

# MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

**MAY 5, 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 the regularly scheduled quarterly meeting of the Advisory Committee on Immunization Practices (ACIP) on May 5, 2021. The meeting took place remotely via Zoom and teleconference. This summary document provides a brief overview of the meeting, which focused on the topics of rabies vaccine and dengue vaccine.

## WEDNESDAY: MAY 5, 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 one potential conflict of interest (COI) was declared by voting member Dr. Camille Kotton, who served on a data safety monitoring board (DSMB) for pneumococcal vaccine for Merck. A list of Members, *Ex Officios*, and Liaison Representatives is included in the appendixes at the end of this summary document.

**Dr. Amanda Cohn** (ACIP Executive Secretary) welcomed everyone and noted that an agenda for the day soon would be posted to the ACIP website. She indicated that the next virtual Emergency ACIP meeting was scheduled for May 12, 2021. She explained that there would be an oral public comment session at approximately 1:00 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-2021-0025. Further information on the written public comment process can be found on the ACIP website. As noted in the ACIP Policies and Procedures manual, ACIP members agree to forgo participation in certain activities related to vaccines during their tenure on the committee. For certain other interests that potentially enhance a member's expertise, CDC has issued limited conflict of interest (COI) waivers. Members who conduct vaccine clinical trials or serve on 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, and no votes were taken during this meeting.

### RABIES VACCINE

#### Introduction

**Dr. Sharon Frey** (Chair, ACIP Rabies WG) introduced the Rabies Session during which she provided an update on the activities of the Rabies Vaccines Work Group (WG). To recap the WG's activities during the February 2021 ACIP meeting as they related to Pre-Exposure Prophylaxis (PrEP), the WG addressed questions raised by the ACIP about PrEP costs; summarized clinical guidance presented at previous meetings; and recapped policy questions, evidence tables, and Evidence to Recommendation (EtR) Frameworks. Additionally, the ACIP committee requested a fourth group to be added to the PrEP table so that persons with risk for rabies  $\leq 3$  years would be included in their own risk category. Also during that meeting, ACIP

voted on 2 PrEP policy questions for persons  $\geq 18$  years of age and deferred the vote for persons  $< 18$  years of age to a future ACIP meeting.

Dr. Frey shared/reviewed the new table with the fourth group added. The first two groups include individuals with elevated risk for unrecognized and recognized exposure. The difference between the first two groups is that the risk of virus exposure is continuous in the first group and episodic in the second group. The third group has elevated risk of a recognized exposure that is sustained. The fourth group has elevated risk of recognized exposure that is not sustained. The fifth group was the group that was requested to be added during the February 2021 ACIP meeting, which is at low risk of contracting rabies (i.e., the general population).

Since the last ACIP meeting, the WG continued to discuss topics related to PrEP and post-exposure prophylaxis (PEP), including discussing questions raised by the ACIP about rabies PrEP and children. In addition, they discussed communication of updates to the 2008 ACIP recommendations according how, when, and through what channels to make these communications to stakeholders and how to ensure communications are clear and can be smoothly implemented by end-users. Specific to PEP, the WG discussed which additional topics should be considered by the WG. For example, they are looking at immunogenicity in children and may look at immunogenicity in the elderly.

The WG's goal for this session continued along the same lines for PrEP, with presentation of the data reviewed by the WG about PrEP and children, presentation of the two policy questions voted on during the February meeting for adults and the proposed questions for children in anticipation of a vote during the June 2021 ACIP meeting. In addition, this session included a presentation of background information about PEP and a general approach to PEP. In terms of the anticipated timeline, the WG anticipates entertaining an ACIP vote on PrEP as it relates to children; presenting the WG's interpretation of data about Rabies Immune Globulin (RIG) and PEP schedules, including Grading of Recommendation Assessment, Development and Evaluation (GRADE) and EtR during the June 2021 ACIP meeting; and presenting clinical guidance PrEP and PEP schedule deviation. This work may continue into October 2021 depending upon what transpires.

### **Rabies PrEP in Children**

**Agam Rao, MD** (CAPT, USPHS; Co-Lead Rabies ACIP WG; CDC/NCEZID) presented on rabies PrEP in children. There are multiple levels to prevent human rabies in the US, including avoidance of risky behavior such as avoiding international tourist destinations that are known to have rabid animals, vaccination of pets and wildlife, and proper use of personal protective equipment (PPE) when handling bats for occupational responsibilities. Over the course of a lifetime, the average person in the US has no rabies exposures simply because these measures are in place. Therefore, the average person has no need for PrEP. If those barriers fail, there is PEP. PEP involves rabies immune globulin and an affordable vaccine series. Prompt and appropriate PEP alone and response for an exposure is typically enough to save lives when an exposure occurs. While PrEP is indicated for specific populations in the US, this does not negate the need for PEP if an exposure occurs.

The ACIP does not recommend PrEP for the general US population. It is given before an exposure, but does not negate the need for PEP if an exposure occurs and is indicated for only select populations and for specific reasons. There are 3 reasons that PrEP is recommended for select populations. The first is that when rapid PEP administration is not enough. This can occur when someone is exposed to an extremely high concentration of rabies virus exposure or an unusual rabies virus exposure like an aerosolized exposure. Aerosolized exposures do not occur naturally. They typically would occur only within a laboratory under unusual circumstances. Second are unrecognized rabies exposures. These can happen when, for example, someone who frequently interacts with bats and frequently feels them brushed up against them may not realize when they have had a bite from a bat. That can go undetected, given that a very small puncture wound from a bat tooth is only about 2 to 10 millimeters and the bite strength is approximately 2 pounds of pressure. Someone might awaken from sleep and not realize they have been bitten, or a biologist might enter a high-density bat environment like a bat cave may not find it atypical when they get swarmed by bats. The third reason that PrEP is recommended for select populations is challenges with the access to PEP. RIG is not available in some developing countries. Rabies vaccines may be available only in a capital city of a developing country, resulting in a delay of PEP administration. For that reason, travelers, particularly children, are recommended to get PrEP.

In recognized exposures, the reason for PEP is clearly different from the previous reasons mentioned and the primary reason that children ever would receive PrEP. A sequence of events for many travelers illustrates what could happen to a traveler. An ideal scenario would be one in which someone receives a bite from a rabid dog while within the capital city of a developing country, quickly receives thorough wound washing with soap and water, and has quick access to PEP. While PEP should be administered promptly, there is no specified time period within which PEP should be administered after an exposure. The ideal scenario is for a person in a capital city with access to RIG and vaccine to complete the entire series by Day 45. The problem occurs when someone is visiting/bitten in a rural area and does not begin traveling to a major city where PEP is available until the following day and it may take a significant period of time before they can actually identify a source for rabies vaccine and there may not even be RIG available, which would delay their care. It is for the second scenario that rabies PrEP is recommended. The Yellow Book specifies that PrEP should be recommended for travelers based on the occurrence of animal rabies in the country of destination; availability of anti-rabies biologics; intended activities of the traveler, especially in remote areas; and the traveler's duration of stay. Children, in particular, should be offered PrEP when indicated. PrEP in children is an important issue. The Yellow Book states the following:

“Children are at higher risk for rabies exposure and subsequent illness because of their inquisitive nature and inability to read behavioral cues from dogs and other animals. The smaller stature of children makes them more likely to experience severe bites to high risk areas, such as the face and head. Also contributing to the higher risk is their attraction to animals and the possibility that they may not report an exposure.”<sup>1</sup>

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<sup>1</sup> \*Yellow Book; <https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/rabies>; accessed on 4/20/21

The benefits of receiving PrEP is that no RIG is needed if an exposure occurs. Only a 2-dose PEP vaccine series is needed once an exposure occurs. Those are given on Day 0 and Day 3 instead of the 4-dose PEP rabies vaccine series which is given at Days 0, 3, 7, and 14. This can be beneficial for travelers to some developing countries where RIG may not be available, where the rabies vaccines may take time to access, and where a 2-dose series is easier to get than a 4-dose series because of travel itineraries.

The WG clearly recognizes that children and rabies represent an important issue. For that reason, they took the approach of setting some expectations for what they would consider to be acceptable in a PrEP series. First, primary immunogenicity had to be demonstrated by given series. That is, the minimum acceptable antibody titer threshold would have to be reached within 14 days of series completion. Second, the WG determined that a high proportion of patients will have to achieve primary immunogenicity. The rationale behind this point was that if primary immunogenicity or seroconversion is achieved after completion of the vaccine series and an exposure then occurs, there will be a rapid anamnestic response. This anamnestic response would occur regardless of the time from PrEP to exposure. As long as primary immunogenicity was reached, the WG could be confident that an anamnestic response would occur after an exposure.

The WG felt that factors that do not impact an anamnestic response are the number of vaccine doses over that needed to achieve primary immunogenicity, the number of bites or scratches to a patient, the severity of bites or scratches, the location of those, and the size of the exposed person. Anamnestic response is an all-or-none response that occurs quickly after an exposure. That is why the number of vaccine doses to push the titer up higher than the minimum antibody titer does not contribute to the response. Recognizing that children are an important population for rabies PEP, the WG considered whether there is any reason to believe that children have a different response to rabies vaccines than adults. To that end, the WG performed a systematic review in 2019 to determine if pediatric response to various rabies vaccine series is inferior to that of adults. Over 12 papers were identified from multiple databases that met the WG's search criteria. Of those, 7 involved children <2 years of age and 7 involved children 2-18 years of age. The age ranges of the patients were 2 months to 17 years. The WG concluded that geometric mean titers (GMTs) in children are the same or higher than those in adults for any given series. In addition, GMTs stay higher for longer in children. Thus, there is no reason to suspect suboptimal immunogenicity in children compared to adults.

