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

**FEBRUARY 24-25, 2021**
**SUMMARY MINUTES**

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## MEETING PURPOSE

The United States (US) Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC) convened the regularly scheduled quarterly meeting of the Advisory Committee on Immunization Practices (ACIP) on February 24-25, 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, dengue vaccine, tick-borne encephalitis (TBE), Ebola vaccine, hepatitis vaccine, pneumococcal vaccines, zoster vaccines, influenza vaccines, cholera vaccine, and orthopoxvirus vaccines.

## WEDNESDAY: FEBRUARY 24, 2021

### WELCOME AND INTRODUCTIONS

**Dr. José R. Romero** (ACIP Chair) called to order and presided over the meeting. He expressed gratitude to outgoing ACIP members Dr. Robert Atmar, Dr. Paul Hunter, and Dr. Peter Szilagyi and briefly summarized their work while serving on the ACIP. Dr. Atmar indicated that serving on the ACIP was a major joy, privilege, and honor of his professional career. Dr. Hunter said that serving on the ACIP had been the most fulfilling activity of his career and participating in various work groups (WGs) and ACIP meetings had been the most educational experience of his career. Dr. Szilagyi added that serving on ACIP had been one of the greatest honors and privileges of his career and that in his opinion, ACIP's careful and evidence-based process should be a role model for decision-making across the country. All three expressed their gratitude to CDC and ACIP Voting Members, *Ex Officios*, and Liaisons for their incredible knowledge and passion for preventing disease and serving this country, which has been especially evident during the pandemic.

**Dr. Amanda Cohn** (ACIP Executive Secretary) welcomed everyone and acknowledged the enormous amount of work that has been done over the last year during the COVID pandemic, especially by the ACIP team. She indicated that a virtual Emergency ACIP meeting was scheduled for February 28-March 1, 2021 and the next regularly scheduled ACIP meetings would be convened on June 23-24, 2021 and October 20-21, 2021. She explained that there would be an oral public comment session at approximately 12:30 PM Eastern Time (ET). Given that many 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-2021-0008. Further information on the written public comment process can be found on the ACIP website.

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

instructions for submission of names of potential candidates to serve as ACIP members is now available on the ACIP website. Applications for ACIP membership are due no later than July 1, 2021 for the 4-year term beginning July 2022.

**Dr. Romero** (ACIP Chair) conducted the roll call. A list of Members, *Ex Officios*, and Liaison Representatives is included in the appendixes at the end of this summary document. The following COIs were declared by voting members:

- Dr. Wilbur Chen has current funding from Emergent, the manufacturer of the cholera vaccine to be discussed and voted upon during this meeting.
- Dr. Sharon Frey serves as a Principal Investigator on several COVID-19 vaccines trials.

## RABIES VACCINE

### Introduction

**Dr. Sharon Frey** (Chair, ACIP Rabies WG) introduced the Rabies Session, with a reminder that the Rabies WG was formed in October 2018. Between October 2019 and February 2020, the WG reviewed vaccine safety and WG considerations for changes to pre-exposure prophylaxis (PrEP); gathered feedback from the full ACIP about data they would need to make changes to the 2008 ACIP recommendations; conveyed WG conclusions about pediatric patients having similar responses (if not more robust) than those of healthy persons; showed evidence to support the WG's move to use data from intradermal series to influence intramuscular series recommendations; explained why 0.5 IU/mL should be the minimum rabies antibody titer cut-off; redefined risk categories for PrEP; and presented Grading of Recommendation Assessment, Development and Evaluation (GRADE) and Evidence to Recommendation (EtR) for two PrEP policy questions.

Since the last ACIP meeting, the WG assessed PrEP costs, including those incurred by PrEP recipients. In terms of post-exposure prophylaxis (PEP), the WG considered the development of guidance for front line clinicians who make decisions about whether PEP is indicated; evaluation of two rabies immune globulin (RIG) products licensed since the 2008 ACIP recommendations; assessment of data about the current ACIP recommendation for RIG infiltration around a wound and for administration of the remainder intramuscularly (IM); and evaluation of immunogenicity of PEP in persons aged ≥ 65. Dr. Frey indicated that the goal of the WG for this meeting in terms of PrEP was to address questions raised by the ACIP about PrEP costs; summarize the clinical guidance presented at previous meetings; recap policy questions, evidence tables, and the EtR frameworks; and entertain a motion/vote on two proposed policy questions. The goal for PEP was to provide background information about PEP and convey the WG's conclusions about RIG.

### Rabies PrEP: Background and EtR

**Agam Rao, MD** (CAPT, USPHS; Co-Lead Rabies ACIP WG; CDC/NCEZID) summarized strategies to prevent rabies in the US, including PrEP and PEP, and described recognized and unrecognized exposures. Timely PEP alone is effective in preventing rabies; however, there are challenges to reliance on PEP alone. These include uncertain access to prompt PEP for some travelers, the potential for unrecognized or high concentration exposures for select populations, and risk for multiple rabies exposures for persons who work with rabies virus or suspect rabid animals. The PrEP schedule for naïve persons includes RIG plus rabies vaccine IM [0, 3, 7, 14

days], while the PrEP schedule for vaccinated persons involves only rabies vaccine IM [0, 3 days]. The role of PrEP is to provide some coverage if PEP is delayed because of access issues for example or is inadvertently not given because of unrecognized exposure; eliminate the need for RIG, which is expensive and is not always easily accessible internationally; and shorten the PEP series. For a person receiving PrEP after an exposure, only 2 doses of vaccine would be needed.

The risk for rabies in the US is 1500 per hundred thousand, so it is a relatively rare event for a high cost treatment in a country that has a robust system for detecting and treating exposures. For the general population, ACIP historically has not recommended PrEP for this reason. Dr. Rao shared the updated table reflecting the ACIP rabies PrEP recommendations, noting that this session would focus on the first 3 categories: 1) research laboratorians and diagnostic laboratorians; 2) persons who frequently handle or come into contact with bats because of entry into high density bat regions; and 3) animal care professionals and others who frequently handle terrestrial mammals in regions with terrestrial rabies; animal care professionals and others who frequently handle terrestrial mammals in regions without terrestrial rabies; and students, spelunkers, travelers, and short-term animal care professionals. The current ACIP recommendation for these 3 risk groups is a 3-dose series IM [0, 7, 21/28 days]. To ensure long-term immunogenicity, serial titers are recommended for most people in these groups. Titer checks ensure that titers remain ≥ 0.5 IU/mL, which prompts a booster if not. However, titer checks are not recommended for students, spelunkers, travelers, and short-term animal care professionals.

The proposed change described during the October 2019 ACIP meeting was for the primary series for all 3 risk groups be replaced with a single 2-dose series. For diagnostic laboratorians, the WG thought the titer check should be changed to every 6 months from the 2 years currently recommended due to the type of work they do. For the large category of veterinarians and other animal care professionals working in regions with terrestrial rabies, the WG proposed having an option of either 1 titer check at 1 to 3 years after the primary series or a booster. The implications of the proposed 2-dose primary series IM [0, 7 days] is that while there are fewer vaccine doses, the efficacy is equivalent. In terms of long-term immunogenicity, research laboratorians are already recommended by ACIP to have titer checks ever 6 months. The implication of the proposed change for diagnostic laboratorians is that it makes sense to consider all laboratorians equally. There would be no change for risk category #2, bat biologists. For risk category #3 with terrestrial rabies, the implications of the WG's proposed titer 1 to 3 years after the primary series OR a booster no sooner than 21 days and no later than 3 years would be fewer vaccine doses and/or titer checks. Those in regions without terrestrial rabies or the other groups (students, spelunkers, travelers, and short-term animal care professionals), PrEP would be considered complete after the 2-dose series. The WG thought that all 3 of these would be well-regarded. This brought the WG to propose the following 2 policy questions:

*Policy Question #1: Should a 2 dose pre-exposure prophylaxis (PrEP) series involving human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV) IM [0, 7 days] replace the 3 dose series IM [0, 7, 21/28 days] for all those for whom rabies vaccine PrEP is recommended?*

*Policy Question #2: Should an IM booster dose of rabies vaccine (PCECV or HDCV) be recommended as an alternative to a titer check no sooner than day 21 and no later than 3 years after the two-dose pre-exposure (PrEP) series IM [0, 7 days] for those in the #3 risk category who receive PrEP?*

Dr. Rao explained that the reason the WG proposed only the booster in the policy questions is because titer checks are considered to be clinical guidance and do not require a recommendation or a vote, and that the only items up for a vote during this session would be the WG's proposed changes to the primary series and titer checks. She then summarized the EtR framework for the rabies PrEP vote. During a 2019 ACIP meeting, the WG reported that they reviewed in great detail the response that various populations have to rabies vaccine. A systematic review of the literature found that that children, pregnant women, and persons ≥65 years of age mounted responses similar to those of healthy adults regardless of the series unless they were immunocompromised. Similar to ACIP's conclusions in the past, the WG concluded that efficacy can be a concern in persons with altered immunity. If PrEP has to be administered while a person has altered immunity, a titer should be checked after completion of the primary series to ensure an appropriate titer level. This is very commonplace in the US, with 3 laboratories that check titers in-person. Clinicians provider boosters until titers are ≥ 0.5 IU/mL. Therefore, the WG concluded that the recommendations to be voted upon during this session would apply to all persons who receive PrEP and that persons with altered immunity would be managed in the same way they always have been and for which there is clinical guidance.

As a reminder, 2 rabies vaccines are licensed in the US that have been used for decades. The first is the HDCV, IMOVAX®, that is manufactured by Sanofi Pasteur and administered intramuscularly (IM) at a potency of ≥2.5 IU of rabies antigen. The second is the PCECV, RabAvert® that is manufactured by Bavarian Nordic and administered IM at a potency of ≥2.5 IU of rabies antigen. Based on the WG's review, there have been no changes in the favorable safety profiles of these 2 vaccines.

During a previous meeting, ACIP requested that the WG characterize the population for whom the PrEP recommendations in the US apply. The WG created a mathematical model based on workforce statistics produced by the Bureau of Labor Statistics (BLS) and market research provided by Bavarian Nordic. The model estimated that 170,000 doses of PRrEP are given each year in the US, including 500 doses estimated to be given as booster doses after titer checks. The numbers of people who receive PrEP is estimated to be about 60,535 per year. In terms of the numbers by risk group, travelers and other risk groups make up the larger sector at over 41,000; veterinary technicians: 13,860; veterinary students: 3,500; animal control: 1,178; rabies laboratory personnel: 480; and wildlife biologists: 400.

Regarding adherence to the PrEP recommendations, veterinary students and laboratory personnel are known to be 100% compliant with the ACIP recommendations because it is enforced by their veterinary schools and by laboratory directors, respectively. For the remaining careers, the WG found answers from an unpublished CDC report. The data in this report were part of a survey that was completed a few years ago by Dr. Jesse Blanton, who is co-leading this WG with Dr. Rao. Most of the findings were published in the manuscript, but the data pertaining to veterinary technicians and staff showing 69.3% did not align with other published studies that found much lower adherence of at 30 to 40%. The WG hypothesized that all of the numbers in the Blanton study represent an over-estimate of the compliance because of who was surveyed. The survey was sent to about 2,000 members of professional organizations who were certified providers. There are a lot of uncertified animal care technicians practicing who would not have been reached by this survey. The particular population to whom the survey was sent all belonged to the professional organizations and may have been more compliant with ACIP recommendations, given all of the activity that they had. The intent of sharing this information was to show that a lot of people for whom ACIP recommends PrEP are seemingly

not receiving it. That is an important point the WG wanted to make since it was part of their EtR Framework in October.

**Rabies PrEP: Summary of EtR**

**Dr. Rao** (CAPT, USPHS; Co-Lead Rabies ACIP WG; CDC/NCEZID) next summarized the EtR summary for the two policy questions. For Policy Question #1 regarding primary immunogenicity, the population is persons for whom rabies vaccine PrEP is recommended. The intervention is a [0, 7 days] rabies vaccine PrEP schedule and the comparison is a [0, 7, 21/28 days] rabies vaccine PrEP schedule. The only outcome for this policy question was primary immunogenicity because as mentioned previously, the safety profile for these vaccines has remained favorable. This is an important issue because rabies is nearly always fatal. PrEP is an important component of preventing human rabies in the US. PrEP is critically important to some persons, including those with an unusual exposures (e.g., aerosolized) or high concentration virus; those with unrecognized exposures; those with frequent exposure to potentially rabid animals; and those who travel abroad to canine-rabies endemic regions without quick PEP access.

Rabies modern cell culture vaccines are very effective and ACIP had recommended them for PrEP for decades. The non-compliance among some for whom it is recommended is of concern. The WG hypothesized that out-of-pocket costs are related to that and some occupations do not require the vaccine even though it is recommended by the ACIP. It is also known anecdotally from speaking with travel clinicians, including travel medicine clinicians in the WG, that people tend to book these travel clinic appointments without much time for the third dose of the rabies vaccine to be given.

To summarize the WG's interpretations of the various EtR domains, the WG concluded that the benefits of this series are minimal because people have 100% seroconversion for both the proposed 2-dose series and the current 3-dose series. The WG thought the harms were minimal because there are no safety concerns, and that the benefit/harm ratio favored both the 2-dose dose and 3-dose series. The WG found the overall certainty of the evidence to be moderate, Level 2, due to concerns for risk of bias as shown in the GRADE table during the last ACIP meeting.

In terms of costs, the reimbursement price for a rabies vaccine dose is approximately $331 dollars according to Center for Medicare and Medicaid Services (CMS). Additional costs are variable depending on the location where PrEP is given. Based on a figure from the same unpublished study that Dr. Blanton pursued as mentioned earlier, professionals go to a variety of facilities to get their PrEP vaccines (e.g., doctor offices, travel medicine clinics, occupational health clinics, veterinary schools, public health clinics). In addition, 2% of respondents reported going to the emergency department (ED) for PrEP doses. Some of the WG confirmed this to be true based on their experience as well.

