FOOD AND DRUG ADMINISTRATION (FDA)
Center for Biologics Evaluation and Research (CBER)
Vaccines and Related Biological Products Advisory Committee
155th Meeting

OPEN MEETING

FDA White Oak Campus
Great Room Salon C
Silver Spring, MD 20903

March 7, 2019

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CALL TO ORDER/INTRODUCTIONS

DR. EL SAHLY: I want to welcome you all to the 155th meeting of the Vaccines and Related Biological Products Advisory Committee. The topic of discussion today is to discuss and make recommendations on the safety and effectiveness of Dengue Tetravalent Vaccine (Live, Attenuated) [Dengvaxia], manufactured by Sanofi Pasteur.

We will begin by introducing the attendees of the Advisory Committee today. Please state your name, your affiliation and your area of expertise. We will go around the table. I'll begin by myself, Hana El Sahly, Baylor College of Medicine, Clinical Vaccine Development and Adult ID.

DR. SWAMY: Good morning. Geeta Swamy, OB-GYN, faculty member at Duke University, and work in Maternal Immunization and Adult Vaccines.

DR. WHARTON: I'm Director of the Immunization Services Division. I'm an Adult Infectious Disease Specialist, and work in the Domestic Immunization

Program in the United States.

DR. BECKHAM: Good morning. My name is Tammy Beckham. I'm the Acting Director of the National Vaccine Program Office. I'm a DVM by training with a specialty in infectious diseases. Thank you.

DR. EDWARDS: My name is Kathy Edwards. I'm a Professor of Pediatrics at Vanderbilt University. I'm trained in pediatric infectious disease and have spent my career evaluating a number of different vaccines.

DR. MESSER: My name is Bill Messer. I'm an Adult Infectious Disease Specialist at Oregon Health and Sciences University. And I studied in the laboratory, dengue immunity and dengue virus evolution.

DR. MUNOZ-JORDAN: Good morning. I'm Jorge Munoz, and I'm the lead for the Diagnostic Research Lab for the CDC Dengue Branch, San Juan, Puerto Rico.

MR. TOUBMAN: Good morning. I'm Sheldon Toubman. I'm an attorney at New Haven Legal Assistance Association in New Haven, Connecticut. I represent low income folks mostly, in the medical area

-- or Medicaid, I should say, more specifically. Thank you.

DR. FOLLMANN: I'm Dean Follmann, head of Biostatistics at the National Institute of Allergy and Infectious diseases.

DR. NOLTE: I'm Hendrick Nolte. I'm the Industry Representative, I work for ALK. My professional background, I'm a Pulmonologist and also trained as an Allergist.

DR. LEBLANC: I'm Ralph LeBlanc, and I'm a Medical Officer at FDA Office of Vaccines Research and Review.

DR. GRUBER: Good morning. My name is Marion Gruber. I'm the Director of the Office of Vaccines Research and Review at CBER.

DR. FINK: Good morning. I'm Doran Fink. I am the Deputy Director for Clinical Review in the Division of Vaccines and Related Products Applications, Office of Vaccines in CBER.

DR. OFFIT: I'm Paul Offit. I'm a Professor of Pediatrics at Children's Hospital of Philadelphia,

and University of Pennsylvania School of Medicine. My expertise is pediatric infectious diseases and vaccines.

DR. MONTO: Morning, I'm Arnold Monto, Professor of Epidemiology at the University of Michigan School of Public Health, interested in infectious disease epidemiology.

DR. MEISSNER: Good morning. My name is Cody Meissner. I'm a Professor of Pediatrics at Tufts University School of Medicine. I specialize in pediatric infectious disease.

DR. LEVINE: Good morning. My name is Mike Levine. I'm the Associate Dean for Global Health Vaccinology and Infectious Diseases, at the University Of Maryland School Of Medicine. I'm bordered in pediatrics and preventive medicine.

DR. KURILLA: Morning, Mike Kurilla. I'm the Director of the Division of Clinical Innovation at the National Center for Advancing Translational Sciences, within NIH. Pathologist by training, and focused on infectious disease and vaccine development.

DR. BENNINK: Good morning, I'm Jack Bennink. I'm at the National Institute of Allergy and Infectious Diseases at NIH, and I study viral immunology.

DR. EL SAHLY: Thank you, and welcome to all. Ms. Serena Hunter-Williams -- Hunter-Thomas will read the conflict of interest statement for today.

ADMIN ANNOUNCEMENTS, COI STATEMENT

MS. SERINA HUNTER-THOMAS: Good morning, everyone. I wish I made as much money as her. In any case, I'll start with housekeeping comments, and then I'll read the conflict of interest statement. And I'm a little older than her too. Good morning. Welcome to the 155th VRBPAC meeting. It is my honor to serve as your designated Federal Officer today.

The Committee Management Officer for this meeting is Ms. Casey Stewart. And the Committee Management Specialists for this meeting are Ms. Monique Hill, Joanne Lipkind, and Natalie Mitchell-Funderburk. I would also like to thank our Division Director, Dr. Prabhakara Atreya, for all the help in

coordinating this meeting.

Today's session has one topic that is open to the public in its entirety. The meeting topic is described in the Federal Register Notice that was published on February 5th, 2019.

The FDA CBER Press Media Representative for today's meeting, if you could stand up, Mr. Paul Richards. If anyone has any questions or concerns related to the press, please get in contact with Mr. Richards. The Transcriptionist for this meeting today is Ms. Linda Giles. Thank you.

I would like to remind everyone to please check your pagers and cellphones, and please make sure that they're turned off or in silent mode.

When making your comments, please state your name first and speak up into the mic, so that for the benefit of the transcription, the public and those listening via webcast, we can accurately record your name and comments. I'll proceed now to the conflict of interest statement.

The Food and Drug Administration is convening

today, March 7, 2019, for the 155th meeting of the Vaccines and Related Biological Products Advisory Committee, under the authority of the Federal Advisory Committee Act of 1972. Dr. Hana El Sahly, is serving as the Chair of the meeting for Topic III.

Today in open session, the committee will discuss and make recommendations on the safety and effectiveness of a Dengue Tetravalent Vaccine (Live, Attenuated) [Dengvaxia], manufactured by Sanofi Pasteur. This topic is determined to be a Particular Matter Involving Specific Parties, or PMISP.

With the exception of the industry representative, all participants of the committee are special government employees, or regular federal government employees from other agencies, and are subject to the federal conflict of interest laws and regulations.

The following information, on the status of this advisory committee's compliance with federal ethics and conflict of interest laws, including but not limited to 18 US Code 208, is being provided to

participants at this meeting and to the public. This conflict of interest statement will be available for public viewing at the registration table.

Related to the discussions at this meeting, all members and consultants of this committee have been screened for potential financial conflicts of interests of their own, as well as those imputed to them, including those of their spouse or minor children; and for the purposes of 18 US Code 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts and grants, CRADAs, teaching, speaking, writing, patents, and royalties, and primary employment.

The FDA has determined that all members of this Advisory Committee are in compliance with federal ethics and conflict of interest laws. Under 18 US Code 208, Congress has authorized the FDA to grant waivers to special government employees, and regular government employees who have financial conflicts, when it is determined that the agency's need for a

particular individual service outweighs his or her potential financial conflict of interest.

Based on today's agenda, under Topic III, a conflict of interest waiver was issued under 18 US Code 208b3, for Dr. William Meissner. Dr. Meissner's waiver is related to our research contract between an affected firm, and his employer, Oregon Health Sciences University. The waiver allows this individual to participate fully in today's deliberation. FDA reasons for issuing this waiver are described in the waiver documents, which are posted on the FDA website, and also available in the viewing binder at the reception table.

Dr. Hendrik Nolte, is currently serving as Industry Representative to this committee, for Topic III, today. He is employed by ALK, Inc. Industry representatives act on behalf of all related industry and bring general industry perspective to the committee. Industry representatives are not appointed as special government employees, and are nonvoting members of the committee. Hence, industry

representatives are not screened and do not participate in the closed sessions, and do not have voting privileges.

Mr. Sheldon Toubman, is serving as the Consumer Representative for this committee. Consumer representatives are appointed special government employees, and are screen and clear prior to their participation in the meeting. They are voting members of the committee, and hence do have voting privileges, and they do participate in the closed sessions, if they are held.

Dr. Gabriela Paz-Bailey, is an Epidemiologist in the Dengue Branch Division of Vector-borne Diseases, the National Center for Emerging and Zoonotic Infectious Diseases at the Centers for Disease Control and Prevention, in San Juan, Puerto Rico. Dr. Paz-Bailey, is a leading expert in infectious disease, and is currently the principal investigator for the National HIV Behavioral Surveillance System.

Dr. Anna Durbin, is a Professor in the

Department of International Health at the John Hopkins School of Medicine in Baltimore, Maryland. Dr. Durbin is trained in internal medicine and infectious diseases, and is an expert in the evaluation of a variety of vaccines, including dengue, West Nile, and malaria.

Dr. Jorge Munoz-Jordan, is a temporary nonvoting member, and he is the Director of Molecular Diagnostics and Research at the Centers for Disease Control and Prevention in San Juan, Puerto Rico. Dr. Munoz-Jordan designs projects and studies to help identify ways to better describe the impact of dengue infections in Puerto Rico, and to reduce intra-household spread of dengue virus infections and medical complications in case fatality rate.

At this meeting, there may be regulated industry speakers and other outside organization speakers making presentations. These participants may have financial interests associated with their employer and with other regulated firms. The FDA asks, in the interest of fairness, that they address

any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals were not screen by the FDA for conflicts of interest.

The FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms, its products, and if known, it's direct competitors.

We would like to remind members, consultants and participants that if the discussions involve any other products or firms not already on the agenda, but which an FDA participant has a personal or imputed financial interest, the participant need to inform the DFO and exclude themselves from such involvement with their exclusion, which will be noted for the record.

This concludes my reading of the conflict of interest statement for the public record. And I would like to hand the meeting back over to our Chair, Dr. Hana El Sahly. Thank you.

DR. EL SAHLY: Thank you, Serina. We will begin with an introduction and presentation of the

questions from Dr. Kirk Prutzman, from the Division of Vaccines and Related Products Applications at CBER FDA.

INTRODUCTION/PRESENTATION OF QUESTIONS

DR. KIRK PRUTZMAN: Good morning, everyone. Today we are here, on March 7, 2019, in the Vaccines and Related Biologics Products Advisory Committee meeting. We're going to discuss Sanofi Pasteur's biologics license application for Dengue Tetravalent Vaccine Live, also known as Dengvaxia. My name is Kirk Prutzman, I'm with the Office of Vaccine Research and Review, in CBER, at the FDA. And I'm the Chair of the review committee for this BLA.

A brief overview of today's agenda; I will start the day with an introduction and presentation of the questions. I will be followed by Dr. Anna Durbin, from Johns Hopkins University, who will present the clinical considerations of dengue. That will be followed by Dr. Gabriela Paz-Bailey, from the CDC who will be giving a presentation on the epidemiology of Dengue. Then Sanofi Pasteur will give their Sponsor

Presentations.

We will break for lunch, and we will reconvene at 1:15pm for an open public hearing. That will be followed by the FDA presentation, by Dr. Ralph LeBlanc, who is the clinical reviewer on this BLA file. The committee will then discuss and vote on the questions, and we will adjourn.

A brief outline to my introduction. I will give a discussion on the current treatment of dengue disease, a description of Dengvaxia, an overview of the biologics license application for Dengvaxia, and I'll conclude with questions to the committee.

So, a brief overview of the current treatment for dengue disease. The management of dengue disease is supportive with rest, control of fever and pain with antipyretics and analgesics, and adequate fluid intake. Management of severe dengue disease includes supportive intensive care and fluid management. Preventative measures are limited to mosquito vector control and personal protection measures. Importantly, there are no vaccines and are no

antiviral drugs that are licensed, in the United States, for the prevention of or treatment of dengue disease.

Dengvaxia is a live, attenuated, tetravalent, chimeric virus vaccine containing the replication genes and the capsid gene from the attenuated yellow fever virus -- that is strain 17D -- and the pre-Membrane and Envelope genes from each of the four dengue serotypes. These chimeric viruses are referred to as the CYD viruses, which stand for Chimeric Yellow Fever Dengue virus.

Each CYD virus is cultured separately in Vero cells under serum-free conditions; they're purified and then mixed, sterilized by filtration, and filled in vials and freeze-dried.

This is a pictorial representation of Dengvaxia. The yellow fever genes are indicated in blue, and the dengue genes, the pre-Membrane and Envelope genes are indicated in red, yellow, green or black. I've also indicated, in the red box, the NS1 gene. Please note, that in Dengvaxia, the NS1 gene

comes from the yellow fever virus and not from the dengue virus.

You will see in presentations today, analyses of antibodies elicited to the dengue NS1 protein. It is important to note that antibodies elicited to the dengue NS1 protein have to come from a dengue wild type virus infection, and cannot come from the vaccine. This is important because the sponsor, Sanofi Pasteur, used this property to understand subject's baseline dengue serostatus. And understanding the baseline serostatus was an important part of understanding the safety and efficacy of Dengvaxia.

Dengvaxia is supplied as a vial of lyophilized powder, which contains each of the four CYD virus components, which are reconstituted at the time of use with the accompanying vial of diluent, which is 0.4 percent sodium chloride. After reconstitution, each 0.5 milliliter dose of Dengvaxia contains 4.5 to 6.0 log 10 cell culture infectious dose 50 of each of the different CYD viruses indicated here. Dengvaxia is

then administered subcutaneously in three doses at month 0, month 6, and month 12.

The sponsor submitted their biologics license application with the following proposed indication. Dengvaxia is a vaccine indicated for the prevention of dengue disease, caused by dengue virus serotypes 1, 2, 3 and 4, in individuals 9 through 45 years of age, with laboratory-confirmed previous dengue infection and living in endemic areas. Previous dengue infection can be accessed through a medical record of a previous laboratory-confirmed dengue infection, or through current serotesting.

The proposed indication also contains the following limitation of use section. Dengvaxia is not recommended in persons who have not been previously infected by any dengue virus, or for whom this information is not known. Those not previously infected are at increased risk for hospitalization, or severe dengue infection, when vaccinated and subsequently exposed to dengue virus.

Sanofi Pasteur submitted their BLA for

Dengvaxia on August 31 of last year. The clinical package includes data from three randomized, placebo-controlled, observer-blind clinical endpoint studies, which evaluated the vaccine safety and the vaccine efficacy in subjects 9 through 16 years of age. These studies are CYD15, which enrolled subjects 9 through 16 years of age living in Latin America; that included over 1300 subjects living in Puerto Rico. Study CYD14, which enrolled subjects 2 through 14 years of age living in Asia Pacific. And CYD23, which enrolled subjects 4 through 11 years of age living in Thailand.

Please note, as I showed in previous slides, the sponsor is requesting an indication for individuals 9 through 45 years of age. And CYD14 and CYD23 have subjects enrolled younger than nine years of age. For the purposes of licensure, we consider the subjects 9 years of age and older for our decision making. The sponsor, Sanofi Pasteur, also included additional supportive studies, and there was a total vaccine exposure of over 35,000 persons; this includes all age groups 2 through 45 years of age.

The clinical package also included data from three randomized, placebo and active controlled, observer-blind studies, which evaluated vaccine safety and immunogenicity in subjects 18 through 45 years of age. They are studies CYD22, CYD28, and CYD47, which enrolled subjects from Vietnam, Singapore and India respectively. The immunogenicity data from CYD22, CYD28 and CYD47 were reviewed in the context of the immunogenicity data from CYD14, CYD15 and CYD23.

We have the following questions for the committee, they are:

Question 1: Are the available data adequate to support the effectiveness of Dengvaxia for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4, in persons 9 through 45 years of age with laboratory-confirmed previous dengue infection and living in endemic areas? We will ask you to please vote yes or no.

Question 2: Are the available data adequate to support the safety of Dengvaxia when administered to persons 9 through 45 years of age with laboratory-

confirmed previous dengue infection, and living in endemic areas? We will ask you to please vote yes or no. Thank you.

DR. HANA EL SAHLY: Thank you, Dr. Prutzman, for setting the stage for today's meeting. Any questions to Dr. Prutzman? Okay. Thank you, Dr. Prutzman.

Next, Dr. Anna Durbin, from Johns Hopkins University, is going to review Clinical Considerations of Dengue.

CLINICAL CONSIDERATIONS OF DENGUE

DR. ANNA DURBIN: So these are the objectives of the talk. I just want to present to you the clinical presentation of dengue, as well as there are two classification systems that have been traditionally used in terms of classifying dengue. And I'm going to discuss both of them because they provide a little bit of different information. And I'll go through why those severity classifications changed, and what we can gain from each of them.

I'm going to discuss just a little bit about

confirmatory testing of acute dengue. Dr. Paz-Bailey's going to go into more details on the testing and confirmation of previous dengue infection, and what serological assays we currently have available. And then I'm going to discuss the management of dengue.

So dengue is a very broad, viral illness. It can range in terms of having no symptoms or very few symptoms, to severe disease that can lead to hospitalization, and in some instances even death. It's easily confused with other viral illnesses, particularly it can look like measles; it could look like influenza, yellow fever, a lot of other viral illnesses that are endemic in the areas where dengue is endemic.

We talk about the more severe forms of dengue disease, as dengue hemorrhagic fever or dengue shock syndrome. And you'll see later in the talk, these terms come out of the previous case classification system of dengue.

Dengue can have a mortality rate that is very

low, less than one percent, or it can be as high as 20 percent, if left untreated, or treated appropriately. And I often tell students, when I'm talking, that if you get dengue you really don't want to be treated at Johns Hopkins Hospital. You want to be treated in Ho Chi Minh City, where you have people who actually know how to treat dengue. And I think that's very important, because appropriate treatment of dengue is critical in terms of ensuring that there aren't complications that can lead to more severe disease or even death.

This is just to show the clinical spectrum of illness. At the very top of the pyramid, I have the more severe forms of dengue, dengue hemorrhagic fever, shock syndrome. This occurs in a very small percentage of the overall number of cases. Really, we think in fewer than 5 percent of dengue infections actually result in what we would consider to be severe disease. The problem is that we can't predict who is going to come down with severe disease and who's not. And you'll see that when I go through the case

classification system.

Then we go into classic dengue fever, which is really an acute febrile illness that has different morbidity, severe muscle and joint pains, small bleeding manifestations. A lot of these cases are hospitalized. And that's really where the complications in terms of health management and health systems come in, and is really that the public health impact of dengue; is that during an outbreak of dengue, because we can't really predict who's going to go on to have severe disease, there's tremendous amount of hospitalizations and stress on the healthcare systems during outbreaks.

And this is really where the importance of the safe and effective dengue vaccine comes in; is to try to prevent, during outbreaks, severe illness that leads to hospitalization that can really shut down health systems in endemic areas. And then we have the undifferentiated febrile illness, or people who really don't present with many clinical signs or symptoms at all.

So, when I talk about classic dengue fever, I'm talking about what used to be known or sometimes still known as breakbone fever. Classic dengue fever was generally a disease in adults. And this is before we had all four dengue serotypes circulating at the same time. So people with their primary dengue infection, is they got their primary dengue infection as an adult, would present with severe fever, headache, pain behind the eyes, severe muscle and joint pains, which gave it it's synonym as breakbone fever.

Generally it's interesting, children with their primary infection may be less symptomatic or even have different symptoms. So if you read the literature you'll see children presenting even with respiratory symptoms, that then turn out to be dengue, sore throat, that sort of thing.

Dengue hemorrhagic fever, shock syndrome, or severe dengue, dengue vascular leak syndrome, which we'll talk about when I go through the case classification system, really occurs most commonly in

secondary dengue infections. And Dr. Paz-Bailey is going to discuss that when she discusses the epidemiology of dengue. At the very end of my talk, I'll discuss a little bit about what we think the immunopathogenesis of that may be.

So where we really see severe dengue, is in hyperendemic areas. And when I say hyperendemic areas, I mean areas where you have multiple dengue serotypes circulating at the same time. We see this because it generally occurs as I said, with the secondary infection. So in areas of hyperendemicity, such as Southeast Asia, Thailand, and now Latin America, particularly Brazil, we see this as a disease of children, because children are infected in areas of high endemicity early on, and then they get their second infection also generally in adolescence or early adulthood.

Where you see this can also depend upon the epidemiology of dengue. So dengue in Brazil has more recently become hyperendemic. So we do see severe disease in adults. And it's important to note that

you can see severe disease children, adults. You can see severe disease even in a primary infection, but it's less common than in a secondary dengue infection.

This slide is just sort of a graphic to demonstrate the time-course of dengue, and some of the clinical signs and symptoms that occur with dengue. So, what we have in Day Zero is really the time that symptoms start. And I put that as Day Zero because often you'll see in the literature, when people are trying to describe the course of infection, and relate severe dangly with different blood markers and such, we use Day Zero as the day of symptom or the day of fever onset.

So prior to that you have the incubation of the virus in the human, following mosquito bite, that can be two to 14 days. Once you have viremia, you start to develop symptoms of dengue, and that can include fever, headache, rash, which is quite characteristic. Petechiae, you see low white count and low platelet count. And that can be seen even in people who don't go on to develop severe dengue or

vascular leak syndrome.

What we see next -- and this is the really most important part about dengue disease -- is the critical phase. And that's what leads to vascular leak syndrome.

What's interesting is multiple epidemiological studies have demonstrated that that critical phase really begins with defervescence. So the patient is going along, the fever breaks, we think that the patient is going to recover, vascular leak develops, the patient's blood pressure crashes, and you've entered the critical phase.

And that's really -- over the next 24 to 48 hours determines the course of events for the patient, whether they're going to get better or whether they're going to succumb to dengue through their vascular leak syndrome. If they recover, we move on to the convalescent phase, which can last three to five days. And you can see a rash that goes on through the convalescent phase. And I'll try to show you a picture of that.

I think what's important to note again is that by the time the critical phase is reached, and even defervescence, viremia has become undetectable. And that's again something that is difficult. When you're following the course of illness, it looks as though the patient is getting better, but then they crash and blood pressure falls. The rash that we see is quite characteristic, and I'll show you a picture of that. Petechiae is a different form of rash, and I'll also go through that so you can see.

Generally, if a patient recovers, or when a patient recovers from dengue, there are few long-term sequelae. What has been described, quite frequently with dengue, is a post-viral illness depression as well as long-term fatigue. But people generally recover from dengue without long-term sequelae.

So this is the febrile phase, it generally last two to seven days. This is important to note when you're trying to make a diagnosis of acute dengue, because you want to collect a blood sample within generally five days of fever onset, to improve

your odds of actually making a diagnosis and detecting viral antigen. The fever can be by biphasic and was typically described as a saddle back fever. That's a fever where you have a high-level fever, it looks like it's getting better, the temperatures is going down, but then the next day the temperature goes back up again, and looks like a saddle back.

You have to monitor the patient very carefully for defervescence and warning signs, because this is critical to recognizing progression of dengue into vascular leak syndrome, or the critical phase. Defervescence generally occurs on days three to eight of illness, and it's defined when the body temperature drops to less than 38 degrees Celsius and remains below this level. Again, we say that because there can be a saddle back fever where it may initially drop below 38 degrees Celsius, but then go back up.

And then we reach the critical phase. Again, I think it's important to note that this is really demarcated by defervescence. So you think the patient's getting better, their fever breaks, but then

their blood pressure drops as they enter vascular leak syndrome. We see with that a rapid decline of platelet count, and arise in hematocrit. And the rise in hematocrit is due to vascular leak syndrome, as opposed to a gross bleed somewhere. And I think that's important.

Although we have the name, dengue hemorrhagic fever, the shock that ensues is due to vascular leak and it's not due to large bleeding. Although you can have small amounts of bleeding during dengue, and occasionally you can have a large bleed.

Generally, you develop a low white count about 24 hours before the platelet drop. I will say you can see low white count and low platelet count, even in people who do not progress to the critical phase. It’s very important to monitor pulse pressure, and increasing hematocrit, as proxies for vascular leak. And when you're on the wards in dengue endemic areas, they go around and measure the hematocrit every few hours, just with generally a capillary tube and a microcentrifuge, just to monitor for signs of rising

hematocrit, which is indicative of a vascular leak syndrome.

Warning signs, and we're talking about warning signs because the 2009 WHO case classification included warning signs as part of their severity classification. So I'm listing them here. There's severe abdominal pain, persistent vomiting, clinical fluid accumulation. This is very key because, again, this is indicative of a vascular leak syndrome.

Mucosal bleeding, particularly, in children, lethargy and restlessness. That's typically how young children who aren't otherwise able to express some of the other symptoms that they're having, they become restless or lethargic, and that's certainly a warning sign.

And then also in the pediatric population, liver enlargement. We generally don't see this in adults, but in some studies out of Southeast Asia. Young kids, pediatric patients who had vascular leak syndrome or severe dengue, more than 90 percent of them had evidence of an enlarged liver. And then of

course, an increase in hematocrit with a rapid decline in platelet count.

Once a patient has entered the critical phase, it's important to monitor them very carefully, and also provide fluid replacement in a very careful manner. The warning signs themselves are thought to be the result of plasma leakage. Clinically significant plasma leakage, usually last 24 to 48 hours, which is the definition of the critical phase.

You have to monitor the patient very carefully because you can end up in a volume overload situation. If you provide too many fluids, the critical phase ends, and then the patient is unable to clear those fluids in an appropriate amount of time, they can actually lead to volume overload. And this was one of the problems in management, particularly of elderly patients and patients that have comorbidities.

So in a recent outbreak in Taiwan, the majority of the patients who developed severe gangue were elderly, because of the interval between primary and secondary infection. And management was very

difficult and they had a high mortality rate, particularly due to volume overload; because the patients were not able to handle the amount of fluid that was administered to treat the vascular leak.

The recovery phase is really a gradual reabsorption of the extra vascular fluid, and that generally takes place over about two to three days. The patient starts to feel better, hemodynamic status stabilizes, sometimes we do see bradycardia in this phase. However, generally the patient does well even with bradycardia. Again, fluid overload can be a big problem in the elderly and others with comorbidities. And it is a leading cause of morbidity, and mortality, in the elderly who come down with severe dengue.

From a laboratory standpoint, what we see is stabilization of the hematocrit. It may actually become even lower. Again, as that fluid reabsorbed, and you get a delusional effect of the hematocrit, we start to see white blood cell count rise and we start to see recovery of the platelet count. It generally occurs later than the white blood cell count, but will

recover over several days to a week.

I did say earlier that the mortality rate of dengue is generally quite low, certainly less than 1 percent. And I will say that clinicians, in endemic areas, who are familiar with how to treat dengue, view the loss of a patient to dengue as something that should never happen. If treated appropriately -- if the patient presents in time, and is treated appropriately, they believe that no one should die from dengue.

But oftentimes people don't present in time, they come in well into their shock period. The disease can be unrecognized, particularly if you have a traveler who comes back from a dengue endemic area and presents to hospitals that aren't familiar with dengue. There can also be unrecognized occult hemorrhage, whether it's in the peritoneal spaces, into the abdomen, that isn't recognized and not treated appropriately. And then you can also have nosocomial sepsis that can lead to death. And this is true, especially in the elderly, and those who have

been hospitalized for several days.

I'm going to go through some of the clinical presentation signs and symptoms of dengue, now. What I'm presenting here on the left, is a typical dengue rash in an adult. I think the key points of this rash are that it is a total body rash, it is very, very uncomfortable. The subject will say that they feel like their skin is on fire, their skin is crawling. It itches intensely, and you'll note that it blanches. So if you apply pressure to an area of the rash, and remove that pressure, you have an area of blanching. That distinguishes it from a petechial rash, which I'll show you in just a minute.

