine for person 9 years of age and older in highly endemic areas. In 2017, additional testing showed increased risk of severe dengue and hospitalization among vaccinated seronegative children compared to controls. Therefore, the WHO revised their recommendations to state that vaccine should be given only to children with laboratory-confirmed evidence of a past infection. The FDA licensed this vaccine in 2019 for children 9-16 years of age with laboratory-confirmed previous dengue infection who live in an endemic area.

The screening test before vaccination is going to be crucial for the safe administration of the vaccine, so the ACIP Dengue Vaccine WG prepared test guidance recommendations on the performance of the test that will be used for pre-vaccination screening. This was based on an international target profile that was adapted for US territories and associated states. The test performance should have a minimum specificity of 98%, sensitivity of 75%, positive predictive value (PPV) of 90%, and negative predictive value (NPV) of 75%. This guidance will be included on the *MMWR* with the vaccine recommendations if there is an ACIP vote on the recommendations. This guidance also would be published on the CDC website and would include a summary of the results of the CDC evaluation. The table could be updated to incorporate any new tests that become available. The WG is awaiting confirmation from the CDC lawyers that this plan is acceptable.

As a reminder, the WG presented previously on the CDC evaluation of commercially available tests. CDC identified 1 ELISA test and 2 versions of the rapid test that had high specificity of between 97% and 98%.The policy question for the EtR Framework was, “Should three doses of DENGVAXIA® be administered routinely to persons 9-6 years of age with laboratory-confirmed previous dengue infection and living in endemic area?” The first element of the EtR framework regarded whether dengue disease is of public health importance. The US territories and freely associated states where dengue is endemic include: Puerto Rico, the US Virgin Islands (USVI), American Samoa, Federated States of Micronesia, Palau, Palau, and the Marshall Island. Most (85%) of the children who would benefit from the vaccine reside in Puerto Rico. As Dr. Cardona explained, dengue epidemics occur every 3 to 5 years. Approximately 95% of the dengue cases in the US territories have been reported from Puerto Rico, and there has been an unusually long period with zero dengue transmission in Puerto Rico since 2014.[6] Part of the reason was the cross-protection from the Zika epidemic. Since the end of 2019 and beginning of 2020, dengue cases started being reported. Over 1000 PCR-confirmed cases have been reported from Puerto Rico since then.[7]

[6] Dengue cases in ArboNET, Jan 2010–May 2021
[7] Dengue passive surveillance system, Jan 2020–May 2021

Seroprevalence data for dengue are available only from Puerto Rico. There have been 3 studies that suggest seroprevalence of between 50% and 60% for this age group:

- Argüello et al: 10-18 years: 2007 (n=345): 50% (95% CI: 44–56)[8]
- Sanofi Pasteur trial data: 9-16 years: 2011 (n=152): 56% (95% CI: 47–64)[9]
- COPA project3: 9-16 years, DENV PRNT>10: 2018 (n=414): 59% (95% CI: 54–63)[10]

Despite the fact that there has been little dengue circulation from 2014 to 2019, there has been high seroprevalence. This means that the incidence must have been quite high during the outbreak years. Therefore, the WG consensus is that dengue is a disease of public health importance.

The benefits and harms domain focused first on the question regarding how substantial the desirable anticipate effects are. Efficacy for this vaccine against virologically-confirmed dengue (VCD) or symptomatic dengue is 82%.[11] The efficacy varies by serotype and is the highest for serotype 4 at 89% followed by serotype 3 at 80%. It is lower for serotypes 1 (67.4%) and 2 (67.3%).[12] Efficacy against hospitalization and severe dengue shown was estimated with 3 different methods: multiple imputation (MI), targeted maximum likelihood estimation (TMLE), and NS1. Focusing on the MI results, the vaccine result is a 79% reduction in hospitalization risk and an 84% reduction in the risk of severe dengue. In terms of duration of protection, data recently published by Sanofi show that the vaccine was still efficacious against hospitalization in Years 5 and 6 post-vaccination.[13] The WG considered the desirable anticipated effects to be from moderate to large.

The benefits and harms domain was next focused on the question regarding how substantial the undesirable anticipated effects are. The most important undesirable effect is the increased risk of hospitalization and severe dengue among seronegative children. The increased risk in seronegative vaccinees compared to controls for hospitalization was 41% greater based on the multiple imputation results. Vaccinees had twice the risk of severe dengue compared to controls.[14] Based on the confidence intervals, these findings were not statistically significant. However, it is important to note that these children fully recovered after their hospital stay. Regarding more traditional AEs, there were no difference in severe adverse events (SAEs) at 28 days. There were fewer AEs in the same group at 6 months and there were no differences in deaths.[15] The risk of hospitalization in seronegative participants was the greatest in Year 3 after vaccination with Hazard Ratio of 2.6. That did not increase in subsequent years. In Year 4, it was 1.68. In Years 5 and 6 combined, it was 1.12. In addition, the DSMB requested Sanofi to follow-up all seronegative children vaccinated in the different trials at least for 10 years after vaccination. Among the nearly 10,000 children followed, Sanofi has reported that there have not been any severe or hospitalized additional cases identified.[16] The WG interpreted the undesirable anticipated effects to be small.

[8] Argüello DF, et al. AJTMH. 2015 Mar 4;92(3):486-91
[9] L'Azou M, et al. TRSTMH. 2018 Apr 1;112(4):158-68
[10] Unpublished
[11] Hadinegoro SR et al. N Engl J Med 2015;373:1195-1206
[12] Sridhar, S, et al. N Engl J Med. 2018 Jul 26; 379(4):327-340
[13] Forrat R et al. CID 2021
[14] Sridhar, S, et al. N Engl J Med. 2018 Jul 26; 379(4):327-340
[15] Gustavo Dayan, Sanofi, personal communication
[16] Multiple imputation: Sanofi Pasteur, personal communication, March 15, 2021

Finally for the benefits and harms domain, the WG considered whether the desirable effects outweigh the undesirable effects. The benefits of DENGVAXIA® are that it prevents symptomatic dengue hospitalizations and severe dengue among seropositive children. The main potential harm is the increased risk of vaccine-induced hospitalizations and severe disease when a seronegative child is vaccinated after a false positive result. Researchers from the University of Notre Dame conducted an agent-based model (ABM) of dengue transmission with humans and mosquitos represented as agents. It was calibrated to simulate dengue transmission in Puerto Rico. It compared pre-vaccination screening and subsequent vaccination of seropositive children 9 years of age to the status quo. The model population is the population of children 9 years of age, with a new with a new cohort of children 9 years of age being vaccinated every year and followed for 10 years to track dengue infections, hospitalizations, and deaths.[17]

Presenting the scenarios of 50% seroprevalence and 30% seroprevalence, the population level benefits are symptomatic and hospitalized cases averted and the risks are vaccine-induced hospitalizations among dengue-naive individuals. With the test and vaccinate coverage of 80% using a test with 75% sensitivity and 98% specificity, the model produced estimates of baseline symptomatic and hospitalized cases. Among children 9-16 years of age in a scenario of 50% seroprevalence, more than 4000 symptomatic dengue cases would be averted and nearly 3000 hospitalizations, there would be 51 vaccine-induced hospitalizations among dengue-naïve children vaccinated after the false-positive result among 102,000 vaccinees who completed the 3-dose series. In the lower seroprevalence scenario of 30%, over 1500 symptomatic dengue cases would be averted and there would be 112 vaccine-induced hospitalizations among dengue-naive children in more than 51,000 vaccinees.[18]

In summary, the population risks of the screen and vaccinate strategy over 10 years in a 50% seroprevalence scenario are 51 vaccine-induced hospitalizations. The benefits are over 4000 fewer symptomatic cases and nearly 3000 fewer hospitalizations. In a 30% scenario, 112 vaccine-induced hospitalizations among seronegative children would be expected. The benefits would be over 1500 fewer symptomatic cases and over 1200 hospitalizations prevented. The WG interpretation of the benefits and harm was that there was a positive balance for benefits versus risk and that this balance varied by the seroprevalence. The WG interpretation was that the balance favored the intervention. Based on the methodology for the outcomes of virologically-confirmed dengue hospitalizations, severe dengue, and death, the certainty of the evidence was considered high for efficacy and moderate for safety.

In terms of the values domain, the WG though that the target population probably feels that the desirable effects are large relative to the undesirable effects, based on the data presented by Dr. Esquilin earlier in the session. The WG also thought that there probably is important uncertainty or variability. The WG considered that the intervention was probably acceptable to stakeholders. Regarding whether the intervention is feasible to implement, the feasibility assessment focused on PR due to the burden there. ACIP heard earlier about the detailed considerations regarding feasibility in Puerto Rico from Dr. Iris Cardona. While there are over 500 vaccine providers and 450 laboratories in Puerto Rico, there are 11 providers in the USVI and less than 5 in the other areas. The WG anticipates that the complexity of implementing vaccination would be more challenging in Puerto Rico, and hopes to apply lessons learned to

[17] Espana G, Leidner A, Waterman S, Perkins A. Cost-effectiveness of Dengue Vaccination in Puerto Rico. https://www.medrxiv.org/content/10.1101/2020.10.07.20208512v1

[18] Espana G, Leidner A, Waterman S, Perkins A. Cost-effectiveness of Dengue Vaccination in Puerto Rico. https://www.medrxiv.org/content/10.1101/2020.10.07.20208512v1. Sensitivity and specificity modified by Espana G. for this presentation

the other areas. In USVI, they were able to coordinate with the health department and conducted a survey to clinicians similar to the one done in Puerto Rico. In summary, the vaccine would be acceptable but more education is certainly needed as only a few were aware that there was an FDA-approved vaccine. For the territories in the Pacific, the WG had a meeting with the Pacific Island Health Officers Association (PIHOA), but COVID has prevented them from being able to coordinate a survey to providers and parents. They are currently planning to do that in collaboration with the CDC and with the University of Georgia. There also is discussion about using a partnership from household-based surveys to do additional dengue testing. One was done in Palau and one in American Samoa. This is currently being negotiated. The WG concluded that the intervention would probably be feasible to implement.

In terms of the resource use domain, the WG sought to answer whether the intervention is a reasonable and efficient allocation of resources. A cost-effectiveness analysis of DENGVAXIA® use in Puerto Rico by the University of Notre Dame showed the incremental cost-effectiveness ratio (ICER) of the vaccine. As a reminder, the ICER is the total cost with vaccination minus the cost without vaccination per unit of the event being prevented. At a cost of $382 for the 3-dose series, the ICER is $122,000 per quality adjusted life year (QALY) gained at 50% seroprevalence. For averted symptomatic cases, the ICER was $11,000 at 50% seroprevalence. For averted hospitalizations, the ICER was $16,000 at 50% seroprevalence. Thus, the ICER increases with lower seroprevalence and with higher cost of the vaccine and of the screening test. The WG considered that this probably would be an efficient allocation of resources.

With the respect to the impact on health equity, the WG considered whether the use of the vaccine would result in an increase in health equity considering the large health disparities between the US territories and the mainland, which are in part due to vector-borne diseases. The WG thought that the desirable consequences probably would outweigh the undesirable consequences in most settings and that there was sufficient information to move forward with the recommendation.

The WG evaluated 3 different policy options for an ACIP recommendation. For Option 1, ACIP does not recommend the intervention, the cons are that a vaccine proven to protect persons with prior dengue infection will not be available to US citizens and it puts off making a difficult decision that will be needed potentially for the next dengue vaccine approved by FDA, which may result in discouraging vaccine manufacturers. In terms of the pros, it would avoid a complicated implementation in the middle of COVID vaccination programs. For Option 2, shared decision-making, the WG was concerned that this type of recommendation may lead to lower uptake, less progress in sorting out feasibility, challenges in terms of test coverage by insurance companies, an increase in health inequities due to unequal health literacy, and the potential for less buy-in for large-scale education and communication. The pros are that it would lessen fears that the vaccine will become controversial and result in increased vaccine hesitancy. For Option 3, a routine recommendation, the cons are that the public and media perception of the risks associated with the vaccine may increase vaccine hesitancy for all vaccines. There is also a potential for public and provider perception that all hospitalizations among vaccinees are related to the vaccine. It is known that most hospitalizations will be related to vaccine breakthrough. In terms of the pros, an effective vaccine will be available for seropositive children. This is especially important since there are few tools available against dengue, though dengue outbreaks continue to occur. A routine recommendation would lead to greater coverage and the reduction in hospitalizations and better buy-in from health department and immunization programs, which will help resolve challenges with feasibility. There likely will be more support for

a broader communication and media campaign, and a routine recommendation likely would result in increases in health equity.

After extensive discussions, the WG decided to propose a routine recommendation to ACIP. The draft recommendation read as follows:

> ACIP recommends 3 doses of DENGVAXIA® administered 6 months apart at month 0, 6, and 12, in persons 9-16 years of age with a laboratory confirmation of previous dengue infection and living in endemic areas.

Discussion Summary: Dengue Vaccine

Comments, Requests, Suggestions from ACIP Voting Members

- More information about false positive results would be helpful.

- Include a detailed description in the education material to give people a better understanding qualitatively of the severity of disease for hospitalized patients, vaccine-associated cases, and the long-term outcomes of these children:

    - CDC confirmed that that they have a group of communicators and behavioral scientists who have been working on key messages for the materials for physicians and parents.
    - There also has been extensive formative work with the focus groups that Dr. Esquilin described.

- Consider addition of this vaccine to the Vaccine Injury Compensation Program (VICP) if hospitalizations in the future are determined to be associated with vaccination, particularly for families who might not be able to pay or who would be greatly impacted financially by hospitalization:

    - CDC confirmed that any vaccine that is routinely administered to children will be covered by the VICP. There is a long process associated with that because there has to be a tax associated with the dengue vaccine, and CDC will work with HRSA to set that process in motion.

- Consider prospectively monitoring equity with regard to implementation to ensure that disparities are being minimized:

    - CDC noted that monitoring coverage of the vaccine could be done by Census tract, geographic area, and potentially by using tools like the Social Vulnerability Index (SVI) to make sure that areas that are more disadvantaged would have appropriate access to the vaccine.
    - It is believed that perhaps the stay-at-home orders and the social distancing due to COVID-19 has had some impact in slowing down the spread from the metropolitan area of Puerto Rico to the rest of the island for this current period of dengue transmission.
    - It also is important to remember that there are FQHCs across the island and in the different health regions that serve Medicaid, uninsured, and under-insured populations and rural communities. Therefore, the more disadvantaged populations

will have access to these facilities where they can receive all of their service in one place.

- Additional information would be appreciated with regard to any known risks or theoretical concerns about the safety of receipt of an incomplete series, beyond not having optimal protection.

- While it is understood that vaccine and testing may not be covered by insurance if ACIP recommends shared clinical-decision making, it seemed to some members that shared clinical decision-making with this vaccine in endemic areas is going to be critically important because the situation is so complex:

    - It was noted that the WG's judgement on this evolved over time and that CDC's Dengue Branch has a very good collaborative relationship with the PRDoH.
    - A WG member who began with the assumption that a shared clinical-decision recommendation would be the best option, that opinion changed after many conversations about the type of vaccine recommendations and after listening to Puerto Rico physicians, the health department, and the insurance companies. In listening to those important key stakeholders, it became clear that shared decision-making would create multiple barriers and actually increase inequity.
    - It has been established by law that the cost of the vaccine has to be covered by insurance companies regardless of the type of recommendation.
    - In meetings with the major insurance companies in Puerto Rico, the companies said that with the routine recommendation, they would favor preventive action and would have no problem covering the cost of the test at between $5 and $10 dollars as reported by Sanofi.
    - There may be some additional paperwork required for a shared decision-making recommendation.