The WG extrapolated that since 3 doses of vaccine are needed for PrEP, the costs are estimated to be $1100 to $3500, taking into consideration that ED costs could be $3500 on average. The WG read anecdotally on veterinary school blogs that some of these costs are sometimes subsidized, but there still seems to be a cost to all of these recipients. The $3500 figure is from unpublished data from a robust analysis by the Minnesota Department of Health several years ago that outlined ED costs related to PrEP. All costs are anticipated to be paid for by employers. As part of the same survey that Dr. Blanton performed, respondents were asked whether their insurance covers all or part of PrEP and titer doses and whether their employers

cover all or part of PrEP and titer doses. There were not full payments by insurance or employers reported among the professionals who responded to this survey, which included about 2,000 people in the US.

All of this contributed to the WG's thoughts about the domains for the EtR. In terms target population sentiments, the target population values protection from rabies and there is likely no important variability. Regarding acceptability to stakeholders, a shorter schedule is preferred by patients and providers. In terms of whether this is a reasonable and efficient allocation of resources, the WG felt that Policy Question #1 would be cost-saving because rabies vaccine shortages have occurred in the US. The WG thought that the impact on equity probably would be reduced because of the decreased cost. Feasibility was thought to be high because of the shorter series and fewer clinic appointments. The WG interpreted that the target population sentiments are probably that the desirable effects are large compared to the undesirable effects. and that the data show that high costs are incurred by PrEP and that persons who should receive for travel are often not receiving it because they make their clinic appointment with less than 21 days before their planned travel. The current 3-dose series stretches out to Day 21.

Taking all of this together made the WG concluded that the desirable consequences probably outweigh the undesirable consequences in most settings, and proposed the following recommendation for an ACIP vote:

> *"ACIP recommends a 2-dose [0, 7 days] intramuscular rabies vaccine series in persons for whom rabies vaccine pre-exposure prophylaxis (PrEP) is indicated."*

In terms of Policy Question #2 pertaining to long-term immunogenicity (e.g., risk for rabies beyond 3 years from the primary vaccination series, the population is persons in the #3 risk category for whom rabies vaccine PrEP is recommended (e.g., veterinarians, animal care workers, travelers, et cetera). It is not for laboratorians or bat biologists. The intervention is a Day 21-Year 3 rabies vaccine booster after the [0, 7 days] rabies vaccine PrEP schedule. The comparison is no rabies vaccine booster after the [0, 7 days] rabies vaccine PrEP schedule proposed, and the only outcome is long-term immunogenicity.

Immunology suggests that an anamnestic response occurs to an exposure that demonstrated primary immunogenicity regardless of the series. The World Health Organization (WHO) did not comment on a need for a booster or titer after the 2-dose primary series when they made a change to their recommendations a few years ago. Because rabies is nearly 100% fatal, the WG wanted to take the most cautious and conservative route. There are data to show that an anamnestic response occurs for up to 3 years, but there are no data in the GRADE table about whether an anamnestic response occurs beyond that. When boosters are given 1 to 3 years after the primary series, titers remain higher for longer. The current PrEP series is a 3-dose series with the third dose as soon as Day 21.

Since language was proposed in late January 2021, new data were published in the *Journal of Infectious Diseases*.[1] That paper evaluated 6 persons after 10 to 11 years who were included in the study who received a 2-dose PrEP series [0, 7 days]. Of those, 5 had titers that were ≥0.5 IU/mL at the titer check 10 or 11 years later. All of them had 4-fold increase in titers after receipt of a booster dose, showing that the series is boostable and that perhaps a lot people may not even need a booster if a titer check is done per ACIP guidance at 1 to 3 years after the primary

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

series. This is encouraging information. More data expected about long-term immunogenicity of 2-dose series because WHO recommendations were made in 2018. Perhaps at that point, it might be possible not to require any titers or boosters for the people in the #3 risk group.

CDC has been talking about ways that they also might be able to assess this in the years going forward if the 2-dose dose series is approved by the ACIP committee. Until then, the WG felt that the benefits of offering a one-time booster as an option for long-term immunogenicity were moderate. A booster at Day 21 is equivalent to getting a current 3-dose series for implementation purposes and is known to provide long-term immunogenicity in 100% of subjects who received a booster between 1 and 3 years. It is already known from the GRADE table the WG presented during the October 2020 meeting that the vaccine has boostability. The WG thought the harms were minimal and there are no expected safety concerns. In terms of the balance of benefits/harms, the WG felt that the intervention was favored in this situation. The overall certainty of the evidence from the GRADE table presented in October was low certainty of evidence (Level 3) because it was considered observational data.

In terms of whether the target population feels that the desirable effects are large relative to the undesirable effects, the WG's interpretation was probably yes. Stakeholders want to avoid acquiring a high-stakes infection and want to avoid their staff from acquiring a high-stakes infection. A booster provides reassurance that outweighs any inconvenience. The WG did not think here was uncertainty about or variability in how much people value the outcomes. The target population values protection from rabies and there is likely no important variability. The WG also thought it was acceptable to stakeholders because they are accustomed to accommodating a third dose of rabies vaccine and will find it acceptable to have the booster as an option. The WG it would be a reasonable and efficient allocation of resources and that the recipients might be encouraged to adhere to the ACIP recommendations given the personal cost-savings that they would experience.

In terms of the cost of titers compared to boosters, this particular policy question is about a booster as an alternative to a titer. The titer is part of the clinical guidance and does not require a vote, but can cost significant less than a booster. For instance, a titer might cost $50 to $75* + cost of blood draw / clinic appointment compared to about $331 for a booster and additional costs associated with a clinic appointment or the ED. Regarding the impact on equity, some PrEP costs are out-of-pocket. Because titer is offered as option, inequity could be resolved by choosing that option. The WG discussed the feasibility to implement receipt of the booster dose at length. This seemed to be the biggest concern for travelers because travelers are not likely to return 1 to 3 years after their primary vaccination series to get a titer check or booster. Those providers may, for ease of implementation, opt to schedule a booster dose as soon as the patient returns from their travel.

The WG concluded that the desirable consequences clearly outweigh the undesirable consequences in most settings, and proposed the following recommendation for an ACIP vote:

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

## Summary of Discussion

- It is challenging in general to think about de-implementation for vaccines.

- Consider mentioning in the clinical guidance that someone who is planning to travel can opt to get their titers tested before they resume travel to determine if they have appropriate protection. If not, they can receive a booster. This type of guidance would be helpful to clinicians.

- Perhaps there would be value in separating the short-term group from Risk Category #3 and creating a Risk Category #4 for people with short-term risk. This will make it very clear that the #3 risk group is only people who have sustained risk for rabies.

- It is important to remember that for short-term risk, there may be intermittent workers, volunteers, travelers, et cetera who are going back to similar places.

- It seems that like one of the biggest issues with immunization is that those who are high risk are not getting vaccinated due to the barrier of cost. There is concern that the reduction of one immunization is not significant enough of a decrease in the barrier to protect the lives of people who are at risk. While this is a nice attempt, it may not be the right place to put the effort. Requiring immunization and payment by providers or employers may be much more appropriate than reducing the number of shots, given that this is a lethal disease:

    - Dr. Rao clarified that the reason the WG was proposing a 2-dose PrEP series was not just for cost savings. There were good data indicating that the efficacy is no different from that for a 3-dose series and that the same thing can be accomplished with fewer vaccines. They did reach out to WHO and no failures have been reported to them related to the 2-dose PrEP series. There also are efforts underway to ascertain what might facilitate insurance companies and employers in paying for PrEP.

- More data are needed for immunocompromised host, given that some immunocompromised hosts many need 1 dose and others may need 4 doses to mount an appropriate antibody titer.

- Children may be at higher risk than adults of exposure as travelers to international settings simply because they do not have the same judgment as adults. They are smaller, lower to the ground, and less likely to be able to defend themselves. If it is N/A for long-term immunogenicity, that removes the opportunity to get what is called a “booster” 21 days after. That would be limiting the child who is likely at higher risk than the adult traveler to only 2 doses. Whereas, as currently proposed, it is 2 doses plus a third at 21 days:

    - Concern was expressed that one of ACIP’s closest partners, the American Academy of Pediatrics (AAP) and the AAP Red Book Committee had not had an opportunity to review these data on their own and weigh in. Some ACIP members stated that they would be very unhappy with an ACIP recommendation that was not consistent with an AAP recommendation. Perhaps it would be prudent to delay applying these proposed recommendations to children until the WG is able to have a more robust discussion with partner organizations and consider this further.

- Dr. Blanton pointed out that the available evidence is consistent that children have the similar or possibly somewhat more robust response to rabies vaccine series in general. If there is an exposure, there is still an expected PEP regimen given. There are robust data throughout the years, maybe not specifically in children for the 0, 7 schedule, but there have been studies with reduced dose schedules in children. There would be no reason to believe that under normal circumstances a child who has had at least two doses of vaccine would not respond robustly with an anamnestic response to a 2-dose PEP series after an exposure.

- It was suggested that children under 18 years of age be removed from this discussion and that the proposed recommendations should be for individuals ≥18 years of age.

- Concern was expressed that adding "persons ≥18 years of age" might disenfranchise some children. It either would not apply if 3 doses continue to be given to children, or could apply and should be done.

- It is important to note that implementation issues (e.g., financial barriers, what insurance pays for, what employers pay for, how the recommendations are being implemented, et cetera) are especially challenging, but are not the purview of ACIP. ACIP has very limited ability to influence those kinds of issues. For non-routine vaccinations such as these, it is oftentimes difficult for CDC to actually monitor some of this:

  - Some of ACIP's Ex Officio partner organizations might actually have a lot more ability to address and follow some of these implementation issues.

  - The CDC website should be pristine, perfectly clear, and very user friendly on these quite complicated and challenging issues.

- At the close of this discussion and with the caveat that minor wordsmithing may be performed after the vote, the wording of the recommendations for an ACIP vote were:

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

  - *"ACIP recommends an intramuscular booster dose of rabies vaccine, as an alternative to a titer check, no sooner than day 21 but no later than 3 years after the second dose PrEP series for those who have sustained and elevated risk for only recognized rabies exposures (i.e., those in risk category #3) of rabies PrEP recommendations table)."*

## Public Comments

The floor was opened for public comment during the February 24-25, 2021 ACIP meeting at 12:30 PM ET. Given that many more individuals registered to make oral public comments than could be accommodated, selection was made randomly via a lottery. The comments made during the meeting are included here. Members of the public also were invited to submit written public comments to ACIP through the Federal eRulemaking Portal under Docket No. CDC–2021–0008. Visit http://www.regulations.gov for access to the docket or to submit comments or read background documents and comments received.

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

Thank you to all members of the ACIP. My name is Sarah Barry. I am an independent pro-vaccine advocate from Ohio. This is my first time giving a public comment, but not my first time applying. The first time I applied was for the February 2020 meetings. Although I was sad that I wasn't picked, I could hardly predict what was to follow in the coming months, which I now feel very compelled to share. It is important to first warn you of the extensive influence of anti-vaxxers in politics. The antivax 501(c)(4) Health Freedom Ohio successfully killed legislation concerning vaccines and is actively in support of bills that would weaken the authority of the Ohio Department of Health. By my estimation, more than half of the Republican Party in Ohio is under the influence of antivax lobbyists. I wanted to exercise my First Amendment right and give testimony on one of these bills to specifically warn of the influence of these anti-vaxxers. To my surprise, the lobbyists from Health Freedom Ohio responded by attempting to literally censor my testimony from being heard in front of the committee. They were even caught on video bragging amongst themselves about how they, and I quote, "worked behind the scenes" unquote to stop me from testifying. The presence of anti-vax lobbyists is troubling for sure. However, when they have become powerful enough that they tried to silence the only person who is criticizing them, I hope we can all agree that a critical point has been reached. So, what next? Well, I think it begins and ends with the portion of my testimony that probably angered the anti-vax lobby more than any other. I genuinely believe that the anti-vaccine community endorses and/or enables the abuse of autistic children. It is because of my efforts that a book teaching parents how to use bleach as an autism cure was removed for sale from Amazon's website. I have watched in dismay as doctors who administer chelation as an autism treatment gave public comment to this committee. As a layperson, I have found that informing average people of these aspects of the anti-vax community, which I've only begun to touch on, is a much more convincing argument than continuing to parrot the same old sound bites that people have heard before. Yes, I agree that vaccines are safe and effective. But that's a really terrible argument for somebody who doesn't really know anything about vaccines. Health Freedom Ohio could have chosen to try and let me speak and then they could publicly debunk what I said for everybody to see. Since they decided to try and censor me, it makes me certain that they are unable to defend themselves against my words. So, I will have to keep repeating these words until the day I die, even if I have to get it tattooed on my body. Anti-vaxxers abuse autistic children. Anti-vaxxers abuse autistic children. Anti-vaxxers abuse autistic children. Thank you so much for your time.

**Emma Schwartz, MPH**
**President, Medical Center of the Americas Foundation**
**Chief Executive Officer, Bio El Paso-Juarez**

Good afternoon. My name is Emma Schwartz. I'm the President of the Medical Center of the Americas (MCA) Foundation in El Paso, Texas and CEO of Bio El Paso- Juárez. I have my undergraduate degree from Stanford University and Master's in Public Health from UCLA, for both of which I studied pandemics and US-Mexico border health issues. I'm here today to shed light on the situation along the US El Paso- Juárez border. Although we are two cities sitting across a river and major geopolitical boundary from each other, we are one community. Our healthcare systems are linked, with many El Pasoans obtaining medical care and products because of the lower cost of care and the high rate of un-insurance in El Paso. Many Juárezans obtain specialty care that they cannot find in Juárez. Our cultures are linked, with many of us flowing between our two cities to visit restaurants, access airports, attend school, visit family,

and shop. Our economies are tied, with 1 in 4 jobs in El Paso directly linked to the manufacturing industry and products and we are major ports of entry. As you all know, at this point in the pandemic, our goal is to achieve herd immunity in order to return to our new normal and re-establish our economy. Our experts estimate that if all goes smoothly, El Paso County, with a population of 850,000, will begin to reach herd immunity levels of 70% over the summer and 80% to 90%, which is much more desirable with the emerging variants, this Fall. We are proud to be one of the cities in the US with the highest percentages of the vaccine administration received, and we have a tremendous appetite for the vaccine. We want to achieve herd immunity and are doing our part to get there. However, if you consider our border location, then we must also consider Juárez's population impact on El Paso. Juárez is a population of 1.6 million. Until 2018, the El Paso Port of Entry handled Northbound border crossing traffic of over 800,000 trucks, more than 12 million cars with 22 million passengers, and more than 7 million pedestrians. In addition, approximately a 150,000 US citizens lived in the State of Chihuahua, all of whom can access vaccines in El Paso much easier than in the State of Chihuahua, but they're not factored into our population count. It is abundantly clear that we will not reach herd immunity in El Paso on the aforementioned timeline if we are only concentrating on vaccinating the El Paso County population. If the goal is herd immunity, then our border areas must be treated differently non-border cities. Thus, my request is two-fold. First, when allocating vaccines across the country, please consider the US population on the Mexican side of the border and the cross-border movement of people with regards to El Paso's allocations. Second, the manufacturing plants in Juárez have committed to funding $12 million dollars to purchase vaccines for their workforce of 350,000—40% to 50% of which have comorbidities such as diabetes. If the US government can help them gain access, the manufacturers will purchase and administer the vaccines. They are not requesting that the vaccine be donated, but they do need assistance in gaining access to the vaccine purchases. These two actions would make a tremendous difference in getting not only our region, but the entire country back to a new normal. Thank you for your critical work that you do and thank you for your consideration of this matter.