On the right, what you see is what we call the rash that's very common in the convalescent phase. And what you see are areas, or islands of sparing. So you see the rash on the calf, and pale areas, circular areas of sparing of the rash. And that can be typical of the convalescent phase. I think what's also important to note is during the convalescent phase, you often see desquamation of the rash, particularly

around the hands and the feet. So you can lose a large amount -- you can desquamate large -- around the fingers and the toes following a dengue rash.

So I'm going to go through some of the hemorrhagic manifestations. What this slide is showing is a tourniquet test. It has fallen somewhat out of favor in terms of a diagnosis of dengue. It was use more commonly when we had the old classification system, which I'll go through in just a minute.

But, essentially how you perform this test, is you apply what looks like a blood pressure cuff and you inflate the blood pressure midway between the systolic and the diastolic pressure. And you leave that on for five minutes, release the cuff, and then you count the number of petechiae that are present within that open space. And if you have more than 20 petechiae, then that's thought to indicate the clinical sign of dengue hemorrhagic fever, and meet the criteria for bleeding manifestation. It's thought to be due to capillary fragility, which allows the

petechiae to form in that area.

In some of the vaccine studies we did, we perform the tourniquet test, and it is not a comfortable test to have the blood pressure cuff inflated for five minutes. But that was one of the early markers of a hemorrhagic manifestation of dengue.

What I'm showing you in this slide are a couple different manifestations. On the left, is a petechial rash. I don't know how well it's projecting, but you can see small purple areas of petechiae that's bleeding into the skin. If you were to apply pressure on the arm, that rash would not blanch; it would maintain because it actually is representing bleeding into the skin.

On the right, you're seeing a larger area bleeding, an ecchymotic area at a phlebotomy site. You see a large bruise like, or ecchymotic area; but you also see a small fluid-filled blister there. And that is actually evidence of plasma leakage, where you're having fluid leak into the skin, into the

subcutaneous space, and form the bullae there.

This slide is presenting a couple of different clinical signs in a pediatric patient. The patient on the left has some petechiae over the bridge of his nose and forehead, but also is very puffy. We describe the baby as very puffy. And this is because there's vascular leakage in the subcutaneous space, really causing some edema around the face. And the little boy on the right, they're marking off his liver edge to show that there's an enlarged liver in this young pediatric patient

This is really the clinical hallmark of severe dengue or dengue-shock syndrome. And that is plasma leakage, particularly into some of the pleural spaces or the abdomen, or even sometimes into the pericardial space. What you're seeing on the left, this is a normal chest x-ray, except instead of standing up the patient is lying on the right side. And in this chest x-ray, for those who aren't familiar with x-rays, air is black, and anything that's more dense is whiter.

So you see on the top of the slide, a nice

black lung airspace; but on the bottom of the slide, what you see is a lot of hazy fluid that's compressing the lungs. So if you look, the lung is only probably about an eighth of its -- or a fifth of its normal size. And you can see that that's a tremendous amount of fluid that has leaked into the pleural cavity. That can lead to difficulty in breathing and of course shock when you lose that much of your intervascular volume into the pleural spaces.

The slide on the right is showing something similar; in a younger patient it's a little bit harder to see. In this slide, if you roll the patient over, and turn them on to their left side, you would see the right lung expand but you would then see compression of the left lung because of that fluid shifting to the different spaces.

So now I'm going to go through the different case classifications of dengue. And I'm presenting both the 1997 case classification system, as well as the 2009, because they give us different information.

The 1997 case definition really was helpful in

terms of classifying cases as dengue, dengue hemorrhagic fever, or dengue shock syndrome. So from an epidemiological standpoint, we were able to have a better accounting of the severity of disease, with the 1997 case classification system. There were problems with the 1997 case classification system, which I'll go through, and which led to the 2009 reclassification system. What's important to know about the WHO 1997 case definition for dengue, is that all four components must be present to have a definition of dengue hemorrhagic fever.

So, the first thing you had to do was have a clinical suspicion of dengue, fever or history of acute fever, lasting for two to seven days. You then had to have a demonstration of hemorrhagic tendencies, and that could be one or more of the following: a positive tourniquet test; petechiae, ecchymosis or purpura, just different amounts of bleeding, essentially, into the skin; bleeding from the mucosa, the GI tract, injection site or other locations; hematemesis or melena. Those would all be accepted as

bleeding criteria.

You then had to have thrombocytopenia, or low platelet count, which was defined as less than 100,000. And you had to have evidence of plasma leakage due to increase vascular permeability. And that was manifested by one or more of the following: either a rise in hematocrit, of greater than or equal to 20 percent above average for age, sex and population. If you didn't have a baseline hematocrit with which you could compare.

After administration of fluids, if your hematocrit dropped by 20 percent or more, that was an indicator of plasma leakage. Or if you had signs of plasma leakage, such as pleural effusions, ascites, or hypoproteinemia. And currently ultrasound is use to make this diagnosis, and it's much more sensitive than the plain films that I showed you. But it's important to note that you had to have all four of those criteria to meet the definition of dengue hemorrhagic fever.

To meet the definition of dengue shock

syndrome, you had to first have a definition, or meet the case definition of dengue hemorrhagic fever. Then you had to have evidence of circulatory failure, which was manifested by a rapid and weak pulse and a narrow post pressure defined as less than 20 millimeters of mercury. Or if you had clinical signs of shocks, such as cold, clammy skin, hypotension for age.

I think what's very important, and what led to criticism of these criteria, is that if you did not meet all four of the criteria for dengue hemorrhagic fever, but you went on to develop shock, you never had hemorrhagic fever, so you never had dengue shock syndrome. And the criteria that was most often missing was the low platelet count, less than 100,000. So this led to a change in the case classification system for dengue, to try to be more inclusive and to ensure that cases of severe dengue were not met.

The 2009, WHO dengue criteria, though, you will see are really more useful for triaging of patients, and for patient care, then necessarily for epidemiological reporting of severe disease. So we

essentially in the new classification system, we have dengue and we have severe dengue. And then we have grouped those into A, B, or C, depending on severity. And then based on the grouping, we'll triage for care.

So Group A can be sent home, they can tolerate oral fluids, and they don't have warning signs. And I'll go through, in more detail, sort of the triaging around these three different groups.

So, if they present with fever, they have suspect dengue, they're able to take oral fluids, and they don't have warning signs, then they can be sent home. They're followed very closely, though. I don't want to imply that they're sent home and not seen again. They're generally seen daily and they're monitored to see if they eventually developed warning signs or just get better.

Group B is referred for hospital management, in-hospital management. So if the patient has warning signs or comorbidities that may make them more susceptible to complications from dengue, than they are referred for in-hospital management.

And Group C is the group that is essentially presenting in shock or with severe disease, so they require emergency treatment. And that can be severe plasma leakage, severe hemorrhage, or severe organ impairment. Again, these criteria are useful for triage, but not really useful for defining severity in a very granular manner.

So this is from the WHO document that went through the new case classification system. You can see on the left, you have dengue with and without warning signs. And then on the right, you have severe dengue. One of the consequences of the new case classification system is that it has led, in many places, to an increase in the hospitalization for dengue. Anyone who presents with any warning sign comorbidity would be referred for in-hospital management. And again, if we're thinking about vaccine trials, that may or may not be indicative of the true severity of disease.

But the criteria for dengue, with or without warning signs, if you look on the left column here you

see probable dengue. And these are some of the signs and symptoms that would make you think of dengue if you were either in an academic area, or you're treating a patient who's returned from a dengue area. There are a couple of new clinical symptoms that have been added to a suspect case of dandy, and that includes nausea, vomiting, and aches and pains. So instead of separating out myalgia and arthralgia, we've combined them into just aches and pains. And again, we've included rash, positive tourniquet test, low white count. And, if we then go to warning signs, we have the list of warning signs.

And again, when a patient presents with presumed dengue and warning signs, the recommendation is that they'd be referred for hospitalization for further management. And the reason for that is, right now we do not have a good way to predict who is going to just get better, if they present with dengue and warning signs, or who's going to actually progress to severe disease. So the recommendation is that they be hospitalized with close monitoring. If they begin to

develop vascular leak syndrome or signs of vascular leak syndrome, then appropriate management ensues, and they're treated, with the goal of actually preventing severe dengue. And, I think that's an important point. You want to prevent shock in these patients, if possible.

So they're referred for in-hospitalization. Some will, in fact, progress to severe dengue. And that is defined, again, as severe plasma leakage, severe hemorrhage, or severe organ impairment. Organ impairment can be due to essentially poor perfusion; or we've also seen -- in some dengue cases -- liver failure due to dengue. Kidney failure, again, most is thought to be due to just poor profusion, but there is a thought that can also be a direct effect of dengue itself. Severe organ involvement is defined as AST or ALT that are greater than 1000, that's liver involvement, and then CNS, if you have impaired consciousness.

There's heart and other organ, and a big area of -- I don't want to say controversy -- but

discussion, is whether or not dengue can really lead to myocarditis and other cardiac disease on its own; or whether it's a result of low blood volume, so vascular leak. So, we have seen decrease cardiac output described in cases of severe dandy; but it's thought to be a result of low preload due to vascular leak, as opposed to direct myocarditis. But this is an area of discussion among dengue experts that has yet to be truly resolved.

So here we go with -- this is dengue without warning signs. The patient presents, you've made a diagnosis of presumptive dengue. Based on these clinical symptoms and signs, you're going to refer the patient home as long as they can maintain -- they can eat and drink and maintain their volume load.

If they develop warning signs -- listed here -- then they will be referred for in-patient management. And then they will meet the definition of severe dengue if they essentially develop shock or severe vascular leak, organ impairment or severe bleeding.

How do we confirm dengue? So, I think it's important to note that a lot of places don't have point-of-care diagnosing. So that means that you have to send the lab test out. Generally, in a lot of areas, it's to a central laboratory for testing. We can only confirm dengue by detection of viral antigen or by serology. Viral antigen testing, can be detected for five to seven days, post-symptom onset. So again, you have a relatively narrow window to detect antigen.

You can detect it by nucleic acid in serum blood plasma, CSF, or other body fluid or tissue, by a validated PCR test. You can also detect dengue antigen in tissues by validated immunofluorescence or immunohistochemistry staining. You can detect in serum or plasma, dengue NS1 antigen. And you heard in the earlier presentation, the NS1 protein, and that is the yellow fever NS1 protein for Dengvaxia. But when we're looking for wild type dengue, we're actually looking for the dengue NS1 antigen. And that can be done either by ELISA or a rapid NS1 test.

The beauty of the rapid NS1 test, is that it can be done at the bedside and you can have a diagnosis in real time. There is not a rapid NS1 test that is approved for use in the United States. These are tests that are used in other dengue endemic areas, but none is approved for use in the United States. You can also, of course, do the old-school virology and actually grow up the virus from serum plasma, or CSF, if you have the laboratory facilities to do that.

But again, the majority of these tests require that the specimen be sent to a central laboratory for testing, whether or not those tests actually make it back to the patient before they're diagnosed, generally doesn't happen. A lot of it is done for epidemiological purposes as well. And I know in some endemic areas, for instance, only a small proportion of patients will actually have specimen sent for confirmatory testing.

The reason for that, as was mentioned earlier, is we don't have a specific antiviral that we can administer. We're going to be treating

symptomatically and supportively, and a confirmed diagnosis of dengue is not going to change that. So in a lot of dengue endemic areas, the diagnosis is really never actually confirmed.

You can do serological confirmation of a suspected case, and Gabriela is going to talk about that in her talk. Essentially, if you're looking for acute dengue, then you're going to be looking at IgM assays, for a confirmation. You can do IgG assays using paired acute and convalescence serum. It's difficult; one, there's a lot of cross reactivity between dengue and other flavivirus, particularly Zika, that may confound this diagnosis. So, if you can do the acute antigenic testing, it's felt to be more reliable. But Dr. Paz-Bailey is going to talk about serological assays for dengue in her talk, so I'm not going to go into that in great deal.

So how do we manage dengue? We manage it really symptomatically and supportively. It's based on the severity classification, and the clinical signs and symptoms.

So again, Group A, if you're presenting with suspect dengue, and you can maintain your own oral fluid intake, and you don't have warning signs, then you can be sent home. You'll be advised to maintain your oral intake. We recommend treatment of fever with paracetamol or acetaminophen. We do not recommend nonsteroidal anti-inflammatories, because of the antiplatelet effect. So you don't want to give them to people who have low platelets. You want to make sure that the platelets that they have are working appropriately.

Then they're monitored daily for worsening signs and symptoms, and also their CBC to look for changes in hematocrit. And they are advised to return immediately if they develop any warning signs.

Group B is dengue with wanting signs. Again, they're referred for inpatient hospital care. They're encouraged to maintain fluid intake. If they cannot do that, then crystalloid intravenous fluids will start to be administered at a maintenance rate. They'll obtain a reference hematocrit at the time of

admission, prior to fluid therapy, because they want to monitor that over time. And then their clinical status will be reassessed. They'll repeat the hematocrit frequently, and they'll review the IV infusion rates. It's very important that these patients do not get fluid overloaded, because that can result in morbidity itself.

And then for Group C, severe dengue, again, that requires emergency management. They will get a CBC to look for the hematocrit. They'll begin IV fluids. They begin with crystalloid fluids. It doesn't generally require anything special, lactated ringers are frequently used. They have very defined algorithms for the treatment of dengue, based on pulse pressure and hematocrit. They're going to monitor them continually, because they really want to avoid any chance of fluid overload.

If hemodynamic status fails to improve, and the hematocrit continues to decrease, then a bleeding complications should be considered. I will say platelet counts can get very very low in dengue, below

20,000. And it's generally not recommended that platelet infusions be given. It hasn't been shown that they're all that effective. Of course, if somebody is bleeding, then platelet transfusion may be indicated. But in general, platelet transfusions aren't given, even for people with very low platelet count.

The thought is that these platelets work very well. And as long as you keep the patient sort of without risk of fall or injury then they shouldn't have a bleeding complication on their own. I will say that there have been several studies to look at the role of steroids and the treatment of severe dengue, and none of them has shown any efficacy.

So what's the etiology of severe dengue? Again, Gabriela is going to talk a little bit about this in her talk. But studies have demonstrated that dengue is more common with secondary heterotypic, or different dengue infection. And we think that that's due to the phenomenon of antibody dependent enhancement of infection, which I'll talk about in

just a bit.

Severe dengue can occur with primary dengue infection. This was first noted in very young children, and was thought to be due to the effect of maternal antibody. But we also see this in adults with their primary infection. It's thought that if the viral load is high enough, then that can result in primary dengue infection, regardless of whether it's your primary or secondary infection.

What's interesting is, that epidemiological studies have also demonstrated that severe dengue rarely occurs with their third or fourth dengue infection. And the thought is that the secondary dengue infection may broaden your immunity such that you're no longer at risk for severe dengue with your third or fourth infection. It can happen with your third infection or your fourth infection, but it's exceedingly rare.

Some studies have associated more severe dengue with a higher viral load, or higher virus titer. Unfortunately, one of the problems that we

have, as I said earlier, is that by the time somebody enters the critical phase, we really can't detect viremia. So you have to be able to measure that viremia earlier in their clinical illness. So it is very dependent upon when they present for clinical care.

And then we also know that there are other factors that may contribute to severe dengue, including cross-reactive T-cell responses. Viral virulence factors; we know that some strains of a particular dengue serotype are more virulent than other strains. And then, of course, there's always host factors.

So I'm just going to go through antibody dependent enhancement of infection, for those who aren't familiar with it. Essentially, what I'm showing here is you have a dengue virus. I'm going to call that dengue virus Serotype 2. You've already had a primary dengue infection, your first dengue infection with dengue virus Serotype 1. That dengue 1 antibody combined to the dengue 2 virus, but it won't

neutralize it, it won't inactivate the virus.

But it can bind to the virus. And then that antibody virus complex can bind to the Fc gamma receptor on monocytes and macrophages. We think that when the virus enters through that FC gamma receptor pathway, it's able to evade the immune response; and therefore, replicate to higher viral titer, leading to a higher viral release that can then lead to severe disease. And there certainly are other mechanisms, but this is one of the leading theories of why we see more severe dengue associated with secondary dengue infections.

So I'm going to wrap-up now, and just give a very brief summary. Dengue is an acute illness. It has a very wide spectrum of illness. This can make it difficult to diagnose, because it can be one of many different things. It's important to note that there are not any approved antiviral agents for dengue, such that treatment is supportive and really just treating symptoms.

If treated properly, it can have a very low

mortality rate. One of the things that you really want to avoid, though, is fluid overload. That can cause a great deal of morbidity and even mortality in dengue patients.

Right now we are unable to predict which patients may progress from dengue to severe dengue. And that really is a very big area of research in the dengue field, trying to find a marker that will help tell us that a patient is going to progress to severe disease. Because we can't predict, we have the recommendation, if you present with warning signs, hospitalized and monitor very closely. And again, good fluid management is critical for treating severe dengue. And you want to avoid nonsteroidal anti-inflammatories in the treatment of fever for dengue patients.

And that's all I have. I thank you. And I'll take any questions you may have.

DR. EL SAHLY: Thank you, Dr. Durbin, for this very informative talk. I guess I'll begin by asking, given a particular incident in a region, with the

understanding that it's a variable cyclical situation, what is the age-related incidence of severe disease? By my age?

DR. DURBIN: So that's a very good question. Again, it depends on where you are and changing epidemiology. So for instance, if you're in Bangkok, or you're in Thailand, the greatest hospitalizations for severe disease were in adolescent. And it used to be as early as young as age nine. We've seen that age going up a little bit, and it's thought that that can be due to varying reasons, including lower birth rate, and apartments with screens and things like that.

But if you have an area like Bangkok, like Thailand, where you have all four serotypes circulating at the same time, then you're going to get your first dengue infection quite young, and you're going to get your second dengue infection young. So that's why in areas like Bangkok or Thailand, we tend to see severe disease earlier in, as I said, adolescence. Right now it's gone from age nine up to about, I think, age 11 or 12. But that's true for

most of Southeast Asia, the Philippines, areas where you have all four serotypes circulating.

Now if you go to Brazil, and Brazil is interesting because Brazil is not just Brazil, there's many different regions and there's different endemicity of dengue in different regions of Brazil. But if you look, for instance, in the Northeast of Brazil, where you have a lot of dengue circulating, you have multiple serotypes of dengue circulating, you'll see epidemiology or severity of disease, kids hospitalized, much like you'll see in Southeast Asia.

But in other parts of Brazil, where more recently you've had new serotypes come in, you'll see severe disease or hospitalizations for severe disease, in adults, young adults, even up into the 30s, 40s or 50s.

Then if you look at a place like Taiwan, where you have very intermittent dengue infections -- so Taiwan is an island much -- or like Cuba, it's mostly adults because there's long periods of time between the primary and the secondary infection.

So you can have different prime ages of hospitalization for severe disease, depending on not only the country you're in, but the region of the country that you're in. If you're, for instance, in a mountainous region, you're not going to have dengue circulating because mosquitoes won't survive at high altitude. So, it makes it very difficult, because you can have communities relatively close to one another that have very different incidences of dengue.

DR. EL SAHLY: Dr. Meissner.

DR. MEISSNER: Thank you. Can you give us a sense of the burden of disease in countries where dengue is endemic? And I realized that it varies a great deal. But I'm thinking, specifically, how many patients are admitted with warning signs and do not progress to severe disease, versus the number that do progress? And then, is there a seasonality to dengue as there is with Japanese encephalitis virus?

DR. DURBIN: There is definitely a seasonality with dengue. So, for instance, in Latin America, Brazil, we're in the height of the dengue season now.

It’s in their summer, our winter. It's seasonality in Bangkok as well, following the rainy season, you'll get a lot of dengue. So there's definitely a seasonality, although you can, of course, have cases out of season, so to speak.

So yes, the vast majority of patients, so the majority of patients who are admitted with warning signs, do not progress to severe disease. So, as I said, severe disease really is fewer than 5 percent of all of the infections.

And again, this is where some discussion about the new case definition system has come up, is that some feel that we're over hospitalizing, that more people are coming in. And that, really also -- you'll see that in different places.

So, I believe, for instance, in Asia, they were less likely to hospitalize, even with warning signs, because they felt very comfortable managing. Whereas in Latin America, more cases with warning signs were hospitalized, so they had more hospitalized cases. And again, I think when we're trying to get

some granularity into severity of disease, that makes it difficult.

I will say -- and I didn't put it in the presentation because I don't think that it's really relevant -- but NIH and WHO put together a consultation to try to come up with case definitions for severity of disease, specifically for vaccine trials, trying to capture some of that granularity. Because I think it's difficult -- all hospitalized dengue cases are not the same severity of disease, that is absolutely true.

But because of this inability to predict, we do see a lot of hospitalization, and it's really lead to overwhelming of some of the healthcare systems during a dengue epidemic. So in Brazil, a few years ago, there were, you know, more than a million cases of dengue. And, those are cases that presented for clinical care and were thought to be dengue. So it really fills up beds that could be used for other diseases.

DR. MEISSNER: Thank you. Yeah, and you got

at the point that I was thinking about, that is unnecessary hospitalizations in countries with limited healthcare resources. It's unfortunate that children, or individuals, or patients are admitted, and they may not need that hospitalization. And so do you have a sense of during a peak, how often that -- how many patient, I mean, does that --

DR. DURBIN: I think Dr. Pas Bailey may be able to answer that, more specifically, with her -- at least with her experience in in Puerto Rico.

DR. EL SAHLY: Dr. Follmann.

DR. FOLLMANN: Yeah, I was interested in your slide on antibody dependent enhancement. You talked about prior exposure, or prior infection by dengue. What's known about prior infection by say, Zika? Does that have an aspect or does that behave like -- will that cause antibody dependent enhancement, if they're first exposed to Zika and then exposed to one of the four dengue serotypes? What's known about that?

DR. DURBIN: You've touched a nerve. No, that was a great deal of -- that question was asked a lot

during the dengue outbreak. What is known about antibody dependent enhancement of infection is that, in a test tube, or in an immunodeficient mouse, any flavivirus antibody can enhance the infection of any other flavivirus. In epidemiological studies, even in the in the post-Zika era in Brazil, we did not see enhancement of Zika in areas where there had been known to have several dengue outbreaks.

So we don't think, in humans, that Zika enhances dengue, or dengue enhances Zika. There's just not enough similarity. You can see that in a test tube, and you can see it in immunodeficient mice. But there are some studies out of Brazil that actually showed dengue may be protective against Zika; and studies that look specifically to see if dengue enhanced Zika illness, or vice versa. And that they were not able to see that in epidemiological studies.

DR. FOLLMANN: Right. But your epi-studies, they were more for dengue first, as dengue primary exposure and had Zika infection. And I guess there's less data about the reverse, where you have primary

Zika and then maybe dengue. Is that fair to say, there's less data about Zika then dengue?

DR. DURBIN: There is less data. What we do know from Brazil is that it has been a very low dengue season, for the two years following Zika. So we don't know whether that's some cross protection from Zika. We don't know if that's just variability in the circulation of dengue viruses. All we can say is that we've seen reduced dengue transmission in the two years post the Zika outbreak.

DR. EL SAHLY: Dr. Kurilla.

DR. KURILLA: Anna, with regard to the NS1 serology, and its utility during acute infection, is that an issue of the sensitivity of available diagnostic tests, or is it a fundamental aspect of the immune response? And then, what's the long-term titer levels of NS1 to see past exposures?

DR. DURBIN: So, in acute infection we're looking at NS1 antigen, not antibody. So the antibody is a marker of previous infection. One of the issues that we have with NS1 antigen testing, is we know that

it is less sensitive during secondary infection. The rapid test is less sensitive than the ELISA, where you send it off to a laboratory that does it. But it is helpful if it's positive, because it gives you a diagnosis at the bedside.

DR. EL SAHLY: Is it serotype specific?

DR. DURBIN: So the rapid test is not. Some people are trying to develop serotypes-specific NS1 testing, but it's not in routine use.

DR. EL SAHLY: Dr. Bennink.

DR. BENNINK: I know we're going to have something on Puerto Rico later, but are there other aspects of what you've been talking about in terms of treatments in the U.S., in Puerto Rico, and in Florida, and Texas, in things -- how it's handled here?

DR. DURBIN: You know, Puerto Rico is certainly an endemic area, and Gabriela will discuss this. I think it is far more like Brazil or Bangkok, than Florida or Texas. Texas and Florida do have cases, but they're very very infrequent. Puerto Rico

is an endemic area with a high burden of disease. So I think when we think about dengue, and where a vaccine would certainly be useful, Puerto Rico has a high burden of disease. They have hospitalizations for dengue, and as I said have a high burden.

So when I talk about dengue, and the management and all of it, this really is, I think, more relevant to Puerto Rico because they see a lot of dengue in Puerto Rico. There are a few cases in Florida, Hawaii, Texas, but it's a minimum burden of disease, particularly when compared to like Puerto Rico.

DR. EL SAHLY: I can speak to the Texas-Mexico border, in that there's a large disconnect between the seroprevalence and the disease. I don't think it's quite understood yet why there's a high seroprevalence, but just no disease -- or I should say subclinical.

DR. DURBIN: Right.

DR. EL SAHLY: Any other questions? Okay. Thank you so much.

DR. DURBIN: You're welcome.

DR. EL SAHLY: From the Dengue Branch, at the Centers for Disease Control and Prevention, Dr. Gabriela Paz-Bailey will do the next presentation on the epidemiology of dengue, with a focus on Puerto Rico.

THE EPIDEMIOLOGY OF DENGUE

DR. PAZ-BAILEY: Good morning, and thank you so much for the opportunity to present to you at VRBPAC today. I am the lead epidemiologist at the Dengue Branch, and I'm located in San Juan, Puerto Rican.

So I'm going to talk to you about the global epidemiology of dengue. And I will also go through a few considerations on dengue testing. I will specifically be talking about IgG testing, as a vaccine under consideration requires pre-vaccinations serostatus screening. And I will review the data on dengue epidemiology in the U.S. and its territories to consider where dengue vaccine may be beneficial.

So what is the global epidemiology of dengue

and where is it a public health problem? Dengue virus is transmitted by Aedes species mosquitoes, primarily Aedes aegypti and Aedes albopictus. Aedes aegypti is a more efficient vector. And it's arguably the most important arbovirus in terms of Worldwide morbidity and mortality, with an estimated 390 million infections every year, and about 100 million infections that present clinical symptoms, half a million hospitalizations, and about 20,000 deaths.

Dengue virus is a public health problem throughout the tropics and subtropics, with 128 countries being affected. It is endemic in Asia, Latin America, including the Caribbean, Africa and the Pacific. And most of the burden of disease is in Asia, but the numbers here give you an idea of the annual number of infections. So, for example, in India, they may expect between 7.5 and 32.5 million infections a year. With rising temperatures, and with more connectivity regarding travel, now there are more areas that may be at risk for dengue infection.

So infections can occur with any of the four

distinct dengue virus serotypes. Natural infection results in lifelong protection for that stereotype; but in theory, a person can be infected with dengue four times in his or her lifetime.

The risks of developing disease after infection is low for tertiary and quaternary infections, medium for primary, and high for secondary, as you can see in the diagram here. So the risk of disease and severe disease is lower for post-secondary infections, is medium for primary, and then it's higher after secondary infection.

In terms of the clinical spectrum, about 25 to 35 percent of infections are symptomatic. And we heard from Dr. Durbin, the classical symptoms that include abrupt onset of fever, headache, retro-orbital pain, and muscle and bone pain. That's why it's called breakbone fever. And often there is a rash. Of those symptomatic, between 10 to 20 percent are hospitalized, and severe dengue happens in one to five percent of symptomatics.