- While this recommendation does not pertain to travel, it is important to recognize that a number of children spend summers or extended periods of time with family in Puerto Rico:

    - The WG has had several discussions about trying to define what would qualify in terms of number of months of the year and number of years in an endemic area. The opinion from the WG was that this probably would need to be assessed and defined by providers. The vaccine is intended for people who continuously live in Puerto Rico and not travelers or Puerto Ricans who just visit over the summer for a short period of time.

- This will be a very challenging implementation process for which there is no precedent in terms of the need to perform a laboratory test before vaccinating. For the providers who do not have in-house laboratories, this will result in patients having to make several visits. Perhaps COVID-19 could serve as a model as some progress has made in terms of providers sending test or vaccination orders and receiving test results by text or by email.

Comments, Requests, Suggestions from ACIP Liaison Representatives

- The American Academy of Pediatrics (AAP) and the Committee on Infectious Diseases (COID) have been very impressed over the last 3 years with the progress that has been made in addressing the many concerns that they have had regarding the issues raised throughout this session. Certainly, they do not believe that this is going to be an easy process as there are many logistical issues to be dealt with. However, the engagement of key stakeholders (e.g., the public health department, local providers, the community, families) and involvement of the local AAP chapters will be critical in helping to disseminate information. If COVID-19 has taught one thing, it is that weighing the risks and benefits is critical. While the risks sound uncomfortable and there will be administrative obstacles to move through, this is extremely manageable. Dengue is clearly a critical issue that has arisen over the years, especially in tropical areas. With this vaccine in front of them and other vaccines that will be coming online in the future, it is important to consider this unusual nuance with the second infection issue. One of the biggest breakthroughs was having a highly sensitive test available and recommendation to vaccinate on certain children. The AAP and COID are confident that many of their issues and concerns have been addressed and they will continue to be engaged with Dr. Paz-Bailey and the community as this moves forward.

VFC Resolution: Dengue

Dr. Jeanne Santoli (CDC/NCIRD) reviewed the proposed resolution that aligned with the discussion about the recommendations. The purpose of this resolution is to add a vaccine for the prevention of dengue to the VFC program. The eligible groups are children 9-16 years of age with laboratory confirmation of previous dengue infection and living in endemic areas (i.e., Puerto Rico, American Samoa, and the US Virgin Islands), which are the areas in the US that are both endemic and also participating in the VFC Program. There is a note that the VFC resolution will be updated as necessary if dengue-endemic areas in the US or its territories change. The recommended vaccination schedule and intervals is 3 doses administered 6 months apart at 0, 6, and 12 months. For recommended dosages, the language refers to the product package inserts.
The language will state that:

Contraindications and precautions can be found in the package inserts that are available at: https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states

The reference is included in all of the VFC resolutions also will be included, which reads:

[If an ACIP recommendation regarding dengue vaccination is published within 6 months following this resolution, the relevant language other above (except in the eligible groups sections) will be replaced with the language in the recommendation and incorporated by reference to the URL].

Vote: Dengue Vaccine

Dr. Gabriela Paz-Bailey (CDC/NCEZID) presented the following proposed wording for an ACIP vote:

> *ACIP recommends 3 doses of DENGVAXIA® administered 6 months apart at months 0, 6, and 12, in persons 9-16 years of age with a laboratory confirmation of previous dengue infection and living in endemic areas.*

Motion/Vote: Dengue Vaccine

Dr. Sanchez made a motion to approve the proposed language for an ACIP vote on DENGVAXIA® as presented. Dr. Lee seconded the motion. No COIs were declared. The motion carried with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

14 Favored:	Ault, Bahta, Bernstein, Chen, Daley, Frey, Kotton, Lee, Long, McNally, Poehling, Romero, Sanchez, Talbot
0 Opposed:	N/A
0 Abstained:	N/A
0 Absent:	N/A

Vote: Dengue Vaccine VFC Resolution

Dr. Jeanne Santoli (CDC/NCIRD) posted the proposed resolution language that aligned with the discussion about the recommendations.

Motion/Vote: Dengue Vaccine VFC Resolution

Dr. Bahta made a motion to approve the VFC resolution for dengue vaccines as presented. Dr. Poehling seconded the motion. No COIs were declared. The motion carried with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

14 Favored:	Ault, Bahta, Bernstein, Chen, Daley, Frey, Kotton, Lee, Long, McNally, Poehling, Romero, Sanchez, Talbot
0 Opposed:	N/A
0 Abstained:	N/A
0 Absent:	N/A

Discussion Points

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

Dr. Ault said he was thinking while they were listening to the dengue presentations that they really need to hear back from the WG as this is getting implemented. He is finishing his third year on the WG and there are so many unique aspects to the screening, geography, and

stakeholder input that he would like to hear updates. He acknowledged that ACIP meetings are very crowded and that he certainly had come to appreciate that more after 3 years, but this should be a priority as this gets rolling in Puerto Rico.

Dr. Daley said that would appreciate special attention to what is defined as "laboratory confirmation" within the dengue *MMWR* so that it does not get taken out of context for the listed and approved laboratory tests.

Dr. Bernstein commented that while he thought that the dengue vaccine should be recommended for endemic areas, there is a lot of information. He initially he thought that a shared clinical decision-making recommendation would be the most appropriate, particularly with many of the elements of the evidence EtR Framework listed as "probably" by the WG. Conversely, while it is likely that this vaccine will require complex implementation with education and communication for families and providers alike, he felt that universal recommendation would likely make implementation somewhat easier. That is why he shifted from a preference for a shared clinical decision-making recommendation to a universal recommendation in an endemic area.

INFLUENZA VACCINES

Introduction

Dr. Keipp Talbot (ACIP, WG Chair) thanked everyone, acknowledging what an incredibly busy year this has been. Even though influenza was not circulating like it normally does, ACIP members, *Ex Officio* Members, Liaison Representatives, and consultants have really worked through the influenza issues that ACIP would hear about during this session. Recent WG discussions have included the development of proposed updates to the ACIP influenza statement for 2021-2022 including timing of vaccination, co-administration of influenza vaccines with COVID-19 vaccines, contraindications and precautions, and a change in indication of a Flucelvax® Quadrivalent (ccIIV4) down to a younger age group. In addition, they heard a presentation of the results from immunogenicity and safety study of Flucelvax® Quadrivalent among children 6-47 months of age, which is currently approved for children 2 years of age and older. This session include presentations on the Flucelvax® Quadrivalent (ccIIV4) Phase 3 randomized controlled trial (RCT) on immunogenicity and safety in Children 6 through 47 months of age and the WG's considerations and proposed recommendations.

Flucelvax® Quadrivalent (ccIIV4) Phase 3 Randomized Controlled Trial—Immunogenicity and Safety in Children 6 through 47 Months

Dr. Gregg Sylvester (Seqirus) briefly described Flucelvax® Quadrivalent (ccIIV4) Phase 3 RCT immunogenicity and safety in children 6-47 months of age. This RCT was the first immunogenicity and safety study that included infants and toddlers 6-23 months of age. However, it is already licensed for children 24 months of age and above. The results of this study were already submitted to the FDA. Seqirus™ is asking for a label expansion down to the 6 month age group. For simplicity, Dr. Sylvester used the name Flucelvax® throughout the presentation.

As a reminder, influenza causes considerable morbidity and mortality in young children. In the US, the CDC estimates that 20,000 children under 5 years of age are hospitalized every influenza season due to influenza complications. Vaccination remains the most effective means of preventing influenza disease. Flucelvax® is the only cell-based influenza vaccine licensed in the US and avoids egg adaptation by being manufactured in mammalian cells. Thus, cell-based vaccines may be a closer match to the annual FDA selected influenza virus strain.[19] As noted, Flucelvax® was approved for use in March 2021 in persons 2 years of age and older.

This study was conducted as a non-inferiority study. FDA has established clinical data guidelines when employing this type of design. Using the FDA recommendations, the investigators pre-specified that the geometric mean titer (GMT) would not exceed 1.5 and the seroconversion rate differences would not exceed 10 percentage points for the upper bound of the 95% confidence intervals for each of the 4 influenza strains. That means that 8 co-primary endpoints are used by the FDA to assess vaccine efficacy (VE) in a non-inferiority clinical trial. As with all vaccine trials, local and systemic AEs and solicited and unsolicited AEs will be collected. This Phase 3 trial compared Flucelvax® to a US licensed influenza vaccine, Afluria® Quadrivalent.

This study was conducted during the 2019-2020 Northern Hemisphere influenza season in 47 centers in the US. Immunogenicity was assessed using hemagglutination inhibition assay (HAI) for influenza A/H1N1, B/Yamagata, and B/Victoria strains and a microneutralization assay for the A/H3N2 strain. Children were randomized to receive either Flucelvax® or the comparator vaccine in a 2:1 ratio (ccIIV4:IIV4). That is, twice as many participants received Flucelvax® as those receiving Afluria®. Children were stratified by vaccine status. Infants and young children who were not previously vaccinated or who had an unknown influenza vaccination history received 2 doses of influenza vaccine. The first dose was given when they enrolled on Day 1. They returned a month later (29 days) to receive their second dose. All AEs were collected and evaluated during the entire study period, including new onset chronic disease (NOCD) and SAEs. “Previously vaccinated” was defined as anyone who had received 2 or more doses of influenza vaccines at least 4 weeks apart. Blood sampling was done in a similar fashion for immunogenicity and that was performed on Day 1 and 30 days after vaccine. Safety assessments were collected and evaluated in the same manner as for those who were not previously vaccinated.

The more common key inclusion criteria used in this clinical trial included healthy children ≥6 to ≤47 months old, the ability to comply with study procedures, and informed consent/assent provided by the parent or legal guardian. Acute subviral illness or fever was defined that as an oral temperature of 100.4^0 F or above, which was an inclusion criteria in the study. Exclusion criteria included fever, history of hypersensitivity to any of the vaccine components, history of Guillain–Barré syndrome (GBS) or demyelinating diseases, history of immunodeficiency or impaired immune function, receipt of an influenza vaccination or documented influenza in the 6 months prior to informed consent, receipt of blood products or immunoglobulins within 180 days prior to informed consent, and receipt of an investigational medical product within 30 days prior to informed consent.

[19] 1) Centers for Disease Control and Prevention. https://www.cdc.gov/flu/prevent/cell-based.htm (accessed March 15, 2021); 2) Rajaram S. et al. Ther Adv Vaccines Immunother. 2020 Feb 22: 8:2515135520908121

In terms of the demographics of the children participating in this study, the 2 groups were well-matched. The mean age of the study population was just a little over 28 months. There was a greater preponderance of children over the age of 24 months in the study. There was a near equal distribution of boys and girls in the study. Nearly two-thirds of participants were white and over 25% were black or African American. When evaluating ethnicity, nearly 30% stated that they were Hispanic or Latino. Slightly less than half of the children were not previously vaccinated, which means that slightly more than half were.

In terms of the results, 8 co-primary endpoints were evaluated to assess immunogenicity. None of the 4 vaccines exceeded that predefined margin of 10 percentage points of the upper bound of a two-sided 95% confidence interval on the difference between seroconversion rates. All 4 strains met all 8 predefined co-primary endpoints. Solicited AEs were assessed during the 7-day period after vaccination. The most commonly reported local AEs were similar in both groups. Tenderness and erythema were the second most commonly reported AEs for local solicited AE. The most frequently reported systemic AEs were irritability and sleepiness in both groups. The vast majority of the solicited local and systemic AEs were considered to be mild or moderate in severity.

To summarize the unsolicited AEs, only 4.5% within each group were determined to be related to the vaccine. Both groups reported similar SAEs at less than 1% or 0.9%. None of the SAEs were assessed as being related to the study vaccine. AEs leading to NOCD were reported at 1.4% for Flucelvax® and 1.6% for the US licensed comparator. AEs leading to study withdrawal were reported by 3 participants in the ccIIV4 group and 3 participants in the Flucelvax® group. Unfortunately, 2 of the children died. One of them died of adenovirus-associated encephalopathy and the other died in a car crash. The third withdrawal was due to new onset seizure. None of these withdrawals were related to the vaccine.

In summary, Flucelvax® met all 8 predefined co-primary endpoints as compared to IIV4. The immunogenicity data were consistent against all 4 strains. Flucelvax® was well-tolerated when comparing AEs amongst both groups. This safety data is consistent with previous reported data in older children. Looking forward, Seqirus™ expects an FDA approval of this expanded age range for Flucelvax® in mid-October 2021 prior to the October 8th ACIP meeting. It is their hope that ACIP will vote to expand Flucelvax® coverage down to 6 months of in the VFC program.

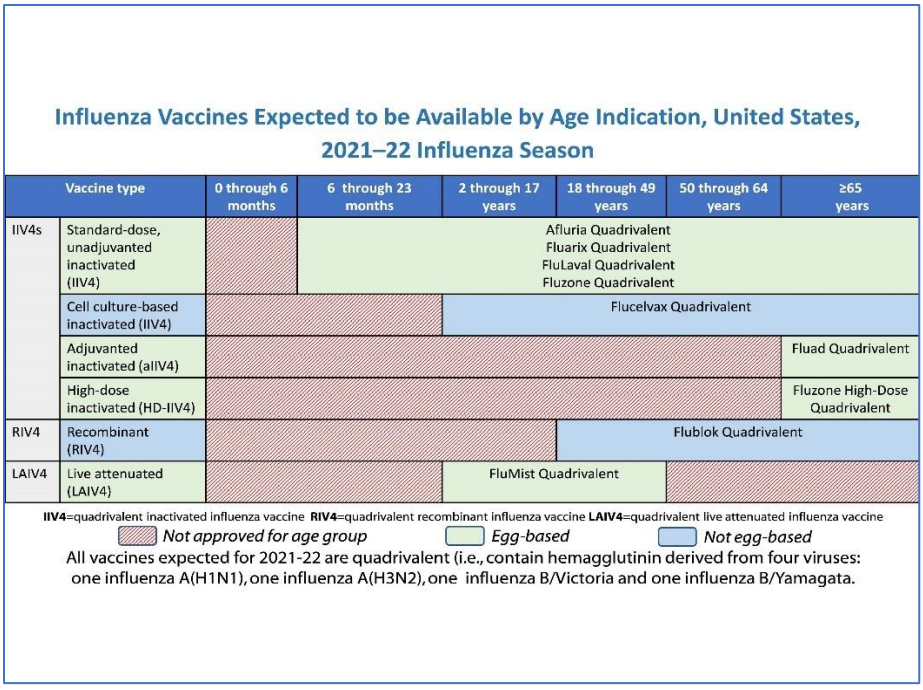
Work Group Considerations and Proposed Recommendations for the 2021-22 Influenza Season

Dr. Lisa Grohskopf (CDC/NCIRD) expressed profound gratitude to everyone who contributed to this work over the course of the year, despite more than a year of having a lot of other very high priority responsibilities. The WG has been blessed to have had amazing turnout and exchange of information and dialog on every call twice a month. During this session, she presented the proposed updates for the ACIP influenza statement for the upcoming 2021-2022 influenza season. As noted earlier by Dr. Talbot, there has not been much influenza activity over the last year.