To point out a few key items in the manuscripts reviewed by WG that indicated robust response in children, diverse ages are represented in these manuscripts. The first study by Chatchenet et al (2017) involved children <2 years of age and there were 68 subjects. This study concluded that comparison to 18-24 year old subjects in Thailand studied similarly, "these findings suggest that the immune responses of the toddlers were better than those of young adults." This is evidence for long-term induction of protective antibodies by PrEP.<sup>2</sup> The second study by Fridell et al (1984) had children <5 months of age to 15 years of age. This study concluded that, "There was good antibody response with titers (EU/mL) higher than those in adults."<sup>3</sup> The third study by Kamoltham et al (2011) included 703 children aged 5 to 8 years. In this study, 100% of children had titers >0.5 IU/mL at 1, 3, and 5 years after ID booster to 2 or 3

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<sup>2</sup> Chatchenet et al; 2017 "Long-term protective rabies antibodies in Thai children after pre-exposure rabies vaccination"; SE Asian Journal of Trop Med & Public Health

<sup>3</sup> Fridell et al (1984) "Pre-exposure prophylaxis against rabies in children by human diploid cell vaccine"; Lancet

dose ID primary series 14 days after booster and that this was safe and immunogenic.<sup>4</sup> The remaining studies and numbers of children in each are listed below:

- ❑ Lang et al (1999 and 1997): 84 Vietnamese children 24 months of age<sup>5</sup>
- ❑ Lang et al (1999): 240 children in Vietnam who were 2, 3, and 4 months of age<sup>6</sup>
- ❑ Kamoltham et al (2007): 206 school-aged children in Thailand<sup>7</sup>
- ❑ Lang et al (2009): 72 children 2, 3, 4 months and 1 year<sup>8</sup>
- ❑ Li et al (2015): 243 children 6 to 17 years of age<sup>9</sup>
- ❑ Pengsaaet al (2009): 200 healthy children aged 12 to 18 months in Thailand<sup>10</sup>
- ❑ Sabchareonet al (1998): 190 school children aged 5 to 12<sup>11</sup>
- ❑ Sabchareonet al (1999): 400 schoolchildren; 100% of children had titers >0.5 IU/mL at day 21 (i.e., 14 days after the 2nd vaccine)<sup>12</sup>
- ❑ Shanbaget et al (2008): 175 school children 6 to 13 years of age; 100% had RVNA concentrations above 0.5 IU/mL after completion of the 3 dose series<sup>13</sup>
- ❑ Vienet et al (2008): 4 to 8 months primary series and 16 to 20 months later; all children mounted an anamnestic response to challenge<sup>14</sup>

The WG came away from this convinced of the conclusions that have been made in the Yellow Book stating that, “Pregnancy is not a contraindication to PEP. In infants and children, the dose of HDCV or PCEC for preexposure or PEP is the same as that recommended for adults. The dose of RIG for PEP is based on body weight (Table 4-18)” and also in the 2008 ACIP recommendations stating that, “Children should receive the same vaccine dose (i.e., vaccine volume) as recommended for adults.” Notably, the reason that there are so many very young included in some of these studies is that the idea of introducing rabies vaccine PrEP into the routine childhood vaccine series was being considered. That is why the vaccination schedule for children has not deferred for from those for adults.

<sup>4</sup> Kamoltham et al; 2011 “Immunogenicity of simulated PCECV Post-exposure doses 1, 3, and 5 years after 2-dose and 3-dose primary rabies vaccination in schoolchildren; *Advances in Preventive Medicine*

<sup>5</sup> Lang et al; 1999 and 1997 “Booster vaccination at 1 yr with rabies vaccine associated with DTP-IPV in infants living in rabies endemic country” *Journal of tropical pediatrics* “Randomized feasibility trial of pre-exposure rabies vaccination with DTP-IPV in infants” *The Lancet*

<sup>6</sup> Lang et al; 1999 “Immunogenicity and safety of low-dose ID rabies vaccination given during an Expanded Programme on Immunization session in VietNam: results of a comparative randomized trial; *Transactions of the Royal Society of Tropical Medicine and Hygiene*

<sup>7</sup> Kamoltham et al; 2007 “Pre-exposure Rabies Vaccination Using Purified Chick Embryo Cell Rabies Vaccine Intradermally is Immunogenic and Safe.” *Journal of Pediatrics*

<sup>8</sup> Lang et al; 2009 “Pre-exposure purified vero cell rabies vaccine and concomitant routine childhood vaccinations: 5-year post-vaccination follow-up study of an infant cohort in Vietnam” *Journal of trop Pediatrics*

<sup>9</sup> Li et al; 2015 “Immunogenicity and safety of purified chick-embryo cell rabies vaccine under Zagreb 2-1-1 or 5-dose Essen regimen in Chinese children 6-17 yrsold and adults >50 yrs: a randomized open-label study *Human vaccines and immunotherapeutics*

<sup>10</sup> Pengsaa et al; 2009 “A Three-Year Clinical Study On Immunogenicity, Safety, and Booster Response of Purified Chick Embryo Cell Rabies Vaccine Administered Intramuscularly or Intradermally to 12- to 18-Month-Old Thai Children, Concomitantly With Japanese Encephalitis Vaccine” *Pediatric Infectious Diseases Journal*

<sup>11</sup> Sabchareon et al; 1998 “Persistence of antibodies in children after ID or IM administration of PrEP primary and booster immunizations with purified Vero cell rabies vaccine.” *The Pediatric Infectious Disease Journal*

<sup>12</sup> Sabchareon et al; 1999 “A New Vero Cell Rabies Vaccine: Results of a Comparative Trial with Human Diploid Cell Rabies Vaccine in Children” *Clinical Infectious Diseases*

<sup>13</sup> Shanbag et al; 2008 Protecting Indian schoolchildren against rabies: pre-exposure vaccination with purified chick embryo cell vaccine (PCECV) or purified verocellrabies vaccine (PVRV); *Human Vaccine*

<sup>14</sup> Vien et al; 2008 Long-term anti-rabies antibody persistence following intramuscular or low-dose intradermal vaccination of young Vietnamese children *Transactions of the Royal Society of Tropical Medicine & Hygiene*

After the WG confirmed that the approach was that any PrEP schedule recommendations made for adults would be applicable to children as well, they presented the following 2 recommendations to the ACIP (as a reminder, ACIP voted on and passed both of these recommendations for persons  $\geq 18$  years of age only):

1. ACIP recommends a 2-dose [0, 7 days] intramuscular rabies vaccine series in immunocompetent persons for whom rabies vaccine pre-exposure prophylaxis (PrEP) is indicated.
2. ACIP recommends an intramuscular booster dose of rabies vaccine, as an alternative to a titer check, for immunocompetent persons 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's thought process in developing this first recommendation was that with the primary [0, 7 days] IM series there are robust data demonstrating the boostability for up to 3 years. This was presented in the GRADE table during the October 2020 and February 2021 ACIP meetings. The advantages for travelers, including children, are that travelers typically do not have enough time to receive the 3-dose series because Dose 3 is due no sooner than Day 21. Often, travel medicine clinic appointments are not scheduled far enough in advance to get the third dose. It is known from the travel experts who served on the WG that in many cases, they do not initiate PrEP because they cannot complete the entire series. Another advantage for travelers is that the proposed recommendation is believed to facilitate more travelers getting vaccinated when it is indicated to do so.

To highlight a couple of key items from the previously presented GRADE and the EtR, the evidence profile in the GRADE assessment for the outcome of "immunogenicity" as measured by a titer  $\geq 0.5$  IUs/mL, the WG assessed the body of evidence from randomized controlled trials (RCTs) and not non-randomized study separately and concluded that there is moderate certainty (Level 2) about immunogenicity for the RCTs. A total of 264/264 people seroconverted with the [0, 7 days] series compared to the [0,7, 21,28 days] series that also achieved 100% seroconversion. The WG could have stopped at that because the certainty was Level 2; however, they moved forward to evaluate the observational studies identified in the search as well.

For PrEP Policy Question #1, the WG identified 10 additional studies that compared a 2-dose to a 3-dose primary series. The mean age of children in the Sabchareon et al (1999)<sup>15</sup> was 10 years of age, with a range of 5 to 13 years of age. The intervention included 190 persons. After a [0, 7 days] series, 100% of these children had antibody titers  $\geq 0.5$  IU/mL and 100% had titers  $\geq 0.15$  IU/mL. The reason the authors included both  $\geq 0.15$  IU/mL and  $\geq 0.5$  IU/mL was because they estimated that  $\geq 0.15$  IU/mL was closer to the ACIP recommendation for the minimum antibody titer level. However, the ACIP is planning to move toward the  $\geq 0.5$  IU/mL as well. Regardless, this study showed that appropriate titers were reached 100% of the time in these children.

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<sup>15</sup> Sabchareon A, Lang J, Attanath P et al. A new vero cell rabies vaccine: Results of a comparative trial with human diploid cell rabies vaccine in children. Clin Infect Dis. 1999; 29: 141-9.

The WG's thought process for the second recommendation was that based on what is known about immunology, there is every expectation that boostability is preserved beyond 3 years. However, because rabies is nearly 100% fatal and ACIP advised the WG during previous meetings to ensure that there were robust data for any proposed change to the existing recommendations, the WG took the very conservative and cautious approach. The WG knows from the data they have reviewed that the titer value at 1-3 years is indicative of long-term titer levels. A titer check and booster if titer is under cut-off at 1-3 years will ensure long-term immunogenicity and provide that extra level of certainty. Additionally, since the titer level has been raised to  $\geq 0.5$  IU/mL, this option will ensure high titers. The WG also wanted to make sure that a booster can be given as an option instead of a titer check, given the realization that some people will prefer a booster dose rather than waiting for a titer check and then potentially having to wait additional time to get a booster anyway. The booster can be given as soon as Day 21 and as late as Year 3, given the current scheduling of the 3-dose PrEP series. The evidence table for duration of immunogenicity has a certainty of Level 3.

In summary, the WG reviewed the primary immunogenicity of rabies vaccine in children. There was no difference between primary immunogenicity in children compared to adults, including for young children, for any given schedule. For the specific schedule proposed to the ACIP, the WG had data from one observational study that involved the proposed PrEP series and US rabies vaccine. That study showed that 100% of the children aged 5 to 13 years of age mounted titers over the  $\geq 0.5$  IU/mL cut-off after the primary series. Regarding long-term immunogenicity, several of the same studies that the WG evaluated to understand rabies vaccine in children showed that titers in children may stay higher for longer. Since boostability is not a concern for adults, the WG concluded that it would not be a concern for children.