This is a study by Messina and co-authors that

mapped the global distribution and the co-circulation of each dengue serotype, from 1943 to 2013. And please take this data with the caveat that serotype diagnostic availability has changed over time. But what it shows is that the detection of the virus serotypes has expanded worldwide, together with growing hyperendemicity. And hyperendemicity means that multiple serotypes are circulating in an area.

So until the 1980's the majority of areas had only report one serotype, one or two. And, most recently, all four virus serotypes frequently co-circulate. And those are the dark orange areas in the map.

An example of this is Puerto Rico, which has monitored serotype distribution for over three decades. And, in addition to co-circulation of multiple serotypes, you can note from the graph that the proportion of each of the four serotypes circulating varies over time, with one or two serotypes predominating every year.

This slide is to emphasize that dengue

transmission is dynamic, that is constantly changing, and that seroprevalence that is measured 10 years ago does not necessarily reflect seroprevalence today. The data come from a cohort study in a particular Managua district, in Nicaragua, and show how seroprevalence, by age group, has changed substantially between 2004 and 2015.

The y-axis in the graph shows the proportions seropositive, and you can see in the x-axis age. And I want you to focus on the yellow line, that is 2004, and the dark blue line, that is 2015. So while 50 percent of children were seropositive by age 4.5 in 2004, 50 percent seroprevalence is only reached by age 11, in the dark blue line, in 2015. So determination of the optimal age to start vaccination needs to take into consideration the changes in the force of infection over time.

So we heard a lot about severe dengue from Dr. Durbin, but I want to highlight that of the estimated $8.9 billion global financial burden of dengue, most of this, $5 billion, come from hospitalizations and

deaths. Age co-morbidities, host genetics, virus strains are risk factors for severe dengue, with heterotypic secondary infections being the greatest risk for dengue hemorrhagic fever and dengue shock syndrome.

So how secondary dengue infections increase the risk of severe dengue is thought to be explained by the phenomenon of antibody dependent enhancement that Dr. Durbin already explained. And the mechanism is that a specific antibody concentration, heterotypic antibodies bind but do not neutralize virions from the subsequent infecting dengue type. And this leads to higher viremia, and to an imbalance, inflammatory response that ultimately results in vascular leak and severe dengue disease.

So it was only recently demonstrated at what specific range of antibody titers there was this association with the increased risk of severe dengue. And this graph is also from a longitudinal analysis of the Nicaragua cohort, showing the risk, or hazard, of severe dengue disease, by preexisting dengue antibody

titers.

For dengue hemorrhagic fever and English shock syndrome, they showed a hazard ratio of seven, compared to having no previous dengue infection, that is the dotted reference line. And the cumulative hazard was 11 percent for that middle range antibody that in this case is from 1:21 to 1:80, compared to 1.6 for dengue naïve children and 1.5 for children with high titers. So having no antibodies, or a lot of antibodies, is better than just having a little bit.

So there is a question about what percentage of primary, secondary or post-secondary infections result in hospitalizations and in severe disease. And Sam Clifford and Stefan Flasche from the London School of Hygiene and Tropical Medicine, kindly shared these modeling results that were fit to the Dengvaxia Phase III trials. And the table shows the proportion of first and second infections that progresses to different disease outcomes; so including symptomatic, virologically confirmed dengue, hospitalization, and

severe virologically confirmed dengue, for different follow-up periods: two years for symptomatic VCD, and five years for hospitalization and death. And the data show that after first infection, 19 percent progress to symptomatic VCD, 3 percent are hospitalized, and .3 percent result in severe dengue.

After secondary infection, this is higher. 35 percent progress to symptomatic VCD, 10.6 percent are hospitalized, and about 2 percent result in severe dengue. And you can see that there is uncertainty in the estimates shown by the confidence intervals. They also estimated this for tertiary and quarterly infections, but there was very little data to support this modeling result, so we chose not to present it.

So the current dengue vaccine candidate requires screening for dengue serostatus before vaccination, and IgG testing will likely be used to determine serostatus. Also, seroprevalence surveys that are needed to determine the optimal age groups that would benefit from vaccination, also employ IgG testing.

So I'm going to talk a little bit about IgG testing. You already heard about molecular and antigen testing, and IgM testing from Dr. Durbin, so I'm going to focus on IgG testing.

So IgG titers rise about a week after primary infection, and rise earlier and to higher levels in secondary infections. And the titers decline, somewhat, after three months, but remain detectable, presumably for life. This graph is from a cohort study that shows antibody levels up to three years after infection. And there are very, very few of these cohorts.

31 companies have marketed 56 dengue IgG ELISA tests, and at least seven rapid tests; but none of these tests are approved for their use in the United States. Performance is reported only among a subset, among 14 tests, including 10 ELISAs and four rapid tests. And the sensitivity ranges from 33 percent to 100 percent, and specificity from 92 to 100 percent.

This is a list of the tests for which specificity and sensitivity are reported. And a

disclaimer, or a statement on cross-reactivity, is only included in a few of the package inserts. The composition and the size of the clinical evaluations is limited in most cases. And the samples sizes vary between 30 and several hundred samples, when they report them. It's not always reported.

Distinction of primary and secondary status in terms of the performance of the test is not made in most cases, and the only exception is the first one in this list. And that is the sensitivity range shows the different sensitivity after primary and secondary infections.

So we note the following limitations in evaluations of dengue IgG test sensitivities and specificities. The performance evaluations, when available, are done with small or specified sample sizes, with a few exceptions. The specificity is measured differently by the various companies, with different panel compositions. And these evaluations were conducted before the Zika epidemic. And now, of course, we have greater challenges with flavivirus

cross-reactivity.

The companies have marketed this test for diagnosis of symptomatic cases; and therefore, the evaluations have been calibrated for detection of high IgG values. And we're talking about using these tests in asymptomatic people. So, few of these tests were assessed independently. The performance is as reported in the package insert, by the manufacturers.

So commercial IgG tests have not been evaluated for long-term detection of confirmed primary and secondary infections, detection of previous infection in asymptomatic persons, and differentiating between previous dengue and Zika virus infection.

So when thinking about test performance, sensitivity and specificity are not the only targets for assay development. Positive and negative predictive values are important too. So tests with a given sensitivity and specificity are more likely to misclassify truly seronegative individuals in low transmission settings than in high transmission settings because of the pretest probabilities being

lower.

And in this example of a 20 percent seroprevalence with a test specificity of 90 percent, and a sensitivity of 70 percent, in the green box you can see that 36 percent of persons that test positive would be false positives, or actually true negatives.

In a higher prevalence setting of 80 percent seroprevalence that is presented here, the positive predictive value is higher, 97 percent; and then only 3 percent of persons testing positive, would be misclassifications, and would actually be false positives.

The problem here is then with the imperfect sensitivity, because then more than half of those that test negative are actually true positives and could benefit from a vaccine. So both the positive and the negative predictive value are important, and both sensitivity and specificity need to be kept high.

So, now I'm going to talk about dengue epidemiology in the United States and its territories, and in consideration of which areas may benefit from a

dengue vaccine. So the framework on dengue risk centers on the presence of the vector, and history of and potential for virus transmission.

Puerto Rico is endemic for dengue. The Virgin Islands and Pacific territories also have high, if not endemic, levels of transmission. Southern U.S. states, such as Texas and Florida, have experienced dengue outbreaks in recent years, as has Hawaii. And a number of other southern states, such as southern border states, are potentially at risk, because they have the presence of the vector; they have Aedes aegypti, and there may be imported infections because of their proximity to endemic areas. In areas where the vector is not present, then only imported cases can occur.

So I just wanted to mention quickly sort of the framework that WHO uses to classify risk. And economists and modelers, in collaboration with WHO, have proposed levels of risk based on seroprevalence, to identify areas that could benefit from vaccine, and also where the risk of false negatives would be low.

Areas with 10 percent, are classified as very low; 30 percent, low; 50 percent, moderate; 70 percent, high; and 90 percent, very high. And this would be seropositivity at the target age group to start vaccinating, in this case, nine-year-olds.

So, ideally, we would have seroprevalence data, to determine risk and to determine endemic areas. But, as for the rest of the world, there is limited seroprevalence data available in the United States and its territories. So, we're proposing to use the dengue risk definition in the CDC Yellow Book that provides information to travelers, and it's updated every two years.

The Yellow Book defines areas with frequent or continuous transmission, as areas with 10 or more dengue cases in at least three distinct years, over the most recent 10-year period. For those areas that do not classify as frequent or continuous risk, if they report at least one reported locally acquired case in the previous 10 years, those are considered sporadic or uncertain risk. And then in many areas,

there is actually no data. So, those are classified as no evidence of risk, if there are no reports of dengue transmission.

So based on this criteria, the areas that would be defined as endemic in the U.S. territories, would include American Samoa, Puerto Rico, and the U.S. Virgin Islands, and then the U.S. affiliated Federated States of Micronesia, and Palau.

So, let me describe the U.S. territories that would fall into frequent and continuous risk. I'm going to talk a little bit about dengue epidemiology in Puerto Rico. These are the dengue incidence rates for suspect cases, comparing Puerto Rico to a few countries in Latin America. And just to show you that the rates in Puerto Rico are very similar to other countries in Latin America. Brazil has 10 times those rates; and therefore, we're using a different y-axis for the Brazil data.

But surveillance practices vary a lot by country, so some of the quality of the surveillance activities may explain some of these differences.

The map shows the confirmed and probable cases in Puerto Rico, by municipality. And you can see that dengue transmission occurs through the island, but there is local heterogeneity. Areas with higher population density, such as San Juan in the northeast, and Ponce in the south, have the highest number of cases.

For each of the territories, I'm going to present the number of cases and the rates per 1,000 persons, for the most recent years when there was transmission. So the most recent years when there was transmission in Puerto Rico, is 2010, and 2013. Passive surveillance data from Puerto Rico, from 2010 to 2013, shows that the highest number of cases, and the highest rates are in the 10 to 14 age group, and 15 to 19 age group.

So the top graph is the number of cases. You can see on the y-axis on the left side, the number of cases, and then the rates on the other y-axis, that is the black line. And then the bottom graph is the number of hospitalizations.

And again, there were 9,000 hospitalization for that period of time total. The number of hospitalizations was the highest in the same age group, 10 to 14, and 15 to 19. And I want to make a couple of considerations here. First, although the 10 to 14, and 15 to 19, were the age groups that were the most affected, still close to 50 percent of the cases occur in adults. So there is disease in adults and there are hospitalizations in adults. And there is a high degree of underreporting in Puerto Rico, and probably in other countries.

So, we have estimated that for every reported case, there are a hundred cases that are not reported. And for every hospitalized case, there are between five to 10 cases are not recorded. So this is just the tip of the iceberg. There's a lot more infections, and a lot more clinical disease, and a lot more hospitalizations that are not monitored by this surveillance system.

With regards to dengue associated deaths, the case fatality rate has varied by outbreak year, and

this graph shows the number of deaths by age group. In contrast to the higher number of cases in children and adolescents, only six of the 64 lab-confirmed deaths in this period where children, and only one death was in the 15 to 19-year-old age group. So death mainly occurred among adults 20 to 88. 90 percent of lab-positive deaths were in adults in this period, 2010 through 2013.

So this is one of the few recent seroprevalence surveys that are available for Puerto Rico, and it was done in 2007, in Patillas. That is in the southeast of the island. And the seroprevalence among 10 to 11-year-olds was 43 percent. By 16 to 18 years of age, about 60 percent were seropositive.

And I would like to provide you some information on how dengue test results are processed in in Puerto Rico. Persons who are symptomatic and seek care, will visit their health care provider in a private office, or they will go to an emergency room. And then if the provider suspects dengue, a dengue

test is ordered, and the patient is usually referred to a clinical lab for the collection of the specimen, unless he or she is at a hospital. And testing for dengue is centralized, so all the testing happens at the public health laboratory and their PCR testing and IgM testing is conducted.

So the results are then sent back to the name in the form that appears the provider. That could be the doctor who ordered the test, or it could be the clinical lab. So if it goes back to the clinical lab, then it's returned to the patient, and the patient has to give it back to his provider. So this means that not all these results go back to the patient chart. And anecdotally, we know that in many cases they don't. However, all these test results are centralized in the passive surveillance system that is managed by the Puerto Rico Department of Health. So there is a database that has all the historical dengue test results available.

And in terms of how vaccines are managed in Puerto Rico, there is an immunization registry, and

there are about 220 providers for the Vaccines for Children program. This covers most of the vaccines administered, about 60 percent of vaccines, and there are also 300 private providers. Many of them are organizing vaccination centers. And they provide about 40 percent of the vaccines in Puerto Rico.

So the immunization registry covers both children and adults, and it's pretty complete. About 70 percent of the private providers are reporting, and this is increasing, and they have 100 percent coverage of the VFC providers.

So moving now to U.S. VI, the past 25 years have seen several periods of increased dengue virus transmission in the U.S. Virgin Islands, and the most recent one was in 2012 to 2013. There was a seroincidence study that was conducted in schools in St. Croix, in 2012, and about 20 percent of school-aged children and adolescents, and 17 percent of teachers were found to have recent infection, testing positive for IgM or PCR. There was no IgG testing done as part of this survey.

In the most recent years where there has been transmission, in U.S. VI 310 cases were reported. And you can see here the age distribution of the cases, and the incidence per 1000 persons. Again, here there's sort of a slight increase in the 10 to 14-year age group, but more cases occur in adults. About 70 percent of the cases in U.S. VI occur in adults.

The U.S. Pacific territories, and affiliated independent states, include American Samoa, Guam, the Northern Mariana Islands, Palau, the Marshall Islands, and the Federated States of Micronesia. And periodic dengue outbreaks have been detected among the Pacific territories since 1958, usually with only one serotype circulating at a time.

So, whether continuous endemic transmission occurs in any of the islands, it's unclear, because it could be introductions of the virus. However, a 2010 survey that was done in American Samoa, among adults, found that 96 percent of the sample population were IgG positive, and therefore, had been exposed to dengue. In 2016 and 2018, there was a large outbreak

in American Samoa, with over 1,000 lab-confirmed cases reported.

Again, this is data from passive surveillance showing confirmed and probable cases in the upper graph, and hospitalizations by age in the lower graph. And you can see a pattern, similar to Puerto Rico, with higher number of cases and rates among the 10 to 14, and 15 to 19 years of age.

So, I will talk now about the U.S. states that have sporadic and uncertain transmission. There have been large dengue outbreaks historically in Hawaii, and more recently in 2015 and 2016, there were 264 cases reported due to dengue 1, on the Big Island of Hawaii. The outbreak strain was dengue 1. And it was different from a big outbreak that happened in 2001, and sort of suggested a recent introduction

There is some seroprevalence data available. There was a serosurvey done in 2001 that showed 14 percent had evidence of recent infection, and 70 percent had evidence of past infection, or were IgG positive.

Several counties in southern and central Florida have reported locally acquired cases. In 2009 and 2010, nearly 90 cases were reported. And in 2013, a locally acquired outbreak took place and there were 21 cases reported.

There was a serosurvey done in Martin County in 2013, where they reported 2 percent being IgM or PCR positive; and also the same year in Key West, with 4 percent IgM positive and 7 percent IgG positive. And then after 2013, there have been just a handful of locally acquired cases reported.

Since 1980, Texas has detected a number of outbreaks. And what happens in Texas is that there a few locally acquired cases in the cities in the border on the U.S. side, and then huge outbreaks on the Mexico side. So there is a, sort of a big difference on what happens on the U.S. and the Mexico side. And in 2013, there were 24 locally acquired cases reported.

So this is to sort of highlight the issue of the different risk, and it's a seroprevalence study

that was done in Matamoros, on the Mexico side, and then in Brownsville, on the Texas side. And for recent infections, you can see the difference by age group. In Matamoros that range from 20 to 70 percent seropositivity. And in Brownsville, it was from one to 10 percent.

For past infection that is highlighted by the red boxes, this is IgG seropositivity. In all age groups it was close to 70 percent or greater than 70 percent for the Mexico side. It was a lot lower in Brownsville, ranging between 17 to 56 percent, but it was 40 percent seropositive in total.

This is a little bit on dengue among travelers in the U.S., about 800 dengue cases a year are reported among U.S. travelers. And the most common travel destination has been the Caribbean; although recently there have been some changes with dengue cases reporting travel to Asia, more frequently than the Caribbean.

The CDC Advisory Committee on Immunization Practices, or ACIP dengue vaccine workgroup, will be

reviewing the available data for foreign-born our territory-born travelers, to consider these groups when making any dengue vaccine recommendations.

So, to summarize, dengue is a public health problem throughout the tropics and subtopics, including the Americas. Seroprevalence data is unfortunately very limited. No IgG tests are currently licensed in the U.S., and the performance evaluations were done before Zika. Seroprevalence affects assay performance.

U.S. territories with frequent or continuous risk include Puerto Rico, U.S. VI, American Samoa, and some of the U.S. affiliated Pacific Islands. And the cases and incidents rates in Puerto Rico, U.S. VI, and American Samoa are the highest in the 10 to 19 age group, but many cases also occur among adults.

And then I just want to acknowledge, especially Steve Waterman, who's the lead for the ACIP dengue workgroup, and then other colleagues at the Dengue Branch at the Puerto Rico Department of Health and at the London School.

DR. EL SAHLY: Thank you, Dr. Paz-Bailey. Quick question, the 20,000 deaths worldwide, are these based on modeling, or are these based on confirmed cases?

DR. PAZ-BAILEY: Yes, those estimates were actually done for 2010, they're a little bit outdated, yes. And is a result of gathering all the data that is available, but also the modeling exercise. So it's very hard to rely on the surveillance systems for it, because of the underreporting.

DR. EL SAHLY: And you showed the slide from Puerto Rico regarding the seroprevalence. It was also a little older, 2013; am I right?

DR. PAZ-BAILEY: No, even older; 2007.

DR. EL SAHLY: 2007. And what was the overall? I saw by age range, but I missed reading the overall seroprevalence based on those --

DR. PAZ-BAILEY: It was 54 percent overall, I think.

DR. EL SAHLY: 54, okay. Dr. Edwards.

DR. EDWARDS: Thank you. That was very, very

informative. I wanted to talk a little bit about the fatal cases of dengue in Puerto Rico. And certainly, it seems that they are, at least 50 percent or more are adults. And older adults, the rates are even higher. So, what do you know about those cases? Are these first cases, are these second? Are these people who are immune, or are there data to address that?

DR. PAZ-BAILEY: Yes, so there is a surveillance system in place in Puerto Rico, EFASS, an enhanced fatal case surveillance system, to monitor deaths. And there was a publication describing most of these cases, 54 of the 64. Most of them are in adults, all except four. And these cases, in many cases, there were comorbidities present, mainly asthma and diabetes.

It was interesting that for 50 percent of those cases, when they showed up at the hospital, they were sent back home. So there was a lot going on, in terms of recognized dengue infection. Most of them had vascular leakage, about 90 percent. About 70 percent had severe hemorrhages. And in about a third

there was also evidence of fluid overload.

So I think, you know, comorbidities were definitely a risk factor contributing to these deaths, maybe poor clinical management at the time, and not enough recognition of dengue warning signs. Of those that were sent home, most of them had dengue warning signs; and if the guidelines had been followed, they would have been hospitalized.

DR. EDWARDS: But, do you have any information about their serologic status, or were these primary or secondary or is that known?

DR. PAZ-BAILEY: I mean, my guess is that they would more likely have been secondary infections, but I don't think that the study actually reports on primary versus secondary. They do have a lot of detail on confirming the deaths, with histopathological findings and with PCR testing; but yes, my guess is that most were secondary. And mainly because these were all adults, so by that time they were probably have been infected with dengue.

DR. EL SAHLY: Dr. Kurilla.

DR. KURILLA: Yes, you highlighted one issue of a prior exposure evaluation. Most of those performance tests have all been done pre-Zika. I'm wondering, though, do we have good evidence that past vaccination for yellow fever does not complicate the ability to detect a past, a prior dengue exposure?

DR. PAZ-BAILEY: Yes, I think that past vaccination with yellow fever would complicate detection of dengue infection, since there is cross-reactivity.

DR. EL SAHLY: Certainly, not as much as Zika. I mean, there's some, but --

DR. PAZ-BAILEY: And I don't know if Jorge Munoz, from the Dengue Branch, may want to expand on that.

DR. MUNOZ-JORDAN: Yes, the previous yellow fever vaccination can affect the results of serological tests such as IgM and a few tests, to some extent. I'm not sure about a difference between Zika and yellow fever, because I haven't been able to compare those yet. But historically, something like a

good 20 percent of people who had yellow fever vaccination would have a confusing test result for dengue.

DR. EL SAHLY: Dr. Levine.

DR. LEVINE: Yeah, it seems to me that the development of a highly sensitive and highly specific point-of-care rapid diagnostic test would be potentially, extremely important here. The few rapid diagnostic tests that you mentioned, are they done with finger stick blood, or are they done with separation then to get serum? Can you tell us a little bit about those tests? And can you also tell us, if you're aware, what's going on in development to convert some of these ELISAs, a few of which show very high sensitivity and specificity. If there were a tool that could achieve that with a point-of-care test, that could be an enormous breakthrough, and have important practical implications for the use of this vaccine.

DR. PAZ-BAILEY: Yes. So I'm going to pass these very important questions to Jorge, because he's

a lab expert. And he kindly put together these slides for me to present today.

DR. MUNOZ-JORDAN: Yeah, are you asking specifically about those IgG tests, or in general -- or for point-of-care diagnostics?

DR. LEVINE: So what I'm thinking of is, if there is an ELISA, based on serum -- an IgG ELISA that has high sensitivity and specificity, then in theory, folks who do lateral flow amino assays, in theory, could come up with – if there's a good ELISA that could be a good rapid test, the next problem is would it be done with whole blood, finger stick being the easiest. And there are techniques to either lyse the red cells, and the test is then done in the immunoassay, with the lysed material or to filter.

So those techniques are available. They're used for various kinds of biomarkers. My question is, are you aware of work going on to develop a rapid point-of-care test, either with blood or with sera? You could also collect blood and go through the step of centrifuge, even in the field, to get a serum and

then test with serum. That's less than the point-of-care, but that's all possible. Getting the high sensitivity and high specificity, with consistency in the field, that would be what one wants.

DR. MUNOZ-JORDAN: Right. So there are rapid test, point-of-care tests that have already been developed for dengue IgG detection. And some of them were mentioned on the table that Gabriela showed. The specificity and sensitivity of those tests vary. And some of them have relatively good sensitivity and specificity.

With that said, not many of them have been recently evaluated in areas where Zika has been circulating. And the sampling size and the composition of the clinical panels evaluated changes.

You know, so the definition of specificity, which is the percent of expected results versus the percent of correctly identified results, will vary depending on the composition of panel, obviously. So, if you have clear-cut negatives in the panel, there

will always be negative in test. But if you have confusing flavivirus that are expected to be negative, the question is, will they be negative by the test.

So, very few of those tests have been evaluated extensively with, you know, potentially confusing illnesses such as Zika or yellow fever, and so such.

In terms of the discovery of this, you know, you pointed to the path of, you know, having an ELISA formulation first, and then moving into rapid test, and that's the natural course of the development. And I think that is ongoing. One of the lessons we have learned recently, in terms of test development, is the antigen composition used in the test. And also the use of ratios between the reactivity for the vital antigen that you're trying to detect, like dengue, in this case, versus another cross-reactive flaviviruses, as opposed to just using just one antigen.

So there's a lot of work going on, on using specific epitopes, as opposed to whole virus antigens. The rest of the tests that have been developed before

were for whole virus antigen, or for NS1 antigen. And some of the recent work shows that an antigen such as the main three of the E protein are very specific.

I think, what's challenging about dengue, is that you have four serotypes. So vaccine companies – sorry, vaccine companies not – but developers have a hard time putting four antigens together that are very specific for each of those viruses. But if you put them together it would not be as specific any longer, because you now have four. And so that has been very challenging; but I think it is work in progress that will improve these in the near future.

DR. EL SAHLY: Mr. Toubman.

MR. TOUBMAN: So, my questions are coming from a lay person. The questions for the committee are premised upon a clear requirement of laboratory-confirmed previous dengue infection. And so that assumes that we're going to be able to do that. And so there's a big question, of course, about compliance, especially in areas with limited resources, how they're going to be able to do that.

But putting that aside -- we'll have that to discuss later -- in terms of your slides on the test that are available: First, I understand that none of the IgG tests are approved by the United States.

Second, there's a slide that says there's been no independent evaluation. It's relying solely upon the manufacturers for the stated effectiveness of these tests. And there's been no -- they've not been evaluated specifically for detection of previous infection in asymptomatic persons, which is, I understand, the kind of tests we're talking about as the requirement for this.

So what's significance of the fact that there's been no independent evaluation of the effectiveness of this test for the very purpose we're talking about?

And then my other question is related to your next two slides that talk about false positives, even as reported. And my understanding for Puerto Rico, which is really, I think, the focus, it's a little more than 50 percent of folks are seropositive.

So, the two examples are 20 out of 100, there you're going to see 36 percent false positives; whereas, in a place with 80 out of 100 patients, you'll see 3 percent false positives. But if it's like 50 percent, it's going to be somewhere in between there, presumably, so we're still going to have a significant number of false positives. And, of course, that means these people will be vaccinated even though, by what we've seen, that's probably not a good idea. So if you could address those two things I'd appreciate it.

DR. PAZ-BAILEY: Yes. So the first question regarding the implications of this test being validated for a different scenario, for cases that aren't symptomatic, I think, I mean, the implications are huge, right? Because then, again, the test may have been, as I mentioned in the talk, calibrated for higher titers that you could expect soon after the infection; and then their performance may be completely different later on.

And I just have to clarify that this is sort

of a preliminary review of the tests available that, again, Jorge and his group put together for this presentation. But I supposed Sanofi is also going to share new data on their evaluation of the test. And all the other diagnostic tools that we have, like PCR testing, and antigen testing, that only serves for a very short window after infection happens.

So, for PCR testing, you will not be able to detect RNA, possibly at five days, at the maximum seven days. So we're talking about a completely different scenario of an asymptomatic population. And with regards to IgM, duration is probably for three months. So again, those are tools to detect recent infections.

The second question about seroprevalence in Puerto Rico, Puerto Rico has a strong surveillance system. It has the presence of the CDC Dengue Branch there. And we're working into generating additional seroprevalence data. But, of course, it's tricky because we had a large Zika epidemic, and the available tests that we have, are going to have

cross-reactivity. So, there will be seroprevalence data available. But right now we have to use what is there, that is mainly old surveys that show that seroprevalence, at 10 years of age, was 40%.

And again, as I showed you in Nicaragua, the force of infection will change with time, and we haven't had dengue transmission, or at least detected cases, since 2013. We had the last epidemic in 2013, and then there was the Chikungunya epidemic in 2014, and then there was the Zika epidemic in 2016.

Now there is a lot of dengue circulating in the Caribbean. There's an epidemic in Jamaica. There are cases in the Dominican Republic. So maybe the time has come and we will have another dengue epidemic in Puerto Rico soon.

But the performance of the assay, I cannot tell you exactly what's going to be the scenario, but you know it's -- and the target age group to start vaccinating is also crucial. Although the indication right now is for 9 to 45, it may be that an older age is more appropriate to start vaccinating. But

unfortunately, I don't have current seroprevalence data to provide you.

DR. EL SAHLY: Dr. Fuhrman,

DR. FOLLMANN: This question is kind of related. The question to the committee is to approve the vaccine in, so forth and so on, living in endemic areas. So we're being asked to approve for people living in endemic areas, given a very nice slide about how the seroprevalence really has a huge impact on the false positive rate.