The core recommendation for the upcoming season remains unchanged and states that, “Annual influenza vaccination is recommended for all persons aged 6 months and older who do not have contraindications.” However, the draft statement contains updates in a number of areas that will address the following:

- ❑ Influenza vaccines expected to be available for the 2021-2022 season
- ❑ The US influenza vaccine viral composition for the 2021-2022 season
- ❑ The change in age indication for Flucelvax® Quadrivalent from ≥4 years to ≥2 years
- ❑ Several changes to the Timing of Vaccination language
- ❑ New information on co-administration of influenza and COVID-19 vaccines
- ❑ Some changes to the Contraindications and Precautions language, specifically concerning persons who have had a previous severe allergic reaction to either influenza vaccines or a component of influenza vaccines

As previously, there are 3 main types of vaccines: inactivated vaccines (IIVs), recombinant influenza vaccines (RIV), and live-attenuated influenza vaccine (LAIV). All 3 categories are expected to be available. One change this year is that all of the vaccines are going to be quadrivalent. This means that they will contain hemagglutinin (HA) derived from 4 different viruses: 1 influenza A(H1N1), 1 influenza A(H3N2), 1 influenza B/Victoria, and 1 influenza B/Yamagata. This will be the first season that this has occurred. Last year, there were 10 vaccines available, one of which was trivalent. The trivalent vaccine will no longer be available. The second change is that the age indication for Flucelvax® Quadrivalent has been changed from 4 years and up to 2 years and up. This was approved by the FDA in March 2021. In the following chart, green denotes egg-based vaccines and blue denotes non-egg-based vaccines. Out of the 9 vaccines, 7 are egg-based meaning that they contain influenza viruses that have been propagated in eggs. The other 2 are cell-culture-based, Flucelvax® Quadrivalent that virus propagated in canine kidney cells and Flublok® Quadrivalent RIV vaccine that does not use viruses. RIV contains HA produced by introduction to the HA in protein genes sequenced into an insect cell line using a viral vector. This chart summarizes the 9 influenza vaccines that are expected to be available for the upcoming season, by their approved age indication:



For the 2021-2022 US influenza season, the FDA met in early March 2021 to make recommendations about the vaccine viral strains that are to go into US licensed influenza vaccines. For this season, they are recommending a composition for the vaccines that contain updates in both the influenza A(H1N1pdm)09-like virus and the influenza A(H3N2)-like component. The B components are the same. Since for this season only quadrivalent vaccines are expected, there is not an option for the second B as both are included. In the last couple of years, there have been separate recommendations for the egg-based and non-egg-based vaccines, but this does not mean the composition of the vaccine is different in any meaningful way for any subtype of virus that is recommended. There are generally a number of antigenically similar viruses that can be used. Since the development and further development of the cell culture-based vaccines, it is now actually possible to use cell-based reference strains in the cell culture-based vaccines, so sometimes there will be separate recommendations though the vaccine is not different. In this case, only one difference is specified for the influenza A(H1N1)pdm09-like virus. That is, egg-based IIV4s and LAIV4 contain an A/Victoria/2570/2019 (H1N1)pdm09-like virus and cell-culture-based IIV4 and RIV4 contain an A/Wisconsin/588/2019 (H1N1)pdm09-like virus.

In terms of the change in age indication for Flucelvax® Quadrivalent (ccIIV4), in addition to the presentation earlier in the session on data for this vaccine for children 6-47 months of age, ACIP heard a presentation of data in October 2020. This vaccine was previously licensed for ages ≥4 years, was approved by FDA in March 2021 for ages ≥2 years. The change was supported by RCTs conducted among over 4000 children aged ≥2 through <18 years over 3 influenza seasons who were randomized 1:1 to get ccIIV4 or Flucelvax® Quadrivalent and a non-influenza control vaccine. Overall VE was 54.6% for reverse transcription polymerase chain reaction (RT-PCR) or culture-confirmed influenza associated with CDC-defined influenza-like illness (ILI), and was somewhat higher for matched strains at 62.7%. Again, these data were presented to ACIP in October for proposed draft language of a new age indication reflected in the text and in Table 1. As is generally done when there is a change in age indication, there is a paragraph on it in the section in the recommendations about licensure changes.

In terms of co-administration of influenza vaccines with COVID-19 vaccines, COVID-19 vaccines were not yet available at the time of the publication of the last statement in August 2020. Since this is first influenza season for which co-administration of influenza COVID-19 vaccines can occur, the WG has been closely following the recommendations coming from the COVID-19 Vaccine WG on co-administration. Initially, it was recommended that COVID-19 vaccines be spaced at least 14 days apart from any other vaccines. However, this was recently updated and is posted under the Critical Considerations for Use of COVID-19 vaccines on the CDC webpages. There is a section in the ACIP influenza statement on co-administration of influenza vaccines with other vaccines, which has been updated to reflect the most recent guidance for the COVID-19 vaccines.

In discussing this topic and considering what recommendations to make, one consideration discussed by the WG was the potential for increased reactogenicity, particularly with co-administration of some influenza vaccines that might be more likely to cause any kind of reactogenicity symptoms. There was greater frequency of reactogenicity with adjuvanted and high-dose inactivated vaccines compared with standard-dose, unadjuvanted inactivated vaccines in some studies. Some of those studies have shown a slight increase in some reactogenicity symptoms, though they were generally mild. In the US, both of those vaccines are only licensed for 65 and older. Individuals 65 and older tend overall to have less reactogenicity than younger people and neither of these vaccines is licensed for children.

Another area that was discussed was the importance of not missing opportunities for vaccination, which easily could be happening and be more of a concern if people are not able to get vaccines at the same time. This has been a particular worry and has been discussed regarding children. It is going to be a concern for adults who require influenza vaccinations, so this was another concern that was discussed and considered by the WG. In the end, the language arrived at the draft statement is consistent with the most recent COVID-19 vaccination guidance. The language also refers providers to the most recent guidance for any updated information in the event that anything should change over the course of the summer and into the fall. Here is the guidance from the interim clinical considerations for the use of COVID-19 vaccines currently authorized in the US:[20]

- "COVID-19 vaccines were previously recommended to be administered alone, with a minimum interval of 14 days before or after administration of any other vaccines. This was out of an abundance of caution and not due to any known safety or immunogenicity concerns. However, substantial data have now been collected regarding the safety of COVID-19 vaccine currently authorized by FDA for use under EUA…COVID-19 vaccines and other vaccines **may now be administered without regard to timing**."
- "Administer the COVID-19 vaccines and vaccines that may be more likely to cause a local reaction (e.g., tetanus-toxoid-containing and adjuvanted vaccines) in different limbs, if possible."

The following is the proposed language for 2021-2022 Influenza Statement, which essentially mirrors the current COVID-19 vaccination guidance:

- Current guidance concerning administration of COVID-19 vaccines with other vaccines (https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html) indicates that these vaccine may be given with other vaccines, including influenza vaccines. No data are currently available concerning coadministration of currently authorized COVID-19 vaccines and influenza vaccines. Providers should be aware of the potential for increased reactogenicity with coadministration, and should consult CDC guidance at the referenced link for updated guidance as more information becomes available. If coadministered, COVID-19 vaccines and vaccines that might be more likely to cause a local reaction (e.g., aIIV4 or HD-IIV4) should be administered in different limbs, if possible.

The next topic is timing of vaccinations, which is always a complex issue. This time, there are several updates. So before launching into the updates, there is some background on this topic and 2 factors that have some bearing on decisions regarding timing of influenza vaccinations. The first concerns timing of the influenza season. The ideal time to be vaccinated against influenza each season cannot be predicted because the timing of the onset and peak of the influenza activity beginning varies from season-to-season. Timing of activity onset also can vary geographically, with the circulation of influenza viruses varying in different parts of the country. In the US, localized areas of increased activity occur as early as October. Over the 36 seasons[21] between 1982-1983 and 2017-2018, peak activity occurred in December during 7 (19%) of seasons, in January during 6 (17%) seasons, in February during 15 (42%) seasons, and in March during 6 (19%) seasons. While February is the most popular of the seasons for the influenza peak to occur, there is a spread in the distribution. In fact, there have been a

[20] https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html
[21] https://www.cdc.gov/flu/about/season/flu-season.htm

couple of seasons when the peak activity was actually quite early. While this occurred only 1 season each in October and November, it has happened.

A second factor is waning protection from vaccines and vaccinations with time following vaccination. Since approximately the 2013-2014 season, the influenza statement has included a fairly lengthy discussion of the evidence for waning protection following vaccination during the influenza season. Declines in VE over the course of the season have been observed in many observational studies and while there is some variation in the findings among the studies, it generally appears that waning is more common and more pronounced among older adults. There has been less evidence of waning among children. Based upon these factors, the current 2021 statement contains a discussion of evidence for waning protection following vaccination. Vaccination has been recommended to be offered by the end of October for several seasons, and has been recommended to continue as long as influenza viruses are circulating locally. The language for the past couple of seasons also has included a recommendation that July and August are probably too early in most influenza seasons, especially for older adults. The reason probably comes down to having to do with the variability in the timing of the onset and peak of the season. An exception to this July and August language has been made for children 6 months through 8 years of age who require 2 doses for the season because they are vaccine-naïve, for whom receipt of the first dose is recommended as soon as possible after vaccine is available since doses must be ≥4 weeks apart.

In discussing timing of vaccination language this year, the scope was broadened somewhat this year. The WG discussed recent literature concerning waning of immunity to influenza vaccines. Other considerations discussed included protection of infants during the first months of life since there are licensed influenza vaccines for children under 6 months of age, and avoiding missed opportunities for vaccination. The language that resulted from this discussion contained several changes concerning timing of vaccination for children, persons in the third trimester of pregnancy, and adults. An addition was made for pregnant persons given the fact that it has been demonstrated in a number of trials that vaccination during later pregnancy can result in increased protection to the infants from influenza during the first few months of life. This is generally a period of time where they are not going to be eligible for influenza vaccines because there currently is no policy for vaccinating children under 6 months of age, nor are any vaccines licensed for children under 6 months of age. The language for non-pregnant adults was modified because all the other groups were taken out and because the language was strengthened with regard to July and August. Dr. Grohskopf reviewed the proposed language differences for each of these groups, shown in red:

Children

- Similar to Previous Language:
  *"Children aged 6 months through 8 years who require 2 doses should receive their first dose as soon as possible after the vaccine becomes available to allow the second dose (which must be administered ≥4 weeks later) to be received **ideally** by the end of October."*

- New:
  "Children of any age who require only one dose for the season should also ideally be vaccinated by the end of October; vaccination of these children may occur as soon as vaccine is available, as there is less evidence to suggest that early vaccination is associated with waning immunity among children as compared with adults."

Pregnant Persons in Third Trimester

- New:
  "Vaccination soon after vaccine becomes available may also be considered for pregnant persons during the third trimester, as vaccination of pregnant persons has been shown to reduce risk of influenza illness of their infants during the first months of life[1-4] (a period during which they be too young to receive influenza vaccine)"

1. Madhi et al N Engl J Med. 2014 Sep 4;371(10):918-31
2. Tapia et al Lancet Infect Dis. 2016 Sep;16(9):1026-35
3. Steinhoff et al Lancet Infect Dis. 2017 Sep;17(9):981-9
4. Eick et al Arch Pediatr Adolesc Med. 2011 Feb;165(2):104-11

Non-Pregnant Adults

- New:
  "For non-pregnant adults, influenza vaccination during July and August should be avoided unless there is concern that later vaccination might not be possible."

The last area where the WG proposed modifications concerned updates to influenza vaccine contraindications and precautions. These changes pertain specifically to severe allergic reactions, such as anaphylaxis to either influenza vaccines or their components. All vaccines, including influenza vaccines, include multiple components that potentially can trigger severe allergic reactions (e.g., anaphylaxis). Serious allergic reactions to influenza vaccines and vaccines in general are fortunately rare. A Vaccine Safety Datalink (VSD) study by McNeil et al from 2016 estimated the rate of post-vaccination anaphylaxis among cases that involved administration based single vaccine as 1.31 cases per million doses for all vaccines and 1.35 cases per million doses for IIV3.[22] One of the complexities of severe allergic reactions to vaccines is that they can occur in people who have no prior history of allergic reaction to a vaccine, or perhaps even to anything. When a recipient experiences a severe reaction, it can be difficult to know which component was responsible for the reaction. One of the things mentioned in the ACIP "General Best Practices" document is that referral of the individual to an allergist for evaluation is usually indicated to try to determine the component responsible before making decisions regarding administration of the additional doses of the same vaccine or other vaccines that have the same components. This language is not specific to influenza vaccines, but it is representative of the uncertainty sometimes in determining what caused and reaction and trying to decide the best course going forward.

The 2020-2021 language concerning severe reactions to influenza vaccines is located currently at the end of the egg allergy section. It was originally placed there for the 2011-2012 season in order to make clear the difference in management between individuals who have egg allergies and individuals who have had a severe allergic reaction to an influenza vaccine previously. This is consistent with the contraindication language that is in most of the egg-based IIV vaccine package inserts. The current language and package insert for egg-based IIVs read as follows:

[22] McNeil J Allerg Clin Immunol 2016;137:868-878

Current (2020-21) language (from egg allergy section):
"A previous severe allergic reaction to influenza vaccine, regardless of the component suspected of being responsible for the reaction, is a contraindication to future receipt of the vaccine."

Package insert contraindications language for egg-based IIVs:
"History of severe allergic reaction (e.g. anaphylaxis) to any component of the vaccine (including egg protein), or after a previous dose of any influenza vaccine."