**Mary Izadi, JD**
**Constitutional Policing Advisor**
**Orange County Sheriff's Department**

Good afternoon. I am the Constitutional Policing Advisory for the Sheriff's Department in Orange County California. First, I would like to thank the ACIP committee and the CDC for your tireless efforts as it relates to the COVID-19 pandemic. Although I have submitted written comments, my focus today is to request clear direction from the CDC regarding COVID-19 vaccine prioritization for those incarcerated in county jails. The CDC's "Frequently Asked Questions" recommends vaccinating those who are working and living in corrections environment at the same time. However, unfortunately there is one oversight in Section 1b of the COVID-19 vaccine allocation program. Phase 1b enumerates Corrections Officers, but not those incarcerated. That omission has resulted in hurdles for those working directly to promote ethical principles in vaccine distribution and mitigate health inequities regarding vaccine prioritization at county jails. The CDC guidance must state with specificity that those incarcerated are in the 1b category. I recognize the need for flexibility at the local level, but listing corrections employees in 1b while omitting incarcerated persons results in a direct injustice that I wholeheartedly believe this committee did not intend. Without edits to the current vaccine allocation programs to match CDC guidance, state and local governments do not have the clarity needed for an ethical vaccine distribution plan that is consistent with CDC recommendations and Constitutional principles. If the CDC recommends Corrections Officers and those incarcerated should be vaccinated at the same time, then there must be adequate specificity to that effect. Two days

ago, the American Journal of Preventive Medicine published their research on the disproportionate COVID-19 case burden among correctional workers. Their research urged priority vaccinations to benefit workers, incarcerated people, and community members alike. Sheriff's departments across the nation have a Constitutional duty to care for the well-being of incarcerated persons. The CDC's current guidance and simultaneous vaccination is consistent with the Constitutional mandates under the 8th and 14th amendments. With one necessary correction, the CDC can rebalance inequity in vaccination distribution. The CDC cannot prioritize those who work in a facility without also prioritizing those who live in that same facility. I recognize there are limited resources and numerous valid competing interests. However, the harsh reality is with everyone trying to get to the front of the line, there is no financial incentive or political capital earned by prioritizing those who are innocent until proven guilty. In fact, over 75% of the population housed in Orange County jails are pretrial and are not convicted of a crime. Nelson Mandela said, "No one truly knows a nation until one has been inside its jails. A nation should not be judged by how it treats its highest citizens, but its lowest ones." Thank you again for the opportunity to speak to you today and for the invaluable CDC guidance that assists our nation in these unprecedented times.

**Nissa Shaffi, MS**
**Associate Director of Health Policy**
**National Consumers League**

Good afternoon. I'm Nissa Shaffi. I will be presenting public comment on behalf of the National Consumers League (NCL). For over 120 years, NCL has championed vaccine education and access for consumers who depend on these life-saving medical interventions. We extend our gratitude to the Advisory Committee on Immunization Practices for the opportunity to serve as a voice for consumers. NCL remains committed to educating consumers on the value and safety of immunizations. During the COVID-19 pandemic, immunization rates have dropped drastically, which means that our work is needed more than ever. Even under ordinary circumstances, vaccines are underutilized in adult populations, especially among racial and ethnic minority communities. Health disparities contribute largely to a burden for Hepatitis B infections, with Asian, Pacific Islander, and non-Hispanic Black communities having the highest rates of HBV-related deaths. Despite vaccine recommendations, there is an estimated prevalence for chronic HBV infection in the US of nearly 1.6 million persons. NCL is concerned that the updated guidance for those over 60 years of age with diabetes getting vaccinated only upon shared decision-making with their providers will not address the health disparities that persist. The populations at risk for Hep B infection are those that are more likely to lack access to healthcare and not have a primary care medical home. NCL would like to see the CDC support a large-scale education and outreach campaign to raise awareness of the risk of Hep B in older adults and call for increased Hep B screening in high-risk communities across the country. NCL similarly shared its disappointment in response to ACIP's 2019 recommendations for the pneumococcal vaccine PCV13 to be administered for those over 65 years of age with shared decision-making, based on the rationale that childhood vaccinations have dramatically reduced the spread of the disease. However, pneumococcal disease continues to result in an estimated 150,000 hospitalizations per year. Adults over the age of 65 remain at an increased risk. In light of the drop in childhood immunizations induced by the pandemic, the CDC may want to issue caution to providers that herd immunity may have diminished compared to years prior for many of the diseases we target with the most commonly recommended vaccines. As a commitment to our advocacy, NCL continues to reaffirm that vaccines save lives and we continue to support increased immunizations for preventable diseases. In closing, we encourage ACIP to maintain effective public messaging and strong vaccine recommendations to instill vaccine confidence so that the American public feels safe and informed in their decisions to vaccinate across the life

span. Thank you for your consideration of our views on this important public health issue. Thank you so much.

**Marla Dalton, CAE**
**Executive Director & Chief Executive Officer**
**National Foundation for Infectious Diseases**

Thank you and good afternoon. I am Marla Dalton, Executive Director and CEO of the National Foundation for Infectious Diseases, or NFID. On behalf of NFID as a long-standing partner of CDC, thank you to all of the members of ACIP for the valuable work you all do. As you know, influenza activity for the current flu season has been low, which is largely attributed to infection control measures implemented during the COVID-19 pandemic, as well as the limited number of children interacting in-person and schools across the US. But even though flu activity has been low, we remain aware that it could increase at any time. As we look ahead to the 2021-2022 respiratory season, we recognize that more children will likely be back at school learning in-person; there may be less attention to social distancing, face masks, and hand hygiene; and family and friends who have stayed apart throughout the pandemic will reunite. Flu will be back and we must prepare. Flu kills tens of thousands of people in the US every year. In addition, pneumococcal disease can be deadly, especially for adults aged 65 years and older. Many of the same individuals who are most vulnerable to serious complications of COVID-19, including older adults, those with chronic health conditions, and under-represented minorities are also at greater risk for complications from flu and pneumococcal disease. In the US, communities of color bear a disproportionate burden of serious flu illness and related outcomes, along with historically lower flu vaccination rates. A recent NFID survey of us Black adults found that only 54% had received or plan to get a flu vaccine during the current flu season, and the top reasons cited were concerned about potential side effects and the misconception that you can get flu from the vaccine. We all must make it clear that there are safe vaccines available to help prevent flu and you simply cannot get flu from the vaccine. Additional information about the survey as well as webinars and other resources to help health care professionals address these misconceptions is available on the NFID website at www.nfid.org. As we all continue to fight the ongoing COVID pandemic, we need to prioritize prevention and treatment of all infectious diseases, including flu and pneumococcal disease. Annual flu vaccination as recommended by CDC can reduce hospitalizations and can help save lives. With new vaccines to prevent pneumococcal disease on the horizon, we all must work to ensure that patients understand the burden of these diseases and the importance of prevention through vaccination. Now more than ever, the work of ACIP in guiding US immunization policy is vital to protecting public health. On behalf of NFID, thank you all for your dedicated service.

**Cesar Ochoa**
**Mesa de Contingencia COVID**

Thank you. Good afternoon. My name is Cesar Ochoa. I live and work in Ciudad Juárez, Mexico across the border from El Paso, Texas. I am here as a member of the Mesa de Contingencia COVID Chihuahua, a private-public task force put together to address the many problems created by the pandemic in our region. Thank you for allowing me to present their concerns for this scientific forum. This presentation tends to give you a vision from the issues raised by my colleague Emma Schwartz. I will be speaking about my area of the border, but remarks should be substantially true for all of the twin cities located on both sides of the US-Mexico border. Allow me to emphasize that the appeal the Miss Schwartz and I are making has enormous economic, political, and humanitarian precautions, but is primarily a scientific one. I have been preparing for this presentation for three days because lives are at stake. Hundreds of lives can

be saved if our hypothesis is correct and if Emma and I can convince you to work together to address its consequences. Our hypothesis is that herd immunity through actual calculations for the American border towns must consider the population of the Mexican side of the border as well. We believe that your country's program to vaccinate the population that lives on the American side of the US border will not fully succeed unless we work together to vaccinate the people on the Mexican side of that same border. In other words, the herd is not only the population of El Paso. It is the combined population of El Paso and Juárez. Assuming this is correct, if you vaccinate 100% of the citizens of El Paso for example, you will have vaccinated less than one third of the herd because Juárez has 1.6 million citizens. Between-border cities are quite literally "joined at the hip." Our destinies, including the epidemiological ones, are inextricably linked. The border that separates the cities is permeable—very, very permeable. It would be naïve to think that the virus will honor any border wall. Now one statement of fact. Mexico's official sources indicated on February 19th that the total number of vaccines administered as of that date country-wide was 167,000 doses. We are your partners and we need help. Therefore, we respectfully come before you with an invitation and a promise. Our invitation is to work together to determine if our hypothesis regarding the border herd immunity threshold is correct. Our promise is that if our hypothesis is correct, you will find in our group a tireless ally who will overcome every single one of the many obstacles in the path to achieve the required herd immunity in our region, US and Mexico. We have a commitment with the region and we will work with the Mexican federal government, with you, and with anyone else who is willing to help. Thank you for your consideration.

**Motion/Vote #1**

**Dr. Rao** (CAPT, USPHS; Co-Lead Rabies ACIP WG; CDC/NCEZID) posted the following proposed recommendation for a vote, which Dr. Romero read aloud:

> *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.*

**Motion/Vote: Rabies PrEP Recommendation #1**

Ms. Bahta made a motion and Dr. Poehling seconded to accept the recommended language as written for Rabies PrEP Recommendation #1. No COIs were declared. The motion carried with 14 affirmative votes, 1 negative vote, and 0 abstentions. The disposition of the vote was as follows:

| | |
|---|---|
| **14 Favored:** | Ault, Bahta, Bell, Bernstein, Chen, Daley, Frey, Kotton, Lee, Long, McNally, Poehling, Romero, Sanchez |
| **1 Opposed:** | Talbot |
| **0 Abstained:** | N/A |

**Motion/Vote #2**

**Dr. Rao** (CAPT, USPHS; Co-Lead Rabies ACIP WG; CDC/NCEZID) posted the following proposed recommendation for a vote, which Dr. Romero read aloud:

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

**Motion/Vote: Rabies PrEP Recommendation #2**

Dr. Long made a motion and Dr. Ault seconded to accept the recommended language for Rabies PrEP Recommendation #2 with a suggested edit to read, "ACIP recommends an intramuscular booster dose of rabies vaccine, as an alternative to a titer check for immunocompetent persons ≥18 years of age who have sustained and elevated risk for rabies only from 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 second dose PrEP series." No COIs were declared. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

| | |
|---|---|
| **15 Favored:** | Ault, Bahta, Bell, Bernstein, Chen, Daley, Frey, Kotton, Lee, Long, McNally, Poehling, Romero, Sanchez, Talbot |
| **0 Opposed:** | N/A |
| **0 Abstained:** | N/A |

Following the vote, ACIP members were invited to comment on the rationale for their votes:

Dr. Lee re-emphasized the importance of clear clinical guidance, particularly with regard to Proposed Recommendation #2. She remains concerned about the gaps that might occur with implementation and wants to ensure that all of those who might fall in the booster category are optimally protected, particularly Risk Group #3, with the knowledge that travelers are typically proactive about getting vaccinated or ensuring that they are protected. It is the non-traveler groups who are particularly important in terms of implementation.

Dr. Chen indicated that as a travel medicine physician, he feels on a daily basis the intricacies of trying to implement rabies vaccination. Sometimes with short notice of travel, they are unable to deliver the full rabies series with the 3 doses. Therefore, he appreciated the intent where they are data-driven in making the decision for having a 2-dose series and the discussion to parse out some of the questions regarding missing data that they would like to explore to further develop these recommendations.

Dr. Frey thanked the committee for all of their input regardless of how anyone voted because she understands that this is a very serious disease that has almost 100% mortality, with the exception of one or two people that are known of. The WG understands the concerns having spent a lot of time going back and forth with these discussions, which were quite rigorous.

ACIP's input allowed them to make changes that probably improved what the WG presented and improved the vote.

Dr. Bell reiterated Dr. Lee's comment and noted that this is not an unfamiliar situation from an implementation perspective. Effective implementation will require CDC to reach across the experts in the travel medicine, pediatrics, and veterinarian communities and people who understand clear communication to make the website crisp in order for this to be effectively communicated and to work.

Dr. Long said that found this process to be very reassuring and thought it was important for ACIP to diminish or add vaccine doses as appropriate. To maintain the trust of the populous in that, careful ACIP deliberation and confidence among rabies experts are needed. It is terrific to be able to decrease a dosage once in a while that cannot give further benefit.

Dr. Romero expressed gratitude to Drs. Frey, Blanton, and Rao for an outstanding job. He noted that he sat on this WG and entered the committee with some trepidation as to whether this was an appropriate step. He thought they amassed a large set of data which support these recommendations and that this was an appropriate thing to do. He noted that given the marathon session of the morning, the additional two topics upon which Dr. Rao was intended to present, PEP and RIG would be tabled. Given that ACIP wants to foster and never stifle discussion and because the discussions leading up to the votes were so robust and important, they decided to keep going. These two topics will be brought back before ACIP at another time.