And so, we'd like to, you know, have the vaccine rolled out in places that are very high seroprevalence. But we're asked about putting it in endemic areas, and so I was wondering if you or someone had thoughts about what does endemic mean in terms of seroprevalence? Would it mean between 50 and 100? Would it mean between 30 and 80, or 30 and 100? So, to me the relevant issue seems seroprevalence, but the charge is for endemic.

DR. PAZ-BAILEY: Yes, we have had a lot of discussion, at the ACIP dengue vaccine workgroup, on

how to define endemic areas. And sort of the epidemiological textbook definition, these are areas where there is ongoing transmission without the need for external introduction of the virus.

With dengue this is very tricky, because epidemic occurs in cycles every three to five years; so you could have very quiet periods with no transmission, and then you can have a huge outbreak that is going to overwhelm the healthcare system. And depending on recent clinical management, or the absence of it, it may result in high number of deaths.

So, I agree with you that defining endemic areas, based on seroprevalence, would be ideal. But we have a situation where there is very -- I showed you the seroprevalence. So, there is very little, and it's old.

And this is not unique for us. You know, WHO also based recommendations suggesting vaccination in endemic areas, but didn't go as far as defining which were those endemic areas. There are these ranges for seropositivity, that is what WHO is suggesting to be

able to make a difference between low, moderate, and high endemicity. But countries are like, well, I don't have that seroprevalence data, what can I do? Right?

So, although I agree with you that that would be the way to go, and we would have more precise information using seropositivity, what we're suggesting is using this imperfect indicator that is number of cases captured by surveillance systems, and following a system that is updated every two years, because also the endemic areas in the United States may change.

So, it is a rough measure of defining endemic areas as 10 cases or more in every year for three years in the past 10 years. But with the data that we have at hand right now, I think that that is as good as it can get. And we, again, we're working on getting more seroprevalence estimates, but also the diagnostic side of things poses additional complications.

DR. EL SAHLY: Dr. Follmann, I think, I can

share with you the WHO, but I think they designated the cutoff at 70 percent or more, for this to have impactful long-term implications, and understanding all the limitations Dr. Paz-Bailey indicated already.

DR. PAZ-BAILEY: And can I just add regarding that 70 percent cut off from WHO, that was when they develop the first set of recommendations, that was before the long-term follow up data, and sort of the safety issues came up. And they, sort of -- as you will know, they had to review that recommendation on vaccinating areas with 70 percent or more seroprevalence. And then suggested screening before vaccination, and didn't actually come up with the figure.

Now modelers groups are sort of developing spreadsheets so that countries can make their own decision and understand at a certain seroprevalence range, how many additional hospitalizations you're going to have in the seronegative, wrongly vaccinated, and then make the decisions locally.

DR. EL SAHLY: Okay, we have, I think, Dr.

Meissner, Dr. Bennink, and then Dr. LeBlanc.

DR. MEISSNER: Thank you. We're being asked to evaluate this vaccine in terms of efficacy and safety among individuals 9 through 45 years of age. And that's certainly when most of the disease occurs and the deaths in adults. But I noticed on your slides that the age group from 5 to 9 seem to have a reasonable burden of disease. And can you comment on excluding that age group from the target population?

DR. PAZ-BAILEY: Yes. I mean, ideally we would have a vaccine that could be administered to all age groups, regardless of serostatus. And there is the burden of disease among that age group, 5 to 9.

So, you know, I think it's sort of due to the considerations that the company had to do with regards to the safety signal and sort of dengue hospitalizations and increased risk of severe dengue among seronegatives. But, yeah, I don't know if there are plans to evaluate the possibility of using the vaccine in the younger age group. But there is definitely cases and hospitalizations among that

group, despite the fact that it's sort of the 10 to 19, the ones with the highest numbers

DR. EL SAHLY: Dr. Bennink.

DR. BENNINK: Yeah, this is a little bit of a difficult question, but do you know in the 9 to 45 age group, how many of those people have been multiple infected, versus only having one infection? Do you know, what that percentage of that is, of the percent that had been infected at any time?

DR. PAZ-BAILEY: So the short answer is no; but the fact that the passive surveillance data show sort of this increase in the 10 to 14, and then the 15 to 19, and then it drops, sort of suggests that by age 20 almost everyone has had two infections, and then they're sort of less likely to be symptomatic.

DR. BENNINK: Which would mean that the vaccine would be more important for that younger group even then, then up to 45, or something, that or at least one thought of that.

DR. PAZ-BAILEY: Yes.

DR. BENNINK: The other thing, in terms of the

cycle of three to five years or something, of outbreaks and stuff like that, another thing is, has anyone ever done any examination, for example, of mosquito control? And does that affect whether you get those outbreaks or something like that?

For example, when Zika first broke out, you know, there was probably tons of mosquito control programs that then began and -- or at other times. Or if you're having outbreaks from 10 to 13, does Puerto Rico then say okay, we've really got to control this. So they begin to really get more effective at doing that. And does that have a massive impact on how many cases you see?

DR. PAZ-BAILEY: Yes. So, traditionally, traditional vector control tools like spraying and repellent use, have sort of failed to control outbreaks. And in a big part is because of insecticide resistance. In the case of Puerto Rico, none of the available insecticides -- and the mosquitoes are resistant to all of them. So that is not an available tool. And it was a significant

challenge during the Zika epidemic.

There are novel mosquito control techniques that are now being evaluated. But it's sort of in very early stages, and we're planning a cohort study to evaluate that. So I could talk to you for hours about this. But some of them are related to Wolbachia infected mosquitoes, where you liberate males infected with Wolbachia. And then when they mate with the wild females, they are sterile. And then that's a method for population control. And they're genetically modified mosquitoes.

And other strategies that seem extremely promising, but have not been evaluated to determine their epidemiological impact, they show that they have an impact in the mosquito population. We don't know if they're going to prevent outbreaks. So, sadly, we don't currently have vector control tools that could stop outbreaks. And the Zika epidemic in Puerto Rico is a clear example of that.

DR. EL SAHLY: Dr. LeBlanc.

DR. LEBLANC: Just two comments with regards

to your question about seroprevalence and on a countrywide level. It's my understanding -- tell me if I'm getting this wrong -- that as of September 2018, when the World Health Organization SAGE committee, considered the most recent data, they most strongly recommended the laboratory confirmation of a prior dengue infection should be the predicate upon which this vaccine is given.

As a secondary comment, they said you could consider vaccination in an area that had 80 percent seroprevalence, so they bumped it up from the 70 percent. But if you just recall the slide that was shown for Puerto Rico, you had seroprevalence by – I don’t know if you call them municipalities or counties. And it varied widely. You had a couple of deep purple areas, then you had a whole lot of areas where there was very little dengue.

So, if you're looking at a vaccine and only the level of advocacy vary by seroprevalence, that might be fine. You’d have less efficacious if you were in a municipality that had a low seroprevalence.

But when you're looking at a vaccine that has a safety risk, and that safety risk is a function of whether you're dengue immune or nonimmune at baseline, that really altars that consideration.

DR. EL SAHLY: Any additional comments or questions to Dr. Paz-Bailey? Thank you, Dr. Paz-Bailey. Thank you so much. Next, we will break for let's say 10 minutes and reconvene at around 11:05. Thank you.

BREAK

SPONSOR PRESENTATION

DR. EL SAHLY: Dr. David Greenberg from Sanofi Pasteur will be presenting the sponsor's presentation today.

DR. GREENBERG: Good morning. I'm David Greenberg, Associate Vice President and Regional Medical Head, North America, for Sanofi Pasteur. I'm also an Adjunct Associate Professor of Pediatrics at the University of Pittsburgh School of Medicine. I'd

like to thank the FDA and members of VRBPAC for the opportunity to present our data on Dengvaxia, the first vaccine to help prevent dengue.

Our proposed indication is for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3, and 4 in individuals 9 through 45 years of age with a laboratory-confirmed previous dengue infection who are living in endemic areas. Previous infection can be assessed through medical record of a previous laboratory-confirmed infection or through current serotesting. Dengvaxia is administered subcutaneously in a three-dose schedule at six-month intervals.

I'd like to take a moment to explain the rationale for our proposed indication. First, our pivotal clinical studies demonstrated that Dengvaxia provides significant protection against all four serotypes of dengue and against symptomatic, severe and hospitalized dengue for at least five years in persons 9 through 16 years of age who have been previously infected with dengue.

Our immunogenicity studies support a level of

protection in adults up to 45 that is similar to the protection observed in adolescents. Additional analyses indicated a risk of hospitalized or severe dengue in seronegative individuals. While Dengvaxia showed a favorable safety profile in our clinical program, we are requiring laboratory confirmation of prior dengue infection as a safety precaution, and we are targeting individuals living in endemic areas because they are at higher risk for symptomatic and severe disease, including hospitalizations.

Dengue is an acute, systemic, viral infection, the most common mosquito-borne viral infection in humans. It has no treatment, it is potentially lethal, and the incidence is growing around the world. As recognized by the World Health Organization, there is a need for a safe an effective vaccine against each of the four serotypes of dengue to help protect people in endemic areas, including Puerto Rico, where dengue has been endemic for decades.

Dengvaxia is the culmination of more than 20 years of research. It is a tetravalent,

live-attenuated viral vaccine. The capsid and non-structural proteins of yellow fever virus 17D serve as the backbone of this vaccine. Precursory membrane and envelope genes are isolated from each dengue serotype and inserted into the yellow fever backbone, resulting in four separate RNA chimeric genomes, one for each serotype. The four chimeric dengue vaccine viruses are combined into a single vaccine preparation that induces protective antibodies and offers protection against each of the four dengue serotypes.

The Dengvaxia global clinical development program was initiated in 2002. The program includes 26 completed clinical studies, with more than 41,000 subjects enrolled in 16 countries. The U.S. has been part of all phases of our clinical program. This has included Puerto Rico. More than 28,000 subjects have received Dengvaxia in our clinical trials, with approximately 21,000 subjects 9 through 45 years, the age group specified in our proposed indication. Dengvaxia is currently licensed in 19 countries and

the European Union.

Shown here is the agenda for our presentation. Next, Dr. Stephen Thomas will discuss the unmet medical need for a dengue vaccine in the United States. Dr. Sanjay Gurunathan will then present our efficacy results. Dr. Cesar Mascareñas will present our safety results. Dr. Corinne Jouquelet-Royer will present our risk management plan. Dr Su-Peing Ng will present the benefit-risk assessment and close our presentation. And finally, Dr. Carlos DiazGranados will moderate the Q&A session. Our external expert has been compensated for his time and travel. We also have a number of other experts here to answer your questions. I will now turn the lectern over to Dr. Stephen Thomas.

DR. THOMAS: Thank you, Dr. Greenberg. Good morning. My name is Stephen Thomas, and I'm the Chief of the Division of Infectious Diseases and a Professor of Medicine and a Professor of Microbiology and Immunology at the State University of New York, Upstate Medical University. I have worked on dengue

for more than 20 years and have been involved in the development of multiple dengue vaccine candidates. I advise a number of groups on issues related to dengue, including governments, NGOs, academic groups, and industry. I am here to describe the unmet need for a safe and effective dengue vaccine in the United States.

Dengue is the most common mosquito-borne viral disease on the planet and is transmitted, primarily, by 80 mosquito species. When an uninfected mosquito feeds on an infected person, that mosquito has the potential to become infected and then has the potential to infect several additional people. These infected people can then function as viral reservoirs for other non-infected mosquitos to feed and become infected, continuing the transmission cycle.

As with many viral infections, most dengue virus infections are clinically inapparent. The first dengue infection in endemic countries, often occurring in children, is typically asymptomatic or mild. When symptoms are present, they can be very debilitating.

They include high fever, nausea and vomiting, severe headache, muscle and bone pain, rash, and a variety of other symptoms.

In some patients, their signs and symptoms become even more severe. Sever dengue may include abdominal pain, bleeding, confusion, and/or shortness of breath. The primary driver of severe disease is plasma leakage, where endothelial cell linings of blood vessels become permeable. Proteins and fluids leak from inside the blood vessel into the extravascular space, causing pleural effusions or ascites.

Dengue infection can also disrupt the coagulation system, resulting in significant bleeding. If the intervascular volume is not properly maintained, organ profusion declines, and organ dysfunction and failure can ensue, with the potential for shock and death.

So why do some individuals get severe disease? There are numerous potential risk factors for developing severe disease, including age, sex,

infecting serotype and genotype, and the individual's nutritional status and genetic background. However, the largest body of data supports that two sequential infections with different dengue serotypes predict the highest risk of severe disease. This is primarily because of two factors: the limitations of cross-protection after the first infection and the individual's antibody titers present at the time of the second infection.

Looking first at cross-protection, as you heard from Dr. Greenberg, there are four antigenically distinct dengue serotypes that often co-circulate in geographically defined areas. Infection with one serotype confers long-term protective immunity against that type, but only short-term, cross-protective immunity against the other serotypes.

To demonstrate this waning of cross-protection, let's look at this hypothetical example of what happens after a dengue naïve individual is infected with a primary dengue infection.

Anti-body titers, depicted on the y-axis and

by the blue line, rise quickly and are maintained above the protective threshold, depicted by the dotted line. Although in this illustration the infection is with serotype one, there will also be immune responses to the other three dengue serotypes. Here, two of them rise above the protective threshold. The period of time the titers remain above the threshold is the period of cross-protection. But, as you can see, this cross-protective response does not persist.

Moving on to the more specific impact of antibody titers, in this graph, we see PRNT50 antibody titers present before a second infection on the x-axis and the probability of hospitalization on the y-axis. As shown in the blue curve, there is a low risk of hospitalization in those without any antibody, depicted by the open circle, and an even lower risk in people with high antibody titers, over 100. However, as the curve shows, those with antibody titers between 1 and 100 experience a significantly higher risk of hospitalization. Similar findings were seen in a cohort in Latin America.

So, to summarize these data, the risk of severe dengue is increased when there are two sequential dengue infections with different serotypes, and we believe this is due to waning cross-protective antibodies, which have the potential to worsen infection and clinical outcomes. These outcomes can become severe, to the point of being fatal.

While other communicable diseases have seen improvement in mortality over time, dengue has not. This table, from the Global Burden of Disease study in 2017, shows that all age deaths from dengue increased by 65 percent in the ten-year period from 2007 to 2017. When adjusted for age, the increase over the same period was 40 percent. Additionally, unrecognized deaths due to dengue may be common. In a study from Puerto Rico, there was a two to three-fold higher dengue mortality rate compared to previous reports.

It’s also important to note that there is no specific dengue antiviral available, nor is there a therapeutic which targets the immunopathologic

responses thought to play a role in severe dengue. Current dengue prevention focuses on reducing mosquito populations and avoiding mosquitos. Treatment for uncomplicated dengue usually occurs in the outpatient setting and includes rest, antipyretics, oral fluid replacement, and close monitoring. Severe dengue often requires hospital admission and intensive monitoring, intravenous volume repletion, occasional blood products, and, in some cases, intensive care unit admission.

Even non-hospitalized dengue represents a significant public health burden. Frequent clinic visits are not unusual, as medical providers assess and reassess for signs of severe disease. Although often managed in the outpatient setting, dengue still may require patients and their caregivers to miss, on average, seven days of work or school. People may also have a post-infection syndrome, which lasts for weeks or longer, impacting overall personal productivity. Disability related to both hospitalized and not hospitalized dengue has been steadily

increasing over the last 30 years, representing a significant global public health burden.

Approximately half of the world's population lives in endemic areas and is therefore at daily risk of a dengue virus infection. Models estimate approximately 400 million infections occur every year. About one-quarter of these result in clinically apparent disease. Half a million people require hospitalization for their infections, and tens of thousands of people succumb to severe dengue.

Dengue is endemic in numerous countries in the Americas. As you can see, there is frequent or continuous transmission in U.S. territories, including American Samoa, the U.S. Virgin Islands, and Puerto Rico. Most dengue cases in U.S. citizens occur in Puerto Rico. Among the endemic U.S. territories, Puerto Rico has the most robust data to support endemicity.

Here, we look at the age-specific dengue burden in Puerto Rico. These are the number of lab positive dengue cases between 2010 and 2012, with case

numbers on the y-axis and patient age on the x-axis. The peak was observed in the 10 to 19-year age range, though nearly half of all cases were in adults.

Different age ranges are associated with different risks from dengue. Children typically can't tolerate severe disease as well as adults can, but adults may have comorbidities, such as heart or lung disease or diabetes, which may increase their risk of a bad clinical outcome. In fact, most dengue deaths occurred in adults 19 to 64 years of age, with an estimated dengue mortality of 0.42 per 100,000 for those younger than 19 and 1.17 or more for those older than 19.

In addition to persistent endemic transmission in Puerto Rico, indicated by the lighter bars, the country has periodic epidemics, indicated by the darker bars. This figure shows passively collected suspected dengue cases reported in Puerto Rico from 1986 to 2013. The epidemic threshold is just below 10,000 cases per year.

Numerous factors contribute to these patterns,

including the co-circulation of multiple dengue serotypes, as mentioned earlier. During each of the periodic epidemics, you can see that three or four dengue serotypes were co-circulating, represented by the color dots.

This pattern of highly variable transmission over time is not limited to Puerto Rico. This is observed in many dengue endemic countries, such as Brazil, Colombia, and Honduras. There are numerous potential drivers of this variable transmission pattern, including climate, tourism and travel, changes in mosquito populations, and herd immunity to the dengue serotype circulating in the area. Of interest, it is believed that the introduction of the Zika virus into the Americas may have provided transient cross-protection against dengue, potentially accounting for the widespread low dengue incidence rates in 2016, ’17, and beyond.

Despite these fluctuations, one thing is clear. Once dengue establishes endemicity in a region, it seems to persist. Extended periods of low dengue

incidence are not cause for celebration, but rather for concern that a large outbreak may soon occur.

In summary, dengue symptoms can be debilitating, and dengue related disease and mortality are increasing. Dengue is endemic in the Americas, including Puerto Rico, where multiple serotypes co-circulate, increasing the risk of clinically severe disease. A vaccine that can reduce dengue severity and sequential heterotypic infections, those infections with the greatest risk of more severe disease and death, would represent an important public health tool.

Thank you for your attention. Dr. Gurunathan will now come to the lectern to present the efficacy data for Dengvaxia.

DR. GURUNATHAN: Good morning. Thank you, Dr. Thomas. My name is Sanjay Gurunathan. I'm the Head of Global Clinical Sciences at Sanofi Pasteur. I'm a clinician with training in infectious disease and immunology. The data I will present will demonstrate that Dengvaxia provides protection for at least five

years against severe dengue, hospitalized dengue, and symptomatic dengue in people 9 to 45 years of age who have been previously infected with dengue. I'll show the key efficacy results of our two pivotal, randomized controlled trials. I will also present the signal observed in year three of Study 14, which lead us to conduct two additional analysis, one by age and one by serostatus. Let's start with Studies 14 and 15.

Both studies were randomized, observer blind controlled studies. These studies were placebo controlled and similar in design. Study 14 was conducted in 11 centers in five countries across Asia Pacific. Approximately 10,000 subjects were randomized two to one to receive either Dengvaxia or a placebo. Study 15 was conducted in 22 centers in five countries in Latin America, including Puerto Rico. Approximately 20,000 subjects were randomized two to one to receive either Dengvaxia or a placebo. Baseline blood samples were only obtained in a small subset of the population in each of the studies. This

was consistent with the WHO guidelines for clinical evaluation of dengue vaccines, which informed the design of the studies.

In both studies, subjects in both groups were scheduled to receive three injections, each six months apart. The entire period, from the first injection to month 25, is referred to as the active phase of the study, where surveillance was aimed at detection of symptomatic dengue regardless of severity or hospitalization. From month 25 onwards, surveillance was aimed at detection of hospitalized dengue; and in your briefing materials, this is referred to as the hospital phase, or long-term follow-up.

The primary efficacy of the vaccine evaluated the risk of symptomatic dengue one year after the last injection. We also evaluated efficacy during the entire active phase, from month zero to month 25. Throughout the study, the risk of hospitalization and severe dengue was evaluated.

The primary endpoint of both studies was to assess the efficacy of three injections of Dengvaxia in

preventing the occurrence of symptomatic, virologically-confirmed dengue cases. Asymptomatic case had to have had the presence of fever and laboratory confirmation. Symptomatic cases were those occurring more than 28 days after the third injection during the active phase. Key additional endpoints included the occurrence of confirmed dengue cases by serotype, as well as severe cases and those that required hospitalization.

We tested a hypothesis that vaccine efficacy against any serotype would be greater than 25 percent. The Per-Protocol Analysis Set is the primary efficacy analysis population. That includes all subjects who received three injections and had no protocol deviations. The Full Analysis Set for Efficacy includes all subjects who received at least one injection. Overall, more than 95 percent of the subjects received three injections of Dengvaxia or placebo.

Next I'll describe the results of the two studies individually, starting with Study CYD14. In Study 14,

the demographics were comparable between the Dengvaxia and the control groups. The study was conducted in children 2 to 14 years of age, which is consistent with the overall peak incidence of dengue illness in the region. The mean age at enrollment was approximately nine years. There were similar proportions of males and females in each group. The proportions of immune subjects at baseline was high in both groups. Approximately two-thirds were dengue immune against at least one serotype.

Study 14 met its primary endpoint. The incidence of dengue in the Dengvaxia group was 1.8 percent, compared to 4.1 percent in the control group. As shown in the forest plot, the overall vaccine efficacy was 56.5 percent. The lower bound of the 95 percent confidence interval was well over 25 percent, therefore meeting the primary objective of the study.

Overall, key additional endpoints evaluated over the active phase support the primary analysis of the study. As shown in this forest plot, values to the right of the null value favor Dengvaxia. All point

estimates and the lower bound of the confidence intervals exceed the null value.

When analyzing efficacy by serotype, it should be noted that all four serotypes contributed to the overall efficacy. Additionally, the incidence of clinically severe cases and of hospitalized cases was lower in the Dengvaxia group compared to the control group. The efficacy was 70 percent against severe dengue, and 67 percent for hospitalized cases of dengue. This forest plot displays the relative risk of hospitalized and severe dengue cases over five years of follow-up. Values less than one that or to the left of the dashed line are favorable for Dengvaxia. Overall, the relative risk of hospitalized and severe dengue are favorable. However, there's less precision in the estimates for severe dengue due to fewer events.

Next, let's look at some of the data for Study CYD15. Study 15 was conducted in Latin America in children ranging in age from 9 to 16 years of age, which is consistent with the overall peak incidence of

dengue illness in the region. Demographic characteristics were comparable across treatment groups. The mean age was 12 in both groups, with nearly an even split between males and females. Approximately 80 percent of the subjects were dengue immune at baseline.

The primary endpoint in Study 15 was also met. The incidence of dengue in the Dengvaxia group was 1.5 percent compared to 3.8 percent in the control group. The vaccine efficacy against dengue due to any serotype was 60.8 percent, with the lower bound, again, over 25 percent.

All key additional outcomes across the active phase favored the Dengvaxia group. Again, each of the four serotypes contributed to the efficacy of the vaccine. In the active phase of the study, there were a total of 12 cases of clinically severe dengue. Of the 12 cases, only one was in the Dengvaxia group, corresponding to 95.5 percent vaccine efficacy. The efficacy against hospitalized dengue was 80.3 percent.

This forest plot displays the relative risk of

hospitalized and severe dengue cases in Study 15 over five years of follow up. Again, values to the left of the dashed line favor Dengvaxia. Similar to results for Study 14, the relative risk in this study is favorable for both hospitalized and severe dengue over five years of follow-up.

Before we move on to the long-term follow-up data, I'll take a moment to summarize our two randomized control trials. These two independent studies met their endpoints and demonstrated that Dengvaxia is efficacious in prevent dengue against all serotypes, against severe cases, and against hospitalized cases of dengue. They were conducted in two distinct endemic regions of the world, spanning the pediatric age group from 2 to 16 years of age. The results of the active phase were positive. And in reviewing the long-term follow up data, we observed a signal of increased risk of hospitalized dengue in year three.

Our protocol included a pre-specified analysis, by age, according to IC age categories. These age strata are shown on the slide. This analysis highlighted an

increased risk of hospitalized dengue in subjects two to five years of age. Additionally, not shown here, there was a similar imbalance observed with severe dengue.

To better understand the impact of age, we show the hazard ratio of hospitalization on the y-axis against age as a continuous variable on the x-axis. There was a pattern of lower risk of hospitalized dengue due to any serotype with age. As you can see on the graph, beginning at around six years of age, the confidence intervals fall below one.

We did a similar analysis for severe dengue. The results were imprecise but revealed a lower risk of severe dengue after eight years of age. Taken together, these analyses, as well as other stratified analyses done using various age cutoffs, led us to evaluate a cutoff of nine years of age. We reevaluated data from Studies 14 and 15 and found the relative risk of hospitalizations between Dengvaxia and control was lower amongst subjects nine years or older in year three of the studies. This justified

the use of nine years as our lower age cutoff for initial licensure in endemic countries.

However, age is not the only factor we have to consider. As we can clearly see in these data from Study 14, there's a clear relationship between age and dengue exposure. In other words, the older you get, the more likely you've been exposed to dengue at least once. Therefore, while the signal could have been explained by age alone, it is also important to account for serostatus.

To explore this, let's look at two scenarios. The first one is a typical course for a person infected with wild-type dengue virus. As you heard from Dr. Thomas, people who have had one wild-type dengue infection are at greatest risk of symptomatic and severe disease if they're infected a second time. Now, let's look at scenario two.

Here, a person who has not had had a pervious wild-type infection is vaccinated. We hypothesize that the vaccine may mimic a natural first infection. This puts the individual at risk for more severe

disease upon first exposure to the actual wild-type infection. At that point, we had two factors to consider in accounting for the signal we saw: age and serostatus. That's why we initiated the NS1 Study to tease out the effects of age and serostatus in explaining the signal.

We needed baseline blood samples to establish baseline serostatus; but, as mentioned earlier, we only had them from 10 to 20 percent of subjects. We did have blood samples from month 13 after vaccination for almost all subjects. However, the traditional assay used to assess serostatus, the PRNT assay, cannot distinguish between vaccination and prior dengue infection. We needed an assay that was not meaningfully affected by the vaccine. This was not available in 2015 when we first observed the signal. Therefore, to infer baseline serostatus from these month 13 blood samples, we developed the NS1 antibody assay between 2015 and 2017.

Our approach was based on the fact that Dengvaxia was constructed with the yellow fever backbone, as Dr.

David Greenberg discussed earlier. This means that Dengvaxia is encoded with non-structural, or NS1, protein from yellow fever, which is different from the dengue NS1 protein found in each of the dengue serotypes. Therefore, the month 13 blood samples from individuals vaccinated with Dengvaxia would only have meaningful antibodies against dengue NS1 protein if they were previously infected with dengue. So we measured NS1 antibodies in month 13 samples, along with other variables, to infer previous exposure to dengue. This was the basis of the NS1 supplemental study.

The NS1 study was a case cohort design that included a random sub-cohort using 10 percent of the subjects from each of the original efficacy studies. All events of interest were included in the case cohort. We imputed baseline serostatus using two methods to make sure our estimates were consistent. We also estimated risk and efficacy by two methods: Cox regression and TMLE. Both yielded similar results and have been published in the *New England Journal of*

Medicine.

Here, I will present the results of the multiple imputation method as it is more widely used. We analyzed the data based on baseline serostatus for both outcomes of hospitalized and severe dengue over the cumulative five to six years of the studies. We noted that Dengvaxia had a different profile in seropositive and seronegative subjects. The data showed a favorable hazard ratio for seropositive subjects, with all points consistently to the left of the null value, and an unfavorable hazard ratio for seronegatives, with all points consistently to the right of the null value. These patterns were consistent above and below the nine-year cutoff, with some difference in the magnitude of the effect.