The implications of not aligning the recommendations for children and adults was discussed by the WG. The thought was that ACIP recommendations for PrEP have always been the same for children and adults. If this new precedent is set, adult travelers may get a 2-dose [0, 7 days] IM series before travel. Child travelers belonging to the same family may not have enough time for the 3-dose series and may not get vaccinated at all. The end result would be that adults will have received PrEP and children will not have received PrEP, even though the children are the population at higher risk. Therefore, the WG proposed the same two recommendations to the ACIP that were voted on and passed during the February 2021 ACIP meeting, but for persons under 18 years of age as shown here:

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.
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 an 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.



## **Summary of Discussion**

- ACIP requested a breakdown of the number of children under 2 years of age who were included in the 12 studies reviewed by the WG. Dr. Rao indicated that the exact number could be calculated for the June 2021 ACIP meeting.
- Dr. Kimberlin (AAP Redbook) thanked CDC and the WG for a much more robust presentation about what is known of use of rabies vaccines in children. He recalled raising a personal concern during the February 2021 ACIP meeting. He emphasized that this could be considered a flexible 3-dose schedule such that the booster can be given as soon as 21 Days following the primary PrEP series of the 2 doses, assuming this is extended down to children. This made him more comfortable compared with the issues he personally raised previously. He expressed gratitude for the thorough assessment and concise presentation made between last time and this session.
- On behalf of the American Academy of Pediatrics (AAP), Dr. Maldonado expressed appreciation to the ACIP and the investigators for addressing the concerns and questions the AAP's Committee on Infectious Diseases (COID) had, and for the added information. The COID had a robust discussion during their recent committee meeting and felt comfortable with the data as presented. The COID raised the same issues around advising its pediatric providers regarding these new recommendations so that they are clear on the pediatric traveler.

## **Background and Approach to Rabies PEP**

**Dr. Rao** (CAPT, USPHS; Co-Lead Rabies ACIP WG; CDC/NCEZID) next presented the components of rabies PEP, summarized the role of rabies epidemiology in decisions about PEP, and described a proposed approach to PEP for clinicians. For persons who have not previously received PEP or PrEP, PEP in response to an exposure involves RIG and 1 dose of vaccine soon after the exposure, which is referred to as "Day 0." To complete the series, the patient receives 3 more doses of vaccine on Days 3, 7, and 14. A previously vaccinated person is defined in the 2008 ACIP recommendations as a person who received either: 1) one of the recommended PrEP regimens of human diploid cell vaccine (HDCV), purified chick embryo cell vaccine (PCECV), or rabies vaccine adsorbed (RVA)—all of which are cell culture vaccines known to be safe and efficacious; 2) one of the recommended PEP regimens of HDCV, PCECV, or RVA; or 3) another vaccine and had a documented rabies virus neutralizing antibody titer afterward. The implications of being previously vaccinated on PEP management is that it eliminates the need RIG entirely and decreases the number of PEP vaccine doses. Someone who is considered previously vaccinated needs only to receive 2 doses of rabies vaccine given on Day 0 and Day 3. RIG is not indicated and the number of vaccine doses shortens from 4 doses to 2 doses and is completed sooner.

There are a lot of complexities that go into who should receive PEP. The challenges of determining who should receive PEP is perhaps best illustrated by the large amount of PEP that is used in the US to prevent human rabies, with approximately 55,000 people receiving PEP each year in the US. The impacts of this are unnecessary administration of vaccines, the high costs associated with these vaccines and with rabies immune globulin in particular, emotional distress involved in a patient believing that they have been exposed to a high mortality illness and need to receive these vaccines in order to prevent death, and less availability to persons who need it during vaccine shortage events. There are just 2 papers that describe inappropriate

and appropriate administration of PEP in the US.<sup>16, 17</sup> They both evaluated whether the ACIP recommendations were followed and found that PEP was sometimes inappropriately administered. The Moran et al paper published in 2000 was a prospective case series study of patients presenting with an animal exposure related complaints from July 1996-September 1998 at 11 university-affiliated urban emergency departments (EDs) as part of the EMERGENCY ID NET. The authors found that 40% of cases of PEP administration were inappropriate, owing often to factors associated with an incorrect understanding of the role of rabies epidemiology and clinician decisions about PEP. The Moran et al study also found that in 6% of cases, PEP was inappropriately withheld due to misunderstandings about circumstances for which PEP should be administered. Recognizing that it can be confusing for clinicians to know which exposures were at PEP, Dr. Hunter suggested during a previous ACIP meeting over a year and a half ago that the WG consider outlining these considerations in the updated ACIP recommendations. The remainder of this presentation was the WG's effort to outline these considerations.

To do so, an understanding of rabies epidemiology was first presented to explain some of the fundamentals. Human rabies is transmitted from infected mammals by a bite, scratch, or contamination of mucous membranes or an open wound with saliva or neural tissue. It is not transmitted by exposures to blood, urine, or feces. Exposures to those should not warrant PEP. There have been some rare cases after organ and tissue transplants, but the remainder of this presentation focused on rabies after animal exposures. Few animal species are reservoirs for rabies (i.e., few species can sustain the circulation of rabies). Rabies virus variants (RVV) are named for the animal reservoir species in which their circulation is sustained, and RVVs are confined to geographically definable regions. However, it is important to understand that infection can be transmitted from the reservoir species to any other mammal and may not stay within the reservoir species. For example, the raccoon RVV can spread from a raccoon to a cat and then to a human. This specific RVV does not denote the animal to which the human was exposed, but rather the reservoir for that specific variant.

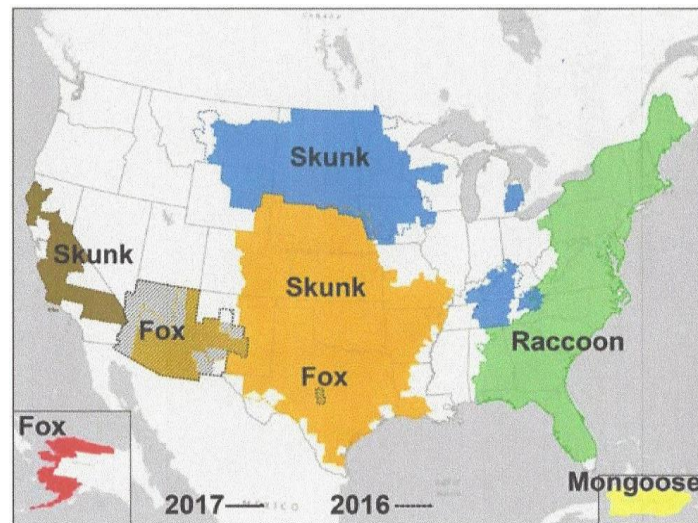
To illustrate host shift and effects on rabies epidemiology, raccoon RVV on the East Coast of the US spread to various unvaccinated animals through bites in 2014-2015. The rate of the raccoon RVV in Florida spread within this species. The variant circulated among raccoons and then built up in this highly susceptible host population such that it was transmitted to individual mammals in more resistant host populations of unvaccinated dogs, foxes, or skunks exposed to a raccoon through a bite. Host shift events can also occur with rabies. Cross species transmission occurs, sometimes all over the world, but nearly every time the virus dies out in the non-reservoir host. Occasionally, the virus gains foothold. Sometimes this is because the virus mutates and adapts to the new host and sometimes it is because the virus gets lucky and finds a host that is genetically primed for viral circulation. When this happens, it is referred to as a "host shift event."

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<sup>16</sup> Steinberg HD, Bemis K, Frias MM, Christiansen D. Inappropriate Administration of Rabies Postexposure Prophylaxis, Cook County, Illinois, USA. *Emerg Infect Dis.* 2020 Oct;26(10):2515-2517. doi: 10.3201/eid2610.200232. PMID: 32946729; PMCID: PMC7510732.

<sup>17</sup> Moran GJ, Talan DA, Mower W, Newdow M, Ong S, Nakase JY, Pinner RW, Childs JE. Appropriateness of rabies postexposure prophylaxis treatment for animal exposures. *Emergency ID Net Study Group. JAMA.* 2000 Aug 23-30;284(8):1001-7. doi: 10.1001/jama.284.8.1001. PMID: 10944646.

While it is hypothetical that a host shift event could occur from raccoons to skunks, it is of concern. The last time there was a host shift event was in the 1950s in Florida when a bat rabies virus shifted into the raccoon population, which is the reason there is raccoon RVV on the East Coast. This spread from Southern Florida into Canada and created what today is called the raccoon rabies variant and reservoir area. It is estimated that 75% of human and pet rabies exposures occur in this area largely due to the interactions with animals infected with this viral variant. This illustrates why it is very important to understand the epidemiology. This map illustrates the different RVVs and geographic regions of the US:



Raccoon RVV in the Eastern part of the US is a result of the post-shift from bats. There are 3 skunk RVV delineated in brown, orange, and blue as a result of host shifts from dogs or bats. There are mongoose and fox RVV as well. This illustrates that mammal reservoirs vary by geography. Terrestrial (wildlife) rabies is due to the RVV for which wildlife are the reservoir. Non-terrestrial rabies is the RVV for which bats are the only reservoir. Terrestrial rabies is restricted to the regions colored on this map. Non-terrestrial rabies is in all US states except Hawaii, which is free of all rabies. An understanding of the biogeography of rabies is essential to clinical decisions about whether a specific exposure warrants rabies PEP. For example, a bite from a raccoon in Washington State may be managed differently from a raccoon bite in Pennsylvania. One region has only non-terrestrial rabies and the other has a lot of raccoon RVV.

Fortunately, despite inappropriate PEP use in the US, there still are relatively few cases of rabies in humans for the time period of 2009-2020. There were 25 human cases of rabies among persons in the US, of which 17 occurred due to domestic exposures and 8 occurred from international exposures. Among the 17 domestic exposures, 12 were bat RVV, 3 were raccoon RVV (including kidney donor and recipient), 1 was mongoose RVV, and 1 was unknown RVV. Of the 8 international, 7 were due to dogs (Philippines, Guatemala, Brazil, Afghanistan, Haiti, India) and 1 was bat RVV (Mexico). A rabid dog has not been a source of human rabies after domestic exposure for a very long time because canine rabies has been eliminated in the US. None have been due to occupational exposures or in people who received PrEP or PEP during the time period 2009 to 2020.