## DENGUE VACCINES

### Introduction

**Dr. Kathy Poehling** (ACIP, WG Chair) provided an introduction to the Dengue Vaccines session, extending a special thanks to all of the members of the ACIP Dengue Vaccine WG for their very robust conversations. She explained that the Dengue Vaccine WG has had quite a history. As a reminder, the 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 Food and Drug Administration (FDA) approval. In 2020, the focus was on vaccine acceptability, WHO's global position, feasibility, and health equity. In 2021, the focus is on dengue immunoglobulin G (IgG) test evaluation, the EtR Framework, and a draft recommendation anticipated to be presented to ACIP later in the year.

Since November 2020, the Dengue Vaccine WG group has discussed whether zika virus infection (ZIKV) enhances future risks of severe dengue disease, an update on the developmental status of a new dengue IgG rapid test to determine past infection, the feasibility of the recombinant, live-attenuated, tetravalent chimeric dengue vaccine (CYD-TDV) vaccination program, CYD-TDV and health equity, and evaluation of commercial dengue IgG tests. In addition, a straw poll and discussion have begun on EtR sections. CYD-TDV vaccine presents novel challenges due to being the only vaccine requiring pre-vaccination screening. A test for pre-vaccination dengue screening needs to be specific to minimize vaccination of seronegative children, as well as sensitive to maximize identification of children who can benefit from the vaccine. The WG group is reviewing data and considering including recommended test

performance characteristics in the *Morbidity and Mortality Weekly Report (MMWR)* accompanying future ACIP recommendations. Anticipated for the 2021 calendar year are further WG discussions to finalize the EtR Framework, presentation of the EtR and draft WG recommendations during a spring ACIP meeting, and an ACIP vote on CYD-TDV in June 2021.

## Evaluation of Commercial DENV (DENV) IgG Tests for Pre-vaccination Screening

**Dr. Freddy Medina** (CDC/NCEZID) presented on evaluation of commercial DENV IgG tests for pre-vaccination screening. This work was done at the CDC Dengue Branch Surveillance and Research Laboratory for which Dr. Jorge Munoz serves as the Laboratory Director. Dr. Medina explained that dengue fever is caused by 4 closely related but distinct virus types. In theory, a person can be infected with DENV 4 times in their lifetime. One of the main findings of the Phase 3 dengue vaccine study shows that in individuals without previous dengue exposure (seronegative), the vaccine can mimic a primary DENV infection and increase the risk for hospitalization due to severe dengue. In individuals with prior exposure to DENV (seropositive), the vaccine shows a protective effect that reduces hospitalization in severe dengue.[2]

In May 2019, the FDA approved Sanofi Pasteur's vaccine named Dengvaxia® to prevent dengue disease caused by all 4 dengue serotypes types in children 9 through 16 years of age living in areas where DENV is endemic (e.g., Puerto Rico, American Samoa, Guam, and the US Virgin Islands) who have laboratory-confirmed previous dengue infection. Before vaccination, healthcare providers (HCP) must evaluate children for prior DENV infection using medical records of a previous laboratory-confirmed infection or through serological testing prior to vaccination. Uninfected or seronegative children should not be vaccinated. To develop a target product profile (TPP) for a dengue IgG dengue vaccination screening test, meetings with experts in country representatives from Latin America and Asia Pacific regions were organized by the Partnership for Dengue Control (PDC). A preliminary draft is available of the TPP resulting from this meeting.[3]

To provide an example of the positive and negative predictive value using a population with a DENV prevalence of 50%, similar to what is observed in Puerto Rico, a test with 70% sensitivity and 98% specificity would have a 97% positive predictive value (PPV) and a 77% negative predictive value (NPV) resulting in a benefit for 352 positive individuals for every 1000. The risk of potential harm by inadvertently vaccinating seropositive individuals would occur in 10/1000 individuals. The true negative individuals who should not be vaccinated is 490 out of 1000. Those who should be vaccinated but are not identified due to a false negative result are 150. Raising the sensitivity of the test from 70% to 90% raises the predictive value above 90% and increases those who would benefit from vaccination. This reflects the need for high test performance in areas with moderate DENV endemicity.

There are problems with the currently available DENV IgG tests. First, the current commercial kits were developed for the detection of high IgG antibody levels such as those typically found in recent or acute secondary infection. Second, only a few studies have evaluated IgG test performance using specimens from remote (>1 year) primary and secondary infections. Third, many DENV IgG tests were developed prior to the zika virus outbreak so most of them have not been evaluated for cross-reactivity with zika virus in endemic areas. The challenge is to find DENV IgG tests with high sensitivity for low levels of dengue IgG and with high specificity and no cross-reactivity with ZIKV antibodies.

[2] Sridhar, S, et al. *N Engl J Med*. 2018 Jul 26; 379(4):327-340
[3] https://www.fondation-merieux.org/wp-content/uploads/2019/10/dengue-pre-vaccination-screening-strategies-workshop-2020-report.pdf

Previous evaluations of DENV IgG tests have potentially been biased by the selection of specimens. The strategy these studies use consisted of using plaque reduction neutralization test (PRNT)-confirmed flavivirus samples from West Nile virus (WNV), Japanese encephalitis (JE), and ZIKV and then performing a test to detect IgG antibodies against the DENV structural protein NS1. If the sample was positive, it was considered as having been exposed to DENV. This may have resulted in the exclusion of flavivirus specimens that are cross-reactive with DENV and could have resulted in artificially low levels of cross-reactivity among the validated DENV IgG screening tests.

Therefore, the objective of the Dengue Branch's study was to perform an independent evaluation of sensitivity and specificity of selected DENV IgG tests for their potential use in pre-vaccination screening with an emphasis on detection of monotypic DENV infections long after exposure and cross-reactivity of anti-ZIKV antibodies and DENV IgG tests. This study was limited in scope and size and was not intended as a large-scale evaluation. The methods were to: 1) review manufacturer and peer-reviewed independent evaluations of more than 30 anti-DENV IgG tests made for the detection of recent DENV infection; 2) evaluate 7 tests with the best performance data using samples from recent DENV or ZIKV from 7 to 30 days after symptom onset; 3) further evaluate 5 tests with low ZIKV cross-reactivity and moderate to high sensitivity for the detection of remote DENV infections that occurred at least a year after infection; 4) add to the evaluation 1 newly available rapid test in two versions, rapid test 3a and 3b, made for the specific detection for anti-DENV IgG in remote infections; 5) evaluate the best performing test with challenging samples from early convalescence and with high ZIKV IgG and neutralizing antibodies; and 6) compare evaluations from the CDC and the manufacturer of the new rapid test. All tests were purchased by CDC without established agreements with manufacturers, and sample selection was made independently and confidentially by CDC.

The composition of the sample panel for remote infections included unexposed (N=8), PRNT50 negative (titer ≤4) specimens from Puerto Rico and Alaska. Remote infections of those that were collected over a year after infection included DENV primary (N=13) PRNT50 neutralization of a single serotype; DENV secondary (N=9) PRNT50 neutralization of two or more serotypes; ZIKV primary (N=14) PRNT50 neutralization of ZIKV >80 and no DENV serotypes (N=7); and ZIKV RT-PCR positive case, DENV and ZIKV IgG negative (days post onset [DPO] 0-5), specimen collected 3-4 years after infection very limited DENV transmission in between (N=7). The top 3 tests with the best performance were evaluated with additional specimens. For this, specimens were added that included unexposed PRNT50 negative specimens from Puerto Rico (N=21) and Alaska (N=20); and remote ZIKV primary specimens that were obtained from a cohort in Nicaragua (N=22) that included a reverse transcriptase polymerase chain reaction (RT-PCR)-positive case and a DENV and ZIKV inhibition enzyme-linked immunosorbent assay (ELISA) negative specimen collected approximately 1.5 to 2.5 years after the infection. Because ZIKV is the main cause of cross-reactivity in areas of [inaudible] with DENV, an additional panel was developed to further challenge the best performing test, which included cases of ZIKV confirmed by RT-PCR with no previous dengue infections. These samples were selected for high IgG ELISA and PRNT titers and were obtained 3 or 4 months after infection. These samples were included to effect test performance in the scenario of ZIKV transmission potentially could affect pre-vaccination screening.

In terms of the performance evaluation and results from the initial evaluations that included 7 commercial tests and the CDC IgG ELISA and the specificity panel composed of unexposed ZIKV primary specimens, no false positive were observed in the unexposed population. However, false positives were detected in the primary ZIKV population. The highest cross-reactivity was observed in the CDC IgG ELISA where 13 out of 14 specimens tested positive. While most of the testing or evaluation had low cross-reactivity, the CDC IgG ELISA that uses virus-like particles (VLP) of antigens, detected the maximum number of positives but is highly cross-reactive and meant to be used in combination with PRNT confirmatory testing. In the sensitivity panel, the ELISA test 2 and rapid test 3a and 3b performed well. The ELISA test 1 had high sensitivity, but exhibited higher cross-reactivity with ZIKV than desired. ELISA test 3 and rapid test 1 had very low sensitivity such that more than half of the DENV specimens were missed and no DENV primary specimens were positive. Rapid test 2 did not detect any DENV specimens despite performing well in the initial evaluation with acute DENV specimens.

Based on these initial findings, the investigators decided to add additional negative and DENV primary specimens to further evaluate ELISA test 2 and the two versions of test 3. In terms of the performance of DENV IgG test percentages with the initial 44 specimens used in the panel plus the additional negative and ZIKVA primary specimen added to further evaluate ELISA test 2 and rapid tests 3a and 3b, the sensitivity for the DENV IgG ELISA was high but the specificity is low. ELISA test 1 had moderate sensitivity and specificity. ELISA test 3 and rapid tests 1 and 2 performed poorly. ELISA test 2 and both versions of rapid test 3 displayed moderate sensitivity ranging from 68% to 82% and very high specificity above 97%, despite the inclusion of ZIKV and other negative specimens.

Regarding cross-reactivity of ZIKV specimens and the DENV IgG test evaluated, the level of ZIKV cross-reactivity and the CDC DENV IgG ELISA was high at 93%. Moderate cross-reactivity was observed in ELISA test 1 and low cross-reactivity was observed in ELISA test 3 and rapid test 1 and 2. The level of ZIKV cross-reactivity was low and ≤ 8% in ELISA test 2 and both versions of rapid test 3. ELISA test 2 and rapid test 3 also were evaluated with a selection of challenging ZIKV primary samples with the highest ZIKV IgG OD values in neutralizing antibody titers. These samples were collected approximately 3 to 4 months after ZIKV and represented a worst case scenario in the event of the emergence of ZIKV. ELISA test 2 had the highest level of cross-reactivity with these challenging specimens and nearly 4 times higher than what was observed in the evaluation using remote specimens, while the results from both versions of rapid test 3 were similar to that seen using remote specimens.

Turning to a side-by-side comparison of CDC and manufacture evaluations for rapid tests 3a and 3b, the results from the manufacturer's evaluation were presented to the Dengue Vaccine WG in May 2020. As noted earlier, the manufacturer and CDC evaluations were performed independently and the specimen panel sources are different. The sensitivity observed by the manufacturer was higher than that observed by CDC for both versions of the test and could be in part explained by the higher proportion of monotypic specimens using the CDC evaluation. The specificity observed by the manufacturer was 98% in rapid test version 3a. They decide to make modifications in this test to increase its specificity, which increased to 99% in version 3b. The CDC evaluation observed no difference in specificity between the two versions of rapid test 3.

Looking at a side-by-side comparison of ZIKV cross-reactivity and rapid test 3 evaluation by the manufacturer and CDC, the manufacturer did not see any cross-reactivity of ZIKV specimens in the 3a version, while the 3b version has not yet been evaluated. CDC did see a low level of cross-reactivity of 6% for both versions of the test. The ZIKV remote specimens are from cohorts in Puerto Rico and Nicaragua. There is RT-PCR confirmation in acute specimens in 29 out of 36 cases. The other 7 ZIKV specimens were from Puerto Rico and were selected based on virus mutualization testing. Data were provided to CDC by the manufacturer of rapid test 3 showing that the cross-reactivity with other relevant flaviviruses is low in the rapid test version 3a. The cross-reactivity of all flaviviruses was less than 3% in the test.

The limitations of the CDC study are that the number of the specimens in the evaluation was small, particularly for sensitivity. The sensitivity of DENV IgG tests may be underestimated due to emphasis in remote primary DENV infections. A high proportion of ZIKV samples included in the specificity panel are greater than the prevalence in the target population. The cross-reactivity with ZIKV has been addressed in the context of past infection but may need additional testing of early convalescence specimens.

In conclusion, there are commercial tests currently available that potentially could be used for pre-vaccination screening. Three pre-anti DENV IgG tests performed with high specificity of 97% to 98% and moderate sensitivity of 68% to 82% with low ZIKV cross-reactivity of 6% to 8%. Half of the commercial tests evaluated performed poorly, with sensitivity of less than 30% for the detection of anti-DENV IgG antibodies long after exposure despite their demonstrated use to diagnose recent infection. Test sensitivity was higher for multitypic DENV infections than in monotypic DENV infections.

## Dengue Vaccine WG Interpretation

**Dr. Gabriela Paz-Bailey** (CDC/NCEZID) presented the Dengue Vaccine WG's perspective. As Dr. Medina said, the CDC evaluation of the DENV IgG test was small (N=107) and generalizability is limited. Given that previous evaluations could have been biased by excluding DENV IgG positives from the specificity panels, the goal of this evaluation was to address problematic areas that could be affecting the estimates of sensitivity, specificity, and cross-reactivity. The results suggest that most of the tests that are intended for acute diagnosis did not perform adequately for detection of DENV IgG antibodies in the context of pre-vaccination screening, especially in terms of sensitivity. One ELISA assay and two versions of a rapid test performed best. The CDC evaluation results may be conservative, meaning that they may represent minimum performance, as the samples were selected to highlight problematic areas for sensitivity and specificity. There is a large proportion of monotypic infections in the estimates for sensitivity, and there is a large proportion of ZIKV samples in the specificity panel. The manufacturer is planning to conduct a large prospective evaluation of the rapid test in Puerto Rico and the mainland, with a goal to recruit about 650 participants beginning this year.