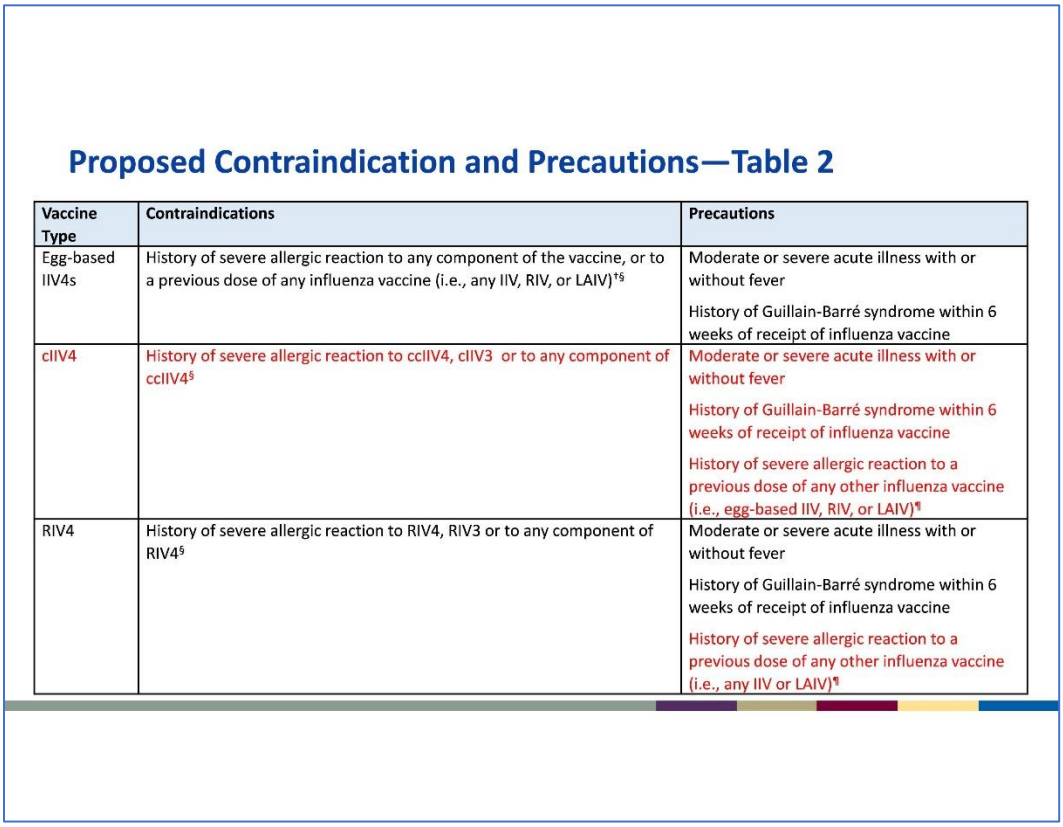
At the time this language was developed, it was based on the vaccines available when there were not newer non-egg-based vaccines. Some of the package inserts do not state anaphylaxis per se, but otherwise that is still the standard language across egg-based influenza vaccines. The package inserts for 2 relatively newer influenza vaccines, RIV4 (Flublok® Quadrivalent) and ccIIV4 (Flucelvax® Quadrivalent), have somewhat different caution contraindication language in the package inserts. They instead read, "History of severe allergic reaction (e.g., anaphylaxis) to any component of vaccine" and do not include history of a severe allergic reaction to any influenza vaccine as a contraindication. In the current statement, in the table of Contraindications and Precautions for all IIVs, including the cell culture-based inactivated vaccine, are grouped together with contraindication language mirroring that of the egg-based inactivated vaccine stating, "History of severe allergic reaction to any component of the vaccine, or to a previous dose of any influenza vaccine." For RIV4, the table acknowledges that the language in the package insert is different, "History of severe allergic reaction to any component of the vaccine." While this accurately reflects the package insert language, it presents inconsistency with the language that comes from the egg allergy recommendations indicating that a severe allergic reaction to any influenza vaccine is a contraindication to future receipt of the vaccine.

In discussing this, the WG considered several points with regard to allergic reactions to influenza vaccines. There is a desire to have consistency and simplicity of the recommendations to the extent possible. Simplicity is both especially important to aim for and a particular challenge to get to in the context of multiple vaccines with differences in labeling. Grouping a similar vaccine within a category with the same language, for example as with the inactivated vaccines, helps simplify the recommendations but sacrifices differences between the specific vaccines. Another point was the need for harmonization with the influenza vaccine package inserts, which also poses a challenge to simplicity. Also discussed were the relative components of the currently available influenza vaccines based on the components listed in each package insert and their similarities and differences with one another. An additional point regarded the desire to be able to extend vaccinations to those who had had a severe allergic reaction to an influenza vaccine if an alternative vaccine could be safely used. Finally, there was some discussion of potential need for allergy or immunology consultation. While this was recognized to be a useful step in determining causative components of a reaction and then identifying a potential alternate vaccine, it was also noted by some in the WG that allergists in some parts of the country are in relatively short supply and are not always easily accessible in all communities.

Another consideration the WG discussed were reviews in the VAERS data that were published by Woo et al that examined reports of AEs, including allergic reactions following RIV. Before summarizing these data, there are some important reminders about limitations of VAERS. VAERS is a passive surveillance system that has a potential for reporting bias, inconsistent data quality, and incompleteness of data. In general, VAERS data cannot be used to assess

causality. The reviews by Woo et al[23] evaluated reports in VAERS of cases of allergic reactions, including severe allergic reactions following RIV. The focus was on such reactions as a whole, but there was some focus on some of the severe allergic reactions. The vast majority of reactions that were found were not severe. This vaccine is egg-free, contains no antibiotics or gelatin or preservatives, and has relatively fewer components than many other vaccines based on the ingredients or components listed on the package insert. It was noted that there were cases of allergic reactions, including some meeting Brighton Criteria for anaphylaxis, including some among persons who had reported a history either of allergic reaction to eggs or to a previous dose of influenza vaccine. This vaccine does not contain egg, so the authors were not trying to make a point that it was something to do with eggs. What they noted in the papers was that the occurrence of such reactions might reflect an underlying predisposition to atopy, which might be to reactions following any vaccine or medications, rather than to indicate the specific causative relationship to the constituents or components of any specific vaccine.

Given all of this discussion, the WG arrived at essentially a copy of the draft Table 2. LAIV has been removed from it because no changes have been proposed there, so the following table basically contains only the relevant sections for the ACIP conversation during this session. One thing that became necessary was to try to be as clear as possible that the cell culture-based inactivated vaccine is now pulled out into its own row in the table. RIV4 was always in its own group:



Proposed Contraindication and Precautions—Table 2

Vaccine Type	Contraindications	Precautions
Egg-based IIV4s	History of severe allergic reaction to any component of the vaccine, or to a previous dose of any influenza vaccine (i.e., any IIV, RIV, or LAIV)†§	Moderate or severe acute illness with or without fever History of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine
cIIV4	History of severe allergic reaction to ccIIV4, cIIV3 or to any component of ccIIV4§	Moderate or severe acute illness with or without fever History of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine History of severe allergic reaction to a previous dose of any other influenza vaccine (i.e., egg-based IIV, RIV, or LAIV)¶
RIV4	History of severe allergic reaction to RIV4, RIV3 or to any component of RIV4§	Moderate or severe acute illness with or without fever History of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine History of severe allergic reaction to a previous dose of any other influenza vaccine (i.e., any IIV or LAIV)¶

[23] Woo et al, Clin Infect Dis 2015;60(5):777-780; and Woo et al, Vaccine 2017;35:5618-5621

In addition to the proposed contraindications and precautions changes, there are some proposed footnotes concerning the precautions:

- ❑ If ccIIV4 or RIV4 is administered to an individual with a history of severe allergic reactions, (e.g., anaphylaxis) to any other influenza vaccine, vaccination should occur in an inpatient or outpatient medical setting and should be supervised by a healthcare provider who is able to recognize and manage severe allergic reactions.
  - Providers can also consider consultation with an allergist to help determine the vaccine component responsible for the allergic reaction.

Discussion Summary: Influenza Vaccines

- ACIP expressed interest in additional information from Seqirus™ on the following: 1) breakdown of the results of immunogenicity and safety by race and ethnicity; 2) the child with overwhelming adenovirus-associated encephalopathy in terms of whether there were any comorbidities; 3) any known risk factors for new onset seizure disorder; and the price point for Flucelvax®:

  - Dr. Sylvester indicated that for NOCDs, the reports they got back were 3 children with asthma, 2 children with seasonal allergy, 2 children with ear infections that may have been otitis media, and 2 children with allergic dermatitis among the Flucelvax® participants. There were 2 cases of cardiac murmur among the comparator participants. He will take ACIP's requests for additional information back to his clinical development colleagues and would report it back to Dr. Grohskopf.

- Key discussion points regarding Dr. Grohskopf's presentation of the Influenza Vaccine WG's considerations:

  - Concern was expressed that continuing to state that vaccines may be given with other vaccines does not make it more correct or indicate that there is more evidence. There is no information at the moment about concurrent administration of coronavirus vaccines and the newest influenza vaccine. In addition, there is increased risk of myocarditis vaccines among adolescents related to COVID-19 vaccines for which the pathophysiology is not yet understood.

  - Dr. Grohskopf indicated that there would be a study by the Immunization Safety Office (ISO) and CISA beginning in the Fall. The WG discussed, and it is indicated in the wording of the COVID-19 recommendations, that the reason for spacing of vaccines in the beginning of administration was out of an abundance of caution and to have the ability to sort out safety. Collecting distinct safety data on COVID vaccines helped to keep the picture from being muddied by somebody having received COVID-19 vaccine and another vaccine simultaneously, making it difficult to sort out safety.

  - Dr. Cohn added that there is a preprint study that looks at co-administration of other vaccines with seasonal influenza vaccines that show similar immunogenicity and safety, with no changes in antibody titers. There are some other ongoing studies from which data are anticipated earlier than the Fall. Certainly, any concerning issues that may arise from either this study or from any reports of AEs that occur in persons who have received co-administered vaccines will be investigated.

- Concerning a question about a second dose of mRNA vaccine for adolescents and young adults should be more than 4 weeks apart and/or if the second dose should be lower in an effort to mitigate AEs, Dr. Cohn pointed out that this inquiry related to COVID vaccines, not influenzas vaccines. She indicated that there is a lot of work underway assessing varying doses of COVID vaccines, including activities occurring with the companies, to try to understand the risk factors for AEs such as myocarditis such as whether there is a relationship related to the number of days between Dose 1 and Dose 2. At this time, there is not a lot of safety or efficacy data on the second doses of COVID vaccines outside the 42-day window. CDC will continue to keep ACIP apprised of additional data as studies progress.

- Concern was expressed that the language pertaining to history of severe allergic reactions is very specific in terms of inpatient or outpatient medical settings and could be too restrictive. Perhaps this should be reframed to emphasize that anyone who administers vaccines should be prepared to deal with anaphylaxis, given that many vaccines are delivered in pharmacy settings, nursing homes, school settings, and other community vaccination settings. Rather than focusing on site, perhaps the focus should be on the capability to be able to support and manage anaphylaxis appropriately.

- There was support among ACIP members that additional studies of the safety and immunogenicity of co-administration of COVID vaccine with influenza vaccines should be strongly encouraged. It is likely that most adolescents will be vaccinated with COVID vaccination in the summer and may receive influenza vaccination in the Fall, but they may need a COVID booster at that time. Better understanding co-administration among adults is very important as well since adults do not present to their practitioners as frequently as children, so it is important to maximize the opportunity to keep adults current on the vaccine schedule at every single appointment. Perhaps CDC and/or FDA could provide a review during a future ACIP meeting on the post-marketing safety surveillance activities with regard to influenza, including a particular focus on ccIIV and all of the various candidates that are available.

- An observation was made that the language seemed negative in terms of considering postponing vaccinating until September and October rather than stating to make sure to vaccinate in September and October. Perhaps this can be phrased in a different way to make it very specific and clear. What is happening in the community is that other vaccinators, non-physicians, are getting the vaccine dosages early before the doctors do and they are giving them out right away to patients. By the time people present to their providers, they may already have been vaccinated in July or August. Physicians may not receive their supplies until September to appropriately vaccinate.

- Concern was expressed about the potential for a pregnant person to receive 2 influenza vaccines during a pregnancy, meaning that one fetus receives 2 doses. While the overall influenza vaccine safety data among pregnancy are reassuring, there do not seem to be any specific data on the number of times 2 doses have been administered during a single pregnancy by happenstance. The American College of Nurse Midwives (ANMA) pointed out that the 40 weeks of pregnancy overlaps 2 influenza seasons in almost two-thirds of pregnancies, so it is completely reasonable

that a woman would receive 2 different influenza vaccines within each gestation and it happens frequently.

- Dr. Cohn suggested that perhaps CDC could look into its vaccine systems to assess the frequency with which a pregnant persons receives 2 vaccines during a single pregnancy and present the findings during a future ACIP meeting.

- AAP expressed gratitude for CDC's continue guidance on all of these issues. The AAP continues to work in collaboration with the ACIP, CDC, other federal agencies, and societies to try to ensure that the vaccine schedule for children is as safe and effective as possible in preventing morbidity and mortality from diseases, as well as preventing AEs as much as possible. If there are AEs, the AAP is in the forefront along with the CDC in making sure that those are addressed rapidly and information disseminated to AAP's 67,000 members. It is important to understand that these are not unilateral decisions. Various groups are all working together. There are unknowns about COVID-19, but children are definitely getting this disease. HHS issued a statement the previous day and AAP continues to believe that the best way to deal with COVID, as well as the other diseases that are known to affect children and adolescents, is to make sure that everybody is as up-to-date on their immunizations as possible. Obviously, they always have in mind the potential for AEs and discuss those with CDC, ACIP, and within AAP and its leadership.

Vote: Influenza Vaccines

Dr. Lisa Grohskopf (CDC/NCIRD) presented the following language for the ACIP vote on influenza vaccines:

> *ACIP affirms the updated statement "Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices—United States, 2021-2021 Influenza Season."*

Motion/Vote: Influenza Vaccines

Dr. Daley made a motion to approve the proposed recommendation for influenza vaccines. Dr. Ault seconded the motion. No COIs were declared. The motion carried with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

14 Favored:	Ault, Bahta, Bernstein, Chen, Daley, Frey, Kotton, Lee, Long, McNally, Poehling, Romero, Sanchez, Talbot
0 Opposed:	N/A
0 Abstained:	N/A
0 Absent:	N/A

Vote: Influenza Vaccine VFC Resolution

Dr. Jeanne Santoli (CDC/NCIRD) indicated that the purpose of this resolution was to update the table of IIV in the VFC program and update the section on contraindications and precautions for both IIV and LAIV. No changes were proposed to the eligible groups or to the recommended vaccination schedule and intervals. Table A was updated to reflect the currently approved IIV vaccines in the VFC program and to include the age indications and updates that Dr. Grohskopf reviewed, with the Flucelvax® Quadrivalent being indicated for ages 2 years and older. Another footnote was added at the bottom to make clear and distinguish the IIV and LAIV vaccines as being egg-based and Flucelvax® Quadrivalent as being cell-based. The recommended intervals and dosages were unchanged. Contraindications and Precautions were changed to divide the contraindications for egg-based from cell-based vaccines on to include an updated link for egg-based vaccine. A new contraindication was added for cell culture-based influenza vaccines to read, “For cell culture-based vaccines: History of severe allergic reactions (e.g., anaphylaxis) to cell culture-based IIV or to any component of the vaccine.” A new precaution was added reading, “For cell culture-based IIV only: History of severe allergic reaction to any other influenza vaccine.” No changes were made to the LAIV section of the resolution. There were no changes to the eligible groups or recommended vaccination schedule, intervals, or dosage. The link was updated for the contraindications to be the 2021 ACIP Statement, and no changes were made to the paragraph regarding updated recommendation published for influenza vaccination within the next 6 months that that would be incorporated into this resolution by reference.

Motion/Vote: Influenza Vaccines VFC Resolution

Dr. Poehling made a motion to approve the VFC resolution for influenza vaccines as presented. Dr. Bernstein seconded the motion. No COIs were declared. The motion carried with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

14 Favored:	Ault, Bahta, Bernstein, Chen, Daley, Frey, Kotton, Lee, Long, McNally, Poehling, Romero, Sanchez, Talbot
0 Opposed:	N/A
0 Abstained:	N/A
0 Absent:	N/A

RABIES VACCINES

Introduction

Dr. Sharon Frey (ACIP, WG Chair) reminded everyone that in May 2020, the Rabies Vaccine WG provided presentations on rabies pre-exposure prophylaxis (PrEP) and children in terms of antibody response to rabies vaccine in children of all ages being similar to that of adults and the WG's preference for the PrEP recommendations for children to align with those for adults as they have in the past. The WG also presented information on post-exposure prophylaxis (PEP) in terms of the components of rabies PEP for previously vaccinated and naïve persons, and the factors that should be considered before administering PEP. A draft flowchart also was discussed. Since that time, the WG has discussed rabies immunoglobulin (RIG) products that have been licensed since the 2008 ACIP recommendations were made, and also began discussions about changes to the PEP schedule.