Differing epidemiology in the 50 US states is one of the reasons that drafting a one-size-fits-all PEP algorithm is challenging. Concern for an exposure in a terrestrial rabies region differs from that in a non-terrestrial rabies region, and rabies vectors and RVV differ by region. In addition, health departments in different regions of the country have differing management styles for these exposures. For example, health departments can differ in recommendations about PEP after an exposure in regions without Fox RVV. As another example, many (but not all) health departments advise against PEP for exposures to squirrels, chipmunks, and mice. Given that some regions have had occurrence of rabid squirrels, a general national algorithm advising against PEP after section exposure would be too simplistic.

The differences in health department guidance are impacted by the degree of oversight and case management of animal bite investigations. Guidance on health department websites can vary as well. Some health department sites provide detailed and complex algorithms recommending or not recommending PEP depending on various characteristics of the exposure, while others provide limited online guidance and recommend consulting the health department for case-by-case advice. The comprehensiveness of online guidance also can differ. Some of them omit guidance about caged rabbits, hamsters, and other so-called “pocket pets.” Others provide a very long list of animals that could be risky. Since health departments are an incredible resource and a huge source of thorough details about the local biogeography, creating a national algorithm would overstep and result in confusion since some health departments provide more information than others on their websites. Those that do not provide information on their websites expect one-on-one consultation.

Beyond rabies epidemiology, there are other issues considered by health departments when advising against PEP. The WG took those into consideration in addition to the expertise that the health departments have about local rabies, biogeography, and the benefits of a general framework so that clinicians could understand what factors should be considered before giving PEP in an attempt to balance the two. The WG tried to balance providing some sort of general framework for the clinician so that they realized what factors were important, but also not providing too prescriptive a guidance since there are a lot of nuances that go into a decision about whether someone should receive PEP.

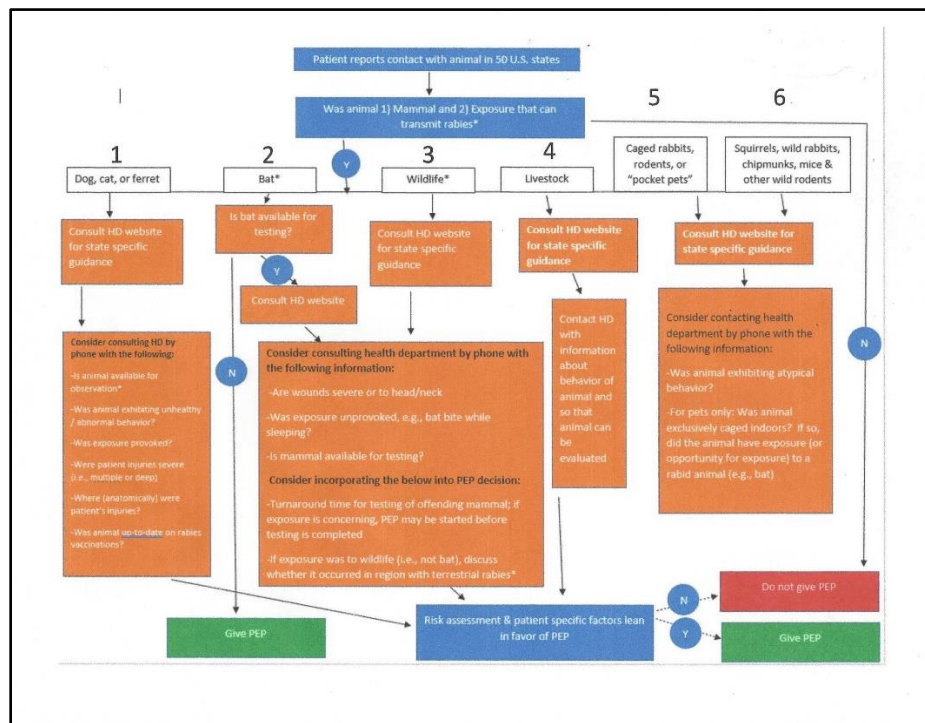
In terms of a general approach to PEP, the WG’s objective was to enable clinicians to handle “easy” cases quickly, with no need to contact the health department. The approach is intended to defer to the health department for guidance for the most definitive answers. Consultations with health department are known to decrease the odds of inappropriate PEP administration by 87%.<sup>18</sup> Therefore, taking that away would not be good. The WG also wanted to outline the multiple considerations needed for decisions about PEP depending upon the exposure type. Clinicians should be able to collect the important history before the health department consultation to understand the factors that weigh into the decision, participate in the decision-making, and be better able to counsel affected patients.

The 2008 ACIP recommendations considerations when making a decision about whether to give PEP, including: 1) whether it was a bite or non-bite exposure, the type of animal to which the exposure occurred (bat, domestic dog, cat, ferret) or wild animals; 2) local animal rabies epidemiology; and 3) the circumstances of the biting incident in terms of whether it was provoked or not provoked, the behavior of the animal, and the vaccination status of the exposing animal. Table 3 in the 2000 ACIP recommendations details animal types, evaluation

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<sup>18</sup> Steinberg HD, Bemis K, Frias MM, Christiansen D. Inappropriate administration of rabies postexposure prophylaxis, Cook County, Illinois, USA. *Emerg Infect Dis.* 2002 Oct; 26 (10): 2515-2517

and disposition of the animal, and the PEP recommendations. Taking all of that into consideration (health department consultation, local biogeography, clinician understanding), the WG drafted the following algorithm that Dr. Rao walked through step-by-step:



Exposures outside of the 50 US states are more challenging. There are approximately 30 known reservoirs for rabies worldwide, including mongoose, dog in a canine rabies endemic region, bats outside of the US, monkeys, and exotic animals (Australian Dassie). Given that it is very difficult to develop any kind of algorithm for these cases, the WG concluded that the general guidance should be to consult the health department for case-specific advice and to collect information about the type of exposure, whether an exposure was provoked or not provoked, and the behavior of the animal and take those cases directly to the health department for case-by-case consultation.

In summary, the WG determined that deciding which human exposure necessitates PEP can be very challenging. The health department has a critical role in the US and consultation is available, including during off hours for consultation about complex cases. They really are the experts in local biogeography and also are the ones who can facilitate laboratory testing and animal observations if needed. At the same time, based on feedback the WG received from previous ACIP meetings and from some clinicians, some sort of framework or general algorithm could be useful to clinicians and would not replace the nuanced advice from public health veterinarians that is listed on their websites or that may be obtained through one-on-one consultations. The WG was somewhat split about whether the proposed algorithm would be helpful, but thought it might be of some benefit to provide this general guidance and request input from the ACIP.

## **Summary of Discussion**

- Some ACIP members were much less worried about overuse of prophylaxis than underuse. Whatever diagram, chart, or recommendation ACIP puts forth should err on the side of caution since this is a fatal disease and it is preventable. While it is okay to test the animal, if someone cannot be reached for 48 to 72 hours, it should be clear that it is okay to start prophylaxis and then perhaps stop it if it turns out not to be appropriate.
- The algorithm could be helpful in that some patients/clinicians may not know that local biogeography is important in deciding whether to administer PEP or that they should consult with the local health department. The algorithm, review of the health department website, and potentially a consult with the health department could arm the clinician with enough information to make decisions for the patient sitting in front of them.
- Some concern was expressed that in certain circumstances, the algorithm may complicate rather than simplify the guidance. For instance, there has not been any evidence of transmission from squirrels on the West Coast so the risk is extraordinarily low. Yet, the algorithm could give the impression that clinicians/health departments should be thinking through every squirrel, mouse, or wild rodent bite. They certainly do not want the algorithm to create unintended consequences in which health departments are inappropriately consulted for every squirrel bite.
- Physicians/clinicians liked the algorithm and thought that it would be useful, but suggested that it needed to be more nuanced. While some thought it seemed somewhat complex as a rabies decision support tool, rabies consultations are probably one of the most common consultations that state and local health departments get and CDC also receives a lot of calls:
  - Given that some of these questions arise in the middle of the night when not everybody is answering phone calls, the algorithm could be very helpful to at least get through the night.
  - It would be helpful to highlight the importance of consulting the health department website for state-specific guidance for each of the 6 animal categories. CDC/ACIP certainly do not want to negate the health department's advice, so including something like that for every category makes sense.
  - Sentiment was expressed that there is a necessity/responsibility in state and local health departments to be able to respond in any hour of the day or night. One model is the Arkansas Health Department, which has a veterinarian who is specifically tasked with receiving these calls 24/7 for her to adjudicate the exposure.
  - Perhaps there could be a national automated decision support tool, such as the poison control hotline, readily accessible for patients.

## **Next Steps**

**Dr. Rao** (CAPT, USPHS; Co-Lead Rabies ACIP WG; CDC/NCEZID) recapped the WG's next steps. In terms of ongoing WG discussions, there are some newly licensed RIG products since the 2008 ACIP recommendations were published. There is also a lot of discussion internationally about the location of RIG administration. The World Health Organization (WHO) changed their recommendations during their most recent update to limit RIG administration to just infiltration around the wound and to not give the remainder intramuscularly. The WG has

been discussing the data surrounding those issues and will present on them at the next meeting. The number of doses for the PEP vaccine series is constantly being evaluated. WHO shortened the number of PEP vaccine doses from a 4-dose series to a 3-dose series. The WG is aware that the considerations for ACIP will be different and that there will need to be a lot of robust data to confirm long-term immunogenicity since PEP is used as the equivalent of PrEP for any subsequent exposure and would need to be boostable if given years previous to an exposure so that the patient could only get a 2-dose vaccine series. The WG is evaluating the available data in order to present the WG interpretation to the ACIP during the next meeting.

There are also numerous clinical guidance topics under discussion, some of which need modification/updates of wording or phrasing in the ACIP recommendations. Topics include PrEP and PEP schedule deviations; PEP initiated abroad (e.g., administered intradermally, with vaccine unavailable in US, or according to schedule not outlined by ACIP); excessive RIG use; and theoretical concerns about administering PEP in a patient with rabies symptoms. The WG has been discussing the plan for implementation of updates. They realize that clear messaging must be drafted for the updated recommendations. There are many stakeholder questions, so discussions have begun about how to engage with stakeholders (e.g., professional societies, public health veterinarians, travel medicine providers) to ensure that implementation strategies are in place and revisions are clear. The CDC rabies website needs to be updated with clear guidance, and consultation support will need to be provided to clinicians and health departments when recommendations are published.