To look at this another way, we analyzed time to hospitalized dengue. In seropositive subjects 9 to 16 years of age, we saw an early separation between Dengvaxia and placebo that was sustained for the duration of the studies. This benefit against hospitalized dengue in subjects previously exposed to

dengue, which is an important clinical outcome, is observed for all four serotypes. In this plot, the upper bound of the confidence interval for each serotype is below one. Similar to time to hospitalized dengue, we saw an early and sustained separation of the cumulative incidence curves between Dengvaxia and placebo for severe cases of dengue. Additionally, for both outcomes of hospitalized and severe dengue, the favorable pattern was consistent across studies for seropositive subjects 9 to 16 years of age.

However, even when we account for serostatus, there remains a vaccine effect modification by age. Although the results in seropositives below nine years of age tend to favor Dengvaxia, there are still some uncertainties, particularly in subjects two to five years, as can be seen in this forest plot. Therefore, we believe that the data justify a conservative age indication of seropositive subjects nine years or older while we continue working on the benefit-risk assessment below the age of nine.

We looked at hospitalized dengue in seronegative subjects as well. The curves appear relatively close at the beginning, but around month 30 onwards, the cumulative incidence of hospitalized dengue is higher for Dengvaxia than for a placebo. Again, the same pattern was observed for severe dengue, with the curves crossing at about month 30. These data support our proposal to restrict the indication to previously infected individuals.

To complete the assessment in seropositive subjects, we reanalyzed vaccine efficacy against symptomatic dengue. Vaccine efficacy was consistent among seropositive 9 to 16 years of age across both Studies 14 and 15. Efficacy was approximately 75 percent in each study.

We also showed vaccine efficacy against symptomatic dengue for each of the four serotypes during the active phase in seropositive subjects 9 to 16 years old. This complements the protection observed against hospitalized dengue for each of the four serotypes during the five to six years of

follow-up.

Let me take a moment to summarize the data from the NS1 study. We observed a different profile by serostatus. The data indicated a favorable affect for dengue seropositive subjects and an unfavorable one for seronegative subjects. In seropositive subjects 9 to 16 years old, there was evidence of high protection against symptomatic, hospitalized, and severe dengue. This was consistent across our two Phase 3 studies. There was also protection across each of the four serotypes.

In younger seropositive subjects, those two to eight years of age, there was also evidence of protection, but this was tempered by an apparent age effect. This could be due to an immature immune system preventing the development of protective responses. So the NS1 study supports the indication for individuals 9 to 16 years and older, previously exposed to dengue.

Given the importance of dengue across the age spectrum, let’s now look at the vaccine performance in

adults. We used immunogenicity to bridge the vaccine efficacy we observed in children to adults. To do that, we had to formally establish the relationship between immunogenicity and efficacy. In our studies, we showed that, as antibody levels increased, the risk of dengue declined. This was consistent for all serotypes.

A correlation was observed between the titers after the third injection and the probability of dengue disease and in between the titers and vaccine efficacy. We published these findings in collaboration with the Fred Hutchinson Cancer Research Center and the University of Washington.

Let’s now look at the data. These graphs show vaccine efficacy on the y-axis and the average PRNT50 titer levels across all four serotypes on the x-axis. We can see that vaccine efficacy increases as PRNT titers also increases, both for symptomatic and hospitalized dengue. Therefore, PRNT50 titers, after the third injection, are a reasonable predictor of vaccine efficacy against both symptomatic dengue and

hospitalized dengue. We felt confident using titer levels to bridge the efficacy observed in our trials to an adult population.

Here, we show data from immunogenicity studies in adults compared to data from our pivotal efficacy studies. Studies 22 and 47, those seen on the right, were performed in areas with similar levels of endemicity as the Phase 3 studies. This plot shows average titers across all four serotypes. The results show that antibody levels were similar, or higher, in adults than in the pediatric populations, where efficacy was observed. These data indicate that efficacy in adults is expected to be comparable to that observed in the efficacy trials. Not only were the titer levels comparable, there was also similar antibody persistence over time in 9- to 14-year-olds compared to the older subjects.

On the right, we see adult data from the immunogenicity Study 22, conducted in Vietnam, which compared the data from the Asian efficacy study in children, seen on the left. These studies, conducted

in similar populations, show similar antibody persistence over time. The comparable antibody responses between children and adults, as well as comparable durability, suggests that one can reasonably infer long-term product of adults with confidence.

To conclude our efficacy presentation, in the pediatric population, high efficacy was observed against symptomatic, hospitalized, and severe dengue. We've also shown that Dengvaxia induces antibody levels in adults similar, or higher, to those observed in children where efficacy was demonstrated. Therefore, we can expect comparable protection in adults.

Taken together, the data presented today demonstrate that in subjects 9 to 45 years of age who've had a previous dengue infection Dengvaxia provides protection for at least five years against symptomatic dengue, severe dengue, and hospitalized dengue.

Thank you. Next, I will invite Dr. Cesar

Mascareñas to the lectern to review our safety findings.

DR. MASCARENAS: Thank you, Dr. Gurunathan. Good morning. My name is Cesar Mascareñas, and I am the Global Medical Head for Dengue, Travel, and Endemic Vaccines. In my presentation, we will be focusing on the safety results in the proposed indicated population. I will first provide a safety overview for the 9- to 17-year-old age group, followed by an overview for the 18- to 45-year-old age group.

In our clinical development program, more than 27,000 subjects received at least one injection of Dengvaxia. The majority came from the Phase 3 trials, Studies 14 and 15, but the database also includes subjects from other studies as well. Our full safety analysis is composed of subjects in our targeted age range, more than 19,000 subjects 9 to 17 years of age and about 13,000 subjects 18 to 45 years of age. Reactogenicity was evaluated in approximately 4,300 subjects, and more than 2,300 subjects in the safety set were seropositive.

For safety reporting, participants used diary cards to record the occurrence and severity of solicited injection site reactions for seven days after vaccination, solicited systemic reactions for 14 days, and unsolicited adverse events for 28 days. Adverse events occurring within 30 minutes of an injection were considered immediate adverse events. Investigators recorded serious adverse events, including deaths, under quality assessment throughout the entire study.

Adverse events of special interest were also collected. Allergic reactions and anaphylaxis were collected within seven days of vaccination, viscerotropic and neurotropic events within 30 days, and episodes of dengue fever throughout the entire study.

Let’s start with the 9 to 17 age group. Overall, most of the evaluated safety parameters for solicited and unsolicited events were higher in Dengvaxia than in placebo recipients, but no clinically meaningful difference has been observed between the two groups.

Regardless of the time period, the frequency of serious adverse events was similar in Dengvaxia and placebo groups.

The rates of solicited local reactions and Grade 3 reactions are shown here. In subjects age 9 to 17 years, only injection site pain appeared to be different between groups. The rate of Grade 3 events was low, at about 1 percent or lower, depending on the reaction.

Most injection site reactions occurred within three days post-vaccination and subsequently result within three days. Systemic reactions included fever, headache, malaise, myalgia, and asthenia. There were no meaningful differences between groups. The rate of Grade 3 reactions was low, and reactions typically last less than three days.

The frequency of unsolicited adverse events was also similar between groups. These were mostly medical conditions commonly seen in this population, such as upper respiratory tract infections and gastrointestinal infections. These were mostly

classified as Grade 1 or 2 and lasted mainly one to seven days.

This slide shows the frequency of serious adverse events reported within the 28 days after each dose and from 28 days to six months of follow-up. Irrespective of the reporting period, the frequency of serious adverse events was low and similar between Dengvaxia and placebo. There was also similar rates of related serious adverse events between Dengvaxia and placebo.

Let's have a look at the serious adverse events with fatal outcomes. Overall, the rates were similar between groups. Within six months after vaccination, five and four deaths occur in the vaccine group and placebo group, respectively. None of the deaths were assessed as related to vaccination by the investigator. The incidence of both serious and non-serious potential allergic reaction seven days after each dose was low in subjects receiving Dengvaxia. There were five serious allergic adverse events reported, with two considered treatment related asthma and urticaria with swelling, because time to

onset was compatible with the vaccine effect. Importantly, no anaphylactic reactions were reported.

Looking at the safety profile in both seropositive and seronegative subjects, most of the evaluated safety parameters were higher in Dengvaxia than placebo, but the differences between vaccines and placebo recipients appears smaller in the seropositive vaccinees.

Now let's turn to the adult population. In this age group, control subjects received either placebo or a licensed vaccine, such as flu, Hepatitis A, or yellow fever. Here's a safety overview of Dengvaxia versus control in the 18 to 45 age group after any dose. The frequency of solicited and unsolicited reactions were higher in the Dengvaxia group, except for local reactions, which were more often reported in the control group.

Similar to the younger age group, most solicited injection site reactions in adults were classified as Grade 1 and resolved within three days. Fewer reactions were classified as Grade 3, with a rate of

less than 1 percent.

The most commonly reported reaction in all subjects was pain. Solicited systemic reactions were more frequently reported in the Dengvaxia group than in the control group. However, there were no clinical meaningful differences in the Grade 3 reactions. Most reactions were Grade 1 and resolved within three days without sequala.

The frequency of unsolicited adverse events was also higher in Dengvaxia compared to control. However, these medical conditions are commonly seen in this population. They were mostly classified as Grade 1 or 2 and lasted between one and seven days.

The frequency of serious adverse events was low and similar between Dengvaxia and control groups, irrespective of the reporting period. The more commonly reported serious adverse events were appendicitis, cellulitis, dengue fever, chest pain, and pyrexia. No related serious adverse events were reported within 28 days. After 28 days, there was one serious adverse event considered related by the

investigator but not by the sponsor.

There was a numerical imbalance in potential allergic reactions between Dengvaxia and control groups. The incidence of both serious and non-serious potential allergic reactions within seven days of an injection was low. Six of the non-serious events were considered related to the vaccine. Despite the imbalance, the clinical presentation of the allergic reactions did not differ from that observed in the younger age group. No allergic adverse events reported as serious were considered treatment related; and, importantly, no serious anaphylactic reactions were reported.

Looking now at the safety profile in adults seropositive and seronegative subjects, most of the evaluated safety parameters were higher in Dengvaxia than placebo, but the data show no particular safety concerns in either seropositive or seronegative.

In conclusion, safety was evaluated in more than 20,000 subjects who received Dengvaxia according to the three-dose schedule, and reactogenicity was

evaluated in more than 4,300 subjects.

The rates of some solicited symptoms were higher in Dengvaxia than in placebo, with low rates of Grade 3 events overall. The majority of symptoms were mild to moderate and transient. The rates of serious adverse events and fatalities were low and similar in both groups, and there was no cluster of events identified. No related deaths were reported, and no viscerotropic or neurotropic cases or severe immediate anaphylactic reactions occurred. Allergic reactions and anaphylaxis were considered a potential risk to be monitored in any ongoing or future study and in our post-marketing surveillance.

Thank you for your attention. Next, I will invite Dr. Jouquelet-Royer to the lectern.

DR. JOUQUELET-ROYER: Thank you, Dr. Mascareñas. My name is Corinne Jouquelet-Royer. I'm the Pharmacovigilance Head at Sanofi Pasteur. I'm a physician and a clinical pharmacologist trained in pharmacoepidemiology. I will review the post-marketing safety data from countries where

Dengvaxia is already licensed, as well as a summary of the ongoing and proposed post-marketing plans.

The safety profile of Dengvaxia has been closely monitored during worldwide post-marketing experience. Since Dengvaxia was first licensed in December 2015, 2.9 million doses were distributed, mostly in Brazil and the Philippines where public programs were conducted.

During this period, almost 3,000 spontaneous cases have been reported, including 553 cases considered as serious. The most frequently reported adverse events have been consistent with those observed in the clinical development programs, such as pyrexia, headache, dizziness, vomiting, and rash. Treatment related allergic reactions were reported as at estimated reported frequency of less than 0.01 percent. 134 potential allergic reaction occurred in the first seven days post-vaccination, 69 of which within the first 24 hours after vaccination. There have been three cases of anaphylactic reaction. As a result, allergic and anaphylactic reactions have been

included in the Dengvaxia proscribing information.

Following data from clinical trial and subsequent post-marketing surveillance, we have identified two important risks: allergic reaction, including anaphylactic reactions, and increased risk of severe and hospitalized dengue in individuals with no previous dengue infection.

To monitor and mitigate these risks in real world settings, we have developed a robust global risk management plan that includes long-term safety and efficacy data from the Phase 3 efficacy studies, CYD14 and CYD15. After five to six years of follow-up, no new safety signals have been identified. Routine and enhanced pharmacovigilance, non-intervention and post-approval effectiveness studies, and post-approval safety studies are all ongoing in different endemic countries. This will also help to monitor adverse signal of special interest.

Risk minimization measures are also ongoing or planned, including monitoring their effectiveness via an HCP knowledge survey. And finally, the role of a

booster is currently being evaluated in three ongoing studies. One of these studies is also evaluating shorter vaccination schedules of one or two vaccine doses. We will also conduct a study in HIV positive individuals.

Our surveillance plan includes routine monitoring of spontaneous report from internal and external databases, as well as monitoring of vaccine exposure, clinical and non-clinical data. It also includes weekly signal detection, periodic aggregated review of worldwide safety data, and monthly literature review.

In addition to routine pharmacovigilance, enhanced safety surveillance is in place. This includes using targeted follow-up questionnaires to properly document adverse events of special interest. We also provide education and training for healthcare professionals on how to report adverse events, as well as training on the safety profile of Dengvaxia.

Finally, we foster a systematic two-way exchange of safety information with regulators, in a timely manner, for rapid and effective management of any

potential safety issues.

A large post-authorization safety study is ongoing. It is a prospective cohort event monitoring study to further evaluate the safety profile of Dengvaxia in a real-world setting. The goal is to enroll 30,000 vaccinees and measure selected adverse events and serious adverse events occurring over a period of six months after each dose administration to quantify any association with the vaccine.

We have more than 12,000 subjects in all, in Brazil, Mexico, and the Philippines. There have been no new safety signals detected to date. These subjects will be followed for five years for serious adverse events.

Finally, it is important to note that Dengvaxia is contraindicated for pregnant women, but our plan includes a pregnancy registry to monitor pregnancy outcomes in pregnant women inadvertently exposed to Dengvaxia, which is important given the age range in the proposal indication. This study would be conducted in Brazil and will assess the safety of

Dengvaxia with respect to maternal, pregnancy, birth, neonatal, and infant outcomes. Babies will be followed up for 12 months after birth.

We are also conducting two observational case control effectiveness studies in the Philippines and Brazil. The objective is to assess vaccine effectiveness in reducing hospitalization and severe dengue.

Turning now to the U.S., in addition to the label, an HCP guide will be distributed to educate providers on the increased risk of severe and/or hospitalized dengue following vaccination in individuals not previously infected, the requirement to document previous dengue infection before vaccination, and the detection of clinical early warning signs of dengue disease.

As part of our post-marketing plan, we have conducted long-term safety follow-ups of CYD15 in Puerto Rico, where 1,300 subjects included more than 800 on Dengvaxia, have been followed up for six years.

As in every country, the U.S. post-marketing plan

will also include routine surveillance and enhanced safety surveillance. We will also conduct a survey to evaluate the vaccinator's knowledge and understanding of the indication, which is restricted to the individuals previously infected by dengue.

Finally, a booster study is underway and includes subjects from Puerto Rico.

In summary, the global risk management plan is a mix between active and passive surveillance with data being collected from various sources, taking into account the maturity of the safety surveillance system in each country and vaccine use. To date, with more than 2.9 million doses distributed and ongoing and systemic monitoring of worldwide data, no new safety issues have emerged.

Thank you. Next, I will invite Dr. Su-Peing Ng to the lectern to provide a benefit risk assessment and conclude our presentation.

DR. NG: Thank you, Dr. Jouquelet-Royer. My name is Su-Peing Ng, and I'm the Global Medical Head at Sanofi Pasteur. I'm a pharmaceutical physician with

vaccines, clinical research, and medical experience. I will summarize the benefit risk profile of Dengvaxia in the proposed indicated population and conclude our presentation.

Let's first briefly review the unmet need in endemic areas of the United States and dependent territories as presented earlier by Dr. Thomas.

The global incidence of dengue has grown dramatically in recent decades. Half of the world's population is now considered at risk. In endemic areas, including Puerto Rico, most people have had at least one episode of dengue and are at risk of being re-infected. This increases the risk of symptomatic dengue and severe dengue. There is no specific treatment for dengue disease, and the management of dengue disease, including severe dengue, is supportive only.

None of the current prevention methods, either alone or in combination, has had a significant impact on the incidence of dengue. Hence, there is an unmet need for a safe and effective vaccine against the four

serotypes of dengue virus to protect people in endemic areas; in particular, people who have had a previous dengue infection.

Dengvaxia has shown clear benefit. Vaccine efficacy against symptomatic dengue was demonstrated in 2- to 16-year-old individuals across two Phase 3 clinical studies. Dengvaxia also reduced the occurrence of hospitalized dengue and clinically severe dengue in both studies. In addition, supplemental analyses by age and serostatus demonstrated consistent vaccine efficacy against symptomatic dengue in dengue seropositive individuals 9 to 16 years of age. Dengvaxia also demonstrated clear protection against both hospitalized and severe dengue in each of the Phase 3 studies over a five to six-year period. This supports our proposed indication of vaccination of seropositive individuals nine years of age or older.

As we saw earlier in our presentation, there is also a significant burden of dengue in the adult population in Puerto Rico. In immunogenicity studies,

seropositive adults 18 to 45 years of age living in endemic areas demonstrated antibody levels higher or comparable to subjects in pediatric efficacy studies. The adults also responded well to the vaccine schedule used.

Next, we looked at how this benefit might translate specifically in Puerto Rico. There are two clear approved dengue diagnostic tests in Puerto Rico that could be used to identify individuals with laboratory-confirmed previous dengue infection. Using the more conservative Biocan screening test, on the next slides we show the results of one of the models of the impact of screening and vaccination in Puerto Rico. To approximate the epidemiology of dengue in Puerto Rico, this model assumes two key parameters, 56 percent dengue seroprevalence in the entire 9- to 16-year-old population, which is what was observed in the participants in Puerto Rico enrolled in Study 15 in 2011, 2012. Also, the incidence of severe dengue in Study 15 extrapolated to Puerto Rico over a five-year period. Without vaccination, we would

expect 79 severe dengue infections in the seronegative population and 340 in the seropositive population. With the screen-and-vaccinate approach, we could expect, in the seronegative population, 0.9 percent to be misclassified and vaccinated and 99 percent correctly classified and, therefore, not vaccinated.

Over a five-year period, we would therefore expect 81 severe dengue infections in this population. In the seropositive population, we could expect 66.1 percent to be correctly classified and vaccinated, and 33.9 percent to not be vaccinated due to false negative results. Thus, over the same five-year period, we could expect 147 severe dengue infections in this population. The net result of a screen-and-vaccinate strategy versus no vaccination would be an overall reduction of 191 severe dengue infections. This represents a 46 percent overall reduction in severe dengue infections in the 9- to 16-year-old population in Puerto Rico over a period of five years. The number of cases prevented is expected to be higher if we use the ELISA with the higher test

sensitivity and when you include the adult population.

Having summarized the positive benefit, the data also demonstrate a favorable safety profile for Dengvaxia in 9- to 45-year-old individuals. The rates of some solicited symptoms were higher in Dengvaxia compared to placebo and were transient in nature. Low rates of Grade 3 events were reported.

Serious adverse events were mostly reported as unrelated to vaccination, expected for the age range, and similar in nature to the control groups. There was no cluster of events within 28 days of injection, and no related deaths were reported. A low frequency of allergic or anaphylactic reactions was reported in the post-marketing period. These continue to be monitored through post-marketing surveillance.

We will have a comprehensive strategy in place in the United States to help properly identify individuals eligible for vaccination and support appropriate use of Dengvaxia. First, our proposed indication is for individuals 9 to 45 years of age with previous dengue infection living in endemic

areas. We are targeting this population as it has a higher risk for symptomatic and severe dengue disease, including hospitalization. The limitations of use in our label will help prevent vaccination of seronegative individuals and the counterindications are clearly described.

Secondly, to support vaccine use according to the label, we will implement an educational program and a healthcare provider guide. These tools will emphasis the importance of previous dengue infection prior to vaccination, as well as how to detect early warning signs of dengue disease. Finally, our strategy also includes real-world evaluation through global post-marketing studies and healthcare practitioner Dengvaxia knowledge surveys.

To conclude, the data demonstrate a positive benefit risk profile for Dengvaxia in 9- to 45-year-old individuals living in endemic areas with laboratory-confirmed previous dengue infection.

Thank you for your attention. Dr. Carlos DiazGranados will now come to the lectern to take your

questions. Dr. DiazGranados is a physician with specialty training in internal medicine and infectious disease, and he is the Head of Clinical Sciences for the Dengue Program at Sanofi Pasteur.

DR. EL SAHLY: Okay. I want to thank the seven presenters and welcome Dr. DiazGranados.

DR. DIAZGRANADOS: Thank you.

DR. EL SAHLY: I guess I can begin the questions as everyone's formulating their questions, the first one being there was a third clinical trial that was part of the portfolio that was sent for us to review but was omitted completely from the presentation here. Is there a particular reason that was not included? An efficacy study, it was the one in Thailand.

DR. DIAZGRANDAOS: Yes. The reason is simplicity. We do have the information available. Overall, the information for the indicated population, as proposed, is consistent from that study than what was compared and presented to you in Studies CYD14 and CYD15.

DR. EL SAHLY: But one in the tide overall effect

was not as robust as in the one here? Meaning the efficacy did span -- the confidence interval, if I remember, did span the one -- and I couldn't retrieve it on my computer, and it wasn't presented, so I can't quote the correct numbers.

DR. DIAZGRANADOS: Perhaps I can summarize by presenting that on the screen. So we summarized that from that Study CYD23. This is for the entire age group of 4 to 11 years of age that were included in the study, and this study was done in a single center in Thailand. So, as you can see at the top, that's the efficacy for the primary endpoint in the study; and as you correctly mentioned, the confidence interval across the known value. When we did analysis, including the entire active phase from first vaccination to the end of the two years of follow-up in the study, we saw some evidence of protection. And importantly, also, we saw evidence of protection against hospitalized cases of dengue overall.

What you're seeing there, also, is that there is heterogeneity by serotype in this study, and the

epidemiology for that center in Thailand at that time was dominated by a particular genotype of serotype 2 that was circulating. So that accounted for some of the findings in the study.

Now, importantly for the longer follow-up period in the study, the study was followed up with a study called CYD57, which followed individuals that had participated in the CYD23 study for a total of six years, encompassing the two studies. And the findings for that period of time, I can summarize for you on the screen here, are consistent with the findings that we described in the main presentation for the indicated populations of nine years and above and seropositives.

Here, we present the data for a hazard ratio for hospitalized dengue by serotype. And as you can see, the different point estimates are to the left of the null value of one, favoring Dengvaxia. You cannot see a line for serotype four, but you can see the distribution of the numbers also favor Dengvaxia. And interestingly, for serotype two, what you see is a

similar level of protection against these clinical outcomes then was observed over the six years of the studies that were presented in the main presentation.

DR. EL SAHLY: Okay. Sure.

DR. BENNINK: Okay. I want to follow up on that question for a second, because I also saw that -- it was Table 19 in the data. And the vaccine effectiveness was much lower than that. It was 5.9 for two, and it was minus 1.2 for three. Is that -- I mean, it's limited data, I think, okay, limited numbers, but is that -- I'll ask a different question. Does that have anything to do with differences in antigenicity or anything else in terms of the individual serotypes of what's circulating, what you've chosen to put into the things in terms of the genotype and where -- what did you select for that -- to put into the vaccine?

So, if I ask you a specific question, I would say have you looked and genotyped and done sequencing of things across the globe? And how much variation do you see in sequences in the antigenic epitope areas of the

virus within a given serotype?

DR. DIAZGRANADOS: Yes. Some of this has been done using actual samples collected during our efficacy studies, so this would include data from ten countries and across different regions of the world, encompassing 11 different genotypes of dengue.

The information that we have available indicates that there is some effect of genotype, so there is some effect modification by genotype. And we can certainly show some of the information that we have. We saw specifically an effect modification of -- a vaccine effect modification by genotype for serotype four in the younger age group of two to eight years of age. When we evaluated that in the age group nine and above, we did not see the same genotype effect.

We also evaluated -- so we can show this slide just to summarize, to keep going here. So this presents the genotypes that were collected during our clinical trials, and this is for the active phase of the clinical trials. You can see that the only significant effect modification was observed in

serotype four. This is at the genotype level. And when you look at the data for the individuals nine years and above, you can see that there is no difference in the estimates of vaccine efficacy across genotypes for that particular serotype.

We also did analysis according to amino acids, specific amino acid sites, for different genotypes, and what we observed was effect modification at the amino acid level for serotype four. I can summarize that also on a slide presented here. So essentially, there were eight signature mutations that were observed as modifying vaccine efficacy for dengue four. And the data you see here is for individuals two to eight years of age. So you see that, when there was a mismatch in one of these positions, there was lower vaccine efficacy.

That, however, was not observed when we looked at the same data in individuals 9 to 14 years of age, which is what I'm showing in the slide right now. What you can see there is that, for those same eight signature mutations, the vaccine efficacy is

consistent whether there is a match or a mismatch to the vaccine. Specific for serotype two, we also saw one amino acid mutation that was associated with low vaccine efficacy in the two to eight years of age, but it was not suggested in the 9 to 16 years of age.

So there are different factors influencing the serotype heterogeneity that we have seen. Genotype is one. Level of matching to the vaccine is one, but there are also important host factors that are impacting the serotype heterogeneity. And of course, age and serostatus are important host factors for that.

And what is important to, perhaps, remember is that, in the indicated population that we are proposing on the label, we demonstrated efficacy against the four serotypes for hospitalized dengue over a five- to six-year period of the study with the estimate -- perhaps, you can show slide 53, please. You can see here that the estimates of protection are consistent for the different serotypes; and also you can see that for serotype two we're looking at the

specific age and seropositive population, and there is a good level of protection through five to six years overall.

DR. EL SAHLY: Okay. Dr. Paul Offit patiently waited for his question.

DR. OFFIT: Two questions. The first has to do with my trying to understand better the phenomenon of enhanced disease associated with the vaccination of the seronegative individual. So presumably, if you're infected with wild-type serotype two, and then your second infection is with wild-type serotype four, you don't have any neutralizing antibodies against serotype four. All you have are binding, heterotypic antibodies, which are then going to enhance entry through FC receptors into cells, thus, making it worse. So that part I get.

What I don't understand well, and you can explain it to me, is, when you're vaccinated, you presumably develop neutralizing antibodies against all four serotypes and, in addition, induce memory BNT cells that are often committed to making neutralizing

antibodies against all four types for what is a relatively long incubation period disease, seven to ten days.

So can one assume, then, that the reason that you see enhanced disease when you're then infected with, say, serotype four is because the -- either the quantity of neutralizing antibodies in your bloodstream or the frequency of memory BNT cells that are devoted to making neutralizing measures are so much less than those binding, non-neutralizing heterotypic antibodies, either in the circulation or for memory BNT cells? And that's why you lose, that's why it is that you get enhanced disease. Is that fair to say?

DR. DIAZGRANADOS: So there are probably several factors, and one would be quantity of antibodies; but the other one, as you mentioned, quality of antibodies as well. So we have tried to do some characterization on the quality of antibodies that are seen in people that are seronegative and received the vaccine.

We have done that in collaboration with

investigators at the University of North Carolina, and what we have seen is that in these individuals there is a dominance of omnipotent antibodies seen against dengue four; but, for the other serotypes, although there is some degree of omnipotent antibodies, the majority of the antibodies for the other dengue serotypes are heterotypic.