The WG's goals for this session were to review the EtR Framework presented during the October 2020 ACIP meeting and summarized during the February 2021 ACIP meeting; and review the ACIP votes on 2 recommendations for children, which were passed for persons ≥18 years of age during the February 2021 ACIP meeting. There would then be ACIP votes on 2 recommendations for children, which essentially would be the same recommendations made for persons ≥18 years of age during the February ACIP meeting. In addition, the WG planned to present information on PEP, particularly for RIG on 2 products that have been licensed since 2008, and the WG consideration of recent changes to the WHO recommendations and data about changes to the PEP series and the WG's preference. No vote was planned for PEP during this session. In terms of the WG's anticipated timeline, that plan is to discuss PEP clinical guidance topics in terms of the management of PEP including the schedule deviations for PrEP and PEP and PEP initiated abroad.

Presentations during this session focused on rabies immune globulin, the PEP schedule, and a summary review of the rabies pre-exposure prophylaxis EtR. The proposed recommendations under consideration for this session were as follows:

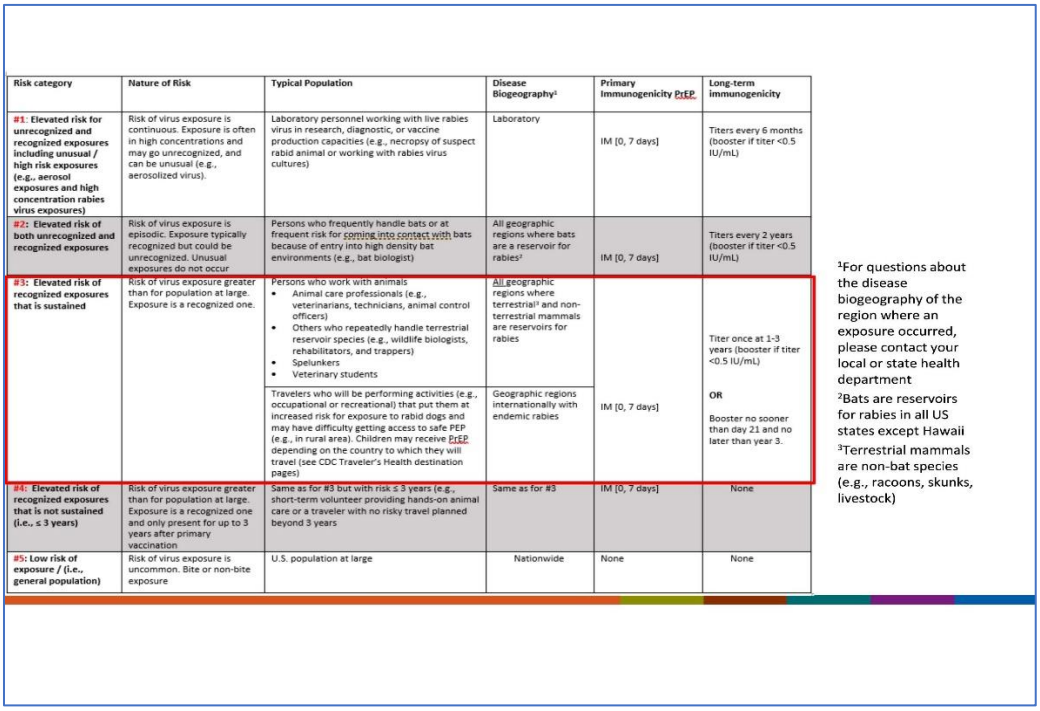
Proposed Recommendation #1

ACIP recommends a 2-dose [0, 7 days] intramuscular rabies vaccine series in immunocompetent persons.

Proposed Recommendation #2

ACIP recommends an intramuscular booster dose of rabies vaccine, as an alternative to a titer check, for immunocompetent persons <18 years of age who have sustained and elevated risk for only recognized rabies exposures (i.e., those in risk category #3 of rabies PrEP recommendations table). The booster dose should be administered no sooner than day 21 but no later than 3 years after the 2-dose PrEP series.

The WG made some changes to the table based on ACIP's recommendations, noting that this session would be focused on Risk Category #3, Elevated risk of recognized exposures that is sustained:



Risk category	Nature of Risk	Typical Population	Disease Biogeography[1]	Primary Immunogenicity PrEP	Long-term immunogenicity
#1: Elevated risk for unrecognized and recognized exposures including unusual / high risk exposures (e.g., aerosol exposures and high concentration rabies virus exposures)	Risk of virus exposure is continuous. Exposure is often in high concentrations and may go unrecognized, and can be unusual (e.g., aerosolized virus).	Laboratory personnel working with live rabies virus in research, diagnostic, or vaccine production capacities (e.g., necropsy of suspect rabid animal or working with rabies virus cultures)	Laboratory	IM [0, 7 days]	Titers every 6 months (booster if titer <0.5 IU/mL)
#2: Elevated risk of both unrecognized and recognized exposures	Risk of virus exposure is episodic. Exposure typically recognized but could be unrecognized. Unusual exposures do not occur	Persons who frequently handle bats or at frequent risk for coming into contact with bats because of entry into high density bat environments (e.g., bat biologist)	All geographic regions where bats are a reservoir for rabies[2]	IM [0, 7 days]	Titers every 2 years (booster if titer <0.5 IU/mL)
#3: Elevated risk of recognized exposures that is sustained	Risk of virus exposure greater than for population at large. Exposure is a recognized one.	• Animal care professionals (e.g., veterinarians, technicians, animal control officers) • Others who repeatedly handle terrestrial reservoir species (e.g., wildlife biologists, rehabilitators, and trappers) • Spelunkers • Veterinary students	All geographic regions where terrestrial[3] and non-terrestrial mammals are reservoirs for rabies	IM [0, 7 days]	Titer once at 1-3 years (booster if titer <0.5 IU/mL) **OR** Booster no sooner than day 21 and no later than year 3.
		Travelers who will be performing activities (e.g., occupational or recreational) that put them at increased risk for exposure to rabid dogs and may have difficulty getting access to safe PEP (e.g., in rural area). Children may receive PrEP depending on the country to which they will travel (see CDC Traveler's Health destination pages)	Geographic regions internationally with endemic rabies		
#4: Elevated risk of recognized exposures that is not sustained (i.e., ≤ 3 years)	Risk of virus exposure greater than for population at large. Exposure is a recognized one and only present for up to 3 years after primary vaccination	Same as for #3 but with risk ≤ 3 years (e.g., short-term volunteer providing hands-on animal care or a traveler with no risky travel planned beyond 3 years	Same as for #3	IM [0, 7 days]	None
#5: Low risk of exposure / (i.e., general population)	Risk of virus exposure is uncommon. Bite or non-bite exposure	U.S. population at large	Nationwide	None	None

[1]For questions about the disease biogeography of the region where an exposure occurred, please contact your local or state health department
[2]Bats are reservoirs for rabies in all US states except Hawaii
[3]Terrestrial mammals are non-bat species (e.g., racoons, skunks, livestock)

Rabies Immune Globulin (RIG)

Dr. Agam Rao (CDC/NCEZID) first reviewed the viral pathogenesis of rabies. Rabies virus is a neurotropic virus. It enters the peripheral nerves, travels centripetally to the central nervous system (CNS), and then flows centrifugally to the innervated organs, including the salivary glands. The incubation period is usually weeks to months, but it can be longer. Death typically occurs within 2 weeks of illness onset. The role of RIG in preventing rabies is that it provides passive immunity before the vaccine-induced humoral immunity occurs from the 3 doses of rabies vaccine given as part of PEP. It is given only to persons who have not received PrEP or previous PEP, because those are the only people who would benefit from it and because RIG can decrease antibody titer levels from rabies vaccine. RIG does not negate the need for the PEP vaccine series because at least some rabies virus is expected to travel to the CNS despite that passive neutralization.

RIG is indicated for 2 scenarios: 1) persons who did not previously receive a complete series of recommended PrEP or PEP prior to their first exposure to rabies virus, which would result in wound washing and PEP of RIG and the 4-dose PEP series; and 2) persons who received previous 2-dose PrEP but did not receive titer or booster within 3 years per the ACIP recommendations approved during the February 2021 meeting, who would be managed the same as a person who had not been previously immunized for the sake of being conservative since there are no data about immunogenicity beyond 3 years unless the titer or booster is checked.

If a rabies exposure occurs and there is virus present at the bite site and if PEP, including RIG is not administered, there is spread and replication of the virus in the CNS and salivary glands. Once onset occurs, there is progression from rabies prodrome, acute neurologic period, coma, and death corresponding with the period of virus replication. On the other hand, when a rabies exposure occurs and RIG is administered, there is some virus neutralization at the inoculation site. When rabies vaccine is administered according to the recommended intramuscular (IM) schedule of 0, 3, 7, and 14 days, there is vaccine-induced humoral response and no signs or symptoms of rabies that occur in that person.

At the time of the 2008 ACIP recommendations, which are the most recent recommendations for prevention of rabies, there were two RIG products licensed in the US. Both were considered equally efficacious and there was no preferential recommendation. Those were HyperRab™ S/D and Imogam® Rabies-HT. RIG was to be administered within the first 7 days of the first rabies vaccine dose being given. It was to be administered at 20 IU/kg regardless of age. Infiltration of the maximal amount of that RIG was to be given around the wound as much as anatomically feasible, and the remainder was recommended to be given intramuscularly at a location different from where vaccine was given. For large and/or multiple wounds, RIG could be diluted in order to ensure that there is appropriate infiltration of as many wounds as possible.

In 2018, WHO updated their recommendations. Their considerations for RIG recommendations included 2 factors that are not major concerns for the ACIP recommendations. Those are first that RIG is limited in supply internationally. It is estimated that worldwide approximately less than 2% of persons with serious wounds (i.e., Category III) receive RIG and RIG is extremely expensive. It is much more expensive than the vaccine, and persons in the US have concerns about that. Second, dog bites are the most common rabies exposures worldwide. Those wounds are large, so a lot of the calculated RIG is probably able to be given around the wound and the benefits from an IM administration of the RIG may be limited. There might be some savings instead.

The 2018 WHO Position Statement prioritizes limited RIG to persons who have the most concerning exposures. This includes people with high risk exposures (WHO Category III), multiple bites, deep wounds, bites to highly innervated body parts, severe immunodeficiency, exposures from confirmed or probable rabies, rabid mammals, and exposures from bats in particular. Perhaps the most notable element of the WHO statement for ACIP purposes is that it limits the RIG infiltration to RIG that can be infiltrated into and around the wound only and no longer has the recommendation for IM administration of the leftover RIG. The maximal dose is still the same at 20 IU/kg regardless of age, and dilution of RIG is still recommended if there are multiple wounds.

RIG products currently licensed in the US include Imogam®, Kedrab™/ Kedrion, HyperRab™ S/D, and HyperRab®. Kedrab™ and HyperRab™ have been licensed since the 2008 ACIP recommendations. HyperRab™ S/D, which is very similar in name to the newly licensed HyperRab®, is being phased out. It may still be on the shelves of individual suppliers and hospitals, but no new product is being sent out. That leaves just 3 products available in the US. Notably, HyperRab® is twice the potency of the other licensed products, so care needs to be taken in knowing which product a specific hospital is using.

All of this led to the following WG considerations for the ACIP update about RIG:

- ❑ There are 2 newly licensed RIGs. Are these new formulations or new products?
- ❑ In terms of RIG administration limited to wound, what are the data? In the US, exposure wounds are often small (i.e., from bat). What are the US implications?
- ❑ Are there data to support any other changes to RIG recommendations?

For the remainder of this presentation, Dr. Rao presented the WG's assessment of each of these separately. Beginning with newly licensed RIG products in the US, the 2 products that have been licensed since the 2008 ACIP recommendations came out, Kedrab™ and HyperRab®, make up most of the market share for rabies immunoglobulin and have no difficulty filling any gaps whenever there have been shortages of other products. Kedrab™ was licensed by the FDA in 2017. It is indicated for passive, transient PEP. It is supposed to be given to people of all ages and should be given immediately after contact with a rabid or possibly rabid animal. The clinical study design and trial results were similar to previously licensed RIG products, so there were really no concerns when FDA reviewed it. There was no referral of the Biologics License Application (BLA) submission to the Blood Products Advisory Committee (BPAC) because there were no concerns or controversial issues that would have benefited from the BPAC discussion. It was thought to be very similar to the other licensed RIG products.

HyperRab® was licensed by FDA in 2018. It is indicated for PEP along with rabies vaccine. Because this product is a higher potency formulation of the previous HyperRab™ S/D, a greater concentration of anti-rabies virus antibodies can be given with each milliliter of volume, which means that less volume is needed to administer the recommended 20 IU/kg. It is twice the potency of currently available rabies immune globulins. There is no FDA post-licensure requirements because it is considered to be a new formulation rather than a new product. There have been improved production and manufacturing processes over the years. HyperRab® now requires dilution with dextrose 5% in water (D5W) rather than normal saline. This is an important difference for this RIG product compared to the others, which clinicians are going to need to be mindful of when administering it.

The WG assessed both of the new products, Kedrab™ and HyperRab® and found that both are prepared from plasma of donors who were hyperimmunized with rabies vaccine and that the safety and efficacy are similar to the previously licensed RIG products. The WG dedicated at least 3 meetings to this discussion and concluded that these newly licensed products are not actually new. It is desirable to have multiple licensed RIG products because shortages have occurred, including within the last few years while the WG has been presenting to the ACIP. HyperRab® is twice as concentrated, resulting in less volume administered compared to other RIGs. The products are equally efficacious, so the WG had no preferential recommendation of a specific RIG product. In terms of selection of a RIG product, the indications are same for all of them. The more concentrated product potentially could be preferable for small wounds like those involved those from a bat bite. Given differences in potency between the products, oversight is obviously needed to ensure that the correct volume is administered for a particular product. There could be errors made and twice the volume inadvertently administered if care is not taken to recognize the fact that one is more concentrated. Clinicians should be aware that D5W is the recommended diluent for HyperRab® even though it is not provided with the product. It is up to individual facilities to decide which product they want to stock. The WG learned that facilities typically stock just one product.

In terms of the US and RIG considerations and the role for RIG, studies indicate that RIG can be advantageous for people before they develop indigenous antibodies. It is not difficult to access in the US unlike many other countries. Most rabies cases in the US are from bat exposures, which create small or barely visible wounds. Therefore, little RIG is administered around a wound. Recommendations about limiting RIG to just around the wound need to be made very carefully. Immunogenicity data suggests that IM RIG is detected in sera about 24 hours later, so there may be a benefit given that it is in the serum. In terms of pathophysiology, RIG infiltrated around the wound likely remains at that site of the injection. There are limited data cited in the WHO Position Statement[24] explaining WHO's decision to limit RIG to infiltration around the wound. It is unclear whether IM administration of RIG provides a significant benefit from their assessment, but it was based on very limited data. The WG felt that the data were insufficient to propose the same recommendations to the ACIP.