During the June 2021 ACIP meeting, the WG plans to present the proposed votes on the two PrEP questions for children; the WG's interpretation of data on RIG and PEP schedules (GRADE and EtR if WG proposes change); and clinical guidance issues identified as frequently asked of health departments and CDC, which could be clearer in the ACIP recommendations.

### **Public Comments**

The floor was opened for public comment during the May 5, 2021 ACIP meeting at 1:00 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-2021-0025. Visit <http://www.regulations.gov> for access to the docket or to submit comments or read background documents and comments received.

#### **Peter Sears, MD Premise Health**

Yes, thank you for having me. I'm a board-certified family physician and been in practice for about three years. And first off, I just want to thank the committee for having me and also thank you for your [inaudible], which has greatly contributed to the US having an extremely safe vaccine supply. So, thank you for your tireless effort. I want to discuss, as you all know, the FDA is set to approve the Pfizer SARS-CoV-2 vaccine hopefully early next week. I just wanted to sort of encourage all my fellow colleagues in pediatrics and family medicine who work with kids of what the critical role children in this population are going to play in achieving herd immunity and how important it is for us to communicate that to the parents of our children. And keep in mind, children under 15 make up approximately 20% of the general population in the United States and it's going to play a critical role, we as clinicians, in helping to achieve herd immunity in the fight against SARS-CoV-2. And as well, I think it's really important that we stay abreast and up-

to-date on things out there and in the social media about concern the parents have about long-term effects, infertility effects, DNA changing, all the things [inaudible]. We need to be able to discuss and address these concerns with our parents in a thoughtful and encouraging fashion and be able to alleviate their concerns as to why these are not issues that they need to be concerned about, but in a way that is understanding toward the parents and empathetic of their concerns. And just wanted to again just encourage us all to know what a critical role we're going to play amongst this pediatric population, as well as adults, as well as the general population as well, of course. And finally, I just also wanted to address the issue of concerns of falling behind on the routine schedule during this pandemic just to remind how important it is for us all to remain vigilant that our patients don't fall behind on the CDC recommended schedule. But again, once again, thank you so much for allowing me to comment and I will leave it at that.

**Sarah Barry**  
**Concerned Citizen**  
**Independent Pro-Vaccine Advocate**

Hello, my name is Sarah Berry. I am an independent pro-vaccine advocate and online I go by the name "42believer." In my first public comment, I talked about how anti-vax lobbyists attempted to censor my testimony. In my second, I began to touch on the rampant abuse of autistic children within the anti-vaccine community. At the risk of sounding like a broken record, I must return to that awful subject as I inform you all about MMS. MMS stands for Miracle Mineral Solution and has long-been touted as a cure-all by a cult known as the Genesis II Church of Health and Healing. Unfortunately, MMS is in fact a type of bleach and is very dangerous for consumption, obviously. The leaders of the cult were finally arrested after claiming that MMS could cure COVID-19, but unfortunately for hundreds of autistic children, that arrest came far too late. It was through the efforts of Kerri Rivera that the book "Healing the Symptoms Known As Autism" was published, giving a detailed guide on how to administer MMS orally, topically, and rectally for the purposes of healing/curing autism. It was through my efforts that I was able to get that book "Healing the Symptoms Known As Autism" banned from sale from Amazon back in 2019. It is disturbing to know that this book was for sale at all—that anti-vaxxers seem to not even notice that such a horrible cure could be touted within their community. I have seen Kerri Rivera present several years at a very well-known autism anti-vax convention called AutismOne. Even after Kerri Rivera was banned from the State of Illinois by the Attorney General from promoting MMS, AutismOne still brought her back to speak virtually, kind of getting around the rules so to speak, because even though MMS is bleach and that is an absolute fact, people in the anti-vax community are unwilling to grapple with this concept that this is abuse. I have actually had to contact Children's Services multiple times because I truly believe it's a fact that giving MMS to an autistic child or an autistic adult is abuse. It's medical abuse. It's neglect you could even say. And unfortunately, all three of those instances where I reported the caregiver, none of those ever resulted in action or removal of the autistic child from that home. So again, I just need to stress that this is a very large part of the anti-vaccine community. It is easier to convince people that anti-vaxxers are wrong if you talk about the side of the community. Until anti-vaxxers grapple with this disconnect, I'm going to continue talking about this problem. Thank you.



## DENGUE VACCINES

### Introduction

**Dr. Wilbur Chen** (ACIP, WG Co-Chair) provided an introduction to the Dengue Vaccines session, extending gratitude to the ACIP members and other members and consultants who have been seminal in the WG's discussions. He noted that for Dengvaxia® (CYD-TDV), the pivotal licensure efficacy data were generated in 2015. This resulted in the WHO's Strategic Advisory Group of Experts (SAGE) making the initial recommendation for the use of this vaccine in May 2016 among individuals 9-45 years of age in high prevalence areas. In 2017, there was disclosure of new information about this vaccine from a case-cohort study showing increased risk of severe dengue among persons who are seronegative prior to vaccination and then have subsequent infection. In April 2018, SAGE revised their recommendations to state that a pre-vaccination screening strategy must be formulated so that only dengue seropositive persons would be vaccinated. In May 2019, the US Food and Drug Administration (FDA) licensed this vaccine.

As a reminder, ACIP's Dengue Epi and Vaccine Development WG was formed in 2017 and was put on hold in 2018 when the Flavivirus WG split and the Dengue WG was formed. In 2019, there was extensive discussion regarding Phase 3 results, safety and pharmacovigilance, GRADE, cost-effectiveness, dengue diagnostics, partially effective vaccines, dengue vaccines in the Philippines, Vaccine and Related Blood Products Advisory Committee (VRBPAC) review, and FDA approval. In 2020, the focus was on vaccine acceptability, WHO's global position, feasibility, and health equity. In 2021, the focus has been on dengue immunoglobulin G (IgG) test evaluation, the EtR Framework, and draft recommendations presented to ACIP. Between February and May 2021, the Dengue Vaccine WG group has discussed performance recommendations for a pre-vaccination screening test, the EtR Framework, and key messages for providers and families.

During the February 24-25, 2021 ACIP meeting, the importance of a specific test for pre-vaccination was discussed. To recap, CYD-TCV vaccine requires pre-vaccination screening. Pre-vaccination dengue screening needs to be specific to minimize vaccination of seronegative children and sensitive to maximize identification of children who can benefit, and test performance characteristics to be included with ACIP recommendations. A CDC evaluation identified 1 enzyme-linked immunosorbent assay (ELISA) test and 2 rapid tests meeting recommended criteria with high specificity and sensitivity. The plan for the May 2021 meeting was for the WG to present the EtR Framework and draft WG recommendations to ACIP, with no vote planned on Dengvaxia® (CYD-TDV) recommendations until the June 2021 ACIP meeting.

### Dengue Vaccine EtR Framework

**Dr. Gabriela Paz-Bailey** (CDC/NCEZID) reminded everyone that dengue virus (DENV) is transmitted by species of mosquitoes, especially *Aedes aegypti* and *Aedes albopictus*. This is the most important arbovirus in terms of worldwide morbidity and mortality, with an estimated 400 million infections every year. Dengue fever can range from asymptomatic or mild to severe disease, and mortality range can go from 0.2% if treated to as high as 20% if untreated. The causes of death are mainly unrecognized or prolonged shock, unrecognized hemorrhage, fluid overload, and nosocomial sepsis. The first infection with dengue is usually mild and will induce antibodies against the 3 other dengue viruses for a period of time. However, the antibody levels

decrease over time and then suddenly go from being protective against future infections to being harmful in a process known as antibody-dependent enhancement (ADE).<sup>19</sup> The theory is that there are not enough antibodies to effectively neutralize the virus, but there are enough to bind the virus and help it enter into immune cells and then activate all types of inflammatory responses. This explains why the second infection is proven to be the most likely to lead to severe disease.<sup>20</sup> It also explains why making a dengue vaccine has been so difficult. If someone does not have immunity to all 4 virus types, there is a possibility that they may have low levels of antibodies that can lead to ADE.

The Phase 3 trials included children 2 to 16 years of age in countries in Asia and Latin America. When the results were published in 2015, there was a safety signal of increased risk of hospitalization and severe disease among children 2 to 5 years of age. Because of that, the vaccine was recommended by the WHO for persons 9 years of age and older in highly endemic areas. It was first licensed in several countries, including the Philippines. In 2016, the Philippines started giving it to all children 9 to 10 years of age. After additional testing of specimens from the trial participants and further analysis, Sanofi eventually found that the increased risk of severe disease and hospitalization among vaccinated seronegative children compared to controls. If the vaccine is given to a child who has not been infected previously, it works as a silent primary infection that does not fully protect against all serotypes. When the child gets naturally infected through a mosquito bite, they get the second infection that is the riskiest for severe dengue. If the vaccine is given to a child who had dengue before, this skips the second infection and the next natural infection they get is like a third or fourth infection.

After this information was released from Sanofi, the WHO revised their recommendation to state that the vaccine should only be given to children with laboratory-confirmed evidence of past infection. Unfortunately, the Philippines had already vaccinated almost 1 million children without doing any testing and the backlash was huge. The suspension of the program broke public trust in the dengue vaccine and in vaccines in general. The hospitalized severe cases that occurred following vaccination were a mixture of breakthrough cases among those who were seropositive and cases among those who were seronegative when vaccinated. Later analysis of the data in the Philippines has suggested that most dengue hospitalizations among vaccinated children were actually breakthrough disease. A small percentage were vaccine-induced hospitalizations. The most important take-home message is that in the case of the Philippines, there was no screening before vaccination. The available data have shown that this is a safe and effective vaccine for children 9 to 16 years of age with evidence of a past dengue infection.