One of the Dengue Vaccine WG's priorities has been assessing that acceptable tests exist or that they will be available for the safe implementation of pre-vaccination screening. This evaluation has helped to clarify that there are a few tests that could be used for this purpose. The WG is currently completing the EtR, which will be presented to ACIP along with draft recommendations in the Spring. Potentially, the WG will present recommendations for a vote in June 2021. The WG also is working in the TPP that would include minimal and optimal performance characteristics of the test used for pre-vaccination screening. The target profile would be included in the clinical guidelines in the *MMWR* with the ACIP recommendations. The

jurisdiction will have to play a role to ensure that recommended test characteristics are met for the test used for pre-vaccination screening.

An example TPP was developed by the PDC and the Global Dengue and Aedes-Transmitted Diseases Consortium (GDAC)[4] after extensive consultations with vaccinologists, country representatives, and key opinion leaders and diagnostic manufacturers. The CDC evaluation findings were added to this example. This TPP proposes a minimal sensitivity of 85% and optimal of 95%. Tests with the best performance had lower sensitivity than that recommended by the TPP. The TPP values for specificity are 95% for the minimal and 98% for performance. The values in the CDC evaluation were higher than the minimal recommended for the 3 tests and met the optimal specificity for the 2 rapid tests. Again, it is important to remember that the CDC evaluation may have resulted in conservative estimates for sensitivity. In terms of the Dengue Vaccine WG perspective, the international target for a profile can be adapted for the US territories context, and specificity is considered to be more important than the sensitivity to "cause no harm." A subgroup from the Dengue Vaccine WG is working on developing a TPP for the Dengue Vaccine WG's review and consideration.

As part of the cost-effectiveness analysis, mathematical modeling[5] was done to estimate hospitalizations averted and additional hospitalizations by erroneously vaccinating seronegatives after screening with the test with imperfect sensitivity. The model simulated a 10-year cohort of 9-year-old children in Puerto Rico and used a pre-vaccination screening test with 80% sensitivity and 98% specificity. The coverage of screening was set at 80% of the population, with all those testing positive being vaccinated. The model assessed various prevalence scenarios among these 9-year-old children, which is the age when vaccination would start. At 30% prevalence, approximately 1655 hospitalizations would be averted after 10 years of vaccinating and 123 additional hospitalizations could be caused for a ratio of 13 averted for 1 additional case. At 15% prevalence of 15%, the ratio would be 60 hospitalizations averted to 1 additional case. At 60% prevalence, the ratio would be 135 hospitalizations averted to 1 additional case.

In closing, Dr. Paz-Bailey posed the following questions for ACIP to consider during the discussion period:

1. Does ACIP concur with including pre-vaccination screening dengue IgG test target product profile in *MMWR* that accompanies ACIP recommendations?
2. Are there other considerations the WG should address?

## Summary of Discussion

- Well-intentioned practitioners in dengue-endemic areas are going to want to test and then vaccinate according to test results. However, they are not necessarily going to be able to appreciate how baseline prevalence affects test performance or the issue of cross-reactivity. ACIP members agreed that in order to provide dengue vaccine safely, pre-vaccination screening dengue IgG test TPP is critically important to include in the *MMWR* that accompanies any recommendations.

[4] https://www.fondation-merieux.org/wp-content/uploads/2019/10/dengue-pre-vaccination-screening-strategies-workshop-2020-report.pdf
[5] 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

- In terms of whether the WG/ACIP might consider making age-specific recommendations for pre-vaccination screening, it was noted that this vaccine is approved for use among those 9 through 16 years of age, which is pretty narrow already.

- With respect to several questions about hospitalizations, Dr. Paz-Bailey confirmed that the takeaway message was that the risk of severe dengue is tied to the second episode of dengue and not necessarily to age. However, she emphasized that hospitalizations and severe dengue occurring among first infection, third, and fourth infections as well. The majority, or higher frequency, of hospitalizations result after secondary infection and has more to do with that than age. For example, there is a shift in severe dengue and hospitalizations in Asia toward older groups because the epidemiology of dengue is changing and incidence has decreased in recent years and now older populations are more likely to be infected. This is a different epidemiology from that observed in Puerto Rico and in Latin America.

- Regarding a question raised about the WG's consideration of potentially recommending re-screening at 2-year intervals, it was clarified that the WG is discussing this as part of the EtR Framework. The children who would be vaccinated would be seropositive and ages 9 through 16 years of age. For instance, if screening were to begin in this age group in 2022, there would be a group of seronegative children who would be screened again in 2 years to be able to detect those who acquired DENV in the interim.

## TICKBORNE ENCEPHALITIS (TBE) VACCINE

### Introduction

**Dr. Kathy Poehling** (ACIP, WG Chair) reported that Pfizer submitted a Biologics License Application (BLA) to the FDA for their TBE vaccine, with licensure possible by the third quarter of 2021. No TBE vaccine has been licensed in the US previously and there is no existing ACIP TBE vaccine recommendation. The terms of reference for the TBE Vaccine WG are to: 1) review information on TBE, including its epidemiology, clinical presentation, diagnosis, treatment, and outcome; 2) review data on infection risk and burden for US civilian and military travelers and laboratory workers; 3) review data on vaccine safety, immunogenicity, and effectiveness; 4) provide evidence-based recommendation options for ACIP; 5) identify areas in need of further research for informing potential future vaccine recommendations; and 6) publish future ACIP recommendations in the *MMWR*. The planned WG timeline for February 2021-October 2021 was to present TBE epidemiology in endemic areas and traveler and laboratory worker risk data during this session, present to ACIP the GRADE on vaccine safety and immunogenicity and EtR in June 2021, and entertain an ACIP vote on vaccine recommendations and finalize the *MMWR* publication in October 2021 assuming licensure has taken place by that time.

### TBE Epidemiology in TBE-Endemic Areas

**Dr. Susan Hills** (CDC/NCEZID) indicated that TBE is a flavivirus in the *Flaviviridae* family and flavivirus genus. The 3 main subtypes of TBE virus are Far Eastern, Siberian, and European. The disease is endemic to parts of Europe and Asia and is transmitted predominantly by ticks. Transmission also can occur occasionally through other means, including ingestion of unpasteurized dairy products, slaughter of animals, blood transfusion, organ transplantation, breastfeeding, or laboratory exposure.

In terms of the clinical features of TBE, asymptomatic infection is common with estimates up to about 80% of infections being asymptomatic. When clinical illness occurs, it can be biphasic or monophasic. Biphasic illness is typical for patients infected with the European subtype of the virus and consists first of a febrile illness phase, followed by remission of symptoms, and then a second phase with neurologic illness. A monophasic neurological illness is more typical with the Far Eastern and Siberian subtypes. Some patients present with only a non-specific febrile illness, which usually lasts 2 to 4 days. The clinical presentations include meningitis, encephalitis, or meningoencephalomyelitis for those who develop neurologic illness.

The case fatality rate and frequency of neurological sequelae vary depending on the viral subtype. The case fatality rate is about 1% to 2% with the European subtypes, about 6% to 8% with the Siberian subtype, and about 20% the Far Eastern subtype. Studies assessing neurologic sequelae provide highly variable rates, but sequelae rates range from 10% to as high as 80% of cases that have been reported. Severity and incidence of disease are highest in older persons. Children typically have a milder illness than adults. Meningitis occurs more frequently than meningoencephalitis, and meningoencephalomyelitis is rare. Estimates of the proportion of children with neurological sequelae vary, but they appear to occur in fewer than 10% of children and only a small percent is severe in each of these. Some studies suggest that cognitive problems like impaired concentration and memory might be underrecognized, and death is very rare.

There are limited reports of TBE in various special populations. Among the small number of reports in women infected during pregnancy, the medical spectrum of illnesses ranges from mild febrile illness to severe neurologic illness. Among infants born to these women, most are reportedly healthy even when the mother has had a severe illness. There are some older anecdotal reports of adverse outcomes in a small number of infants, but no laboratory testing was done in these cases to support TBE virus infection in the infant as the cause. Therefore, transplacental transmission of TBE virus has not been confirmed at this time. One case of TBE virus transmission through breastfeeding has been described, in which the infant purportedly had severe illness and survived with severe sequelae. When immunocompromised persons are infected, the illness is typically severe and there appears to be a higher risk of fatal outcome in these patients.

Being a tick-borne disease, the distribution and activity of infected ticks clearly affects human disease patterns and risk. Infected Ixodes species tick, mainly ixodes Ricinus or ixodes persulcatus, transmits TBE virus to humans. Ixodes ticks are distributed in natural foci, tend to be stable over time, and can be very limited in size with hotspots as small as one square kilometer. They prefer sites near the edges of forests in areas with deciduous trees, low growing dense bush, and low ground cover. TBE virus infection rates of ticks are generally low at typically less than 5% and can be variable over time. Certain recreational activities and occupations result in an increased risk for exposure to ticks. Some of the key recreational activities at increased risk include camping, biking, fishing, cycling, birdwatching and foraging for mushrooms, berries, or flowers. Occupations that are at increased risk include forestry workers and military personnel. TBE viruses have been found in ticks in some urban park land areas and in backyard gardens, but the risk in urban areas is considered to be very limited.

It is quite difficult to assess and compare TBE cases and data by country, which is related to several factors. First, diagnostic tests are not routinely available in many areas and the performance of available assays varies. Second, there are differences in reporting practices by country including different case definitions and case specifications and variability in whether reporting is voluntary or mandatory. It is clear that surveillance data are of variable quality by country and over time. Data must be considered over appropriate timeframes because incidents fluctuates from year-to-year and assessment of data from short intervals can suggest misleading trends. Finally, vaccination impacts case numbers. Although vaccination rates are low in most countries, the availability of data is limited.

In terms of TBE epidemiology in Europe,[6] TBE was added by the European Centre for Disease Prevention and Control (ECDC) to the list of mandatory notifiable diseases in 2012. During 2014 to 2018, reported cases numbered approximately 2,000 to 3,000 annually and reported incidence remained relatively stable from 0.4-0.6 cases per 100,000 population. Almost all cases had disease onset during April to November, with 59% occurring during the warmest months from June through August. Disease was predominant in males with a ratio of 1.5:1. The rate of reported disease was highest in adults 45 to 64 years pf age. A map showing reported locally acquired TBE cases in Europe from 2012-2016 had a range from 0 TBE cases in some countries or areas to at least 15 case per 100,000 population in others. The highest incidences of disease is reported in the Baltic countries.

In terms of understanding risk among travelers, some countries have no surveillance so information on risk is not readily available and there is substantial variability in TBE incidence reported from countries in Europe. The granularity of data in countries is highly variable, with some countries reporting only national data and others reporting data at various subnational levels. When subnational data are reported, the risk is not uniform across the country. It is important to note that a certain area does not necessarily correspond to the risk of infection for travelers. Although infected ticks or animals have been identified in many areas, for instance, no human cases have occurred. Regarding TBE cases in Europe by country and year for a 28-year period of time from 1991 to 2018, there are a few key messages illustrated by a graph of cases shown in a publication by Dobler at al.[7] First, the graph clearly shows the fluctuation in case numbers from year-to-year by country. Second, there are different disease patterns in different countries. Third, trending case numbers have been relatively stable over time in many countries but have increased in a small number of countries and decreased in others.

While there has not been a substantial increase in human TBE case numbers overall, there clearly has been an expansion in the range of TBE virus in Europe. During the last 30 years, the geographic area with infected ticks has increased, including locations further North and West in Europe; locations in higher altitudes, with infected ticks found at elevations over 5000 feet; and with new foci within countries. The specific reasons are unknown and are likely related to a complex variety of factors affecting the tick and affecting their hosts, including climatic, ecologic, and anthropogenic factors. This expansion in the range of TBE virus transmission is not necessarily associated with an increased risk for humans or establishment of endemicity over the longer term. For example, in recent years when there have been newly recognized foci transmission, this is often not being associated with any human TBE cases or only with sporadic cases.

[6] https://www.ecdc.europa.eu/en/tick-borne-encephalitis/surveillance-and-disease-data/annual-epidemiological-report
[7] Dobler et al, The TBE book, 2019 (Russia not included)

Russia was not included on the earlier graph by Dobler et al. of reported TBE cases in Europe, given that its case numbers have been substantially higher than other countries. Looking at TBE incidence in Russia from 1944 to 2018, disease peaked first in the mid-1950s and second in the mid to late 1990s with over 10,000 cases reported in 1996. However, during the last decade, national incidences have significantly decreased. Currently, there are about 2,000 reported cases per year. The average incidence from 2007 to 2016 was about 1.9 cases per 100,000 population. However, this was variable from region-to-region. For example, there were 23 regions with low incidence, 14 regions with moderate incidence, and 6 regions with high incidence.

To complete the epidemiological picture, Dr. Hills briefly discussed the epidemiology of TBE in Asia. In China, incidence is about 0.3 TBE cases per 100,000 population. There are three foci in the Northeast, Northwest, and West. However, the epicenter is in Northeastern China. In Japan, only 5 human cases have ever been reported and all have come from Hokkaido, an island in the Northeast of the country (1 diagnosed in 1993 and 4 cases from 2016 to 2018). In South Korea, no human cases have been identified. Studies have detected TBE virus in ticks and rodents in dispersed areas of the country.

Only about 50% of the countries with risk areas have vaccination recommendations for their local population. When recommendations are made, they are very variable. Austria is the only country with a national recommendation. Some have subnational recommendations based on risk. Some have recommendations for those spending extensive time outdoors in risk areas or for certain occupational groups. When there are recommendations, government reimbursement is provided by less than 30% of the country. Sometimes, it is only partial reimbursement. In some countries, vaccination is covered by private insurance. However, there also is the issue of people actually getting vaccinated. Overall, vaccination rates are generally considered to be low, ranging from a few percent up to no more than 25% in most countries. The only major exception to that is Austria, which has reported rates higher than 80%.