In conclusion, the WG found these 2 new licensed RIG products to be new formulations. In terms of the data regarding RIG administration limited to the wound, WHO's considerations are very different from those of ACIP given the population that with whom they are working. Small wounds would result in very small, if any, RIG infiltration around the wound. Therefore, the implications for the US population of limiting RIG administration to the wound would be significant potentially because no intramuscular administration would mean that the same level would not be seen in the bloodstream. Regarding data to support any other changes to RIG recommendations, there are no changes to any RIG recommendations for the purposes of voting, but the WG has a lot of clinical guidance that will be presented during the October ACIP meeting about RIG an about PEP in general. Some of that includes inadvertent administration of a higher amount of RIG because of a hyperconcentrated product or for other reasons, which do happen. For example, sometimes people will administer all of the RIG intramuscularly and then realize that they were supposed to first administer as much as possible around the wound. The clinical guidance issues will be taken up by the WG. There are no other proposed recommendations that would require a vote.

Rabies Post-Exposure Prophylaxis Schedule

Dr. Agam Rao (CDC/NCEZID) reminded everyone that the rabies PEP schedule for persons who have not previously received PEP or PrEP is RIG plus vaccine on Day 0, whatever day zero might be, and then 3 more IM doses on Days 3, 7, and 14. In terms of the features of an improved PEP schedule, effectiveness is unchanged from the currently recommended series. Fewer doses are required than the current 4-dose schedule, with completion of the series sooner than the current schedule. Ideally, this would be an IM vaccine schedule because that is what is used in the US. There are robust data supporting its use. This would be the WG's expectations if they were to suggest any changes to the PEP schedule. Dr. Rao shared a screenshot from a table in the recent WHO recommendations describing the exposure categories used by WHO and to illustrate which of the multiple recommended schedules could be an improvement to the current ACIP recommendations that would result in a schedule that is completed a week sooner than the current schedule. The WG wanted to assess the particular series that was taken on by the WHO in the form of intradermal (ID) recommendations, so they reviewed a systematic review that was published just 2 years ago that evaluated multiple abridged PEP schedules.[25] The objective of this systematic review was to inform the 2018 WHO update for rabies PEP schedules by evaluating the: 1) immunogenicity and effectiveness of PEP schedules of a reduced dose and duration (the most important to the ACIP discussion); 2) new

[24] Madhusudana et al, Saesow et al, and Wilde et al included in background documents
[25] Kessels et al, Vaccine 37 (2019) A107-A117

evidence on effective PEP protocols for special populations; and 3) effect of changing routes of administration (ID or IM) during a single course of PEP on the immunogenicity of PEP.

In assessing the studies, the WG considered that the current ACIP PEP schedules have not been problematic and that the cost considerations are less critical than they are for WHO. The expectations for ideal data if changes are proposed would include a high seroconversion rate (~100%), effectiveness for all population types, a large number of subjects, impact of RIG on antibody levels considered, vaccines used in the US, the ability to convert the route of administration to an IM recommendation since that is what is used in the US, and whether the animal causing the exposure should be confirmed to be rabid in situations where titers are not evaluated if PEP was administered after an exposure. Based on the studies assessed pertaining to the schedules reviewed that involved potential improvement from the existing 4-dose series, each of the 3 relevant studies[26] involved an ID [0, 3, 7 day] schedule, so the entire PEP series would be completed within a week. However, each of the studies involved a 4-site intradermal series, which is difficult to convert to intramuscular. They also involved purified vero cell rabies vaccine (PVRV), which is a cell culture vaccine that is thought to be equally efficacious to the vaccines available in the US, but is not available in the US. There were other issues such as only adults were evaluated, the impact of RIG on the series was not assessed, et cetera. For all of these reasons, the WG did not feel that a recommendation should be brought forward for shortening the series.

The main study[27] that informed WHO's recommendations was a 2-site each day study, so it was different from the 3 just described. That 2-site intradermal can be roughly translated to 1 dose IM, which is what the WG did when they had discussions with ACIP about the pre-exposure vaccination schedule. PVRV was used in this study, but the bigger issue here is that of the 2,805 subjects that were included in this study, only 129 of the ones who received the 3-dose series instead of a 4-dose series were people who had exposures to confirmed rabid animals. No titers checked in the study to confirm and the authors themselves recommended that a clinical follow-up system be adopted by rabies prevention centers, especially to monitor implementation of any abridged course, including the one that they described in their study. It is a balance of costs, resources, and feasibility. The authors of this paper mention that adopting this abridged series would result in 25% fewer costs and 33% more people treated with the same amount of vaccine. The benefits to the patient would be fewer patient resources and time spent for travel and loss in daily wages, less patient crowding in high throughput clinics, and increased equity. All of these issues are very important to the international population, but less so for the US. The low power for the outcome of importance also was noted by the authors of that systematic review.

The WG concluded that based on reviewing all of this information that more studies are needed before a change can be proposed to the current 4-dose IM series. The studies that they are hoping people will conduct are ones with the features that include a large number of subjects, a variety of populations (e.g., children of all ages), vaccines licensed in the US, either an IM or ID schedule that can be confidently extrapolated to a proposed IM schedule, evaluation of the impact of RIG on antibody titers, titers in human subjects after vaccination, and confirmation of rabies in the offending animal.

[26] Shantavasinkul 2010, Sudarshan 2012, Naranya 2015
[27] Tarantola 2019

As noted earlier, the October ACIP meeting will be dedicated to the WG speaking about clinical guidance issues pertaining to PEP, but they wanted to bring up one issue in case related discussion arose during this session. The ACIP has “General Best Practice Guidelines” for persons with altered immunocompetence. The clinician determines who is immunocompromised. For inactivated vaccines in immunocompromised persons, there are no safety concerns according to these best practice guidelines. However, the immune response may be inadequate. Therefore, options for pre-exposure rabies prophylaxis have been either to either delay PrEP until the person is no longer immunocompromised or consider avoiding activities for which rabies PrEP is indicated. Alternatively, if PrEP has to be administered, it can be administered per the same schedule as for healthy persons, but virus neutralizing antibody titers should be checked and boosters given if the titers are lower than the minimum antibody titer threshold.

The ACIP recommendations from 2008 still say to avoid immunosuppressive agents during the administration of PEP unless essential for the treatment of other conditions, and when PEP is administered to immunocompromised persons, one or more serum samples have to be obtained for rabies virus neutralizing antibody to ensure acceptable antibody response. The ACIP recommendations also say that if the titer is low upon checking, there needs to be consultation with public health. Public health typically recommends booster doses until adequate titers are reached. While some patients will require multiple titers, most do not. The 2008 ACIP recommendations actually recommended a 5-dose series, and the same PEP series was recommended for healthy persons and immunocompromised. A titer check after completion of the series was only recommended for immunocompromised, which is the same as what has always been the case. In 2010, there was an update prompted by a shortage in rabies vaccine. That updated process basically involved assessing the data for a 4-dose PEP series and found it to be effective. A 4-dose series replaced the 5-dose series for healthy persons, but there was not a change made to the immunocompromised group even though previously the recommendations for healthy persons and immunocompromised have been in sync. The only difference between the two was the requirement of the titer.

Therefore, the WG considerations is that for immunocompromised persons, ACIP has always recommended titer checks after completion of the series. More vaccine doses and more titer checks may be indicated accordingly, but since a titer check is needed regardless of what schedule an immunocompromised person receives, the WG brought up the idea of titer check with the fourth dose, which is sooner than the current guidance. That has advantages and is why it was proposed. It might spare some persons from unnecessary additional doses. The recommendations for healthy and immunocompromised persons would be similar except that the immunocompromised people would still need the titer check. There is expected to be no negative impact on patient care because that titer would still be used in order to determine whether additional doses should be given. The that the fourth dose is being recommended is that a person who gets PrEP can generate an animistic response in 2 to 3 days, but it usually takes longer for PEP. Because PEP is priming the immune response in a naïve person, it is a slower response but there is an immediate need for high neutralizing antibody levels, and the most people in clinical trials, including immunocompromised people, typically have titers that are at the appropriate level after 3 doses. That is why checking a titer with the fourth dose will probably spare a lot of people from getting additional doses. Additionally, the criteria of determining if somebody is immunocompromised is really dependent on the clinician, so checking a titer with the fourth dose would be done for all patients regardless of whether they are immunocompromised. This prevents people from getting an additional extra dose if not needed.

With that in mind, the proposed clinical guidance, for which an ACIP vote was not needed, would be as follows:

- ❑ Titers for immunocompromised persons should still be checked after completion of PEP series (as has always been recommended).
- ❑ Titer should be checked with fourth dose and decisions about additional doses made accordingly.
- ❑ Expedited titer checks occur when clinicians contact the laboratory where the titer check is occurring and indicate the importance for clinical decision-making. Titer check can often be completed within 48 hours. Clinician request is needed so that facility is aware.

It seemed like there was really no disadvantage to checking a titer with the fourth dose compared to after completion of a 5-dose series. Some people will require a fifth dose, but the WG's understanding from having spoken to a lot of people who work in these laboratories is that it is not all immunocompromised people will. Unfortunately, there are no good data that the WG could analyze to show that.

Rabies Pre-Exposure Prophylaxis: GRADE/EtR Summary

Dr. Agam Rao (CDC/NCEZID) pointed out that this presentation would be a review of the GRADE and EtR for the PrEP in children in anticipation of a vote later in the session. She basically reviewed all that was discussed during the previous APIC meetings in May and February 2021. As a reminder, the recommendations that passed in February were as follows:

- *ACIP recommends a 2-dose [0, 7 days] intramuscular rabies vaccine series in immunocompetent persons ≥18 years of age for whom rabies vaccine pre-exposure prophylaxis (PrEP) is indicated.*
- *ACIP recommends an intramuscular booster dose of rabies vaccine, as an alternative to a titer check, for immunocompetent persons ≥ 18 years of age who have sustained and elevated risk for only recognized rabies exposures (i.e., those in risk category #3 of rabies PrEP recommendations table*). The booster dose should be administered no sooner than day 21 but no later than 3 years after the 2-dose PrEP series.*

The wording for the proposed recommendations for this session's vote were identical to the language passed during the February meeting, except that they would be for persons <18 years of age. As a reminder, the most common reason that children require PrEP is travel to canine rabies-endemic countries. RIG is not available in some developing countries. Rabies vaccines may only be available in the capital city, resulting in a delay in PEP administration as people travel from rural areas to urban areas to get those vaccines. Children are at increased risk of multiple and severe bites, including to the face and neck for various reasons. An important consideration for PrEP in children is that the costs are usually out-of-pocket for persons who are getting them for travel purposes. Those can be very costly because the schedule recommends 3 doses of vaccine over the course of 21 to 28 days. That can be a large amount of money that is required in a short time period.

The number of people who receive PrEP is about 60,535 per year based on a mathematical model that was used with the help of research provided by Bavarian Nordic. Travelers and "other risk groups" are the largest groups at almost 41,000 of the people who get PrEP in a given year, so this is a very important issue. The conclusions from the presentation about rabies PrEP and children during the May ACIP meeting were that for primary immunogenicity purposes, there is no difference between that in children compared to adults for any given schedule based on the data that the WG presented. The WG showed data from various rabies vaccines and various schedules in children, with a broad range of children included. While it was difficult to ascertain in all of the papers, it appears that over 1,000 of those subjects were persons under 2 years of age and more than half were children under 1 year of age at the time of the first vaccine dose. The WG also showed 1 observational study included in GRADE table for 2-dose series showing that 190 (100%) children aged 5-13 years mounted titers ≥ 0.5 IU/mL cut-off after primary series, which was reassuring. In terms of long-term immunogenicity, titers in children may stay higher for longer. Since boostability is not a concern for adults, the WG thought it should not be a concern for children either.

In terms of the impact of a 3-dose series on PrEP administration, if someone's first travel clinic appointment is on a specific day, referred to as Day 0, when they receive the first dose but they are traveling to a developing country on Day 10 where canine rabies is endemic, this creates problems because rabies PrEP would typically be administered but is not because there is not enough time to give the 3-dose series because the third dose is on Day 21 or Day 28. If a hypothetical exposure occurs during that travel, RIG and a 4-dose PEP are indicated. However, there are some challenges with accessibility to this when traveling. With a 2-dose series of PrEP for children, the first dose of PrEP can be administered during the first appointment. Dose 2 could be given on Day 7 before the person travels. If risk continues for that individual beyond 3 years, they would have the option of the titer or the booster dose. The booster could be given after they return from travel or any point before 3 years. If they have a hypothetical exposure on their trip, they would only need the 2-dose vaccine and no RIG, which would make things a lot easier.

The implications of not aligning the adult and pediatric PrEP recommendations were also presented during the May meeting. Discordant recommendations could mean that parents may get vaccinated but children would not, and children are the ones who are believed to be at a greater risk than adults. It also would set up precedent. There are no previous rabies PrEP or PEP recommendations that have involved a different series for adults compared to children. This could result in people thinking that there is a concern about the number of doses for children when, in fact, the work group was not worried about that.

Moving to the EtR Framework, there were 2 policy questions. The first regarded whether a 2-dose PrEP series involving human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV) IM [0, 7 days] should replace the 3-dose series IM[0, 7, 21/28 days] for children for whom rabies vaccine PreP is recommended. For the PICO question, the population for the vote during this session was children for whom rabies vaccine PrEP is recommended. The intervention is a [0, 7 days] rabies vaccine PrEP schedule, the comparison is the current 3-dose [0, 7, 21/28 days] rabies vaccine PrEP schedule, and the outcome was primary immunogenicity because there have not been safety concerns with these vaccines that have long been available on the US.

The problem is that rabies is nearly always fatal. PrEP is an important component of preventing human rabies in the US. The Yellow Book specifically mentions that children are at a particular risk for rabies because they have inquisitive nature and attraction to animals, might be unable to read behavioral cues from dogs and other animals, and might have an increased likelihood for severe bites to high-risk anatomic regions like the head and face because of their short stature. Children often travel to canine rabies-endemic regions, for example visiting grandparents. Rabies modern cell culture vaccines are very effective, which is why PrEP should be considered in children.

In terms of the EtR Framework, the benefits have been previously presented. Regarding benefits, the WG interpreted the desired anticipated effects to be minimal in that 100% of people seroconvert for the proposed and the previous schedule. Regarding harms, the WG determined that the undesirable anticipated effects would be minimal as there are no expected safety concerns. For the benefit to harm ratio, the WG favored both because they are minimal for both. Regarding the overall certainty of the evidence, the WG found that there was moderate certainty of the evidence, or Level 2, due to concerns for risk of bias.

To present some of the information for the GRADE table, the WG identified two studies in its systematic review. There were 2 RCTs that compared a 2-dose to a 3-dose primary series. Across both studies, 100% of participants met the outcome of interest. There was unclear reporting of randomization and allocation concealment in both trials, which led to some concerns with risk of bias. The WG also looked into observational studies and identified 10 additional studies that compared a 2-dose to a 3-dose primary series. They treated these as observational studies even though they were originally designed as randomized trials because they broke this randomization to extract the pertinent data. The quality of the studies were evaluated with the Newcastle Ottawa Scale. There were minimal concerns identified in 3 of these studies and no concerns identified in the rest. The concerns for risk of bias were factored into the GRADE table. Dr. Rao highlighted the studies in the observational data that included people who were close to the age of children. The lower limit was 18 years of age in the Cramer paper, 17 in Jaijaroensup paper, and children were 5-13 years of age in the Sabchareon paper.