The FDA licensed this vaccine in 2019 for this group of children who live in an endemic area in the US. However, there were no commercially available serological tests at that time that reliably determined whether a child had a past dengue infection. In order to determine if safe implementation of the vaccine was feasible, CDC evaluated commercially available tests to detect dengue antibodies. This evaluation confirmed that there are tests available with high specificity and adequate sensitivity. The Dengue Vaccine WG drafted recommendations on the performance of tests used for pre-vaccination screening that include a minimum specificity of 98% and a sensitivity of 75%.

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<sup>19</sup> Whitehead SS, Blaney JE, Durbin AP, Murphy BR. Prospects for a dengue virus vaccine. *AP, Murphy BR. Prospects for a dengue virus vaccine. Nat Rev Microbiol.* 2007;5(7):518-528. [oi:10.1038/nrmicro1690](https://doi.org/10.1038/nrmicro1690)

<sup>20</sup> Flasche S, Jit M, Rodríguez-Barraquer I, et al. The Long-Term Safety, Public Health Impact, and Cost-Effectiveness of Routine Vaccination with a Recombinant, Live-Attenuated Dengue Vaccine (Dengvaxia): A Model Comparison Study. *von Seidlein L, ed. PLoS Med.* 2016;13(11):e1002181. [doi:10.1371/journal.pmed.1002181](https://doi.org/10.1371/journal.pmed.1002181)

The WG assessed each of the elements in the traditional ETR Framework for the policy question, “Should 3-doses of Dengvaxia® be administered routinely to persons 9-16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas? The questions for each domain were:

EtR Domain	Question
Public Health Problem	<ul style="list-style-type: none"> <li>• Is the problem (Dengue) of public health importance?</li> </ul>
Benefits and Harms	<ul style="list-style-type: none"> <li>• How substantial are the desirable anticipated effects of the intervention (dengue vaccine)?</li> <li>• How substantial are the undesirable anticipated effects?</li> <li>• Do the desirable effects outweigh the undesirable effects?</li> </ul>
Values	<ul style="list-style-type: none"> <li>• Does the target population feel the desirable effects are large relative to the undesirable effects?</li> <li>• Is there important variability in how patients value the outcomes?</li> </ul>
Acceptability	<ul style="list-style-type: none"> <li>• Is the intervention acceptable to key stakeholders?</li> </ul>
Feasibility	<ul style="list-style-type: none"> <li>• Is the intervention feasible to implement?</li> </ul>
Resource Use	<ul style="list-style-type: none"> <li>• Is the intervention a reasonable and effective allocation of resources?</li> </ul>
Equity	<ul style="list-style-type: none"> <li>• What would be the impact of the intervention on health equity?</li> </ul>

In terms of the first question in the EtR Framework regarding whether dengue disease is of public health importance, 90% of the population at risk for locally-acquired dengue resides in Puerto Rico (PR). Other territories that are considered endemic or affiliated states include American Samoa, the US Virgin Islands (USVI), the Federated States of Micronesia (FSM), Palau, and more recently, the Marshall Islands. Dengue epidemics occur in a cyclical pattern every 5 or so years, with 95% of dengue cases in the US territories occurring in PR. There has been an unusually long period with little dengue transmission in PR since 2014. However, dengue cases started being reported again in 2020. Over 1,000 polymerase chain reaction (PCR)-confirmed cases have been reported since the beginning of 2020.

Looking at dengue virus cases and hospitalizations by age in PR from 2010-2020, most dengue cases and the highest incidence occurred in children 10 to 19 years of age. There is a similar pattern for dengue hospitalizations. In contrast, 88% of deaths occurred in adults. Nearly 90% of cases occurred among adults  $\geq 20$  years old. Prevalence data among children are available only from PR and not from other US territories. In 2017, seropositivity was estimated at 50%.<sup>21</sup> There also are data from the Phase 3 trials that Sanofi conducted that suggested that 56% of the children ages 9 to 16 years were seropositive.<sup>22</sup> More recently, CDC found similar results from a survey conducted in 2018 among children in Southern PR, with nearly 60% seropositive among children 9 to 16 and seroprevalence at 9 years of age being 50%.<sup>23</sup> The WG concluded that dengue is a disease of public health importance.

With respect to benefits and harms and the question regarding how substantial the desirable anticipated effects are, survey results from Asia and Latin American show a combined efficacy against virologically confirmed dengue (VCD) among seropositive participants 9 to 16 years of age of about 82%.<sup>24</sup> Efficacy varies by serotypes and is higher for serotype 4 at 89%. Efficacy was lower for serotypes 1 and 2 at 67% and 80% for serotype 3. Efficacy against hospitalizations and severe dengue was estimated as far as the case-cohort study with three different methods (multiple imputation, TMLE, and NS1 testing). Based on the multiple

<sup>21</sup> Argüello DF, et al. AJTMH. 2015 Mar 4;92(3):486-91

<sup>22</sup> L’Azou M, et al. TRSTMH. 2018 Apr 1;112(4):158-68

<sup>23</sup> Unpublished: COPA Project

<sup>24</sup> Hadinegoro SR et al. N Engl J Med 2015;373:1195-1206

imputation results, there was a 79% reduction in hospitalization risk and an 84% reduction in the risk of severe dengue (estimated as one minus the relative risk).<sup>25</sup> The WG considered the desirable anticipated effects to be moderate to large.

With regard to the undesirable effects, the most important one is increasing the risk of hospitalization and severe dengue by erroneously vaccinating a seronegative child. The point estimate for the relative risk is greater than 1.0, suggesting an increased risk of these outcomes when vaccinating seronegative children ages 9 to 16 years. The increased risk in seronegative vaccinees compared to controls for hospitalizations was between 40% to 50% greater risk, and for severe dengue between 2 to 6 times as high as in the controls. The differences were not statistically significant because of the small sample size of seronegatives in the trial.<sup>25</sup> For severe adverse events (SAEs) and deaths, there were no differences for SAEs at 28 days. At 6 months, there were fewer SAEs among vaccinees compared to controls. There were no differences in deaths.<sup>26</sup> The WG considered the undesirable effects to be small.

Regarding whether the desirable effects outweigh the undesirable anticipated effects, the benefits of Dengvaxia<sup>®</sup> are that it prevents symptomatic dengue hospitalizations and deaths among seropositive children. The efficacy against symptomatic dengue is 82%, against hospitalization 79%, and against severe dengue 84%. The main potential harm is increased risk of vaccine-induced hospitalization and severe disease when a seronegative child is vaccinated after a false-positive laboratory test result.

To assess the issue of the balance between benefits and harms, researchers from the University of Notre Dame<sup>27</sup> conducted an agent-based model (ABM) of dengue transmission with humans and mosquitoes represented as agents. The model was calibrated to simulate dengue transmission in PR. It compared pre-vaccination screening and subsequent vaccination of seropositive 9-year-olds to the status quo. The model population was 9-year-olds, with a new cohort of 9-year-olds being vaccinated every year. They were followed for 10 years keeping track of dengue infections, hospitalizations, and deaths. Dr. Paz-Bailey reported results on two scenarios of 50% seroprevalence and 30% seroprevalence. The population level benefits were symptomatic and hospitalized cases averted and the risks were vaccine-induced hospitalizations among seronegative individuals. Using a test with a 75% sensitivity and 98% specificity, the model estimated baseline symptomatic and hospitalized cases among the entire population. Among children 9 to 16 years of age, the model estimated the number tested and vaccinated, symptomatic cases and hospitalizations averted, and the number of additional hospitalizations by erroneously vaccinating seronegatives with a false-positive test result.

In this scenario of 50% seroprevalence, more than 4,000 symptomatic dengue cases nearly 3,000 hospitalizations would be averted annually. There would be 51 vaccine-induced hospitalizations among dengue-naive children or seronegative vaccinated after a false-positive result. In a lower seroprevalence scenario of 30%, over 1,500 symptomatic dengue cases and over 1,200 hospitalizations would be averted. There would be 112 vaccine-induced hospitalizations among seronegative children vaccinated after a false positive result. In summary, the population risk of a screen and vaccinate strategy over 10 years in a 50% seroprevalence scenario would be 51 vaccine-induced hospitalizations. The benefits would be over 4,000 fewer symptomatic cases and nearly 3,000 fewer hospitalizations. In a lower seroprevalence scenario, the population risk would be 122 vaccine-induced hospitalizations

<sup>25</sup> Sridhar, S, et al. N Engl J Med. 2018 Jul 26; 379(4):327-340

<sup>26</sup> Gustavo Dayan, Sanofi, personal communication

<sup>27</sup> 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>

among seronegative children. The benefits would be over 1,500 fewer symptomatic cases and over 1,200 hospitalizations prevented. The WG interpretation of the benefits and harms was that there was a positive balance for benefits versus harm and that this balance varied by the seroprevalence among old 9-year-olds. The WG interpretation was that the balance favors intervention. The WG evaluated the certainty of the evidence following the GRADE methodology for the outcomes of biologically confirmed dengue, hospitalizations, severe dengue, and death. Certainty was considered high for efficacy and moderate for safety.

To answer the question of whether the target population feels that the desirable effects are large relative to the undesirable effects, CDC conducted a survey in Ponce, PR. This study found that 75% of parents said that they were interested in vaccinating their children with a hypothetical dengue vaccine if the vaccine was provided for free, while 68% said they would be interested in vaccinating their children if they had to pay for the vaccine. A total of 342 out of the 1,139 participants said they were unsure or that they would not vaccinate. Among these participants, side effects was the number one concern. The WG interpretation was that probably yes, the study population felt that the desirable effects were large relative to the undesirable effects.

Regarding the question about whether there is important uncertainty about viability and how much people value the main outcome, the WG considered that there was probably important uncertainty or variability. To answer the question pertaining to whether the intervention is acceptable to stakeholders, the University of Georgia (UGA) conducted a survey among 109 physicians in PR in 2020 and showed that 56% were familiar with the vaccine. After describing the need for screening before vaccination, 72% said that they would recommend the vaccine if there was a test with acceptable specificity. The WG interpretation was that probably yes, the intervention was acceptable to key stakeholders.