So this would be somewhat similar to what you would see in somebody that is having a previous dengue infection. The other one is the actual level of antibodies that might be playing a role as well.

DR. OFFIT: One other quick question. So you noted that you were taking a look at this viscerotropic disease because we know that yellow fever vaccine is, itself, a rare cause of viscerotropic disease. It's sort of 0.9 to 2.5 cases per million doses of -- per million vaccines. So that's not something you're probably going to pick up pre-licensure. And it's also more a phenomenon of the greater than 65-year-olds; so again, something you're unlikely to find pre-licensure.

My question to you is there any difference in the replicative or viscerotropic nature of this, your chimeric virus, as compared to just the vaccine virus, either in animal model studies or clinical studies that suggest that the virus, because it's chimeric, because it's genetically altered, that it's different than, and you may be less likely to expect viscerotropic disease?

DR. DIAZGRANADOS: Yes. So some of the tropism that has been described for yellow fever has been associated with the envelope protein of the yellow fever vaccine. So in the chimeric vaccine, that protein is removed. So, hypothetically, there should be lower risk of having a neurotropic or viscerotropic disease.

In addition to the, of course, theoretical point, we have done a lot of pre-clinical characterization of this in animal models and hepatic cell lines. So we have done evaluations of hepatic cell line cultures. We have done studies in mice and non-human primates for neurotropism and hepatotropism with actually, for

example, in mice and non-human primates, actually, intracerebral injection of the CYD vaccine compared to the yellow fever vaccine. And all those indicate a lower risk of viscerotropism and neurotropism.

DR. OFFIT: I see. Your base strain is actually not the yellow fever vaccine, right, because you're using 17Ds? Aren't the two strains about there --

DR. DIAZGRANADOS: 17D.

DR. OFFIT: 17D 204, but is the 17D strain, is that the yellow fever vaccine strain? I thought it was --

DR. DIAZGRANADOS: Yes.

DR. OFFIT: -- 17DD or D204. Isn't -- no? Am I wrong about that? 17D is the yellow fever vaccine?

DR. DIZGRANADOS: Yes.

DR. OFFIT: Okay. 17D. Thank you.

DR. EL SAHLY: Dr. Edwards?

DR. EDWARDS: I have some questions regarding your immunobridging because it looks very much like -- well, I don't see a distribution of the antibody titers in the ages that you're asking for licensure.

And on slide 64, the CYD22 has only 17 serosamples. So could you talk a little bit about the more granularity of the antibody responses between the 18 to 45, and in terms of is it pretty consistent? And then also it seems a little arbitrary, like you would just do this to 45, and maybe you might want to comment on, ultimately, would you look at it in other ages besides 45?

So the two questions, the actual spread of the antibody response between 18 to 45 years; and then, second, why you chose 45 to be your upper limit?

DR. DIAZGRANADOS: Okay. So let's see if we can show you distribution of the antibodies for those studies. Do we have something on that? Okay. So this is -- let's see. These are reverse communicative distribution functions for the antibodies in study CYD22. And what you can see there is two age groups for that same study, so 9 to 16 years and 18 to 45 years of age. And you can see what is the distribution of the titers, probability of having a positive titer -- or a certain level of titer for the

different curves. Is this addressing the point that you --

DR. EDWARDS: No, because you've lumped everything from 18 to 45 years. What I'm asking is what is the distribution of the serologic responses in those people between 18 to 45? Is it quite consistent throughout the range?

DR. DIAZGRANADOS: We don't have more granularity within that age group. Perhaps we can bring that to you after lunch, if it's necessary. We can try to do that.

DR. EDWARDS: Yes. The second question is, then, you chose 45 just because you had data up to 45 and you may, in the future, extend the upper limit or what are your thoughts about that?

DR. DIAZGRANADOS: Yes, so the reason for the upper limit for the indication is the scarcity of the data that we have beyond that age group at this point. So we have only about 241 individuals that we were exposed to the vaccine about -- 46 and above years of age, but we're currently generating more data in two

ongoing studies that will provide the final story, which is targeted for 2020. So we will evaluate that data and see whether it is supportive to, perhaps, go up in the age of indication.

DR. EL SAHLY: Dr. Swamy?

DR. SWAMY: I have two questions as well. So the first is do you have any data on self-report of prior dengue history and then their serostatus from the data you have? And then, do you also have -- I don't know what your -- if you comment on the eligibility criteria on if they had prior dengue, if there was any timeframe that they had to state when their prior infection was or any data like that?

DR. DIAZGRANADOS: So let me -- so the first question is on self-report?

DR. SWAMY: Right. So self-report of the prior dengue infection and their serostatus.

DR. DIAZGRANADOS: Yes. So there is really a very poor correlation between self-report of previous dengue infection by recall and the actual seropositivity to dengue. So we have looked at that

in some of our studies, and that's likely related to the fact that many of the exposures are asymptomatic on the one hand. And on the other hand, when symptoms occur, their symptoms sometimes overlap with other conditions. So there is not really very good correlation on that.

DR. SWAMY: But if they reported that they had a history, do you know if that's a positive correlation with seropositivity?

DR. DIAZGRANADOS: Well, it's definitely a little better than the ones not reporting it. But again, there is some overlap between dengue and other syndromes. And in the dengue endemic areas, there is some areas in which actual confirmation is not done, so there is some still inaccuracies in just basing the previous exposure by recall.

DR. SWAMY: So, in your eligibility criteria, was there any restriction on if they did report they had dengue, that they could be in the study or they had to have some certain timeframe for prior infection?

DR. DIAZGRANADOS: No. And actually, in the Phase

3 studies, there was no restriction for that. The study included individuals that had any type of previous profile for dengue. So it included people that were not exposed to dengue, people that were exposed to dengue before, as well.

DR. EL SAHLY: Dr. Monzo has a question.

DR. MONZO-JORDAN: Yeah. I have a series of questions, probably. So first, I'd like to ask if you could put up the slide on the two tests that you had, because it's not here on my copy.

DR. DIAZGRANADOS: Slide 105, perhaps. Is that one the slide that you wanted, Dr. Monzo?

DR. MONZO-JORDAN: Right. So first of all, I'll ask -- so these are not RDT, so are you going to be basing your test screening in Puerto Rico on clinical laboratories, basically?

DR. DIAZGRANADOS: So we are just providing information about what is available in Puerto Rico, to the best of our knowledge, today. So these two tests are available in Puerto Rico in private laboratories. There is one that is an RDT, the second one, but it's

not used as a point of care test. So that's an important distinction, because these are authorized for use under CLIA and the authorization is for the laboratory specifically.

So they are available for use, currently, in Puerto Rico in those laboratories for the evaluation of previous exposure to dengue. And this is evaluation and with it -- so this evaluation is independent of the test manufacturers. We did this in our global clinical immunology laboratory with samples that we had extensively characterized. And that's the basis for the performance characteristics of the tests that we're reporting in there. So you can see that the sample set is large. You have more than 250 samples assessing sensitivity, and you have more than 330 samples assessing specificity.

DR. MONZO-JORDAN: And those samples that you used to characterize these two tests are from your placebo group or where are they coming from?

DR. DIAZGRANADO: These samples come from different sources, but if I can perhaps summarize for

you the reference negative samples and the reference positive samples, many of those were taken from the clinical trials at baseline or afterwards in placebo recipients. And they were characterized as being, for example, dengue negatives. There were two instances. One, people that participated in the studies in non-endemic areas, for example, the U.S., we still require a sample being PRNT negative for dengue to be classified as a reference negative sample. And if the sample was from an endemic area, we require PRNT negativity as well as NS1 negativity. So that's for the reference negative samples.

For the reference positive samples, the panel consisted of essentially two groups of samples. One were PRNT positive samples from endemic areas, and, second, samples that had been virologically confirmed for dengue with PTR. So that's the basis for the reference panels used for these tests.

DR. MONZO-JORDAN: And have you had the chance to look at the sensitivity and specificity of these tests in places like Puerto Rico after the Zika epidemic,

and do you have a number of Zika positive samples in your analysis?

DR. DIAZGRANADOS: Well, as you know, the studies that we have done preceded Zika; so that was an important challenge and a knowledge gap that was important to fill. So what we did is we started a process of finding Zika positive samples that were dengue negative. We reached to multiple different investigators and laboratories in different parts of the world, travel clinics, et cetera; and we characterized samples that we obtained.

So we have been able to -- it's not been easy to find those samples, but we have been able to characterize 38 samples that are Zika positive and that are dengue negative. And on those samples, 38 samples, we have evaluated the cross-reactivity of these two tests.

So I can tell you, the cross-reactivity of these two tests on those 38 samples is that the first test in there, the somatic ELISA, has a cross-reactivity of 13 percent. So 13 percent of those samples that are

negative for dengue and positive for Zika tested positive with the first test. The second test show only 2.6 percent cross-reactivity with Zika.

Another important point that I want to make related to the fact that it was so difficult to find these samples to do the assessment is that dengue and Zika are somewhat correlated, so it's likely that somebody that is positive for Zika will be positive for dengue. And we actually looked at that in our clinical trials, and we found in study CYD15 that 87 percent of the individuals that were Zika positive at the end of the study had documented dengue seropositivity before, as well.

DR. EL SAHLY: There are many questions remaining, many hands. We're going to take one more question, break, and then we're going to dedicate the committee discussion session to all the remaining questions. There are many. I can see that. Dr. Follmann's last question, and then we'll reconvene for more questions later. Dr. Follmann, yes?

DR. FOLLMANN: Thanks. Yeah, I had a question.

So when you do these studies, you try and get everyone to comply fully. Everyone gets three doses and so on. In the real world, when you roll out a vaccine, maybe not all people get three doses. And I was wondering if you had thought about, or have data, about the potential enhancement of the vaccine for a seropositive who gets maybe one dose? That's the concern, and you have experience with rolling it out in other parts of the country, how common it is for everyone to get three shots. And relatedly, or the same point I made before, is do you see signs of enhancement for people with one shot who are seropositive?

DR. DIAZGRANADOS: Yes. So first on less than three doses, what happens, what's the data on that. So the studies that we did in which we collected clinical outcomes were associated with very high compliance with the three injections; so more than 95 percent of the individuals in the studies received the three injections. We, therefore, cannot have a good idea of mid-term and long-term outcomes in those

individuals.

We do have some information about short-term, clinical outcomes in those individuals. And in analyses that we have done using similar methods to the ones presented earlier, what we have seen is that individuals that are seropositive -- and I'm summarizing it in the screen right now -- individuals that are seropositive and nine years or older have evidence of efficacy starting from the first dose.

And this is substantiated in part with data from immunogenicity studies. So when we looked at the correlation of the antibody levels after the second dose and after the third dose, specifically in seropositives, those levels are very comparable, very similar. So the three doses, we're allowing the improvement of antibody responses mainly for seronegative individuals. In seropositive individuals, as you can see here, two doses are associated with short term protection, or even one dose is associated with short-term protection.

Now, we don't know about the durability, per se,

and we're trying to complement these data with an ongoing randomized control trial that is comparing three doses to two doses and one dose and obtaining durability time points for immunogenicity and the antibody responses.

We're hopeful that that study can result in simplification of the regimen, but we'll await the result next year. So in terms of the second point that you made, which was related to compliance, I believe?

DR. FOLLMANN: Yeah. What's happening to compliance when you -- you've given the vaccine to a lot of people, and what's the compliance you've observed in the field?

DR. DIAZGRANADOS: In one region of the world, where there was a school-based program, we observed very high compliance with the second dose. So to be specific, of the people that received one dose, 85 percent received the second dose and 75 percent received the third dose.

In another area of the world, where there was

another program, what we observed, and this was a community program rather a school-based program, what we observed was 75 percent compliance with the second dose and about 50 percent compliance with the third dose.

DR. EL SAHLY: Is 20 minutes for lunch acceptable?

LUNCH BREAK

DR. EL SAHLY: If we can resume the meeting. Thank you all for cutting your lunch short to leave more time for the numerous questions that remain to be deliberated in this important meeting. At this moment, we will have the open public hearing section of the meeting.

OPEN PUBLIC HEARING

DR. EL SAHLY: Welcome to the open public hearing session. Please note that both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the

open public hearing session of the Advisory Committee Meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance of the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

MS. HUNTER-THOMAS: Thank you, Dr. El Sahly. We will begin with the registered speakers. I will

call you by name, and just a reminder that you have five minutes to speak and it will be timed. If you go over the five minutes, I will raise my hand as such. And then, you have to wrap it up very quickly. The first person that I have is Fernando Ysern.

DR. YSERN: Good afternoon to all. Okay. Yes, my name is Fernando Ysern. I'm a pediatrician in Caguas, Puerto Rico. And although I have positions in various pediatric associations, have been an advisor to the health department vaccine program, currently participating in clinical investigations on other vaccines, and give multiple conferences on vaccines sponsored by manufacturers, such as Sanofi, Merck, Glaxo, MedImmune, and Pfizer, I am currently here on my own personal capacity, representing only myself.

My travel expenses and lodging have been paid by Sanofi, but I'm not receiving any direct or indirect compensations, nor do I have any investments or contracts with any vaccine manufacturer or FDA-regulated company that might represent a conflict of interest.

My interest is to present to you the need for a vaccine against dengue for Puerto Rico. Four years ago, while I was just a medical student, my first patient was a 280-pound second base baseball player, promising baseball player, who, within 24 hours of feeling sick, was admitted into our hospital's intensive care unit with a platelet count of 3,000, and went into shock and, despite an aggressive CPR, died.

I remember when the residents tried to explain to his wife that he died of dengue hemorrhagic fever. She refused to accept the fact that a healthy young man had died due to a mosquito bite since he had no signs of mosquito bites. As you know, the Aedes aegypti mosquito does not leave a mark. You do not feel as it has bitten you because it draws blood but does not inject the formic acid that causes the pain.

Since that time, I have seen children die of what are now vaccine-preventable diseases, like Haemophilus influenzae and meningococcus. I've also seen how vaccines have saved the lives of millions of

people, who do not know that they are alive today because vaccines have protected them from these vaccine-preventable diseases. Dengue is still not a vaccine-preventable disease.

In Puerto Rico, to practice medicine, it is mandatory every three years to take two hours of continued medical education on dengue in order to be familiarized with the symptoms of dengue. Despite this, in 2010, one of our fellow pediatricians, who had twins, had one of them develop a fever. He was taken to the tertiary hospital's ER where she worked, started promptly on IV fluids, taken to the intensive care unit, where it is he went into a hypovolemic shock and died.

His brother developed a fever a couple of days later, who was also taken immediately to the intensive care unit. He developed hypovolemia, but he survived. Both tested positive for dengue. None of them had thrombocytopenia, nor had they had alterations in the WBC count. The second twin lived because the first one died.

Every day, children and adults are ordered labs in Puerto Rico. And many are sent to the ERs, because the doctors see their patient's blood platelet counts dropping, even though the vast majority are due just to viral illnesses. The economic cost of ruling out dengue prior to the hypovolemic stage is staggering and, as you can see, this cost of missing diagnosis can be fatal.

Dengue is endemic in Puerto Rico. Last November, the Paramedic and Health Association and the World Health Association warned us that their dengue was on the rise in South America. Despite our best efforts to diagnose it, the best way is to avoid it -- is to prevent it. Vector control and vaccines are two options. Today, you are considering the approval of one of those vaccines. The safety and efficacy of the vaccines is not for me to judge or to influence you. I am here just to emphasize the need for a vaccine.

When the Haemophilus influenzae vaccine came out in the '80s, it was supposed to be about 80 percent effective in preventing meningitis, and there

was questions whether it was worth it. Since we started immunizing kids with it, the herd immunity took care of eliminating the meningitis, the epiglottitis, and the septic arthritis in Puerto Rico, thus providing protectors to those who were not vaccinated. Having a vaccine that would provide protection to a large portion of the persons against dengue would also protect the transmission via the Aedes aegypti mosquito to those who cannot be vaccinated.

I had dengue in 1983. I still remember the rash, the general malaise on my legs, the pain in the eyes and --

MS. HUNTER-THOMAS: Time.

DR. YSERN: Well, I just want to thank you for your time.

MS. HUNTER-THOMAS: Okay. Thank you, Dr. Ysern. The next person I have on my list is Jose Luis Arredondo Garcia.

DR. GARCIA: I am pediatrician and infection diseases specialist. I'm head of the clinical

research unit in the National Institute of Pediatrics in Mexico. My disclosures: I am a researcher and receive funds from many pharmaceutical companies, including Sanofi Pasteur. Sanofi Pasteur also support my travel here, but has not compensated me for my time.

I testify, in my own name, about experience in terms of the efficacy and safety of the Dengvaxia vaccine in Mexico. Dengue disease continues to be a major problem, a health concern. Vaccination maybe contribute to control the disease in areas with high report of the disease. Until December 2015, the only preventive measures against dengue infection was to rely on mosquito control and personal protection.

In Mexico, in 2018, there were 12,700 cases of confirmed dengue with 45 deaths, and the age of presentation was from 9 to 40 years old. As of April last year, the dengue vaccines, Dengvaxia, has been granted marketing authority in 19 countries in Latin America and Asia. The efficacy of the vaccines against virological-confirmed dengue have been

assessed in two clinical trials in Asia and in Latin America.

The trial was conducted during a 6-year period, in two phases. The (inaudible) from the first injection until the first two years of (inaudible) and subsequent four years long-term safety follow-up period. The countries that participate in Latin American were Brazil, Columbia, Honduras, Puerto Rico, and Mexico. The later participant with 3,400 subjects, and five representative, (inaudible) of the north center of country areas with a high incidence of dengue in Mexico.

This analysis permits an update on hospitalized patients with dengue and clinical severe at year 6 and during the entire study period. During the year 6, there were no cases of hospitalized dengue and severe cases in Latin America. During the entire study period, there were 61 cases in the vaccine group, versus 41 cases in the control group with the cumulative relative risk, 0.32 for hospitalized dengue, and 0.28 for severe dengue.

All subjects with hospitalized dengue in both trials recovered. (Inaudible) on hospitalized dengue and severe dengue, persisted over the 6-year study period in Asia and Latin America. These results from supplemental analysis show evidence of protection in individuals previously infected with dengue virus, and benefit (inaudible) for seronegative individuals with consequent update recommendation for vaccine, only individuals with previous dengue infection and over 9 years old. With these results and more than 10 years of working with this vaccine, we conclude that we need to have these vaccines in areas where dengue is endemic, like Mexico. Thank you very much.

MS. HUNTER-THOMAS: Thank you, Dr. Garcia. The next person I have on my list is Natalia Gomez.

DR. GOMEZ: Hello. Good afternoon. My name is Natalia Gomez. I'm a physician, and I currently work as a disease prevention and immunization program manager at VOCES Immunization Coalition of Puerto Rico. We appreciate the opportunity to submit comment on the advisory committee meeting regarding the dengue

tetravalent vaccine.

Furthermore, I would like to clarify that my travel expenses are being reimbursed by Sanofi Pasteur, but my testimony and time during this meeting is on my own behalf. VOCES is a 501(c)(3) patient advocacy organization, dedicated to raising awareness and educating about the importance of disease prevention through immunization in Puerto Rico. Since founded in 2013, we have played a significant role pronouncing the immunization issues in the island, subsequently advocating for the development and amendments of public policy.

Also, as a coalition, we work as a community-based multisectoral group that has successfully allied more than 46 distinguished individuals and organizations, including government agencies, professional associations, community groups, academia, among others, toward our initiatives and projects. On behalf of VOCES and the community we represent, we would like to thank the agency for the opportunity to provide comment on the open session

about our original community perspective on dengue fever on the proposed vaccine.

Dengue represents an important public health challenge in Puerto Rico, being an endemic disease with periodic epidemics. It is a mosquito-borne disease that can be lethal and kill up to 20 percent of those with severe dengue if left untreated, as described by the World Health Organization. And has been a growing threat for decades. There's no specific antiviral treatment for dengue, and supportive care is the only option available up to now.

At the same time, a study reported in the American Journal of Tropical Medicine and Hygiene, dengue fever is inflicting nearly a 4 million burden on Puerto Rico; consequently not only being a threat to the public health, but to the island economics.

Likewise, as a patient-oriented organization, we would also like to present an example of the patient-experience perspective while suffering from dengue fever through my personal testimony. I was

diagnosed with dengue fever at the age of 14. The virus started with fever, chills, and headaches. Suddenly, my hands and feet erupted with red dots, petechia, rash, and developed an excruciating joint pain with generalized weakness.

My platelets count dropped abruptly, hence I was hospitalized. As a teenager, I felt devastated and captive of my own body. Not only I was feeling bad, but I will miss attendance to school and all of my extracurricular activities. I was admitted for 10 days and treated with supportive measure.

Fortunately, eventually -- fortunately, for me -- I'm sorry -- I fully recovered, but couldn't imagine what could have happened in the eventuality of a development of more severe complication. It is a disease that nobody should die from it.

Therefore, based on imperative need to come with the support of a safe and effective vaccine that can prevent against each of the four serotypes on dengue in the island, dengue vaccine will represent to Puerto Rico an event and sustainable approach to the

primary prevention, which offer confidence for control and prevention of the disease, especially those of severe cases.

VOCES, based on the recommendation of the World Health Organization, is encouraged by its addition as a preventive tool in order to improve one of the issues that affects Puerto Rico's public health and to save thousands of life. Thank you.

MS. HUNTER-THOMAS: Thank you, Dr. Gomez. The next person I have is Scott Halstead.

DR. HALSTEAD: Good afternoon, everybody. I'm Scott Halstead. I'm an adjunct professor at the Uniformed Services University of the Health Sciences. And over the last three years, I have been a short-term consultant on dengue vaccine development to Merck, GlaxoSmithKline, Takeda, and Sanofi. So, I suppose I should sit down. I'd like to discuss two issues with the committee. One is how are we going to identify vaccine harm? And second is what's going on with the seropositives anyhow?

We can no longer argue whether there is

identified harm. In the New England Journal of Medicine study where there were 3,300 seronegative children in the age group 9 to 16, and 700 controls, the hospitalization rate between those two groups didn't differ significantly. But severe dengue, i.e. thrombocytopenia with demonstrated vascular permeability, did occur significantly in the seronegative vaccinated group.

Now, you've seen the adverse events data from Sanofi. They and the World Health Organization and everybody else seems to have a great deal of difficulty coping with the fact that a breakthrough case in a seronegative, which is a vaccine-enhanced disease, is clinically identical to the control, who's had a secondary dengue infection -- monotypic immune with a second dengue infection.

So, we don't have exactly the situation we had with the measles vaccine, where we, as you recall -- there is an antecedent to this phenomena -- where (inaudible) measles vaccine was followed in a matter of years with breakthrough measles cases. But in that

case, the syndrome, apparently, was sufficiently different that it acquired the term atypical measles. But here, we don't have any difference. And the result is that this is not identified as an adverse event. Period. Yet, everybody says we should be on the outlook for cases of this kind.

We know that 850,000 9-year-old children were vaccinated in the Philippines. And who is going to be monitoring them? And what are we looking for? The statistical analysis of the New England Journal of Medicine article says that severe dengue is -- if it occurs in a vaccinated child who is seronegative, is an adverse event. And I think we need to get down to brass tacks, getting some nomenclature to put on these cases so that they'd -- otherwise, how are we going to pursue Phase 4, surveillance?

Now, the amazing thing is that this vaccine protects 75 percent of seropositive children. And as we've seen today, as the age group falls, the protection falls significantly, almost to the point where it disappears in the 2- to 5-year group. Now,

what's going on? And what impact does this have on what serological test is used to classify somebody as seropositive? I mean, is it possible that the monotypic immunity -- you can be immune to any one of the four dengue viruses, and then you get this vaccine on top of it -- the vaccine that appears to broaden the immunity response so that you're protected. But is it possible that a "dengue 1" person would respond differently than, say, a "dengue 3" person? So, I think there are a lot of things that we need to think and be concerned about in going forward with this vaccine. Thank you.

MS. HUNTER-THOMAS: Thank you, Dr. Holstead. Is there anyone else in the public that wanted to speak or would like to speak at this time that hasn't registered? Hearing and seeing none, we will conclude the open public hearing portion of this meeting and I will hand the meeting back over to Dr. El Sahly. Thank you.

DR. EL SAHLY: Dr. Ralph LeBlanc, from the FDA, will present an overview of the product.

PRODUCT OVERVIEW

DR. LEBLANC: Good afternoon and thank you to the advisory committee members for your participation today. I will be presenting a summary of the safety and effectiveness data submitted in support of the BLA for Dengvaxia, a live tetravalent dengue vaccine. My name is Ralph LeBlanc and I'm in the Office of Vaccines Research and Review at the FDA.

An outline of the presentation today will include background with the product description and a proposed indication and usage, overview of selected clinical trials submitted to the Dengvaxia BLA, efficacy in children 9 through 16 years of age, immunogenicity in adults ages 18 through 45 years of age, an integrated summary of safety, a pharmacovigilance plan overview, and an overall summary.

As you have been informed several times today, but we'll go over it one more time, Dengvaxia is a live, attenuated, tetravalent, chimeric virus vaccine. It contains the replication genes and the capsid gene

from the attenuated 17D strain, yellow fever virus and the preMembrane and Envelope genes from each of the four wild-type dengue serotypes.

It is administered as three 0.5 mL subcutaneous injections administered 6 months apart. And the requested indication is prevention of dengue disease caused by serotypes 1, 2, 3, and 4 in individuals 9 through 45 years of age with laboratory-confirmed previous dengue infection and living in dengue-endemic areas.

The laboratory confirmation of a previous dengue infection was very nicely reviewed by two other presenters; but just as an overview, if you have an individual who has a medical history or a potential medical history of a prior dengue infection, laboratory confirmation with compatible clinical history could include direct detection methods, viral culture, RT-PCR, nonstructural protein 1 immunoassays, or indirect methods, single or paired IgM, IgG sera.

For individuals who have no medical history of a previous dengue infection, or it’s unknown,

currently available IgG ELISAs or IgG Rapid Diagnostic Tests may be used to confirm the previous infection. The performance characteristics of these tests -- the sensitivity and the specificity -- should be considered as there is a potential for detecting cross-reactive antibodies to other flaviviruses, at least Zika, West Nile, potentially yellow fever. And that cross-reactivity can lead to false positive results. No serological tests are cleared by the FDA to establish prior dengue exposure at this time.

This slide presents an overview of the selected clinical trials that we're going to review today and has the three clinical efficacy endpoints studies on the first slide. CYD15 and 14 were both Phase 3 -- randomized, placebo-controlled, observer-blind, multi-center trials -- with the primary objective of vaccine efficacy against virologically confirmed dengue due to any serotype, and safety, and immunogenicity.

CYD15 was conducted in five countries in South and Central America and in Puerto Rico, in 9 through

16-year-old subjects. CYD14 had the same design and objectives and CYD15, but was conducted in 2 through 14-year-olds in five Asia-Pacific countries. And CYD23 was a Phase 2 proof of concept study that was conducted in 4 through 11-year-olds in Thailand.

A brief background now. The original clinical development plan for this vaccine anticipated an indication from 2 through 60 years of age. Therefore, 2 through 16-year-olds were included in the endpoint studies.

When we present the data today for the two Phase 3 trials -- actually, and the Phase IIb trial -- we will present the per protocol set for efficacy data as preplanned for the age groups included. However, because the requested indication is 9 through 45, we will then focus on post-tonic or additional analyses in CYD14 and 23 that look at 9 years and above. I just wanted to be clear why we're doing what we're doing.