The Sabchareon paper included 190 school children who received HDCV. After the [0, 7 days] series, 100% of those children had antibody titers ≥0.5 IU/mL. Relevant to this conversation is that 0.5 IU/mL is roughly what the previous ACIP recommendations might come out to. As previously discussed, the ACIP guidance will state that ≥0.5 IU/mL going forward will be the minimum antibody titer. For the GRADE assessment for the outcome of immunogenicity as measured by a titer at or above ≥0.5 IU/mL, the WG assessed the body of evidence from the RCTs and the non-randomized studies separately. Because of the concerns with unclear reporting of randomization and allocation of concealment, the WG rated the RCTs down for risk of bias, but had no other concerns of the certainty of the evidence. This is how they landed on a moderate level, or Level 2 certainty about immunogenicity. All of the 264 persons in the 2-dose arm and 3-dose arm achieved 100% seroconversion. For the certainty level in the evidence of immunogenicity for the non-randomized studies, because the randomized trials had a Level 2 level certainty, the WG did not have to do the GRADE table for the observational studies, but did go forward with that because there was 1 study that involved children. It was comforting to see that the WG found the certainty to be Level 3 because these started as non-randomized studies and therefore started at a Level 3. The WG had no additional concerns and no reasons to upgrade. Therefore, it remained at the Level 3 certainty level.

Moving to the remainder of the EtR values, the WG determined that the target population feels that desirable effects are large relative to undesirable effects of being vaccinated from rabies. In terms of values, the WG determined that there is not important uncertainty about or variability in how much people value the main outcomes. The target population values protection of children from rabies because this population is at higher risk than adults during travel. The WG determined that the intervention acceptable to key stakeholders, given that the shorter schedule is preferred by patients and providers and will enable more children to be vaccinated before risky travel. For resource use, the WG ascertained that the intervention is a reasonable and efficient allocation of resources because travel vaccination costs are typically out-of-pocket. Fewer doses results in lower costs for individuals, and rabies vaccine shortages have occurred in the US. Therefore, using fewer doses will result in efficient allocation of resources. With regard to the impact on health equity, the WG thought that probably equity would be increased because of decreased costs. The WG though that the intervention would be feasible to implement because a shorter series than the current series would be easier to implement before travel. The balance of consequences led to the WG to conclude that the desirable consequences clearly outweigh undesirable consequences in most settings and that the WG preference is for intervention.

Now moving to the second recommendation to be voted on pertaining to long-term immunogenicity. The policy question regards whether an IM booster dose of rabies vaccine (PCECV or HDCV) should be recommended as an alternative to a titer check no sooner than day 21 and no later than 3 years after the 2-dose PrEP series IM [0, 7 days] for children in the #3 risk category of people who receive PreP. Again, the population is children in the #3 risk category, travelers who might be visiting grandparents or have some other reason they might be repeatedly going back to a country with canine-endemic rabies beyond the 3 years from their primary vaccination. The intervention is Day 21 to Year 3 for a rabies vaccine booster after the [0, 7 days] days rabies vaccine PrEP schedule. The comparison is no rabies vaccine booster after the [0, 7 days] rabies vaccine PrEP schedule, and the outcome is long-term immunogenicity.

The problem here is that some children make trips to developing countries beyond 3 years. Immunology suggests that they would have an anamnestic response if an exposure occurred beyond 3 years. The WHO approved a 2-dose series for this population without titers or boosters for this population, but the WG wanted to be as conservative as possible to ensure long-term immunogenicity for the [0, 7 days] series. There are no data beyond 3 years, but there are strong data for long-term immunogenicity up to 3 years. There are data showing that the titer at ≥ 1 year is a marker of long-term immunogenicity, which is why the WG put of all these pieces of information together to propose a titer at 1-3 years. If the titer is ≥0.5 IU/mL, nothing would need to be done. If it was lower, the child would be boosted and confirmed to have had an appropriate response. For people who would just like to cut to the chase and get straight to the booster dose, they could get a booster or that third dose. It can be considered like a flexible 3-dose schedule for what is currently recommended. They could get the vaccine as soon as day 21, which would make it the same as the currently recommended 3-dose series. Or they could wait until much longer up to 3 years potentially defraying costs.

As mentioned previously, there are hopefully data evaluating long-term immunogenicity coming to show that a 2-dose series might be enough. Meanwhile, a study was published in January 2021 in a very small group of people.[28] There were 6 persons (3 male, 3 female) 34-46 years of age who received the [0, 7 days] IM series and were evaluated after 10-11 years. Of the participants, 5 had titers ≥ 0.5 IU/mL before a booster was given and all 6 had a 4-fold increase in titers after a booster. More data are expected about long-term immunogenicity from Europe because of the WHO recommendations made in 2018 for a 2-dose series. Until then, the plan is to have the proposed second recommendation.

In terms of the EtR Framework domains, the WG determined the desired anticipated effects for the benefits to be moderate. Flexibility in receiving that titer check and only a booster if indicated versus a booster over a broad time period (i.e., as soon as day 21 and as late as 3 years) would provide flexibility. 100% of subjects mounted an anamnestic response to a booster at 1 to 3 years. The WG determined the undesirable anticipated effects to be minimal because there are no expected safety concerns. The benefit to harm ratio favors the intervention. The overall certainty for the evidence is Level 3, or low certainty of evidence. The same 2 studies that were included for the previous GRADE table also were included in this study. For the outcome of duration of immunogenicity as measured by a titer of ≥ 0.5 IU/mL after a booster dose, the best available evidence came from the single arms of 2 trials and therefore was treated as non-randomized. No additional concerns existed with the body of evidence. The WG selected Level 3 because the data were observational.

Going back to the EtR Framework and the target population sentiments, the WG said that the target population probably feels that the desirable effects are large relative to the undesirable effects, because stakeholders want to avoid acquiring high-stakes infections. Children have many more years ahead of them and might make future travel plans. A booster provides reassurance that outweighs any inconvenience. The WG determined that there are no important uncertainty about or variability in how much people value the main outcomes. The target population values protection from rabies and there is likely no important variability. The WG felt that the intervention would be acceptable to stakeholders because stakeholders are accustomed to accommodating a third dose of rabies vaccine as is currently the schedule, particularly given the flexibility for when that booster can be given. The WG thought that this intervention would be a reasonable and efficient allocation of resources. Persons who do not have sustained risk for rabies will not require the booster. It is only the people who have sustained risk. Additionally, because of the flexibility in the time point for this booster, it can be arranged at a time when there is no shortage of vaccines.

In terms of the equity domain, the WG felt that the impact on health equity would be increased because some PrEP costs are out-of-pocket. Because titer is offered as an option, inequity could be resolved by choosing that option. Additionally, children without sustained risk for rabies will not need that booster or titer and those who do require it could defer receiving and paying up to 3 years later, diffusing the costs over a longer time period. The WG felt that the intervention is feasible to implement. Administrators could opt to schedule a booster dose at the time of primary vaccination if there is a concern for travelers not remembering to receive the booster dose. In terms of the balance of consequences, the WG felt that the desirable consequences clearly outweigh the undesirable consequences in most settings and indicated a preference for the intervention.

[28] De Pijper et al, Long-term memory response after a single intramuscular rabies booster vaccination, 10-24 years after primary vaccination. Journal of Infectious Diseases. Epub January 2021.

Discussion Summary: Rabies Vaccines

- Regarding an inquiry about whether there is any information on duration of time between bite and presentation that would impact the administration of the immunoglobulin just at the site versus at the site and elsewhere to improve the systemic number of antibodies, Dr. Rao indicated that it takes some time before whatever virus is at the inoculation site travels upwards. No limit has been provided to when rabies PEP can be administered after an exposure occurs. However, RIG should be administered within 7 days of the rabies vaccine since the RIG can bind to the antibodies in the vaccine and result in lower antibody levels than would otherwise occur. There is really no value to RIG administration beyond 7 days because humoral immunity would have mounted at that point.

- In terms of an inquiry about the steps that must be taken to expedite a titer check, particularly given that rabies is fatal, Dr. Rao indicated that there are 3 main locations that do these titer checks: Atlanta Health Associates, Kansas State University, and the CDC. All of these facilities routinely complete rapid turnarounds as part of their normal process.

- Concern was expressed that the titer check could create inequity and could create barriers to getting the vaccine, so it would be helpful to know the percentage of people who are immunocompromised and what their titers are like. Dr. Rao noted that the WG tried to collect such data, but the laboratories that are performing this testing do not get information about the patient. The WG talked during the February meeting about the cost of the titer being around $50 or $75 and about the additional costs for the clinic appointment to get blood draws, et cetera. That is compared to the cost of the vaccine, which is a lot more expensive than that. From an equity standpoint, the WG felt that it would be preferable to check titers with the fourth dose instead of waiting until after the fifth.

- Given the paucity of data on immunocompromised persons, ACIP emphasized that mechanisms by which some research could be conducted would be extremely helpful.

- The International Society of Travel Medicine (ISTM) pointed out that in the past, travelers who could not receive a full series prior to traveling typically would decline to receive any of the vaccine. Having this alternative schedule in which it would be possible for people to receive 2 doses in this way is anticipated to increase the uptake overall of vaccine among those who could benefit from it.

- AAP pointed out that children could fall into more than Risk Category #3. The WG will modify the table to indicate that children could fall into any of the risk groups.

Vote: Rabies Vaccines

Dr. Agam Rao (CDC/NCEZID) presented the WG's proposed language for the 2 recommendations to be voted upon:

> Recommendation #1
> *ACIP recommends a 2-dose [0, 7 days] intramuscular rabies vaccine series in immunocompetent persons <18 years of age for whom rabies vaccine pre-exposure prophylaxis (PrEP) is indicated.*

Recommendation #2

ACIP recommends an intramuscular booster dose of rabies vaccine, as an alternative to a titer check, for immunocompetent persons < 18 years of age who have sustained and elevated risk for only recognized rabies exposures (i.e., those in risk category #3 of rabies PrEP recommendations table. The booster dose should be administered no sooner than day 21 but no later than 3 years after the 2-dose PrEP series.

Motion/Vote: Rabies Vaccines

Dr. Poehling made a motion to approve both of the proposed recommendation for rabies vaccines. Dr. Sanchez seconded the motion. No COIs were declared. The motion carried with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

14 Favored:	Ault, Bahta, Bernstein, Chen, Daley, Frey, Kotton, Lee, Long, McNally, Poehling, Romero, Sanchez, Talbot
0 Opposed:	N/A
0 Abstained:	N/A
0 Absent:	N/A

Discussion Points

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

Dr. Long emphasized that when the stakes are so large, it makes it harder to reduce a vaccine schedule. ACIP is frequently accused of only adding and not taking away. With the careful and surprising amount of data that were gathered on children, she felt very comfortable with this recommendation and was very happy that every once in a while they can do this.

PUBLIC COMMENTS

The floor was opened for public comment during the June 24, 2021 ACIP meeting at 3:45 PM ET. Given that many more individuals registered to make oral public comments than could be accommodated during this meeting, selection was made randomly via a lottery. The comments made during the meeting are included here. Members of the public also were invited to submit written public comments to ACIP through the Federal eRulemaking Portal under Docket No. CDC–2021–0034. Visit http://www.regulations.gov for access to the docket or to submit comments or read background documents and comments received. A single voting session was held after the public comment session was completed for votes on Dengue, Influenza, and Rabies recommendations. However, the votes have been included with their respective sessions for ease of reading. The public comments were as follows:

Mr. Chuck Sheldon, BA, MA
Concerned Individual

My name is Chuck Sheldon. I want to address the mRNA COVID vaccines. I have a BA and MA in biology and years of medical research at Stanford. This committee did exemplary work yesterday examining most of the COVID vaccine benefit-risk equation. Yet, risks of an mRNA vaccines to some groups, such as minors, pregnant women, and the unborn, are still largely unknown since: 1) all of the trials have been very short; 2) most trials have excluded children and pregnant women; and 3) many trials no longer have controls, which are essential to real science. So, I ask you, have we here neglected the unknown risks? Some scientists see risks that may seem too terrible to contemplate, but nevertheless, are this committee's responsibility on behalf of all Americans. For example, has anyone here studied or proved whether the spike proteins generated by the mRNA vaccines could act as prions in the brain? Logically, that kind of risk should vastly outweigh the virtually non-existent risk of COVID-19 in almost everyone under age 30. Let's consider collective immunity. Immunization may not be able to achieve collective immunity without those who choose not to participate, but low-risk collective immunity can be achieved via both children and adults as follows. First, most teenagers and children can contribute essentially risk-free by passively tolerating natural COVID-19 infection, which poses almost no risk to them in the absence of underlying conditions. Second, those adults who passively become infected will contribute via natural immunity and can protect themselves from serious adverse effects by using known effective countermeasures, both prophylactically and as early treatments, usually at home. Proven effective protocols include nutraceuticals, zinc, vitamin D, and glutathione and the off-label use of HCQ (hydroxychloroquine) or ivermectin. Both have ample safety records and have been found very effective with early treatment against COVID-19, with 64%-78% symptom reduction and 72%-81% mortality reduction. This is based on ample studies. In round numbers, HCQ has had 3,000 studies with 400,000 participants in 150 RCTs. Ivermectin has had to 250 studies with 20,000 patients and 35 RCTs. These figures are available to anyone at C19early.com. C19early.com. In most cases, COVID disease with these early interventions does not require hospitalization, thus conserving critical resources. In summary, even taking public health risks into consideration, those under 30 have effective and far safer alternatives to using mRNA vaccines. We all do. Please protect our young people by weighing the risks based on the scientific method, by not relying on trials that lack proper controls and by not excluding unknown risks.

Ms. Jenifer Vincent
Concerned parent & Community Member

Good afternoon and thank you for taking my comment. My name is Jennifer Vincent and I'm calling from California. I have a medical and a scientific background. Today, however, I'm commenting as a parent and a community member. I'm asking this committee to suspend the interim authorization or COVID vaccines for youth ages 12 and older and to not authorize COVID vaccines for younger children until long-term safety studies have been completed. Children are not the primary source of transmission of COVID-19. They have a 99.99% chance of surviving COVID-19. There is no emergency in regard to COVID-19 in children. Additionally, they have successful treatments available, although those treatments have been purposefully suppressed. I find this committee quick to say that side effects are a rare occurrence. However, it's only rare until it happens to your child or loved one. The news media and social media are filled with first-hand accounts of youth and adults with severe side effects, including deaths, attributed to COVID-19 vaccines. No sooner do Facebook, Instagram, YouTube, or Google delete one than a new one pops up. More and more physicians and scientists are coming forward to express their concerns about the safety of these vaccines in larger safety studies. But

again, these doctors' voices are silenced by the media—I suspect at the urging of the pharmaceutical industry. People are not given proper informed consent and do not understand that these vaccines are only authorized under emergency use. They don't understand that they are now part of a long-term safety study. Several states, including California, are using coercion to get people to take these experimental vaccines. Do the physicians on this committee feel it's ethical to pay people to take a vaccine that could potentially kill them? I have no confidence in any of the COVID vaccines. I've seen dozens of news reports about large numbers of fully vaccinated people testing positive for COVID-19. Despite the committee's statements that the benefits outweigh the risks of COVID vaccination, I would argue that none of the vaccines are safe or effective. Our children are not data points. They're living, breathing human beings. I will not allow any of my children to get a COVID vaccine until many long-term safety studies have been done. I implore you to error on the side of caution for your fellow citizens, for our children, and not the pharmaceutical industry that donates heavily to the CDC Foundation. Please suspend interim authorization for youth ages 12 and older and do not authorize COVID vaccines for younger children until long-term safety studies have been completed. Thank you very much for your time.