In terms of whether the intervention is feasible to implement, there are several considerations for Dengvaxia<sup>®</sup>. Implementation of vaccination for Dengvaxia<sup>®</sup> will be more challenging than for other vaccines as 3 doses are required at 0, 6, and 12. Extensive education of providers and parents will be needed. The vaccine costs will be covered by Vaccines for Children (VFC) or insurance, but there still will be out of pocket expenses because of the repeated visits. The requirement for screening before vaccination is not needed for any other vaccines. For screening to be conducted safely, the first step is to have tests available with good specificity. Determining if tests were available was one of the WG's priorities. After the CDC-led evaluation mentioned earlier, 2 versions of the rapid test were identified and analyzed a test with high specificity and moderate sensitivity. Implementation of point-of-care testing in PR is challenging since only laboratory technicians can conduct testing. None of the tests with adequate performance have FDA approval. PR laboratories have experience implementing non-FDA approved tests under Clinical Laboratory Improvement Amendments (CLIA) protocols and can provide results to participants. They have had conversations with insurance companies and Medicaid about covering the cost of the test, which they would do if there is a routine ACIP recommendation. If the recommendation is shared decision-making, they may require proof from providers that the test is needed before reimbursing the cost. Screening before vaccination will result in additional visits to the pediatrician office, laboratory, and vaccination clinics and will affect feasibility.

The Dengue Vaccine WG developed guidance on test performance for pre-vaccination screening. If there is an ACIP recommendation, this guidance would be published as part of the *MMWR* that accompanies the recommendation. The guidance includes that tests should have a sensitivity of 35% or greater and a specificity of 98% or greater. The positive predictive value (PPV) should be 90% or greater and the negative predictive value (NPV) should be 75% or

greater to minimize missing persons who would potentially benefit from the vaccine. The WG also considered that sequential testing using a 2-test algorithm could help improve specificity. It is currently challenging to think about a 2-test algorithm with the limited number of tests available, but it may be an option in the future as more IgG tests become available. A communication plan will be a key component of the implementation of these vaccines, and will include counseling messages for providers on how to communicate the risks and benefits of their vaccine. Dr. Paz-Bailey shared some draft examples of these messages that they have been validating with a series of focus groups—first with WG members and then with dengue clinical experts in PR. There is a third focus group with pediatricians and general practitioners. They are in the process of finalizing these key messages, but she wanted to show ACIP that they have been having a lot of progress in this area. The WG interpretation was that probably the intervention would be feasible to implement.

Turning to the question of whether the intervention is a reasonable and efficient allocation of resources, Figure 5 in the cost-effectiveness modeling from University of Notre Dame shows here the incremental cost-effectiveness ratio (ICERs) for averted symptomatic infections and for averted hospitalizations. An ICER can be interpreted as the cost of the intervention minus the cost of hospitalization and treatment for each quality-adjusted life-year (QALY) gained or for each symptomatic case or hospitalization averted. A lower ICER indicates a more cost-effective vaccine. The ICER goes up with lower seroprevalence and a higher cost of the vaccine. At a seroprevalence of 50% at age 9 and an estimated cost of the 3 doses of the vaccine of \$382, the ICER is estimated to be 122,000 per QALY gained for the 50% seroprevalence scenario and 240,000 per QALY gained for the 30% seroprevalence scenario.<sup>28</sup> To put this ICER into context, Dr. Paz-Bailey used a graph from a review paper in *Pediatrics* of the ICER for other pediatric vaccines. Vaccines were ordered in the graph from the least cost-effective with the highest ICER to the most cost-effective with the lowest ICER.<sup>29</sup> The WG's judgment was between probably yes and yes that the intervention is a reasonable and efficient allocation of resources.

With respect to the question regarding the potential impact on health equity, there are marked disparities in healthcare between PRs and other US citizens. PR has the lowest Medicaid and Medicare per capita annual spending. Mosquito-borne diseases are highly prevalent, and PR has repeatedly suffered natural disasters like hurricanes and earthquakes that affect the risk of vector borne diseases. The WG discussed a number of considerations to ensure that the use of Dengvaxia<sup>®</sup> helps reduce health inequities. First, health insurance and Medicaid should cover the cost of the laboratory test. The cost of the test should be minimal and funds should be available for those who are not covered by insurance or Medicaid. Second, multiple visits to the pediatrician, laboratory, and vaccination site will be challenging and maybe a larger burden for low-income families because of transportation costs and missed days of work. Strategies to reduce the number of visits would be needed to reduce the impact on health equity. The WG considered that the use of the vaccine probably would increase health equity.

In terms of the balance of consequences, the WG considered that the desirable consequences probably outweigh the undesirable consequences in most settings. The WG also considered that there was sufficient information to move forward with a recommendation.

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<sup>28</sup> 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>

<sup>29</sup> Ismael R. Ortega-Sanchez et al. *Pediatrics* 2008; 121:S63-S78

## **Summary of Discussion**

- In response to an observation that parents rather than physicians are the key stakeholders, Dr. Paz-Bailey indicated that they have been studying who the key stakeholders are going to be to implement a vaccination program against dengue in PR and to implement it well. There are different associations of parents and different associations of physicians. They want to work with Tecnología Médica, other healthcare providers, municipalities, the government, and the media. In the process of mapping all of the stakeholders, they have that clinicians are a very important group because they are the ones providing information to parents on the benefits and risks of vaccination and are the ones who the parents trust.
- Regarding an inquiry about why an adjustment was not made to the 2008 dollars used in the cost analysis, Dr. Paz-Bailey indicated that 2008 was the latest survey available comparing hospitalization costs. They have been working closely with the University of Notre Dame who has kindly reviewed the model to provide additional data on a higher specificity and sensitivity. They also could consult with them to find out whether there is an opportunity to update the model with more recent cost estimates.
- Concern was expressed with the lack of endemic disease since 2014 in terms of the ability to understand the antibody signature after vaccine in the absence of repeated infection soon after infection when it was more prevalent and with regard to ADE. Dr. Paz-Bailey pointed out that Dengvaxia<sup>®</sup> does not provide balanced protection against all 4 serotypes. It is primarily a vaccine against dengue 4, which is why it cannot be used among dengue-naïve individuals. It would need to provide protection among all serotypes to prevent the resulting effect of ADE if someone is vaccinated and then is naturally infected by a mosquito. It is known from studying dengue without the vaccine that there are cross-protective antibodies generated after a natural infection that last about 2 years. After 2 years, ADE begins occurring. The longer the separation between the first and the second infection, the more likely it can result in severe dengue. Based on the data provided by Sanofi on the children they have been following, protection against hospitalization is still present in Years 5 and 6 after vaccination and that protection is still effective.
- In regard to what the recommendation would be for a scenario in which someone had a prior infection, was vaccinated, started their vaccination series but in the midst of that series had a breakthrough of dengue, Sanofi said that they would still recommend completion of the vaccination schedule as they have shown that even 1 or 2 doses are effective.
- The epidemiology of many of the diseases that they are trying to vaccinate against change over time, which might change the risk/benefit calculation. The dengue circumstance seems even more prone to changes in risk/benefit based on changes in the epidemiology and seroprevalence. With that in mind, it was suggested that if this recommendation comes to a vote in June 2021 and the vote is favorable, perhaps the EtR should be explicitly re-evaluated more formally 24 months from when the recommendation is made. Dr. Cohn reminded everyone that the epidemiology and ACIP recommendations are always monitored and reviewed. While a formal review could be done, 24 months out might not be sufficient for monitoring trends and assessing changes.

- Dr. Paz-Bailey emphasized that it is important to note that with temperatures rising and increased travel and connectivity, the incidence of dengue has been increasing worldwide. An alteration of that increasing trend was observed likely because of Zika and the cross-protection it may be providing. In 2019, there were huge outbreaks in Latin America, which suggests that dengue continues to be a large threat. While PR was somewhat safe in 2019, they are now seeing increases and are expecting a large dengue outbreak during the mosquito season.
- ACIP members emphasized the critical importance of appropriate education/messaging, as well as long-term surveillance.

### **Draft Recommendation**

**Dr. Gabriela Paz-Bailey** (CDC/NCEZID) reminded everyone of the policy options for ACIP, which are that: 1) ACIP does not recommend the intervention (intervention may be used within FDA licensed indications); 2) ACIP recommends the intervention for individuals based on shared clinical decision-making; and 3) ACIP recommends the intervention. The WG had a lot of discussions about the different options, so Dr. Paz-Bailey shared some of the considerations from the WG for each option in terms of the pros and cons.

Regarding Policy Option 1 (ACIP does not recommend), the cons are that a vaccine proven to protect persons with prior dengue infection is not going to be available to US citizens. It also puts off making difficult decisions that may be needed for future dengue vaccines approved by FDA. The pros are that this option would avoid complicated implementation in the middle of the COVID vaccinations program.

The WG assessed various attributes they considered important for Option 2 (ACIP recommends based on shared clinical decision-making) compared to Option 3 (ACIP recommends, or a routine recommendation). In terms of the impact of the recommendation on the reduction of dengue transmission, it would be unlikely for the vaccine to have an impact on dengue transmission since it mainly reduces disease and severity of disease, but does not prevent infection. Regarding reduction in disease burden, the model that was presented earlier estimated that of all dengue hospitalizations among all age groups, about 6% would be averted in a 10-year period with 80% coverage of the screen and vaccinate strategy and a 50% seroprevalence scenario. With shared decision-making, there will be no measurable benefit in reducing hospitalizations. In terms of harms, the balance shared earlier was that for every 57 hospitalizations prevented, 1 additional hospitalization would occur due to the vaccine. With shared decision-making, coverage would likely be low and among a selected group of patients. Therefore, potentially AEs would be unlikely in terms of vaccinated seronegatives.