The second slide that presents the overview of selected clinical trials shows the three studies --

CYD47, 28, and 22 -- that were submitted in support of immunogenicity and for adult subjects. They were all three Phase 2 studies. They were randomized, placebo-controlled, observer-blind. Their objectives were descriptive immunogenicity and safety. The study in India only included adults; but in Singapore, there were younger subjects. They were not included in the analysis. The analysis for all three of these studies only included 18 through 45-year-old subjects. Further, it only included those subjects who were dengue-immune at baseline. The study CYD22 was conducted in Vietnam.

So the largest of the Phase 3 clinical trials was CYD15. You already understand that it was a randomized, placebo-controlled, observer-blinded trial that evaluated safety and efficacy of Dengvaxia in healthy children 9 through 16 years of age in Latin America. 20,869 subjects were randomized 2 to 1, to receive three doses of Dengvaxia or the placebo, which was normal saline, and those doses were 6 months apart.

It was a multi-center trial at 22 sites across Brazil, Colombia, Honduras, Mexico, and Puerto Rico. Subjects were followed up for up to 6 years post-vaccination, and the follow-up was divided into three phases: an Active Phase, a Hospital Phase, and a Surveillance Expansion Period.

This schematic shows an overview of the phases of the study. It's the exact same schemata for 15, CYD14 and CYD23. What you will notice on the lower horizontal axis is years 1 through 6. And in years 1 and 2, that was the Active Phase. The first year, the three injections were given during the first 12 months. And active case detection for any symptomatic VCD case of dengue was conducted from month 13 to month 25.

The Hospital Phase, which could be characterized as Hospital Phase year 1, if you look at the bottom of the chart, where it says year 3 of the study, that's year 1 of the Hospital Phase. Then year 2, then year 3, then year 4. During the Hospital Phase, as originally planned, active case detection

for severe clinical and hospitalized dengue was conducted.

Because of the identification of an imbalance in severe virologically-confirmed and hospitalized dengue that was observed in year 1 and 2, initially, of the Hospital Phase -- year 1 and 2 of the Hospital Phase and the clinical trials, this imbalance was noted. Because of that, the sponsor decided to further try to characterize that safety signal. And in order to do that, they proposed what they call a surveillance expansion period, which is shown on this slide that, for studies 15 and 14, started towards the end of the second year of the hospitalization, which was year 4 and extended through year 6.

The surveillance expansion period was characterized by reconsenting the subjects -- all willing subjects, and they had a high acceptance rate. About 93 percent agreed to be reconsented, have a blood draw at the time of that reconsenting, resume active case detection for symptomatic VCD of any serotype and continue the hospital surveillance. So,

that's the explanation of that. The data submitted with this BLA cover from month 0 to month 60, or the end of the year 5. We do not yet have the data from the 6th year.

For the CYD15 trial, there was a reactogenicity and immunogenicity subset. Those subjects were recruited in the first two months and were randomized to the subset until 2000 subjects had been enrolled. So, that was basically 10 percent of the total randomized number of subjects were in the immunogenicity and reactogenicity subset. Reactogenicity was for solicited local and systemic adverse reactions, recorded on diary cards daily -- per routine, in a trial like this -- for up to 14 days after vaccination.

Unsolicited adverse events were recorded on diary cards from Day 0 to 29 after each vaccination. And the immunogenicity part of the subset, those -- same subjects. They were the same people that were in reactogenicity and immunogenicity. They had blood drawn at baseline, just 10 percent of the people in

the study. They also had blood drawn 28 days post-dose 2, post-dose 3, and then annually for five years.

The primary objective and endpoint for CYD15 trial -- primary objective was to assess efficacy of 3 doses of Dengvaxia administered 6 months apart to prevent symptomatic VCD dengue cases, regardless of severity due to any dengue serotype.

The primary endpoint definition: a symptomatic VCD case, occurring from 28 days post-dose 3, for 12 months by the per protocol analysis set for efficacy and the prespecified success criteria was at the lower bound of the 95 percent confidence interval for vaccine efficacy; needed to be greater than or equal of 25 percent.

Selected secondary objectives were for efficacy to describe vaccine efficacy against severe dengue disease and dengue hemorrhagic fever.

An additional endpoint was the occurrence of symptomatic VCD cases by serotype.

Safety objectives, to describe rates of local

and a systemic adverse reactions for up to 14 days post-vaccination, to describe rates of unsolicited adverse events for 28 days post-vaccination, and to describe all serious adverse events and deaths for the entire study period.

The case definitions that are relevant -- the first thing I want to point out is, what is virologically-confirmed dengue case. In CYD15 -- and this is exactly the same for CYDB14 -- a case required an acute febrile illness, temperature greater than or equal to 38 degrees centigrade for at least 2 days; and then, virological confirmation would be by dengue RT-PCR and/or dengue NS1 ELISA antigen test. For CYD23, the only difference was they had a different fever criteria, and it was greater than or equal to 37.5 centigrade two times in one day, separated by at least 4 hours. So, just a slightly different threshold for fever triggering concern about a clinical case of dengue.

All I'm going to say about severe dengue and dengue hemorrhagic fever, because you've had excellent

presentations this morning, is that the clinical criteria that goes into calling something clinically severe or clinically severe hospitalized dengue or dengue hemorrhagic fever grade whatever, 1 through 4, by WHO, new or old criteria, the clinical criteria are all the same. It's just what weight's put to each of the elements.

So, suffice it to say that there was a decision to use the 1997 WHO criteria for dengue hemorrhagic fever and their grading scale that was used when results are expressed as DHF cases, and the applicant had their own template for the ICDM to identify severe dengue. It included all of the same clinical criteria, but by their own algorithm. There's not a lot of difference between a case that was characterized as severe or WHO grade 1 or 2. I think that's a lot to have two different endpoints that both reflect severity, but that's the explanation of them.

So, in this study, the study demographics by gender, ethnicity, and race for the safety analysis

set, it showed that there was a proportional percentage of male and female. When subjects were asked about ethnicity, 100 percent of them said they were Hispanic. This was conducted in South America. When they were asked about race, 8 percent said white, non-Hispanic; 3 percent said black; and 16 percent said American-Indian. And they were balanced across the Dengvaxia and the placebo group.

The percentage of subjects by country in this study varied from 46 percent in Columbia to a low 6 percent in Puerto Rico. And there was no prespecified success criteria for efficacy by country. My understanding of the selection of the countries and the balancing of how many people in each country was driven by the epidemiological data that showed certain attack rates and the desire to have, if possible, a certain number of dengue cases in a reasonable period of time; but also to cover some dispersion of countries in South and Central America as the one major geographic location, and then for 14, five different countries in Thailand.

So, the primary endpoint for trial CYD15, which was the symptomatic virologically-confirmed dengue case due to any serotype during that 12-month interval, starting 28 days post-dose 3, by the per protocol set for efficacy, and the point estimate was 60.8 with the confidence intervals that you can see. This was 9 through 16-year-olds, so that entire age range is in the requested indication. This is the per protocol efficacy including dengue-immune and dengue non-immune at baseline.

There was a secondary endpoint of cases in dengue hemorrhagic fever post-dose 1 due to any dengue serotype, and there were ten such cases in the placebo group, one in the Dengvaxia group. The one case in the Dengvaxia group was a Grade 2 dengue hemorrhagic fever; and in the placebo group, there were two Grade 1s and eight Grade 2s. So, in this trial, there was no Grade 3.

An analysis for serotype-specific efficacy was done by the full analysis set for efficacy. So, it was post-dose 1. The full analysis set for efficacy

included anybody who got one injection at least. In reality, there wasn't a lot of difference between the FASE and the per protocol. Most people in this study got all three doses, 95 percent plus.

There is a range of point estimates of efficacy by serotype that you can see on this slide. In a very general way, it can be stated that serotypes 3 and 4 had a point estimate of vaccine efficacy that was higher than 1 and 2. When data was analyzed in a post-hoc analysis for vaccine efficacy against symptomatic VCD, post-dose 3 due to any serotype, but then analysis was done by dengue-immune status, these are the results that you get.

So, for subjects who were dengue-immune at baseline, which was defined by the PRNT-50 assay, dilution of greater than 10, there was an 83.7 percent point estimate. And for those dengue non-immune, 43.2.

There's one slide that I'm going to show on the immunogenicity results from this Phase 3 study in 9 through 16-year-olds. You can see that the results

are divided by dengue-positive at baseline versus dengue-negative. The word dengue-positive and dengue-immune means the same thing. These are post-dose 3 by serotype, and it's clear that there was a substantial fold increase in neutralizing antibodies in the dengue-immune individuals. And when you look at the second red box for the dengue non-immune individuals, there was some increase in titer. There was some increase, but the ultimate post-dose 3 mean titer was substantially lower if you were dengue non-immune to start with.

This slide presents the Geometric Mean Titers in dengue cases and non-cases in the Dengvaxia group from CYD15. What we see here is that subjects by serotype 1 through 4, cases had GMTs in the range you can see in that box, whereas non-cases have substantially different GMTs.

Now, when various analyses were performed to look at relationship between GMTs and efficacy, there was no clearly established correlated protection, then no point at which efficacy could be predicted based on

the antibody titer.

Beyond that, how you want to characterize this relationship, there's numerous ways to do it. The Fred Hutchinson Center who did these analyses used the term "trend," that there was a trend towards higher efficacy. FDA, we're not so sure that's the best word to use. There is a relationship, the titers are higher in non-cases rather than cases, but there clearly are outliers. When you look at the granular data, the majority of cases of dengue had post-dose 3 GMTs that were sero dilution of 1 to 160 or much less than that. But there were a few cases at 1 to 320, 1 to 640. So, those outliers certainly made it difficult to pull the data together and say, oh, here's the correlated protection, but these people, they don't count or they're outside that limit.

So, just to give you a sense of what the data looked like and -- next slide. We're going to go to the study of CYD14 now and, as noted, the study design was the same. The only things that were different between 14 and 15 were the age of the subjects. So,

CYD15 was 9 through 16 and CYD14 was 2 through 14. They're a different area of the world; 14 was in the Asia-Pacific and 15 in Central and South America. Otherwise, the study design elements were the same.

This slide shows the study demographics for CYD14. Philippine had the greatest percentage of overall subjects and Thailand the least, although we note that Thailand also had subjects in -- well, all the subjects in CYD23 were from Thailand. So, there's a little bit more representation of Thailand than what you see from CYD14. But, nonetheless, the pattern is exactly the same as with CYD15. There was no preplanned design to balance enrollment by country. And even though we can look at efficacy data by country or any data we want to, nothing was preplanned by country as far as analyses.

The study demographics by gender and age, in study CYD14, show that male and female were proportionately balanced. There was about 25 percent of the subjects that were 2 to 5, about 53 percent that were 6 to 11, 23 percent 12 to 14, and then we

added the last row, 9 to 14, because 9 to 14 is the age that's going to be potentially included indication. We wanted to give some sense of, well, what was the proportion of subjects in that trial that were in 9 to 14? And it was half of them; 50 percent of them.

The primary endpoint for this trial, which was the exact same as for CYD15, this data, again, is per protocol set for efficacy, the entire age range, 2 to 14. And the vaccine point estimate is 56.5. You can see the confidence intervals.

So, this trial, just like 15, succeeded on its primary endpoint for the entire age range of subjects that were enrolled. In a post-hoc analysis looking at symptomatic VCD, during the 12 months, starting 28 days post-dose 3 due to any dengue serotype but in a subset of children 9 through 14 -- so, just in that 50 percent of the subjects that were in that age range, the point estimate was 69.4.

This slide shows the serotype-specific efficacy, but only in subjects who are 9 through 14.

This isn't the whole age range. And you can see that, again, serotype-specific efficacy varied by the serotype. Again, serotype 2 is on the low end of the four; 3 and 4 are higher. In this particular analysis, serotype 1 was comparable to 3.

This slide shows the post-hoc analysis of efficacy against dengue hemorrhagic fever. And again, it's 9 through 14 only. It doesn't include all the subjects in the study. There were 20 cases in the placebo group; 8 in the Dengvaxia group; and there was one Grade 3 dengue hemorrhagic fever in that placebo group. I've got to look at my paper here to tell you. I'm sorry.

Suffice it to say that was the only Grade 3 DHF that occurred in either of these two studies, and the other cases were Grade 1 and 2. The exact numbers -- so, in the Dengvaxia group, there were two cases of Grade 1 DHF and six of Grade 2. In the placebo group, there were five cases of Grade 1, thirteen of Grade 2 -- oh, and I misspoke. Two of Grade 3. I'm sorry. So, that was the range.

In a post-hoc analysis for vaccine efficacy against symptomatic VCD in that 9 through 14-year age group, by the full analysis set for immunogenicity, you, again, see this pattern of, in subjects dengue-immune at baseline, a point estimate 79.2; and dengue non-immune, 61.8. The confidence interval is quite a bit different for those two point estimates. So, it's the same pattern.

The magnitude of the pattern is a little bit different between 15 and 14. They had different ages included. But, even when you go down to relatively the same age group, a little bit different. But there's serotype-specific variance in efficacy. There's variance in efficacy as a result of whether you're dengue-immune at baseline or not.

So, study CYD23 was the Phase IIb study conducted in Thailand as a "proof of concept" study, and they enrolled 4,002 subjects. The study design elements were essentially identical to that of 15 and 14, with the following differences. It was a Phase IIb study. Subjects were 4 through 11 in this study.

They were enrolled at a single site in Thailand. As already noted, their fever criteria was just a little bit different. It was 37.5, greater than or equal to, at least twice within an interval of four hours, whereas the other two studies, it was 38.0 over two days.

In this study, because it was a proof of concept in the first clinical efficacy endpoint, had a prespecified success criteria of the 95 percent lower bound confidence interval being greater than 0 rather than greater than 25. And those were the main difference between these two studies.

The primary endpoint for the entire study, 4 through 11 years of age, you can see that the point estimate was 30.2, but the lower bound was less than zero. So, evaluated on a per protocol set for efficacy, this study did not achieve its prespecified success criteria.

When analysis were done for a subgroup, 9 through 11 years, the point estimate was 70.1. Number of cases are limited because of the narrow age range

in this study. But 9 through 11, again, is included in the age indication requested. So, we wanted to look at that breakdown. So, a summary of the vaccine efficacy from all three trials -- 15, 14, and 23 -- can be stated that the vaccine efficacy by per protocol set for efficacy analysis that, for the two Phase 3 trials, CYD15 in 9 through 16-year-olds and CYD14 in 2 through 14-year-olds, both met their prespecified success criteria for efficacy with a 95 percent lower bound that was greater than 25 percent.

The vaccine efficacy varied by dengue serostatus at baseline, in post-hoc analyses, with higher point estimates of efficacy in dengue-immune or dengue seropositive versus dengue seronegative. The vaccine efficacy varied by serotype in post-hoc analysis, with, in general, serotypes 3 and 4 having higher point estimates of efficacy than 1 and 2.

There's a few slides here on the immunogenicity data from the three studies in adults. So, if you look on the upper left-hand corner of this slide, there were three studies. They were all Phase

2 randomized, placebo-controlled, observer-blind, descriptive studies. One was in India; one was in Singapore; one was in Vietnam. You can see the number of subjects that were enrolled. And when there were subjects, such as in Singapore and Vietnam, who were less than 18, you can see how many adults were in each study.

Critical points to make: In the clinical efficacy endpoint trials, as previously noted, a specific threshold PRNT50 titer above which vaccine efficacy could be predicted reliably was not identified for any dengue serotype, although neutralizing antibody titers tended to be higher in non-cases than in cases.

Second point: Serotype-specific GMTs were compared descriptively for dengue-immune adolescents from the studies 14 and 15 and dengue-immune adults from these three studies.

So, a descriptive comparison. There was no statistical criteria that was prespecified for assessing that comparability of the GMTs from adults

to the GMTs observed in the clinical efficacy studies. So, there was no non-inferiority on a specific endpoint with a specific boundary limit. The comparison was to be descriptive.

So, this is a little busy slide, but what you see are the GMTs from those three studies. Even though it says 22 and 47, CYD28 is also on this slide. What we have is that, for serotypes in the columns, we have pre-injection 1 GMTs and post-injection 3. We have the age groups 9 through 16. We call them adolescents. Those subjects all came from 14 and 15. You've got your pre-injection and your post-third injection titers. In the lower three rows, in dengue-immune adults, 18 through 45, you've got the results from all three studies.

So, you will notice that for 14 and 15, if you look at the post-injection 3 GMTs -- they're in bold -- and then compare those two numbers to both CYD22 from India, which is in bold red, and CYD47 from Vietnam, that's what we mean when we say we're comparing them descriptively. You're literally

looking at them and saying to yourself, 785, 688. Looking at 703, 437, what do I think? That's the descriptive comparison, and it's similar for each serotype.

You will observe that there is general similarity between the titers from CYD22 and from either 14 or 15. The data's presented for CYD28 in Singapore, and you notice two things. One, their post-dose 3 titers are not as high as from Vietnam and India, across the board at each serotype. But you also notice, if you look at their pre-injection titers, these subjects had much lower pre-injection antibody levels.

A piece of information that may help explain that is that even though Singapore was chosen for this study because it was considered a dengue-endemic region, it's not all that dengue-endemic. So, the seroprevalence in Singapore for the years that you're able to look at is much, much lower than for Vietnam or India. We focused our descriptive comparison on 22 and 47. And just to be real clear about what we're

saying, we're saying, descriptively, those post-dose 3 titers look similar to 14 and 15.

This just kind of summarizes it. Descriptively, in studies CYD22 and 47, post-dose 3 GMTs among vaccinated dengue-immune adults 18 through 45 were similar to post-dose 3 GMTs of dengue-immune vaccinated children 9 through 16 in the clinical efficacy endpoint studies. These data are intended to support effectiveness in dengue-immune persons 17 through 45.

Okay. There's a few slides on safety data and we'll begin those now. So, the safety of Dengvaxia in persons 9 through 45 years of age -- we looked at solicited local and systemic adverse reactions from CYD15. We'll show those findings. They were very similar for 14 and 23, so we're not going to show all those multiple slides.

Serious adverse events and deaths are going to be presented from an integrated analysis of safety based on about 20,426 subjects, 9 to 45, who received the 3 full doses of the final formulation of the

vaccine. And then, there will be analyses of the risk of hospitalized virologically-confirmed dengue presented.

So this is the slide that shows the percentages of solicited local and systemic adverse reactions from CYD15, 9 through 16-year-olds, South America. Within 7 to 14 days after any injection of Dengvaxia, 9 through 16, by their reactogenicity analysis set.

There were some differences between the Dengvaxia and placebo, but not of great magnitude and not of clinical significance. There's higher rates of Grade 3 pain in Dengvaxia, and a little bit higher rate of Grade 3 myalgia. But overall, there's a general comparability on the criteria of any solicited adverse reaction, no matter which one you look at, and on Grade 3.

Unsolicited adverse events within 28 days of vaccination -- non-serious AEs were reported in about 46 and a half -- 46.6 percent of subjects in the Dengvaxia group; 44 percent in the placebo group

within 28 days after any injection. So, it's comparable. Unsolicited non-serious AEs occurred in various system organ classes, but the highest proportion of classified non-serious AEs were infections, infestations, and they were 25.8 in Dengvaxia, 26.4 in placebo. That was pretty balanced. And then the second highest was GI disorders, which were about 12 percent in each group.

The frequencies of adverse events -- these are unsolicited adverse events -- from all other SOCs were less than 10 percent, and they were balanced between the groups. This slide shows an integrated summary of the safety of Dengvaxia, looking at serious adverse events post-vaccination, age 9 to 45. Whether you look at, in the first column, SAEs less than 28 days, where the rate was 0.7, 0.8, Dengvaxia to placebo, or if you look at SAE 28 days to less than 6 months, when you look at serious allergic reaction or discontinuation, those balance in the two groups.

This slide is the first of two that looks at the incidents of hospitalized virologically-confirmed

dengue cases due to any serotype, 9 through 16 years of age. This is from pulled analysis from all three studies -- 15, 14, and 23. And we have a relative risk that's assessed at year 1, 2, 3 -- all three years and the entire study period. What you see is that the relative risk for hospitalized VCD was approximately half in the Dengvaxia compared to the placebo group for whatever time interval you want to look at; a little bit lower than half if you look at the entire study period, which would be month 0 to month 60.

In this analysis, subjects were dengue-immune and dengue non-immune. This is not segregated by immune status at baseline. As noted by the applicant, this relative risk for hospitalized VCD by dengue-immune status at baseline -- the increased relative risk of severe/hospitalized dengue, that was greater in Dengvaxia than the placebo group, was first observed in year 1 of the hospital phases; year 3 of the study. And it was observed at a higher relative risk in subjects 2 to 5. You remember seeing that in

the slide from the applicant; I think it was 7.5 relative risk in that age range. But there was still increased relative risk in the age group 6 to 11.

It was clear that there was some association of increased relative risk with younger age. However, analyses of that relationship were limited by the small percentage of subjects in the immunogenicity subset. You had 10 percent immunogenicity subset in CYD15; 20 percent in 14. Put them together; you had about 14 percent. Severe/hospitalized dengue wasn't that common, so there weren't that many cases.

So, there was a need for further clarification of that signal. But that required knowing dengue-immune statuses at baseline, which we didn't know in 80 to 90 percent of the subjects because they weren't in the immunogenicity subset.

So, what was done and has already been explained, an exploratory analysis was conducted. It was done by a case-cohort method which was described to you. So, a 10 percent sample of subjects from the three studies, and then adding in every single subject

that had a severe/hospitalized dengue.

The objective was to impute the baseline dengue serostatus from the post-dose 3 serostatus, and do that based on the NS1 anagen ELISA, which had the ability to distinguish wild-type NS1 antigen from wild-type dengue, as compared to the NS1 antigen that's in Dengvaxia.

That was one analysis that they ran. They also ran analysis of that post-dose 3 sera based on their PRNT50 assay. So, they got both analysis going and they used multiple statistical methods to impute that baseline dengue serostatus.

The third bullet here: Although there's certainly limitations to the case-cohort design and to the statistical methods used to impute a serostatus, the results of the exploratory analysis using the NS1 ELISA showed the dengue-immune status at baseline was related to the risk of severe/hospitalized dengue. That was the bottom line, with caveats.

This slide shows the comparison between subjects from all three studies who are either

seropositive or seronegative at baseline. It looks at their risk for virologically-confirmed dengue during the entire study period and gives you a hazard ratio on the last column. So, for the seropositive subjects, whether they were from 14, 15, 23, or the pulling of all the studies, the hazard ratio for symptomatic VCD -- just to have VCD -- I'm sorry, hospitalized symptomatic VCD. The hazard ratio is 25 percent or a little bit lower. So, there's protection in the dengue-immune at baseline from hospitalized VCD.

Conversely, if subjects were dengue seronegative at baseline or dengue non-immune, the hazard ratio is essentially greater than 1, and it depends on what study you're looking at, whether it's 14, 15, or all studies combined. But the point estimate is basically right at 1 or above 1, and then the confidence intervals go up to an upper level, as you can see here.

So, being dengue-immune at baseline is associated with protection from severe/hospitalized

dengue and being dengue non-immune is associated with risk. And this is 9 through 16. It's got nothing to do with people younger than 9. 9 to 16 years old, data from all three studies, although that baseline dengue-immune status was imputed in a number of people.

Okay. A summary of the safety data for Dengvaxia in persons 9 through 45: The majority of subjects experienced local and/or general adverse reactions of short duration. Most of those reactions were mild or moderate -- Grade 1 or Grade 2 -- and there was no substantial imbalance in severe adverse reactions between the Dengvaxia and the placebo groups.

Overall, SAEs, excluding hospitalized severe dengue which was an SAE in these studies, but all other SAEs were reported in similar proportions of subjects in Dengvaxia and the placebo groups. The last bullet just made note of there was an increased risk of hospitalized VCD observed in Dengvaxia recipients who were seronegative at baseline in the

clinical efficacy endpoint trials.

We have one brief slide on the pharmacovigilance plan, simply to note that Sanofi Pasteur submitted a Pharmacovigilance Plan to monitor what are termed Important Identified Risks that could be associated with Dengvaxia, and they cited allergic reactions and severe/hospitalized dengue in individuals not previously infected by the dengue virus. Details of the PVP are still under discussion between FDA and the applicant. So that's all we're going to say.

Last two slides, summary of the immunogenicity and safety -- just to recap on immunogenicity, the specific threshold for neutralizing antibody titers with which vaccine effectiveness could be predicted reliably was not identified. There was no correlated protection. However, there was a tendency towards higher post-dose 3 neutralizing antibody titers in non-cases compared to cases in CYD15 and 14.

Descriptively, the 28-day post-dose 3 neutralizing antibody titers that were observed in

subjects 18 through 45 in those three studies, but particularly in 22 and 47 from India and Vietnam -- those titers were similar to the 28-day post-dose 3 neutralizing antibody titers in the subjects 9 through 16 in the clinical trials.

Just recapping what I said two minutes ago. Safety -- again, the increased risk of hospitalized VCD in Dengvaxia recipients who were seronegative at baseline. Solicited local and systemic adverse reactions were generally mild -- Grade 1 or 2 -- and of short duration.

There was no substantial imbalance in severe reactions between Dengvaxia and placebo. Overall, SAEs -- excluding the hospitalized VCD -- and deaths were reported in similar proportions of subjects in the Dengvaxia and placebo groups. There were no deaths in any of these studies that were found to be attributable to the vaccine product. And viscerotropic and neurotropic disease entities were clearly defined and were clearly looked for in the first six months' safety follow-up, and there's no

case of either in any of the three trials.

This is the final slide. It's the summary of the efficacy results. You see study 15, the primary endpoint, its vaccine efficacy estimate, and the confidence intervals. Study 14, full age range, 2 to 14, a little bit lower efficacy estimate, pretty similar confidence intervals. CYD23, as pointed out, if you look at the full age range and their primary endpoint, lower vaccine efficacy estimate, lower bound less than zero. And then, if you look at three post-hoc analyses and focus in on the 9 and above -- for CYD23, 9 to 11 -- all subjects, you get an efficacy estimate of 70.1 with those confidence intervals.

Then, if you look at seropositives instead of the whole group, CYD15, point estimate of 83.7 in those seropositive 9 through 16-year-olds. And in CYD14, if you look at the 9 through 14-year-olds, seropositive point estimate of 79.2.

Thank you for your patience. I'll take any questions anybody might have.

COMMITTEE DISCUSSION/RECOMMENDATIONS/VOTE

DR. EL SAHLY: Thank you, Dr. LeBlanc. I would begin by asking, regarding the test that was used to characterize individuals as seropositives, is the NS1 ELISA an antibody ELISA? And is this test available for use? And how does it perform in post-Zika era?

DR. LEBLANC: Oh, those are good questions. Yeah. I would let the applicant address how it's available for use. I'll let them address how it performs in a post-Zika era. I'm going to let him address both of them.

DR. GURUNATHAN: So the dengue NS1 ELISA test that was used for the case-cohort analysis is -- I'd say that was specifically used for the purposes of addressing a research question. And it's not available for use in the field.

The influence of Zika on the test was evaluated based on a few samples, but the important point is that, for the purpose of the study that was done, which was to characterize the baseline of the

individuals in the studies, at a time when the sample was available, which was the month 13 sample, Zika had not occurred in the Americas yet.

So, for the purposes of addressing the research question at hand, the assay was not influenced by Zika, because Zika was not in the Americas at that time.

DR. EL SAHLY: Dr. Kurilla.

DR. KURILLA: Does that NS1 test distinguish dengue subtypes? The serotypes?

DR. GURUNATHAN: No.

DR. KURILLA: So, do you have any evidence, even if it's limited to animal model -- evidence of the vaccine efficacy after two or more dengue infections, particularly heterotypic dengue infections?