Ms. Lori Ciminelli
Concerned Citizen

A perversion of public health ethics has occurred. This past week, the CDC diverted an established need of discovery on why 1,200 under 30-year-olds, primarily males, were acquiring myocarditis and pericarditis following administration of the Pfizer-BioNTech and Moderna COVID vaccine, publicly stating a rescheduling concerning this discussion due to observation of Juneteenth National Independence Day. I fail to believe that even one celebratory participant of Juneteenth would say, "Postpone these young people if they're coming heart inflammation interrupts our celebration." The WHO's and CDC's own statistics show that the African-American population have been disproportionately affected by this pandemic. Yet your excuse of whatever reason to postpone investigation is given as justifiable by the Juneteenth celebration. Really? Though myocarditis and pericarditis in young people under 30 is not relevant over a national holiday, I'd like the data of new cases in the pause that you chose to take. Your own quotes dismissed 1,200 incidents of heart inflammation by claiming it is rare, with over 300 million shots given. This is where verbiage is essential. It's not 300 million shots administered in this age group, but as of May, it was 600,000 shots. See how the math works you give? I certainly did. Some of these youth remain hospitalized—some in ICU. But as always, the CDC is tramped in the greater good concept of public health, whereas this population doesn't even carry a huge risk factor compared to other populations and similar age groups. This young population were absent of comorbidities—basically healthy. This is a humanity issue now. The greater good is unacceptable, while a twisted campaign of the CDC's recommendations are shouted, jingles changed often, pop-up vaccine centers in our stores, schools, places of worship dot the landscape. Censorship is executed on any scientist, doctor, or citizen who dares question your voting personnel. We're declared misinformed. My God teaches me that we are all equally valuable in his sight. If one is in danger, he leaves the 99 and helps that one. Twelve-hundred young humans matter. Unfortunately, my prior experience observing you tells me that only the greater good matters to you and you will permit this vaccine to continue its post-market status surveillance. You can stop this now and do the right thing. These young people have faces, they are loved, and they matter.

Mr. Kermit Kubitz
Individual

Hello, I am Kermit Kubitz and I want to congratulate the ACP and its members on the success of the review of vaccines for COVID-19 and support expansion of indicated populations to teens and others. As a result of the EUA for Pfizer and Moderna and rapid vaccination updates, overall COVID-19 cases in the US have been declining since January 2021. The San Francisco VA Hospital where I was vaccinated was doing 400 veterans a day beginning in January. Vaccination of more than 170 million people has allowed the economy to recover, businesses to reopen, band concerts in the Corte Madera Town Park to resume, and monthly breakfasts to restore a sense of community at my American Legion Post in Lordsburg, California. My two sisters over 80 have been successfully vaccinated, but my nearly 90-year-old brother still resists vaccination due to misinformation. The unvaccinated are still at risk. The number of Utah residents in the hospital is rising, while Dr. Russell Vinik of University of Utah Health notes that nearly everyone in the hospital with COVID has not been vaccinated. The Cleveland Clinic study recently released found that more than 99% of patients hospitalized with COVID-19 weren't fully vaccinated. Sixty to 65% of patients in the ICU at Mercy Hospital in Springfield, Missouri were under 40. Young people must get vaccinated. The ACIP is also considering influenza formulations for the next flu season. The occurrence of a cluster of oseltamivir resistance and antigenically drifted influenza H1N1 cases suggest the need for continuously monitoring and attention to influenza. It also suggests the need for universal flu vaccine. Recent studies suggest that chimeric hemagglutinin-based universal influenza vaccine may be in sight. NIH and other government agencies should aggressively pursue a universal flu vaccine with adjuvants if necessary to prevent new variants of H1N1, H5N1, H3N2, or other variants from becoming public health threats. See clinical trial NCT-033-0050. The ACIP should also return to the topic of widespread hepatitis vaccines, which is highly transmissible. Keep up the good work ACIP and CDC to stem the current pandemic and prevent future public health threats. Thank you.

Rishanne Golden
Haleigh's Heart

I name is Rishanne Golden. I'm the mother of two and my husband and I are the founders of Haleigh's Heart established after the death of our 20-year-old daughter, Haleigh, stolen 950 days ago from vaccine-induced grand mal seizures. Our days since are full of agony, but Haleigh's journalistic voice remains alive at haleighheart.com. Your recommended poison forever changed Haleigh's life and our family's life. Nearly 5 years ago, we became informed and versed in a horrific truth intentionally hidden from the public. Unlike those paid to speak and counteract our realities, there countless parents, families, and medical doctors who have for years brought to your attention the slaughter and death taking place daily. Yet, you arrogantly ignore and adamantly deny the immense loss and heartache happening to innocent children and adults. Legions have brought you the witnessing of ongoing horror and agonizing loss, and still, you all choose to do nothing, only sometimes commenting, "I'm sorry for your loss," which means nothing without action and meaningful change. Science confirms almost 80% of SIDS cases happen when multiple vaccines are given on the same day, and public-funded studies show children live in aluminum toxicity with the government repeatedly refusing to do the studies or adhering to its own safety guidelines. Your silence and continued lack of conscience, as witnessed again yesterday, makes each of you complicit of murder, the unlawful killing of another from extreme and reckless disregard for life that results in death. Haleigh's beautiful life mattered, as do the countless others senselessly injured and tragically stolen. For years, this committee has been made fully aware of the truth brought before you repeatedly and today, my

family and hundreds and thousands of others in this growing community stand together. We declare, “No more.” We have been lied to for decades, but we are well-versed and very knowledgeable. We wear God’s armor and we are prepared for this battle you created. We wear the belt of truth, the shoes of peace, the shield of faith, the helmet of salvation, the sword of the spirit, and we are strong in wisdom, truth, and love that comes only from goodness. I will pray for each of you, for I am to pray for my enemies. But remember each time you cash your paychecks, you bring home blood money. Each time you get the opportunity to hug a loved one, you remember my Haleigh, my family, and the countless others not able to do the same because of your recommendations increasingly mandated without exemption. A business owner of 27 years, I am now a certified natural health practitioner and soon a practicing naturopath, which means I’m a teacher and I assure you and those alike that I will teach truth about humans who are wonderful, and fearful, and remain in support of nature’s treasures, having no need for your liability-free neurotoxic poisons that bring in trillions for fraudulent makers and their cohorts. Your days of abuse, neglect, and tyranny are soon coming to an end. In closing, it is through our shattered hearts that we choose truth and kindness to honor our loved ones and want each of you to make things right. For you, too, will someday stand before your maker and give account to the monumental injuries and massive deaths of God’s children and that you were told about but repeatedly chose to ignore and disregard. May God help you all.

FRIDAY: JUNE 25, 2021

WELCOME AND INTRODUCTIONS

Dr. José R. Romero (ACIP Chair) called to order and presided over the meeting. He conducted the roll call during which no conflicts 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.

ZOSTER VACCINES

Introduction

Dr. Grace Lee (ACIP, WG Chair) presented

Burden of Herpes Zoster in Immunocompromised Adults

Dr. Tara Anderson (CDC/NCIRD) presenter

Use of Recombinant Zoster Vaccine in Immunocompromised Populations: Overview of Clinical Program

Ms. Robyn Widenmaier (GSK) presenter

Discussion Summary: Zoster Vaccines

PNEUMOCOCCAL VACCINES

Introduction

Dr. Kathy Poehling (ACIP, WG Chair) presenter

Updates on Epidemiology of Invasive Pneumococcal Disease in US Adults

Mr. Ryan Gierke (CDC/NCIRD) presenter

Cost-Effectiveness of PCV15 and PCV20 Use in US Adults

Dr. Charles Stoecker (Tulane University) presenter

GRADE for Age-Based PCV15 and PCV20 Use in US Adults

Ms. Jennifer Farrar (CDC/NCIRD) presenter

EtR Summary of Age-Based PCV15 and PCV20 Use in US Adults

Dr. Miwako Kobayashi (CDC/NCIRD) presenter

Summary and Timeline

Dr. Miwako Kobayashi (CDC/NCIRD) presenter

Discussion Summary: Pneumococcal Vaccines

CERTIFICATION

Upon reviewing the foregoing version of the June 24-25, 2021 ACIP meeting minutes, Dr. José R. Romero, ACIP Chair, certified that to the best of his knowledge, they are accurate and complete. His original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

ACIP MEMBERSHIP ROSTER

CHAIR
ROMERO, José R, MD, FAAP
Arkansas Secretary of Health
Director, Arkansas Department of Health
Professor of Pediatrics, Pediatric Infectious Diseases
University of Arkansas for Medical Sciences
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ACRONYMS USED IN THE DOCUMENT

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ABCs	Active Bacterial Core Surveillance
ABM	Agent-Based Model
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
ADH	Arkansas Department of Health
AE	Adverse Event
AHIP	America's Health Insurance Plans
AI	Autoimmune
AI/AN	American Indian or Alaskan Native
AIM	Association of Immunization Managers
AIRA	American Immunization Registry Association
AMA	American Medical Association
AMI	Acute Myocardial Infarction
AOA	American Osteopathic Association
APhA	American Pharmacists Association
APRN	Advanced Practice Registered Nurse
ASTHO	Association of State and Territorial Health Officers
auHSCT	Autologous Hematopoietic Stem Cell Transplant
BLA	Biologics License Application
BPAC	Blood Products Advisory Committee
ccIIV4	Flucelvax Quadrivalent
CDC	Centers for Disease Control and Prevention
CER	Cost-Effectiveness Ratio
CISA	Clinical Immunization Safety Assessment
CLIA	Clinical Laboratory Improvement Amendments
CMC	Chronic Medical Condition
CMI	Cell-Mediated Immunity
CMS	Center for Medicare and Medicaid Services
CNS	Central Nervous System
COI	Conflict of Interest
COID	Committee on Infectious Diseases
COPA	Communities Organized to Prevent Arboviruses
CSTE	Council of State and Territorial Epidemiologists
DFO	Designated Federal Official
DMARD	Disease Modifying Antirheumatic Drugs
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DSTDP	Division of STD Prevention
DVA	Department of Veterans Affairs
DVD	Division of Viral Diseases
ED	Emergency Department
EHR	Electronic Health Record

ELISA	Enzyme-Linked Immunosorbent Assay
ET	Eastern Time
EtR	Evidence to Recommendation
FDA	Food and Drug Administration
FQHC	Federally Qualified Health Centers
GBS	Guillain-Barré Syndrome
GMT	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
HAI	Hemagglutination Inhibition Assay
HCP	Healthcare Personnel / Providers
HCT	Graft Versus Host Disease
HCW	Healthcare Workers
HDCV	Human Diploid Cell Vaccine
HHS	(Department of) Health and Human Services
HIV	Human Immunodeficiency Virus
HM	Hematologic Malignancies
HRSA	Health Resources and Services Administration
HSCT	Hematopoietic Stem Cell Transplant
HSCT	Hematopoietic Stem Cell Transplant
HZ	Herpes Zoster
IC	Immunocompromised
ICD	International Classification of Diseases
ICD-10-CM	International Classification of Diseases 10 Clinical Modification
ICER	Incremental Cost-Effectiveness Ratio
IDSA	Infectious Disease Society of America
IgG	immunoglobulin G
IHS	Indian Health Service
IIS	Immunization Information System
IIV	Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
IM	Intramuscular
IMD	Immune-Mediated Disease
IPD	Invasive Pneumococcal Disease
IS	Immunosuppressive Therapy
ISD	Immunization Services Division
ISO	Immunization Safety Office
JHU	Johns Hopkins University
LAIV	Live Attenuated Influenza Vaccine
MI	Multiple Imputation
MMWR	*Morbidity and Mortality Weekly Report*
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization Canada
NANASP	National Association of Nutrition and Aging Services Programs
NAPNAP	National Association of Pediatric Nurse Practitioners
NBP	Nonbacteremic Pneumonia
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCHS	National Center of Health Statistics
NCIRD	National Center for Immunization and Respiratory Diseases

NEJM	*New England Journal of Medicine*
NFID	National Foundation for Infectious Diseases
NIH	National Institutes of Health
NMA	National Medical Association
NNDSS	National Notifiable Diseases Surveillance System
NNV	Number Needed to Vaccinate
NOCD	New Onset Chronic Disease
NPV	Negative Predictive Value
OID	Office of Infectious Disease
OIDP	Office of Infectious Disease Policy and HIV/AIDS
OPA	Opsonophagocytic Activity
PCECV	Purified Chick Embryo Cell Vaccine
PCP	Primary Care Provider/Practitioner
PCV13	13-Valent Pneumococcal Conjugate Vaccine
PCV15	15-Valent Pneumococcal Conjugate Vaccine
PCV20	20-Valent Pneumococcal Conjugate Vaccine
PEP	Post-Exposure Prophylaxis
PHAC	Public Health Agency Canada
PHN	Postherpetic Neuralgia
PhRMA®	Pharmaceutical Research and Manufacturers of America®
PICO	Population, Intervention, Comparison, Outcomes
PIDS	Pediatric Infectious Disease Society
PIHOA	Pacific Island Health Officers Association
PPSV23	23-Valent Pneumococcal Polysaccharide Vaccine
PPV	Positive Predictive Value
PRDoH	Puerto Rico Health Department
PrEP	pre-exposure prophylaxis
PVRV	Purified Vero Cell Rabies Vaccine
QALY	Quality Adjusted Life Year
RCT	Randomized Controlled Trial
RHC	Rural Health Clinic
RT	Renal Transplant
RT-PCR	Reverse Transcription Polymerase Chain Reaction
RZV	Recombinant Zoster Vaccine
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts
SAHM	Society for Adolescent Health and Medicine
sBLA	Supplemental Biologics License Application
SCDM	Shared Clinical Decision-Making
SHEA	Society for Healthcare Epidemiology of America
SME	Subject Matter Expert
SOT	Solid Organ Transplant
STM	Solid Tumor Malignancies
SVI	Social Vulnerability Index
TMLE	Targeted Maximum Likelihood Estimation
UAMS	University of Arkansas School for Medical Sciences
UGA	University of Georgia
US	United States
USG	US Government

USVI	US Virgin Islands
VA	(US Department of) Veteran's Affairs
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VFC	Vaccines for Children
VIS	Vaccine Information Statement
VPCI	Vaccine Policy Collaborative Initiative
VRBPAC	Vaccine and Related Blood Products Advisory Committee
VSCDA	Vintage Sports Car Drivers Association
VSD	Vaccine Safety Datalink
WG	Work Group
WHO	World Health Organization
ZVL	Zoster Vaccine Live