With regard to cost, with a routine recommendation, coverage of the screening test and the vaccine by insurance companies and VFC/Medicaid would be achieved and would minimize cost to families. In terms of shared decision-making, insurance companies were less certain about covering the cost of the tests without documented medical indication by a provider. While the vaccine would be covered, the coverage of the test was uncertain. Possibly, there would be higher out-of-pocket expenses for families. In terms of implementation and feasibility, with a routine recommendation there will be greater engagement from health departments with territory-wide policies that would lead to greater coverage. There would likely be a greater push to solve the information systems connectivity and testing and logistical challenges. The health department could centralize testing at a reference laboratory, facilitating access to testing and the logistics of providing results back, with phased implementation. This also would remove



some of the burden of testing and vaccination from providers on making those decisions. It also may lead to implementation of dengue vaccine programs in other countries with a high dengue burden. For shared decision making, it would allow for a quicker but probably limited use of the vaccine. In theory, it would allow for more careful discussion between providers and parents. It could lead to a full recommendation later after the vaccine gains are more acceptable. It does place the burden on providers, leading to delays and maybe missed opportunities for testing and vaccination. This path may be a “dead end” for these vaccines and for any other unbalanced dengue vaccines that can still provide a benefit to a group of the population.

In terms of health equity, the WG considered that a routine recommendation would increase health equity and that shared decision-making likely would decrease health equity since fully empowered and informed patients are those served by informed doctors who would have access to the vaccines. The administrative hurdles and the cost could reduce access for families with low medical literacy and economic means. For education of providers and families, with a routine recommendation, educational materials and training for providers would be more readily available. For shared decision-making, there would be efforts from CDC on educating providers and patients. However, the WG was worried about less buy-in from the health department. For cost-effectiveness, a routine recommendation would achieve higher coverage. It seems that this strategy would be cost-effective in most scenarios. With shared decision-making and very low coverage, it would likely not be cost-effective.

Regarding communication and media, under a routine recommendation, communication would fall to the health department and to CDC. Something that would need to be explained is that hospitalizations among children with a history of vaccinations mainly will be due to vaccine breakthrough and a small percentage will be vaccine-induced. Clinicians and the public could attribute all hospitalizations to the vaccine, so a communication campaign would need to explain this difference. A risk is that faulty implementation could lead to negative perception of dengue vaccines and vaccines in general. This is a particular concern during efforts to achieve high coverage for COVID vaccine. With shared decision-making, there will be slow implementation and limited coverage that would make public relations issues less likely. Vaccine safety concerns may vary by individual, so shared decision-making would lessen fears that the vaccine will become controversial and a stimulus to vaccine hesitancy.

To summarize Option 2 (shared decision-making) the WG considered the cons to be lower uptake, little progress in sorting out feasibility, coverage of tests by insurance companies more challenging, may lead to an increase in health inequities, and less buy-in for large education and communication campaigns. The pro is that it would lessen fears that the vaccine will become controversial and result in increased vaccine hesitancy. In summary of Option 3 (routine recommendation), the WG identified the cons to be the perception that all hospitalizations among vaccinees are related to the vaccine, while most hospitalizations are actually due to vaccine breakthrough. There could be media backlash that could reduce coverage for other vaccines if not managed appropriately. In terms of the pros, it is a useful vaccine for seropositives during a time in which sustainable vector control for *Aedes aegypti* is still years off in the US while dengue outbreaks continue to occur. Greater coverage could be achieved and hospitalizations could be reduced. There likely would be better buy-in from health departments and immunization programs to resolve the challenges with feasibility. There would be broader communications and media campaigns, as well as an increase in health equity.

The WG considered Policy Option 3, ACIP recommends the intervention, to be the best option and presented the following draft recommendation to ACIP:

*ACIP recommends 3 doses of Dengvaxia® administered in persons 9-16 years of age with laboratory confirmation of previous dengue infection and living in endemic area.*

### **Summary of Discussion**

From the consumer perspective, the health equity issue around shared clinical decision-making is significant. In addition to concern about medical literacy, a shared clinical decision-making recommendation would mean that some children who are candidates would be missed because a provider may not raise the issue, which would be consistent potentially with CDC guidance that it is up to the provider to raise the issue. Parents may not know what to ask. Because dengue is a significant public health problem and 75% of parents surveyed said they were interested in having their children vaccinated, a routine recommendation would be more appropriate under these circumstances.

Asked to expand on the insurance company discussions, Dr. Paz-Bailey indicated that these discussions are highly preliminary. They had one meeting with representation from 4 or 5 of the large insurance companies to explain the details of this vaccine and how testing before vaccination is needed, and inquire as to whether insurance companies would be willing to provide coverage for that test. Their response was very positive that if the vaccine was recommended, they would favor preventive strategies and would cover the tests. The companies were specifically asked whether a recommendation for shared decision-making would make a difference, to which the insurance companies responded that they would have to meet with their boards and decide once the recommendation was made. One of the companies mentioned that in some situations similar to this, they require documentation from the provider that the test is indicated. This issue will be revisited once an ACIP recommendation is decided upon. They met with the group managing Medicaid for PR, which said they would cover the test if the cost was low enough. With their current work plan, they would need to submit a request for an amendment on the amount of funds and how the funds are spent based on the estimated cost of the test. The group was provided with information on the size of the population of children 9 to 16 years of age and the estimated cost of the test received from Sanofi of between \$5 to \$10, with a frequency of testing every 2 years. While they thought that the cost of the test would be covered, they still have to assess whether it could be covered under current plans and report back.

In response to a suggestion about providing information about specific tests in the recommendation and/or on the CDC website, Dr. Paz-Bailey indicated the WG discussed refraining from recommending particular brands and specific tests. The proposal is to include a paragraph in the *MMWR* that will accompany the recommendations that will spell out the minimum sensitivity and specificity. She will ask the division about the potential to provide general guidance for providers on the CDC website about the most recommended tests. It is important to remember that due to the wide range of performance of the available tests on the market, the testing is likely to be done in the laboratory, with the health department having more room to regulate. In the context of PR and their regulations about who can perform testing, this testing is mainly going to be performed in the reference laboratory.

It was noted that there is a precedent for CDC recommending certain tests, which occurred in the 1990s when the first commercial human immunodeficiency virus (HIV) tests were coming on the market. Perhaps the WG could conduct a historical review of the *MMWRs* from the 1990s to find that recommendation.

While some ACIP members were leaning toward shared clinical decision-making, they were swayed toward making a firm recommendation due to the compelling argument about health literacy.

It was suggested that perhaps more consideration should be given to people who go back and forth between endemic countries. Some people who mainly live in the continental US and travel to endemic areas would not be covered with the current indication. Perhaps this should be the next step to consider.

Dr. Maldonado (AAP) emphasized that Dengvaxia<sup>®</sup> is an important vaccination strategy for high-risk children in high-prevalence areas and that the data have been much improved over the last few years. However, some of her colleagues in the AAP are not comfortable with the shared decision-making at this point, given that there are so many unknowns (e.g., implementation, when screening would take place, vaccine confidence, high risk for social vulnerability, test development, payment/reimbursement uncertainties, et cetera). On behalf of the pediatricians in the community that AAP serves, she stressed that this recommendation did not seem ready for primetime. More details on all of these issues would be beneficial.

Suggestions for topic areas for the June 2021 ACIP meeting: implementation strategies, vaccine confidence, post-implementation safety monitoring, screening intervals, social vulnerability, test development, and payment/reimbursement.

## CERTIFICATION

Upon reviewing the foregoing version of the May 5, 2021 ACIP meeting minutes, Dr. Jose 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.

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## ACRONYMS USED IN THE DOCUMENT

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
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
ADE	Antibody-Dependent Enhancement
AE	Adverse Event
AHIP	America's Health Insurance Plans
AIM	Association of Immunization Managers
AIRA	American Immunization Registry Association
AMA	American Medical Association
AOA	American Osteopathic Association
APhA	American Pharmacists Association
APRN	Advanced Practice Registered Nurse
AS	American Samoa
ASTHO	Association of State and Territorial Health Officers
BSL-4	Biosafety Level-4
CDC	Centers for Disease Control and Prevention
CLIA	Clinical Laboratory Improvement Amendments
CMS	Center for Medicare and Medicaid Services
COI	Conflict of Interest
CSTE	Council of State and Territorial Epidemiologists
CYD-TDV	Recombinant, Live-Attenuated, Tetravalent Chimeric Dengue Vaccine
DFO	Designated Federal Official
DSMB	Data Safety Monitoring Board
ED	Emergency Department
ELISA	Enzyme-Linked Immunosorbent Assay
EtR	Evidence to Recommendations
FDA	Food and Drug Administration
FSM	Federated States of Micronesia
GMT	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
HCP	Healthcare Personnel / Providers
HCW	Healthcare Workers
HDCV	Human Diploid Cell Vaccine
HHS	(Department of) Health and Human Services
HIV	Human Immunodeficiency Virus
HRSA	Health Resources and Services Administration
ICER	Incremental Cost-Effectiveness Ratio
IDSA	Infectious Disease Society of America
Ig	Immunoglobulin
IHS	Indian Health Service
IM	Intramuscular
ISO	Immunization Safety Office

MMWR	<i>Morbidity and Mortality Weekly Report</i>
MI	Multiple Imputation
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization Canada
NAPNAP	National Association of Pediatric Nurse Practitioners
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCIRD	National Center for Immunization and Respiratory Diseases
NFID	National Foundation for Infectious Diseases
NIH	National Institutes of Health
NMA	National Medical Association
NPV	Negative Predictive Value
PCECV	Purified Chick Embryo Cell Vaccine
PCP	Primary Care Practitioner
PCR	Polymerase Chain Reaction
PEP	Post-Exposure Prophylaxis
PHAC	Public Health Agency Canada
PhRMA <sup>®</sup>	Pharmaceutical Research and Manufacturers of America <sup>®</sup>
PIDS	Pediatric Infectious Disease Society
PPE	Personal Protective Equipment
PPV	Positive Predictive Value
PrEP	Pre-Exposure Prophylaxis
PR	Puerto Rico
PR	Puerto Rico
QALY	Quality-Adjusted Life-Year
RIG	Rabies Immune Globulin
RR	Relative Risk
RVA	Rabies Vaccine Adsorbed
RVV	Rabies Virus Variants
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts on Immunization (WHO)
SAHM	Society for Adolescent Health and Medicine
SHEA	Society for Healthcare Epidemiology of America
US	United States
USG	US Government
USVI	United States Virgin Islands
VAERS	Vaccine Adverse Event Reporting System
VFC	Vaccines For Children
VRBPAC	Vaccine and Related Blood Products Advisory Committee
WG	Work Group
WHO	World Health Organization