In summary, the epidemiology shows some key features. First, TBE can be a severe clinical illness with potentially high mortality and sequelae rates. Second, virus transmission occurs in focal areas during the warmest season when ticks are active. However, risk can be highly variable over space and time. Finally, given the tick-borne nature of the disease, the main risk for infection occurs when humans visit settings that put them at risk for exposure to ticks when recreating or working in tick habitats.

## TBE among US Civilian Travelers and Laboratory Workers

**Dr. Erin Staples** (CDC/NCEZID) indicated TBE is not nationally notifiable in the US and currently, there is no commercially available test to diagnose TBE. However, limited testing is available at certain academic centers, state public health laboratories, and a few US Government (USG) facilities. Some of these laboratories do not have TBE-specific testing, but they do have IgM antibody testing for other closely related flaviviruses (e.g., Powassan virus) that can be positive for TBE IgM antibodies due to cross-reactivity. The CDC does have TBE virus-specific molecular and serologic testing capacities available. Identification of cases relies on clinicians to consider TBE in the differential diagnosis for returning travelers with clinically compatible illness and pursue TBE testing. Because of this, cases are expected to be missed. Since testing is limited mostly to CDC and a few other laboratories, it is believed that there is good capture of cases when testing is performed and found to be positive.

To be classified as a TBE case, a traveler must have both a clinically compatible illness (e.g., either the febrile illness or neuroinvasive disease) and laboratory evidence of infection. Laboratory evidence of infection classifies the case either as confirmed or probable based on the level of certainty. Confirmed cases have to have evidence of a virus, viral antigen, ribonucleic acid (RNA) in the clinical sample, or serologic evidence showing a change in virus-specific neutralizing antibody titers determined PRNT or have IgM antibodies with other tests for closely related arbovirus being negative. For probable case classification, they have to have an IgM positive sample in serum or cerebrospinal fluid (CSF) with no other related virus testing performed.

Prior to the year 2000, there had been only 1 TBE case reported among US travelers in a 4-year-old girl who traveled with her family to Hungary where she became unwell, got better briefly before traveling home, and then developed meningoencephalitis.[8] Since 2000, there have been 11 cases of TBE identified among persons who traveled from the US to an endemic area and then returned to the US. This includes 10 confirmed and 1 probable case. There typically are either 1 or no cases identified per year, with the exception of 2012 when 2 cases were identified. The vast majority of cases among US travelers have been a male and cases have been seen in all age groups, including 3 pediatric cases.

Most of the travelers developed their symptoms of TBE either in July or August. The 11 case of US travelers each had their illness onset in May and June. All diagnosed case patients had neuroinvasive disease, with roughly two-thirds (N=7) diagnosed with encephalitis and one-third (N=4) diagnosed with meningitis. In terms of outcomes, none were reported to die. However, the final status was not known for 2 of the cases. Of the remaining 9 patients who survived, one-third (N=3) reported having long-term sequelae ranging from mild cognitive issues in 2 patients to more pronounced neurologic issues of severe dysarthria and mild bradykinesia in the limbs in 1 patient.

Among the cases, 7 were exposed in Europe (2 in the Czech Republic, 2 in Sweden, 1 in Switzerland, 1 in either Switzerland or Austria, and 1 in Finland). There are 3 cases for which the country of probable acquisition was Russia, namely Siberia or the Eastern area of Russia. Finally, 1 case was associated with travel and exposure in China. The approximate duration of travel was documented for all cases and ranged from 7 days up to 2 months. The median duration of travel was 24 days or roughly 3.5 weeks. The specific activities the travelers took part in were not available for 3 (27%) of travelers. For the remainder, the most common activity reported was hiking, followed by substantial outdoor exposure in rural areas such as frequent picnicking in grassy areas. One each reported camping, fishing, or working on a property. Just over half (N=6) reported a known tick bite. Among those, two-thirds (N=4) report more than one bite.

To summarize TBE cases among US travelers, there have been 11 cases over the last 21 years. This is a relatively low number of TBE cases identified among US travelers. The majority of cases were in male and occurred in both pediatric and adult patients or travelers. None of the cases died, but one-third reported sequelae. Thankfully, a severe outcome was relatively rare. Infection was acquired in late Spring into Summer in countries known to be endemic for the virus. Risk activities like hiking and camping occurred in known tick habitats, with several cases reporting tick bites prior to illness onset.

[8] Cruse et al. *Am J Dis Child*. 1979 Oct;133(10):1070-1

To briefly review what is known about TBE virus infection among laboratory workers, TBE virus should be handled at biosafety level (BSL)-4 or enhanced BSL-3 laboratory. The latter includes precautions beyond BSL-3 such as enhanced respiratory protection, special airflow in the laboratory, and showering in and out of an area where the virus is being worked on. Most of the data on TBE virus infection and disease in laboratory workers comes from review of literature and surveys conducted by the Subcommittee on Arbovirus Laboratory Safety (SALS).[9] The initial survey they conducted was sent out in 1976 to international and national laboratories and repeated in 1978. Since the report by SALS, there has been only one additional case reported in the literature.[10] There have been no additional surveys conducted of laboratories since the late 1970s. Most laboratory personnel who are working with the virus or who might be exposed to the virus in laboratories outside of the US are routinely vaccinated against TBE.

From the SALS report, there were 45 infections or disease cases reported. With one additional case reported in 1995, that means there is a total of 46 known TBE virus infections among laboratory workers. Of these, 36 (78%) resulted in disease, including 2 deaths. Information on the route of transmission was limited among the reports. All known exposures were due to aerosolization either during laboratory procedures or handling infected animal waste. Among the 46 cases, at least 4 occurred among US laboratory workers and 3 of the 4 exposures resulted in disease. Among the 3 cases in laboratory workers, there were 2 known deaths due to TBE and 1 asymptomatic infection. All exposures for US laboratory workers were due to aerosolization. None of the laboratory workers were known to have received the vaccine. Overall, there has not been a large number of laboratory-acquired infections over time, but the likelihood of disease among those with known exposure is high and among US laboratory workers based on the fact that half of the infected workers died.

## TBE among Military Personnel and Dependents

**Dr. Bruce McClenathan** (DoD) presented on the Department of Defense's experience with tick-borne encephalitis. By way of background, TBE has been recognized as a public health and force health protection threat since the 1970s for US Service Members and beneficiaries residing in or traveling to Europe. TBE risk for military families living in some host nations is estimated to be similar to other residents of those areas. Additionally, there may be locations or activities that place certain individuals or units at increased risk of tick-borne encephalitis. Most Service Members stationed in the European Command (EUCOM) areas of operation are transferred there on orders for at least 3 to 4 years and are known as Permanent Party Service Members. Permanent Party Service Member populations stationed within the USEUCOM can be at risk for TBE. In addition, DoD can send Service Members to areas within the (EUCOM) area of operation on temporary duty.

Eastern Europe adds additional temporary force members who rotate approximately every 9 months. Germany is the country in which the greatest number of Service Members and beneficiaries are stationed who might be at risk for TBE. TBE became a notifiable disease in Germany in 2001, and the majority of cases are reported from the southern states of Baden-Wurttemberg and Bavaria, both of which contain US military installations. Military personnel may engage in activities which place them at higher risk for contact with tick vectors to include field training exercises, outdoor work, and recreational activities such as hiking or camping.

[9] The Subcommittee on Arbovirus Laboratory Safety of the American Committee on Arthropod-Borne Viruses. Am J Trop Med Hyg 1980.
[10] Avsic-Zupanc T et al. Clin Diagn Virol. 1995;4(1):51-9

Because of known Service Members and DoD beneficiaries developing TBE and its increasing prevalence, TBE risk assessments have been conducted by various military organizations. The headquarters (HQ) of the USEUCOM tasked its Counter Biothreats Cell to conduct a risk assessment, and they deemed that TBE posed a moderate biothreat. In addition, the National Center for Medical Intelligence (NCMI) conducted a risk assessment with similar conclusions. The need for TBE vaccination for force health protection is supported by high-level DoD leaders to include the USEUCOM, the US Special Operations Command (USSOCOM), and the Joint Chiefs of Staff (JCS). DoD medical leaders advocate that an FDA-approved vaccine in combination with personal protective measures will assure the best available protection for our troops and their families.

Of note, North Atlantic Treaty Organization (NATO) nations offer their Service Members either of the 2 European Medicines Agency (EMA)-approved vaccines. However, the FDA has not approved these vaccines for use by US Service Members currently. Therefore, these vaccines are currently offered on a voluntary basis. Service Members must first obtain a referral from their military provider consulting with a local host nation provider and then obtain vaccine from that host country's Tricare provider. It is very difficult to track overall uptake through this process. In addition, there is no mechanism for civilian contractors and civil servants working in these regions which can be multiyear assignments to obtain TBE vaccines through their insurance.

With that background, Dr. McClenathan transitioned to the DoD's experience with TBE over the last several years from 2006 to the present. Most of the cases have been well-described by Dr. Mancuso and colleagues[11] in the *Medical Surveillance Monthly Report* (*MSMR*) dated November 2019. This article described 8 individuals who developed TBE between 2006 and 2018. Since this publication, a single additional case is known to DoD that occurred in 2020. These cases have some interesting correlations. Dr. McClenathan briefly reviewed the case definitions from the ECDC[12] mentioned earlier by Dr. Staples.

In terms of the known 9 cases of TBE within the DoD from 2006 to 2020, 5 met the case definition for "Confirmed" and 4 met the case definition for "Probable." All patients had neurological illness consistent with the case definition. Virtually all of the individuals reported fever. Other symptoms variably included weakness, mental status changes, nausea, headache, vomiting, diarrhea, and neck stiffness. Many patients had sequelae lasting from days to over a year. For example, there were reports of decline in memory/difficulty concentrating for greater than a year; fatigue, attention/concentration issues for 5 months; fatigue, headache, visual disturbances for 1 month; and reduced psychomotor function and headaches for 10 days.

Among the 9 cases, 1 occurred in 2012 and the remaining 8 cases have occurred since 2017. As expected, virtually all the cases occurred during tick season, which as Dr. Hills mentioned was between April and November. The cases occurred exclusively in Germany, specifically the southernmost space of Baden-Wurttemberg and Bavaria. In terms of demographics, these cases involved a wide age range of individuals 2 to 47 years of age with the median age being 33 years. Of the cases, 8 were male and 1 was female. This mirrors what Dr. Staples mentioned in the civilian population. The 1 female was a child. Looking at the beneficiary status of the individuals, 6 were either Service Members or retired Service Members and 3 were dependent children. When looking at the individual's travel status, all cases of TBE occurred in residents on Permanent Party status. None of the individuals were in a temporary traveling status. Also, none

[11] Mancuso JD, Bazaco S, Stahlman S, Clausen SS, Cost AA. Tick-borne encephalitis surveillance in U.S. military service members and beneficiaries, 2006-2018. MSMR. 2019 Nov;26(11):4-10. PMID: 31804845

[12] https://www.ecdc.europa.eu/en/tick-borne-encephalitis/facts/factsheet (accessed 11 Jan 2021)

of the cases reported receipt of TBE vaccines. The breakdown of cases by occupation was quite varied and did not isolate to one particular military specialty, though infantrymen would be expected to be more exposed to ticks because of their duty, engaging in more field training exercises, and being outside more.

In conclusion, TBE has been documented in the DoD population living in endemic areas. TBE is a public health and force health protection concern for US Service Members and beneficiaries residing in or traveling to Europe. TBE immunization opportunities for DoD may be insufficient without an FDA-approved vaccine.

**Summary of Risks of TBE for US Travelers and Laboratory Workers and Next Steps**

**Dr. Susan Hills** (CDC/NCEZID) summarized the issues that will inform the TBE vaccine recommendations in terms of risk for TBE for US travelers and laboratory workers. In terms of geographic locations where there is increased risk of infection, comprehensive data are frequently limited. The general area of TBE virus transmission extends from Europe through to Japan. The virus typically occurs in focal locations and precise transmission areas can be hard to define. Incidence is variable from country-to-country and in areas within countries. Transmission levels fluctuate from year-to-year and overall. There is a very low risk in urban areas. There is a clear seasonal risk that occurs in the warmer months from April to November when ticks are active.

There are very low numbers of TBE cases among US persons, with only 11 cases reported in US civilian travelers during the 21-year period from 2000-2020 and 9 cases among military personnel in the 15-year period from 2006 through 2020. While TBE occurs at low incidence among US travelers, the disease can have a high impact in terms of mortality and sequelae. Case fatality and sequelae rates vary depending on the infecting TBE virus subtype. In some subtypes, case fatality rates can reach 20% and sequelae rates can reach 80%.

The key risk factors for infection is entering an environment where exposure to ticks can occur, such as habitats in and on the edge of the forest and in other areas where there is low growing dense brush and low ground cover. Exposure to these environments can occur when travelers are involved in certain recreational activities such as hiking, camping, fishing, cycling, birdwatching or foraging for mushrooms, berries, or flowers. Occupational exposure can occur for persons in occupations like forestry work or the military. There is a risk for infection for laboratory workers working with TBE virus who can be exposed through the aerosol or other routes. While there have been only a small number of laboratory infections over time, the likelihood of disease among those with an exposure is high.

The TBE Vaccine WG group will be keeping this epidemiology information in mind as they draft vaccine recommendations. The next steps for the TBE Vaccine WG during the next 4 months are to review vaccine safety and immunogenicity information and relate these data as they prepare to present the EtR Framework and GRADE to ACIP during the June 2021 ACIP meeting. The intent is to have ACIP vote on vaccine recommendations during the October 2021 ACIP meeting. With that in mind, the WG prepared the TBE policy question, which is:

> *Should TBE vaccine be recommended for use in persons aged ≥1 year traveling to or residing in TBE risk areas and in laboratory staff working with TBE virus?*

## EBOLA VACCINE

### Introduction

**Dr. Sharon Frey** (ACIP, WG Chair) introduced the Ebola vaccine session, providing a brief recap of Ebola virus and the Ebola Virus Vaccine WG's activities since the last ACIP meeting. In February 2020, the ACIP recommended preexposure vaccination with Ervebo® for adults ≥18 years in the US population who are at highest risk for potential occupational exposure for to Ebola virus species *Zaire ebolavirus* (ZEBOV)because they are responding to an outbreak of Ebola virus disease (EVD); or they work as HCP at federally-designated Ebola Treatment Centers (ETCs) in the United States; or work as laboratorians other staff at BSL-4 facilities in the United States. As a reminder, the Ervebo® vaccine is a replication-competent vaccine which uses recombinant vesicular stomatitis virus (rVSV) that expresses the glycoprotein of Ebola virus species ZEBOV.

A number of key events have occurred since February 2020. The 10th EVD outbreak in the Democratic Republic of Congo (DRC) ended on June 28, 2020. There were 3400 plus cases, about 66% of which resulted in death. The 11th EVD outbreak in the DRC (Mbandaka Province) was declared on June 1, 2020 and ended on November 18, 2020. Although this outbreak was much smaller, the mortality rate was approximately 42%. On October 14, 2020, the FDA approved Inmazeb® (REGN-EB3) for the treatment of EVD caused by species ZEBOV in adult and pediatric patients. On December 21, 2020, the US FDA approved Ebanga® (mAb-114). Ebanga® is a monoclonal antibody for the treatment for species ZEBOV infection in adults and children. Shortly thereafter on January 7, 2021, *Use of Ebola Vaccine: Recommendations of the Advisory Committee on Immunization Practices* was published in *MMWR Recommendations and Reports*.[13] A month later on February 7, 2021, another EVD outbreak was reported in North Kivu Province. On February 14, 2021, an EVD outbreak was reported in N'Zerekore Prefecture, Guinea.

The WG has identified two additional US populations at risk for potential occupational exposure to Ebola virus for whom potential policy options are under consideration. These include HCP at a designated ETCs involved in the care and transport of confirmed EVD patients and also individuals who work as laboratorians and support staff at Laboratory Response Network (LRN) facilities that handle replication-competent Ebola virus. As a reminder, the published CDC definition of HCP is as follows:

> *Healthcare personnel (HCP) refers to all paid and unpaid persons serving in healthcare settings who have the potential for direct or indirect exposure to patients or infectious materials, including body substances (e.g., blood, tissue, and specific body fluids); contaminated medical supplies, devices, and equipment; contaminated environmental surfaces; or contaminated air. These HCP include, but are not limited to, emergency medical service personnel, nurses, nursing assistants, physicians, technicians, clinical laboratory personnel, autopsy personnel, therapists, phlebotomists, pharmacists, students and trainees, contractual staff not employed by the healthcare facility, and persons not directly involved in patient care, but who could be exposed to infectious agents that can be transmitted in the healthcare setting (e.g., clerical, dietary, environmental services, laundry, security, engineering and facilities management, administrative, billing, and volunteer personnel).*[14]

[13] https://www.cdc.gov/mmwr/volumes/70/rr/rr7001a1.htm
[14] Adapted from: https://www.cdc.gov/infectioncontrol/guidelines/healthcare-personnel/index.html

## Background on State-Designated ETC and LRN Facilities and Survey Results

**Ms. Allison Joyce** (CDC/NCEZID) presented the results of the Vaccine Acceptability Survey that was distributed among the two populations of interest, HCP in state-designated ETCs and individuals who work at LRN facilities with Ebola testing capability. Before the WG could begin discussing the consideration to expand eligibility for Ebola vaccine in these two populations, they requested more information about them and especially their interest in and acceptability of the Ebola vaccine. Therefore, CDC created a Vaccine Acceptability Survey and distributed it to the populations of interest along with excerpts from the package insert to help inform the survey respondents.

The available information on clinical efficacy, duration of protection, and potential adverse reactions of the vaccine were summarized. Background information was provided which reported that across various blinded placebo-controlled studies, arthralgia was seen in 3% to 40% of vaccine recipients, was generally mild to moderate in intensity, and resolved within one week. Arthritis was seen in 0% to 24% of vaccine recipients, mostly of mild to moderate intensity that resolved within several weeks. One study reported severe arthritis, defined as preventing daily activity in 12% of vaccinated persons. Information also was provided on potential transmission of the vaccine virus, including that that vaccine virus RNA was detected in the urine or saliva of some vaccinated individuals at time points ranging from Day 1 to Day 14. Following this background information, survey respondents were asked about their perceived risk of infection with ZEBOV, their interest in receiving the Ebola vaccine, and potential concerns they had about the vaccine.

Before presenting the survey results, Ms. Joyce shared some background on state-designated ETCs and how they differ from federally-designated ETCs whose personnel received approval for a preexposure vaccination during the February 2020 ACIP meeting. Both of these institutions are hospitals that are specially trained and equipped to manage the care of suspected EVD patients for the duration of their illness. There are currently 11 federally-designated ETCs in the US. These facilities receive funding directly from the Assistant Secretary for Preparedness and Response (ASPR), with the exception of the National Institutes of Health (NIH). NIH has a formal agreement with the federal government to provide treatment for a suspect special pathogen patient. Federally-designated ETCs have a specific HHS region for which they are responsible. For example, Cedars-Sinai Medical Center in Los Angeles would provide treatment for an EVD patient from California, Nevada, Arizona or Hawaii.

There are considerably more state-designated ETCs in the US. While CDC was not able to find an official list, they reached out to all 50 states and compiled a list of 51 hospitals that identify as state-designated ETCs. Additionally, these facilities do not receive federal funding. Essentially, these hospitals volunteer to become an ETC and approval is granted by state and local authorities. Some hospitals also can decide to no longer be an ETC, which could give them greater attrition potential as compared to federally-designated ETCs. There is also a question of whether a state-designated ETC would transfer a suspect Ebola patient to a federally-designated ETC. During preliminary discussions with a handful of state ETCs, 4 mentioned that they do not currently have a plan to transfer a suspect Ebola patient should one present to their facility. However, this is subject to change. Based on interviews with 5 of these hospitals, it was estimated that each ETC has a staff of 100 to 150 HCP. Thus, a potential recommendation for this population could involve between 5,000 to 7,500 HCP.

After identifying the list of 51 state-designated ETCs, an invitation to participate in the Vaccine Acceptability Survey was sent to 49 of them. Point of contact information was not available for 2 of the 51 facilities. A total of 364 survey responses were received. However, 66 of them were incomplete and therefore were excluded. This left a total of 298 responses included in the data analysis. The survey population was fairly evenly split between the ages above and below 40 years of age, with 52% above 40. However, women were more likely to respond to the survey and comprised 69% of the survey respondents. Looking at the professional groups of this population, nurses and doctors made up the majority of the survey respondents, with 39% of the survey population self-identifying as nurses and 22% as doctors. There were lower response rates from other professional groups, including respiratory therapists, emergency medical technicians (EMTs), advanced practice providers (e.g., nurse practitioners and physician assistants), laboratory technicians, managers, and environmental services staff.

Survey respondents were first asked, “If you were eligible for vaccination and offered the rVSV Ebola vaccine today, would you choose to be vaccinated?” Among this survey population, 54% expressed interest in receiving the vaccine. It is important to provide context as to when the survey respondents answered this question. “Today” refers to the time between October 14, 2021 through January 22, 2021 when the survey was available to this population. During this time, the Ebola outbreak in Equateur Province, DRC was declared over on November 18, 2020. Survey respondents also were given an option to choose when to get vaccinated and 23% said immediately, 25% said when an Ebola case was imported to the US, 33% said when an Ebola case was imported to their state in the US, and 19% said they would not choose to be vaccinated.

When the question of choosing to receive the Ebola vaccine was broken down and respondents were given the option of choosing when to receive it, the interest in vaccine rose from 54% to 81%. Survey respondents also were given the opportunity to provide free text responses explaining why they would choose not to be vaccinated. The most common responses were their perceived low risk of exposure and concerns about vaccine safety and potential long-term effects.

Looking at interest in the vaccine by age, respondents between 18 to 40 years of age were somewhat more likely to say they were interested in receiving the vaccine, with 57% being interested. For those aged 40 or above, there was not much of a difference. Women were split evenly, with 50% expressing interest in the vaccine. Men were considerably more likely to be interested in the vaccine, with 63% reporting interest. However, it is important to emphasize that a smaller total number of men responded to the survey, so it is possible that this result could be due to the smaller sample size.

There does not appear to be a clear pattern looking at interest in vaccine by profession. It does not appear that closer patient contact results in higher vaccine interest as doctors, nurses, EMTs, and laboratory technicians all were more likely to be interested in the vaccine than not. Advanced practice providers and respiratory therapists, who also have close patient contact, were less likely to be interested in the vaccine. Environmental services staff also were less likely to be interested in the vaccine, but this group was so small at only 3 people that this is not really an interpretable result.

When survey respondents were asked about their perceived severity of EVD and risk of infection, 89% of survey respondents said that they considered EVD to be a very serious disease, while 2 individuals responded that it was not serious. When asked about their perceived risk of infection if an EVD patient were admitted to their hospital, 48% of the survey respondents rated their risk of infection as low. Looking at interest in vaccine by perceived severity of disease, people who reported EVD to be very serious were more likely to be interested in the vaccine compared to people who reported EVD to be serious. The 2 individuals who reported EVD to not be serious both indicated interest in receiving the vaccine, so it is possible there was an error in their response. Looking at interest in vaccine by perceived risk of infection, those who thought the risk of infection was high or intermediate were more likely to be interested in receiving the vaccine, while those who thought the risk was low or next to zero were less likely.

When respondents were provided with a list of potential reasons for not being interested in the vaccine and asked to select all that applied to them, 55% expressed a concern that the risks of the vaccine outweighed the benefits and 42% were concerned about transmitting the vaccine virus to family and friends. When asked about which adverse reaction they were most concerned about, the potential for a serious adverse event (SAE) was the top concern for 32% of respondents, transmission of the vaccine virus to close contacts or patients was the top concern for 26%, and 23% were most concerned about the potential increased risk of arthritis. When asked what additional information would be most important to them, 66% expressed an interest in knowing more about the likelihood and nature of adverse events (AEs), 56% wanted to know more about the likelihood and severity of transmitting the vaccine virus, and 50% were curious if infectious disease experts and their peers were being vaccinated.

Survey respondents also were asked if they thought ACIP should vote to recommend the Ebola vaccine to HCP at state-designated ETCs. It is important to noted that the option of shared clinical decision-making was not included in this question. Among the respondents, 53% thought ACIP should recommend, 9% thought ACIP should not recommend, and 38% were unsure. Survey respondents were provided the opportunity to explain their choice in free text. The most common reasoning for those who thought ACIP should recommend the vaccine was that people should have the right to decide for themselves, HCP should be prepared, and the extra safety is worth it. For those who thought ACIP should not recommend, people's reasoning was that personal protective equipment (PPE) is sufficient to protect against EVD, the risk of exposure is so low, and there would be time to offer the vaccine if the situation in the US changes. Those who were unsure whether ACIP should recommend felt they needed more information on the vaccine, or they were not sure the benefits outweighed the risk.

In summary, 54% of the state-designated ETC survey population expressed an interest in receiving the vaccine today, which increased to 81% when people were given the choice to get vaccinated at a later time. Concern for SAEs and transmission of the vaccine virus to others were top concerns among the study population.

Turning to the results of the Vaccine Acceptability Survey for the LRN population in facilities with Ebola testing capability, the structure of the survey was the same as the one distributed to the state-designated ETCs. The LRN is a large network of laboratories that aim to respond quickly to biological and chemical threats and other public health emergencies. The LRN for biological threats preparedness (LRN-B) has 3 tiers. First, there are thousands of sentinel laboratories. These are largely in hospitals and local public health facilities and perform rule-out testing. Second, there are roughly 130 reference laboratories. These are largely found in state health departments and at various military, veterinary, agricultural, and water testing facilities and they

can do additional testing. Third, there are 3 national laboratories: CDC, the United States Army Medical Research Institute of Infectious Diseases (USAMRIID), and the Naval Medical Research Center (NMRC). Within the LRN, 62 facilities have EVD testing capacity. CDC estimates that 10 to 15 laboratorians per facility would be capable of performing the tests on a suspect EVD sample. Thus, a potential recommendation for this population could involve an estimated 620 to 930 individuals. Based on the numbers previously shared, there are roughly 1,133 facilities within the LRN-B. An invitation to participate in the survey was sent to 62 of these facilities as these were the ones with the capacity for EBV testing. A total of 96 survey responses were received, of which 26 were incomplete. This left a total of 70 responses that were included in the data analysis and this presentation.

Of this survey population, 76% were 40 years of age or above and 64% were female. When asked about profession, survey respondents were given the options of laboratory scientist, clerk or receptionist, environmental services, manager, or other. Of the respondents, 64% self-identified as laboratory scientist, 30% as manager, and 4 individuals self-identified as other. All 4 described themselves as director or laboratory director. Of the survey population, 59% expressed an interest in receiving the vaccine when asked if they were eligible and offered the vaccine today. The survey for this population was available from December 29, 2020 through January 21, 2021 when there were no active Ebola outbreaks in the world. When provided the option of choosing when to get vaccinated, 34% said immediately, 29% said when an Ebola case was imported to the US, 23% said when an Ebola case was imported to their state in the US, and 14% would not choose to be vaccinated. When the question of choosing to receive the Ebola vaccine was broken down and respondents were given the option of choosing when to receive it, the interest in vaccine rose from 59% to 86%. When given the opportunity to provide free text responses to explain their reasoning for choosing not to be vaccinated, the most common responses were their low risk of exposure and concerns about potential side effects. This population of the LRN was especially concerned about the increased risk of arthritis.

Looking at interest in vaccine by age and sex, people between the age of 18 to 40 and men were considerably more likely to say that they were interested in receiving the vaccine than not. In terms of profession, 64% of laboratory scientists expressed interest in receiving the vaccine compared to 52% of managers. This could be explained by laboratory scientists having closer contact with a potential Ebola virus sample than managers. Only 1 of the 4 laboratory directors expressed interest in receiving the vaccine. Among survey respondents, 96% classified EVD as a very serious disease and 59% thought that their perceived risk of infection was low even if an Ebola virus sample was sent to their facility for testing. Interest in vaccine by perceived severity of disease was interesting, with 58% of those who considered EVD to be very serious indicating interest in the vaccine compared to 67% who considered EVD to be serious. Interest in vaccine by perceived risk of infection followed the expected trend—the higher the perceived risk of infection, the more interest expressed in receiving the vaccine.

When asked about some possible reasons for choosing not to be vaccinated, 51% of the LRN survey population said the risks of the vaccine outweigh the benefits and 38% were concerned about transmitting the vaccine virus to family or friends. Potential increased risk of arthritis was a top concern among the LRN population, which differs from what was seen in the ETC population. However, the LRN population also was interested in receiving additional information on the likelihood and nature of AEs from vaccination as well as the likelihood and severity of transmitting the vaccine virus to others.

When asked if ACIP should vote to recommend the Ebola vaccine to staff at LRN facilities, again not providing the option of shared clinical decision-making, 59% said yes. The most commonly provided reason for why ACIP should recommend was that it provides an added layer of protection against a laboratory-acquired infection (LAI) and the LRN population as a whole is at increased risk of exposure to ZEBOV, with 1 person stating it is very likely that LRN personnel will be handling Ebola samples for diagnostic purposes. For the 6 individuals who felt ACIP should not recommend, all listed the low risk of exposure as their reason. For people who were not sure whether ACIP should recommend, the reasons provided were needing more information on the risk of exposure versus the risks of side effects and some felt the LRN may not be a high-risk group and that priority should be given to first responders.

In summary, 59% of the LRN study population expressed an interest in receiving the vaccine today, which increased to 86% when people were given the choice to get vaccinated at a later time. Common reasons for not wanting to receive the vaccine were low risk of exposure and concerns about potential side effects, especially arthritis, which differed from the top concerns of the state-designated ETC population.

## Review of Preliminary WG Discussions

**Dr. Caitlin Cossaboom** (CDC/NCEZID) presented on the ACIP Ebola Vaccine WG's discussion of the proposed recommendation text for the policy options currently under consideration. As Ms. Joyce discussed in her presentation, the ACIP Ebola Vaccine WG identified two additional US populations at risk for a potential occupational exposure to EVD for whom potential policy options are under consideration, HCP at state-designated ETCs who may be involved in the care and transport of suspect and confirmed Ebola patients and individuals who work as laboratorians and support staff at LRN facilities that may receive, process, and perform diagnostic testing on clinical samples from suspect Ebola patients. Dr. Cossaboom discussed the following policy issue:

> *Should preexposure vaccination with rVSVΔG-ZEBOV-GP be recommended for adults aged ≥18 years in the US population who are at potential risk for occupational exposure to EBOV because they are working as:*
> - *HCP[1] at state-designated Ebola Treatment Centers in the United States, or*
> - *Staff in LRN facilities that receive, process, and perform diagnostic testing on suspect cases of EVD?*

She emphasized that these WG discussions are preliminary and that the WG looked forward to feedback from ACIP during this session. The WG has discussed two policy options with regard to recommending the Ebola vaccine in HCP personnel at state-designated ETCs, "Recommend" and "Recommend with Shared Clinical Decision-Making. The considerations are ongoing, but preliminary discussions suggest that the WG favors shared clinical decision-making with regard to preexposure vaccination with the Ebola vaccine in this population.

To summarize the themes behind the discussions of the WG members who favor recommending vaccination in this population, these members believe that there is a comparable level of risk to HCP personnel in state-designated versus federal ETCs for which there was a recommendation issued by ACIP in February of 2020. They believe it is important to provide HCP at state-designated ETCs the same protection as their federal designated counterparts. Additionally, HCP at state-designated ETCs may have a higher risk of being exposed to an Ebola patient without prior notification because there are a higher number of state-designated ETCs at 51 facilities compared to the 11 federally-designated facilities. The federally-designated

facilities are more likely to receive Ebola patients transferred to them, which gives them the advanced notice to prepare. Additionally, these WG members have concerns that a shared clinical decision-making recommendation would essentially pass the responsibility to employees and/or healthcare providers when the individual level of risk within this population is very difficult to assess. Additionally, these WG members discussed that recommending the vaccine for this population would improve general preparedness of frontline HCP for a number of reasons. First, the side effects of the vaccine do not make it amenable for a just-in-time vaccination strategy after an imported case is identified in a facility because, for example, the expected reactogenicity would be difficult to differentiate from symptoms of EVD in the post-exposure scenario. Second, it is difficult retrospectively to identify the movements of potentially infectious materials and who may have been exposed. By recommending the vaccination, the same prevention tools are offered to all personnel who may have a potential exposure. Third, a recommendation would encourage state-designated management teams to be better prepared by evaluating in advance the movements of materials and identifying the persons within each facility who could be at risk of an exposure.

As mentioned earlier, preliminary WG discussions indicate that a majority of WG members seem to be favoring a shared clinical decision-making recommendation for this population for a number of reasons. First, one of the major concerns voiced by the WG is that occupational health programs may require employees to be vaccinated if it is recommended by ACIP. This raises concerns for unintended negative career consequences for persons who either do not want the vaccine or those with contraindications to vaccination. Second, state-designated ETCs may lend themselves to higher attrition rates because they are not federally-funded and can opt out of providing the service at any time. This is related to a general concern for the administration of a large number of vaccines in a population that may be at negligible risk of exposure to EVD. Third, the WG members who favored shared clinical decision-making for this population indicated that they believe the risk versus benefit of the vaccine in this population is not as clear as it is for their federally-designated counterparts. They noted that the vaccine is efficacious but not without some expected side effects and risks. Additionally, not all individuals working at state-designated ETCs are at equal risk. These staff members are trained in proper PPE and biosafety practices, which offer an effective first line of protection. Likely not all personnel in these facilities will want the vaccine, but the vaccine should be available for those who choose to take it. Personnel duties may change, placing an individual at greater or lesser risk with their assumption of new duties. Fourth, the WG noted that health insurance coverage is not necessarily a benefit of recommending this vaccine as it is with others, as this vaccine will be made available at no cost through the USG.

In terms of the WG's considerations for the expansion of Ebola vaccine recommendations to personnel working in LRN facilities that may receive and handle clinical specimens from suspect Ebola patients for diagnostic testing, for the following policy option is under consideration:

> *Should preexposure vaccination with rVSVΔG-ZEBOV-GP be recommended for adults aged ≥18 years in the US population who are at potential risk for occupational exposure to EBOV because they are working as staff in LRN facilities that receive, process, and perform diagnostic testing on suspect cases of EVD?*

The WG has discussed two policy options, "Recommend" and "Recommend with Shared Clinical Decision-Making." Considerations are ongoing, but preliminary discussions again suggests that the WG favors "Recommend with Shared Clinical Decision-Making" with regard to preexposure vaccination with the Ebola vaccine in this population.

WG members who favor recommending the vaccine in this population cited reasons including that recommending would improve general preparedness of frontline laboratory personnel, as LRN personnel would receive the un-inactivated clinical samples from suspect Ebola patients and it is important to provide LRN personnel the same protections as laboratory workers who are affiliated with federally-designated ETCs in BSL-4 facilities for this reason.

WG members who favor recommending the vaccine with shared clinical decision-making for LRN personnel cited similar reasons to those voiced for the state-designated ETCs. First, occupational health programs may require employees to be vaccinated if it is recommended by ACIP, and there maybe unintended negative career consequences for persons who either do not want the vaccine or those with contraindications to receiving it. Second, health insurance coverage is not necessarily a benefit of recommending this vaccine as it will be made available at no cost through the USG. Third, the risk versus benefit of the vaccine in this population is not as clear. Similar to the concerns voiced for the state-designated ETCs, the vaccine is efficacious but not without some side effects. Not all individuals in a given facility are at equal risk. While not all staff at these facilities will want the vaccine, it should be made available for those who choose to take it. Personnel duties may change, placing an individual at greater or lesser risk with their assumption of new duties.

With all of this in mind, Dr. Cossaboom presented the WG's proposed specific policy options for ACIP's consideration:

**1st Vaccination Policy Issue for Consideration**

Should pre-exposure vaccination with the rVSVΔG-ZEBOV-GP vaccine ***be recommended*** for individuals ≥ 18 years of age working as HCP in state-designated Ebola Treatment Centers?

**– or –**

Should pre-exposure vaccination with the rVSVΔG-ZEBOV-GP vaccine ***be recommended with shared clinical decision-making*** for individuals ≥ 18 years of age working as HCP in state-designated Ebola Treatment Centers?

**2nd Vaccination Policy Issue for Consideration**

Should pre-exposure vaccination with the rVSVΔG-ZEBOV-GP vaccine ***be recommended*** for individuals ≥ 18 years of age working as staff in facilities within the Laboratory Response Network that handle replication competent Ebola virus (species Zaire ebolavirus)?

**– or –**

Should pre-exposure vaccination with the rVSVΔG-ZEBOV-GP vaccine be recommended with shared clinical decision making for individuals ≥ 18 years of age working as staff in facilities within the Laboratory Response Network that handle replication competent Ebola virus (species Zaire ebolavirus)?

As a starting point for discussion, Dr. Cossaboom posted the following questions for ACIP's consideration, discussion, and feedback:

1. What are the perceived advantages and disadvantages of ***recommending*** use of rVSVΔG-ZEBOV-GP in these populations?
2. What are the perceived advantages and disadvantages of ***recommending*** use of rVSVΔG-ZEBOV-GP ***with shared clinical decision-making*** in these populations?
3. What additional information will be useful for the committee for decision making?

**Summary of Discussion**

- ACIP members found the survey results and the summary of the WG discussion were incredibly helpful in thinking about these issues.

- In terms of a shared clinical decision-making process, one of the interesting things that the survey results revealed is that people were very interested in knowing about their perceived risk of infection, risk of transmitting the vaccine virus, and risk of acquiring an SAE. This highlights the importance of the provision of informative educational materials.

- It was reported that some facilities rely on volunteers to staff Ebola assessment hospitals. While having vaccine available could help with recruitment of additional staff in terms of making them comfortable to serve in that setting, requiring it potentially could prevent other staff from volunteering given the same concerns raised by the WG about mandatory vaccines.

- A major challenges with the state-designated ETCs, and by extension an even larger challenge with the assessment hospitals, is a huge heterogeneity in terms of what this means. As noted, only 18 of the 51 so-called state-designated ETCs responded at all to the survey despite heroic efforts on the part of the staff to try to understand which of these state-designated centers actually are active. An even larger issue with the assessment hospitals is that this infrastructure was established after the 2013-2015 Ebola outbreaks. Therefore, the "care and feeding" of this effort has been very patchy. This is not a homogeneous group with clear mandates.

- The benefit/risk balance is demonstrably in favor of the benefit. Given the post-COVID experience and the fact that every decision to vaccinate is really a shared clinical decision, a clear statement in favor of a recommendation should be made in this instance. This is a very serious disease and if a vaccine is available, people who want to take it should be able to have access to it.

- It seems critical to clearly define the population in terms of who is truly at risk and who would be eligible in terms of the Population, Intervention, Comparison, Outcomes (PICO) question.

- It is important to recognize that recommending something does not necessarily equate to mandating it, which needs to be clarified. CDC reminded everyone that ACIP is not in the business of issuing mandates. Mandates typically are established by state and sometimes local governments and employers.

- Notably, the survey was sent out in the midst of the COVID-19 pandemic around the time that COVID vaccine was being evaluated. Therefore, it is not clear that the response rate should be interpreted as a clear reflect of interest in the vaccine or not. Facilities were simply very busy.

## HEPATITIS VACCINE

# THURSDAY: FEBRUARY 25, 2021

## WELCOME AND INTRODUCTIONS

**Dr. José R. Romero** (ACIP Chair) called to order and presided over the second day of the February 2021 ACIP meeting. Before beginning the sessions for the day, he conducted a roll call of members only. No new COIs were identified in addition to those declared by Drs. Chen and Frey on the first day of the meeting. A list of Members, *Ex Officios*, and Liaison Representatives is included in the appendixes at the end of this summary document.

## AGENCY UPDATES

Agency updates were provided by CDC, CMS, FDA, HRSA, IHS, NIH, and OIDP.

## PNEUMOCOCCAL VACCINES

The pneumococcal vaccine session included presentations on the current epidemiology of pneumococcal disease and pneumococcal vaccine coverage in US adults, PCV20 Phase 2/3 study results in adults, PCV15 Phase 2/3 study results in adults, including adults with underlying conditions, and considerations for PCV15 and PCV 20 use in adults.

## ZOSTER VACCINES

The zoster vaccines session included presentations on the risk of Guillain-Barré syndrome (GBS) following recombinant zoster vaccine (RZV), an RZV risk-benefit analysis, WG interpretation, and an introduction of the EtR Framework for use of RZV in immunocompromised adults.

## INFLUENZA VACCINES

The influenza vaccines session included an influenza surveillance update and a presentation on WG considerations.

## CHOLERA VACCINE

The cholera vaccine session included an introduction to cholera and cholera vaccines, a presentation on Vaxchora safety and immunogenicity data, and a presentation of the WG's future plans.

## ORTHOPOXVIRUSES VACCINES

The orthopoxvirus vaccines session included presentations on the introduction and use of Vaccinia virus vaccine in persons at risk for occupational exposure to orthopoxviruses, WG considerations, and updated policy questions for the EtR Framework, and plans for next steps.

## CERTIFICATION

Upon reviewing the foregoing version of the February 24-25, 2021 ACIP summary minutes, Dr. Jose Romero, ACIP Chair, certified that to the best of his knowledge, they are accurate.

_____ _____

José R. Romero, MD, FAAP, FIDSA, FPIDS, FAAAS Date
Chair, Advisory Committee on Immunization Practices

## ACIP MEMBERSHIP ROSTER

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Director, Arkansas Department of Health
Professor of Pediatrics, Pediatric Infectious Diseases
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Little Rock, Arkansas
Term: 10/30/2018-06/30/2021

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Term: 12/23/2020 – 6/30/2024

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Term: 12/24/2020 – 6/30/2024

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Term: 10/31/2018 – 6/30/2022

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Term: 7/1/2019 – 6/30/2023

TALBOT, Helen Keipp, MD
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Term: 10/29/2018 – 6/30/2022

## EX OFFICIO MEMBERS

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## LIAISON REPRESENTATIVES

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Medical Director, Dominos Farms Family Medicine
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**American Academy of Pediatrics (AAP)**
Red Book Editor
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**American Academy of Physician Assistants (AAPA)**
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