DR. GURUNATHAN: Yes. We actually did some of those analyses at the request of the European Medicines Agency. For doing that, we utilized the PRNT90 assay to classify individuals in the immune subsets in the studies as monotypic, meaning that they

only had immunity to one dengue serotype, or multitypic, meaning that they have immunity to two or more dengue serotypes.

The data is summarized to -- see if it's going up or not on this screen. Okay. So, this is the summary of the data. And here we have information for the immunogenicity subsets for the two studies pulled and for the age group 2 to 16 years of age. What you have in the top of the slide is the data for symptomatic dengue over a period of zero to 25 months post-vaccination, expresses vaccine efficacy. And at the bottom, you have the information for hospitalized dengue.

First, if you concentrate on the right side of the slide, the placebo data, what you can see there is that the individuals that are classified as monotypic have a higher risk of symptomatic dengue compared to the multitypics, and also a higher risk of hospitalized dengue compared to the multitypics. So, that information is consistent with the dengue paradigm that you have a much higher risk of

symptomatic dengue and more severe forms of dengue if you have a single previous dengue infection.

So then we can take a look at the left side of this slide and the estimates of vaccine efficacy and relative risk. What you can see is that, for monotypic immunes, the vaccine efficacy is close to 80 percent and significant. And the protection or risk reduction against hospitalized dengue is around the same range. Also, it's statistically significant for the subgroup of people that are classified of multitypic.

What is interesting is that you also see protection for the two outcomes of both symptomatic dengue at the top and hospitalized dengue at the bottom. So, the vaccine is providing benefits to the group that needs the benefit the most, which are the monotypic immunes. But the people that have been exposed to two or more dengue serotypes before also start to benefit from the vaccine.

DR. LEBLANC: What I would just add to that, and it's a basic perspective, I think it's important

to keep in mind what these studies were powered for. They were powered for efficacy against any serotype. That was the main thing. Even going to serotype-specific efficacy, you're getting into smaller numbers. Getting into the type of question you asked, which I think is immunologically very important, but you have very few data points. So, I would just question that that type of data needs to be interpreted consciously.

DR. EL SAHLY: Would the Singapore volunteers -- would they have been classified as immune?

DR. LEBLANC: The only subjects whose data were presented in that table, they were all immune. There were non-immune people in each one of those studies; but the comparisons were GMTs post-dose 3 between adults and adolescents who were immune at baseline.

If you remember the data from the CYD15 and the immunogenicity subset, if you're non-immune at baseline, you don't get much of a titer post-dose 3. So, the comparison was in dengue-immune adults,

dengue-immune adolescents. And the people from Singapore were immune at baseline by that greater than 10 threshold, but their pre-injection titers were quite a bit lower than --

DR. EL SAHLY: So I'm trying to put this into context of the bridging data, meaning the Singapore volunteers post-dose 3, their titers were way lower than what we observed in CYD14, 15 and the two other adult studies.

DR. LEBLANC: Correct.

DR. EL SAHLY: So I'm wondering about why different and how do we put this in the context of the bridging data?

DR. LEBLANC: The only explanation I have for you as to why the data from Singapore is different is that they start at a different level. Their pre-injection titers were substantially lower. There's some thinking that that relates to lower overall levels of endemicity in Singapore.

DR. EL SAHLY: But they're still considered immune. We should have given them the vaccine.

DR. LEBLANC: Yeah, but that doesn't mean that they're necessarily immune and protected from getting dengue. There's a difference. The immune definition is a function of the PRNT50 assay.

DR. EL SAHLY: Exactly.

DR. LEBLANC: And that lower threshold's pretty low. But it's a legitimate concern.

DR. FINK: So I'll jump in and clarify that, for purposes of the descriptive comparison between adults in the immunogenicity study and the pediatric subjects in the efficacy studies, we considered that the two studies done at sites where there was known to be an overall higher level of endemicity would be the most appropriate comparisons; apples to apples comparisons for looking at the immune post-dose 3 GMTs in adults versus those in the children in those studies that were also conducted in highly endemic areas.

DR. KURILLA: Are you suggesting, then, that people living in endemic areas are being constantly boosted by repeated mosquito bites even though they're

immune and that's what's keeping their titers higher?

DR. LEBLANC: There is some evidence that suggests that, if you look at the immunogenicity table for CYD15 and you look at subjects who didn't get Dengvaxia and they got placebo, and you look at their post-dose 3, year 1, their titers keep going up. They didn't get the vaccine. And we know that there's repetitive exposure and that they could be getting boosting. So, yes, there's the assumption that their titers are being maintained or even rising a little bit as a function of ongoing dengue exposure.

DR. EL SAHLY: Okay. Dr. Bennink?

DR. BENNINK: Yeah. Part of the issue is that these are averages anyways, as you say, when they're not in the endemic area. It's an average of everyone that you have in the thing. What would be nice, really, is if we had the individual data, particularly the data for people that had a problem after the vaccine. Was that monovalent or was there nothing? What really came out of the vaccination after you had that and then there was a failure? And that's much

more difficult to get a --

DR. EL SAHLY: Okay. Dr. Edwards?

DR. EDWARDS: So do you think that Puerto Rico is more Singapore-like or more Thailand-like? And if we're going to try and make a bridge, then I think it's really important because the efficacy data are in seropositives who have much higher titers. So, how do we interpret what you show us for Singapore?

DR. MONTO: And is it regions in Puerto Rico that are more Singapore-like?

DR. LEBLANC: So, if you look at the baseline epidemiology, Puerto Rico's pretty much midway between Singapore and Vietnam and India. So, Puerto Rico in 9 to 16-year-olds, for the most recent data prior to the studies, was about 56 percent seropositive in the 9 to 16-year-old. It was on the low end for those five studies that were in South America. Brazil, I think, was maybe the highest; Brazil or Columbia. I can't remember the numbers exactly. But they were, like, 70 to 80 percent. So, that does vary. But Puerto Rico is mid-50 percent.

DR. EDWARDS: But we're used to seeing serology in populations that we're going to use the vaccine in and we're used to seeing serology that we can kind of go back to what the efficacy is. And I'm very uncomfortable with the Singapore serology because you say that efficacy is based on the height of the titer, and these titers aren't very high. In fact, these titers are pretty much the same as the seronegative kids that got vaccinated.

DR. GRUBER: So can I -- I'm sorry. This is --

DR. EL SAHLY: Dr. Gruber?

DR. GRUBER: Yes. I actually, at this point, would actually ask and invite Sanofi Pasteur to comment on this. This is a complex subject and topic and I think they need to give the sponsor a chance to comment.

DR. GURUNATHAN: Thank you, Dr. Gruber. Yes, for understanding study CYD28, it is also important to understand a couple of things. Of course, the level of endemicity in Singapore was much lower than the

level of endemicity in the other adult studies that were shown and in study CYD14 and CYD15.

So, to understand the possible implications of that, I think we have to take a look at the baseline and what is affecting the baseline. The baseline PRNT antibody titers are affected by the magnitude of previous exposure to dengue. So, with higher level of exposures, you are expected to have higher baseline PRNT50 antibody titers. That's the first point.

The second point is that there is a clear relationship between the pre-vaccination antibody titers in seropositive individuals and the post-dose 3 antibody titers in individuals; so that if you want to compare the post-dose 3 antibody titers, you have to account somehow for baseline or for magnitude of exposure.

We have tried to do some analysis that adjusts for baseline to compare the studies. So, first, let me just show the relationship I was mentioning about baseline and post-dose 3 that's represented by the figure that you see on the screen right now.

Now, the second point, which was described by Dr. LeBlanc, is that the antibody titers in CYD28 were much lower a baseline than the antibody titers in, for instance, CYD14 studies age 9 to 14, where efficacy was demonstrated. So, that is illustrated in the slides that we are projecting right now on the screen. This is specifically for people that are seropositive. So, we think the -- you know, not all the seropositives are the same. We think the seropositives -- the antibody titers for the adults in CYD28 were much lower than the antibody titers in 9 to 14-year-olds in CYD14.

So then what we did, in collaboration with the University of Washington, was to adjust for baseline. And those analyses that adjusts for baseline, what we have is -- in the slides presented here, is that the differences that we're largely seeing in analyses that were unadjusted are low.

Once you adjust for baseline, you see that the bars are relatively similar for all the other serotypes. And for the average titer records of the

four serotypes, they're also very similar with the ratio for the average titer that is very close to one between the studies -- 28 adults, 18 to 45 years of age, and adolescents or children 9 to 14 years of age in study CYD14 where efficacy was illustrated.

So, a large part of the difference is explained by the differences in baseline between the different individuals, even after classifying them as seropositive. We did a similar analysis trying to adjust for magnitude of exposure as well, looking at only individuals that were positive for a single serotype, using the PRNT90 assay. And the findings are consistent with what I've just shown.

So, this slide is only showing individuals that were characterized as monotypic by PRNT90. And again, you see that the bars are relatively consistent between the adult population in CYD28 and the children, 9 to 14-years-old in CYD14, where efficacy was demonstrated.

When you look at the average titer for the four serotypes, the bars are very similar, also

reflected in the ratios between the studies being very close to one. So, our interpretation is that the data is the way it is when it's unadjusted because the baseline is completely different.

DR. LEBLANC: Dr. Edwards, if I may, there's another point -- two more points, actually, I want to make. And I'm not trying to convince you on something; I appreciate your skepticism. You referenced seroprevalence rate in Puerto Rico, and we're talking about 9 through 16-year-old with the 54, 56 percent, and seroprevalence rate in Singapore and that was 18 to 45. If you remember the slides that were shown about the epi, basically every decade you go up in age in a dengue-endemic area, you're going to have a higher seroprevalence in your 20-year-olds, your 30-year-olds, your 40-year-olds.

So, I can't give you the estimate of seroprevalence in the blended age range, 18 to 45 in Puerto Rico. Maybe the applicant would have that number. But it's not going to be 56 percent. It's going to be higher than that. A little bit, perhaps,

closer -- maybe not as high as what you're going to have from Vietnam and India. So that was point one.

And I understand that immunogenicity data in adults in Puerto Rico indicated adult age range would be desirable. I understand that. Another discussion that we've tried to have, because we grapple with these things, is we tried to look at what we call the biological plausibility of there being protection in 18 to 45-year-olds. Just totally set aside any immunogenicity data at all. Look at the disease.

Is there anything about dengue disease that says to us it's significantly different in 18 to 45 than it is from 9 to 16? Or is there anything we know about the immunology that would suggest that immune responses in adults who are dengue-immune at baseline would be different in a substantial way from adolescents? I'm just kind of making an argument. I'm not saying that --

DR. EDWARDS: I guess I'm used to seeing data rather than hypothesizing whether there could be a difference. And the numbers of people in the 18 to

45, I think, was quite small. It was less than 50.

DR. LEBLANC: It is. It is small.

DR. EDWARDS: Less than 50 people in that slide. That's not usually what we see.

DR. LEBLANC: Yes ma'am. Right.

DR. EL SAHLY: Dr. Wharton?

DR. WHARTON: Yeah, I was just trying to jump in on this discussion about the adult data, just with the either question or observation that there were no adults in the safe group -- or there were no adults from whom we've seen data from, the Western hemisphere, and that's not what I'm used to seeing.

DR. EL SAHLY: All right. First, Mr. Toubman, then --

MR. TOUBMAN: Thank you. I, first, have a question for Dr. LeBlanc. It's going back to the number 23 study. I appreciate that you included all three effectiveness studies. The applicant did not. They excluded C23.

My question -- this -- I have questions for you. I also have some questions for either of you.

But this question is about when the chair asked why it was excluded, the answer was, oh, well, they just, for brevity, they just exclude one of the three studies; and we were told that that study was consistent with the other two.

And I'm looking at their own presentation, the 206-page briefing document where they say that the primary estimate of VE at 30 percent was lower than anticipated and did not reach levels of statistical significance since the lower bound of the 95 percent CI was less than zero.

So, in their document, they seem to be saying, no, it didn't confirm. And I understood you to be saying you agreed with what they said in the documents, most of what they said today, which is that the C23 did not confirm effectiveness. I just want to know if that's -- is that your understanding as well? My first question.

DR. LEBLANC: CYD23 did not meet their prespecified criteria for success in efficacy.

MR. TOUBMAN: Thank you. And then my other

questions, which could be for either, and this is concerning -- I mean, this is, I think -- one of the nubs of it is -- and we can take what WHO says, which is in their September position paper, that countries should consider introduction of the dengue vaccine only if the vaccination of seronegative persons can be avoided. So I think everybody seems to be in agreement on that.

So, I have real practical questions about how that would be done, the testing. Again, I don't know who can answer these questions, but the questions are, first of all, is there a test that's actually available? Because we're being asked to approve this thing when the test may not be available.

Second, if there is a test, does it require a patient to come in twice? Meaning, they come in, they get blood drawn, it gets sent out to a lab, that takes several days, and the person has to come back. I represent low-income folks in an urban area, and according to providers in the clinics, it's hard to get people to come in. People in rural areas, it's a

bigger deal. So, I'd like to know -- that's my second question -- if they do have to come in twice. And this is all about concerns of compliance.

So, the third question is, if that's going to be required in order to even know whether the person can get the vaccine, are there any examples anywhere where a vaccine has been approved with the condition that the person has to be tested first which will require them to come in twice? Has that ever been done, to know whether it's even feasible?

And then the last question is this. I heard a reference to a rapid test or something. Is that, in any way, feasible in the near future such as, perhaps, this thing could -- just throwing it out, this thing could be approved subject to such a rapid testing available? I don't know if that's realistic at all. You can answer any or all those questions.

DR. LEBLANC: You've got four questions. I think Dr. Gruber is going to answer that for you.

MR. TOUBMAN: Okay.

DR. GRUBER: Yeah. Go ahead.

DR. FINK: All right. So let me try to address all of your questions. First of all, we don't have a prior example of a vaccine that has been indicated for use contingent upon a test prior to vaccination. So, this, if approved, would be the first example of that.

We did have extensive discussion within the agency, both during the review of this application and even before receipt of the application, about the consequences and the practical issues of the requirement for a diagnostic test to identify individuals who would be indicated for the vaccine, especially considering the current state of available tests in areas where the vaccine would likely to be used.

There were a number of factors that we considered. First of all, as is mentioned in the proposed indication, laboratory-confirmed prior dengue infection could be documented either by current sero-testing, which is what you're talking about, or through the medical record. So, there may be

opportunity to use the vaccine in individuals who have documented laboratory-confirmed dengue infection by history. And you heard a little bit from Gabriela Paz-Bailey this morning about the systems that are in place in Puerto Rico that might enable that type of paradigm.

The second factor that we considered is that, while the options for current sero-testing are currently limited today, there are ongoing efforts to develop new tests, so availability of such tests may change over time. The performance of such tests, specifically the positive predicted value, may change over time.

So, given that, we are charged with assessing the safety and the effectiveness of the vaccine for the intended indication, which is for use in individuals living in endemic areas with laboratory-confirmed prior dengue infection, and we were asking for your advice or your opinion on whether the data presented today do support the safety and effectiveness.

But if we can conclude that the data do support the safety and the effectiveness for that indication, then it might be left up to public health authorities and recommending bodies, such as the ACIP, to determine, under the current conditions or under future conditions, whether the vaccine should or should not be used. So, that was another consideration.

Finally, you heard a little bit from the applicant about benefit and risk considerations given the performance characteristics of currently available tests. We also considered these, including considerations where we took a more conservative approach to what the positive predicted value might be. And we considered that, even if currently available tests were used to identify individuals who are indicated for vaccination and even if the positive predicted value was not 100 percent, that the benefits might still outweigh the risks of the vaccine. So these were the discussions that we had.

MR. TOUBMAN: I appreciate that. I guess that

I'm particularly worried that there is no examples of this ever, and that you're putting physicians in a situation where they're now going to have access to this wonderful opportunity to prevent some of the horrible things we've heard about, and the fact that there's this two-visit requirement and this testing that it might -- people will slip through the cracks, is what I'm worried about.

I understand what you're saying is you analyzed the possibilities that even if that weren't really in place, maybe the cost benefit analysis warrants, but given the other things I've heard, I'm not sure about that.

DR. EL SAHLY: Okay. Dr. Follmann, then Marion.

DR. FOLLMANN: Yeah, my question is more for Dr. Edwards, I guess. I wanted to -- and then maybe have a question for the sponsor. But I think -- was your concern that Puerto Rico might have -- well, had seropositives but their titers might be kind of low, and you're worried about the vaccine efficacy as a

function of titer even in the seropositives?

DR. EDWARDS: Yes.

DR. FOLLMANN: So I was wondering if the sponsor had done such an analysis where you take seropositives, and amongst seropositives, you look at those with very high titers, medium titers, and low titers, all positive, and look at vaccine efficacy for those two or three groups. And if you see similar VEs, I think that would allay Kathy's concern.

DR. GURUNATHAN: So, in Puerto Rico specifically, as Puerto Rico was one of the countries included in the study CYD15, we do have data specific for Puerto Rico that we can show in seropositive individuals and the indicated age population. That's one point that we don't have for the adult region, but for Puerto Rico, we do have specifically data in these children.

So, this is the summary of the data for you, specific for Puerto Rico, and putting it into context with the overall study CYD15. These are seropositive individuals based on the case-cohort analysis from

Puerto Rico. You can see that the vaccine efficacy from month zero to month 25 estimated is 91 percent, which is generally consistent with a high efficacy observed in the overall CYD15 study. But the relationship between vaccine efficacy and PRNT titer after 3 doses -- I'm sorry?

DR. FOLLMANN: I think the issue was at baseline.

DR. GURUNATHAN: So baseline and antibodies and efficacy?

DR. FOLLMANN: Yes.

DR. GURUNATHAN: Yes. So can I invite Dr. Laurent Chambonneau to address that question?

DR. CHAMBONNEAU: Good afternoon. My name is Laurent Chambonneau. I'm a lead statistician in biostatistics of our department in Sanofi Pasteur. We do have a V curve actually taken into account for baseline. I do have one. Here we are.

So, as you can see, actually, the baseline of which titer is a modifier of vaccine efficacy, not as strong as post-dose 3, of course, but still, a

modifier of vaccine efficacy.

DR. FOLLMANN: And just for my reference, what would be -- these are all seropositives, so what would be the cut-off be for seropositivity?

DR. CHAMBONNEAU: Greater than 10. The limit of quantification was 10 for PRNT.

DR. FOLLMANN: Okay.

DR. EDWARDS: It looks like the efficacy is lower for lower pre-titers.

DR. EL SAHLY: Dr. Gruber?

DR. GRUBER: Yeah, I just wanted to come back for a moment, again, to discuss the availability of a rapid diagnostic test that can be used at point of care and provides rapid results and is of sufficient specificity and sensitivity. We had actually -- and I would like to, again, call upon Sanofi Pasteur to perhaps provide the committee here with additional information. Because we've had a couple of meetings with the applicant to discuss efforts made to really develop such tests in the not-too-distant future. Can I invite Sanofi to provide this information and

summarize the discussions that we've had?

DR. GURUNATHAN: Yes, Dr. Savarino can expand on that, I think.

DR. SAVARINO: I'm Stephen Savarino. I'm in Translational Sciences and Biomarkers at Sanofi Pasteur. As you've seen today, we've evaluated the tests that are available in Puerto Rico. We've also done evaluation of the tests that are available in other parts of the world. Similarly to the tests in Puerto Rico, we find that the specificity in detecting prior dengue infection is relatively high -- very high for all these tests, so we think that's a good starting point.

We have, as a company, made a commitment to develop or codevelop a test that's for this specific intended use of determining prior dengue infection. We are in the process of developing a partnership to do that. And our commitment is to -- our expectation is to bring that test forward by late 2020 to FDA registration.

As was pointed out earlier, the tests that are

available in Puerto Rico to the issue of visits, these are available in a laboratory setting, not at point of care. The intent is to develop the point of care test that could be used in a single visit in the right situation.

DR. EH SAHLY: Dr. Myron Levine.

DR. LEVINE: Okay. I had a few more questions on the rapid diagnostic test as well, but I'd like to get there with my understanding of what I've heard today and what I've read today, and all the information that we have as a background to grappling with the questions to the answer.

So, for Americans and a dengue vaccine, one might think of two major possible uses. One would be a traveler, and the other would be those parts of the U.S. population, such as in Puerto Rico and American Samoa, where there is an endemic disease.

This particular vaccine, from all I've heard, we've read, and what we're grappling with in terms of finding the seronegatives, this is obviously not a vaccine a traveler would take. But there is American

population that's at risk. Of that American population, from what I think I heard this morning from the presentation, is that the overwhelming burden of endemic dengue is in Puerto Rico. And within Puerto Rico, we saw one map today where there are different relative burdens in different states or regions of the island.

So, one would think, if the public health authorities in Puerto Rico want vaccine to help grapple with their problem, one would think that they might start looking at their really high burden areas. And they're going to have to grapple with how they identify the folks who are seronegative. The seropositives, they're going to get vaccine. And one would see what would happen in the context of this piece of the American population that's at risk. For the seronegatives, there has to be a good test, and I'll get to that in a moment.

In terms of how to use a non-point of care test, if it's a really good test -- if -- looking at the one, I don't know exactly what these numbers mean

for the Simetics dengue IgG test, but it claims 100 percent sensitivity with the way you all have tested it with whatever the sera are. To me, 100 percent, 99 percent, really high in this context means the ability of a test to detect a true seronegative. And that's what you want, a test with a very high specificity to find the person who is truly antibody negative and, therefore, possibly at risk of getting this vaccine and being in an endemic area.

One would also like to have high sensitivity so that you don't miss people who are seropositive and would gain benefit from the test, because efficacy data and seropositives are clearly in the positive area.

So, one way, just sitting here today, that I could think one could do this with a test where you have to get blood, bring it to a lab, have it done under clear conditions, see who does and who doesn't have a positive test, and then go back and vaccinate for the school-age population, in much of Latin America, school-based immunization is very, very, very

common, much more so than in the U.S.A.

If the Puerto Rican public health authorities wanted to do this, this is one possibility. It's a captive population. That doesn't help the clinic-based. It doesn't -- that's still cumbersome. And I was wondering whether the folks from Sanofi or others around the table have thought of ways to get at the clinic-based. It may be that that will have to wait for a true point of care test. But at least, seems to me, for school-age, it's a captive population and that's a possibility.

I think that testing people with a reliable test beforehand is very important in relation to the use of this vaccine, and I think that Puerto Rico's the big burden. If there are some folks from public health in Puerto Rico here could comment on that, or if CDC can comment for Puerto Rico, that might be helpful.

DR. EL SAHLY: Anyone can comment on that. I must say, though, you're also asking the schools to do diagnostics then vaccinate. So, how -- it's also

unchartered territory there.

DR. LEVINE: Well, send other -- I have lots of experience with school-based immunization with trials that led to FDA licensure of a live oral typhoid vaccine that was outside usual immunization regimens because it required multiple doses with a short interval between doses. And the only way that one could get at the highest risk population was to do school-based immunization. Those trials were done in Santiago, Chile. Chile has a long tradition of school-based immunization.

It may be that, in Puerto Rico, that's totally incompatible. It may be that because of the results of the hurricane that schools are destroyed. I don't know the local suit, but the Puertorriqueños do. School-based immunization works and it can be done, but it requires that the equivalent of a ministry of education and ministry of health have to get together and agree. You have to put aside a day for testing or half a day. You have to put aside a day for immunization. But I think it's feasible.

DR. EL SAHLY: Dr. Kurilla?

DR. KURILLA: Yeah. So I'm struggling with the restriction in the labeling to endemic regions. I think this has some particular issues going forward because if, in fact, other parts of the United States -- Florida, around the Texas area -- I think that, first of all, calling somebody endemic, it's a little subjective.

To me, it's kind of a squishy definition and there's probably going to be a preference by a lot of communities to avoid being labeled endemic. But it's particularly frustrating in light of the benefit risk analysis that was done which would seem, to me, that if you can define the parameters of testing sensitivity and specificity, and you know your seroprevalence data, you can do a risk benefit analysis for a region without having to wait for it to be declared endemic and it might be more flexible, particularly, in areas.

It may be, going forward, that we will see outbreaks such as occur with many of the flavies

(phonetic) in other parts of the world where they come and go. So, we may have a bad year and we might see a lot of dengue in a particular region. And by the time the decision is made to actually do something, it will be over and it won't come back for a few years. So, we may miss opportunities in order to actually implement something that may actually have quite substantial benefits to communities.

DR. EL SAHLY: And Dr. Messer?

DR. MESSER: Yeah. I just also want to offer a counterpoint interpretation of that, which is that, if the goal of vaccination is to drive down disease transmission and overall burden of disease, an effective vaccine actually stands, again, under the language of the question that we're looking at, turning an endemic region into a non-endemic region. And then how do you approach interpreting your vaccination going forward? It can work in both directions.

DR. EL SAHLY: Any additional questions or comments? Dr. Edwards.

DR. EDWARDS: Do we have any serologic data from Puerto Rico? I know it was only, like, 6 percent or 10 percent of the study. But do we have any serologic data from Puerto Rico from the studies that were done?

DR. GURUNATHAN: We do have the data from Puerto Rico. This is the summary of the data for Puerto Rico. What you see here is the average titer across the four dengue serotypes in Puerto Rico, so these are seropositive. Of course, in the study, everybody was 9 years and above. And you can see the titers throughout the study. Starting with the prevaccination titers and what the kinetics of the antibody responses were over time, also compared to the right side with the antibodies that were in the control group.

DR. EDWARDS: Do you have a geometric titer or the main titer? About 600, is that right?

DR. GURUNATHAN: The dot is the average titer across the four serotypes. So, for example, pre-vaccination, we don’t have exactly a number in

this light, but you see that it's somewhere in between probably 100 and 150, and then that goes up to approximately 400 to 500. It has, then, a period of some decay from the picked titer, post-dose 3, and then maintains levels of antibodies after the year 2.

DR. LEBLANC: Is that the data that you were looking for, Dr. Edwards? Or were you looking for some other kind?

DR. EDWARDS: Oh, I think that's helpful to know what the titers are in that population and kind of put it into context of the other titers that we're seeing.

DR. EL SAHLY: Okay. Dr. Monto?

DR. MONTO: Could I ask what the plans for marketing this vaccine are? Are there any plans to market the vaccine in the continental U.S. plus Hawaii, or is this all going to be in Puerto Rico, American Samoa, Virgin Islands?

DR. GURUNATHAN: For distribution of the vaccine, the target at the moment is dengue-endemic areas as defined by the U.S. CDC. So, the

distribution is going to be linked to that designation as a measure to support, actually, appropriate use of the vaccine. But, of course, if the dengue epidemiology evolves, then that will also evolve. And if some areas in Florida or Southern Texas would be designated as dengue-endemic, then, of course, they would become target for distribution as well.

DR. EL SAHLY: Okay. Dr. Offit?

DR. OFFIT: Let me ask this question. Let's suppose, worst case scenario, that we introduce this vaccine, say, with Puerto Rico, and people just decide to use it off-label. They just gave the vaccine without knowing the serological status of the person who was getting vaccinated. Would you increase the incidence of dengue shock syndrome and hemorrhagic fever? Would that increase that incidence or not? And does it depend on how endemic the virus is in a given region? Whoever can answer that question.

DR. GURUNATHAN: Well, it depends on what's the target population. If you're thinking about the balance between those that are benefited by the

protection of the vaccine and those that are put at risk while being seronegatives and vaccinated --

DR. OFFIT: Say you immunize all 9 to 14-year-olds. Period. You don't know their serological status. You're just immunizing them all. What would happen in the instance of dengue shock syndrome, dengue hemorrhage fever?

DR. GURUNATHAN: It decreases. That's basically what they've seen when you do the analysis, regardless of serostatus. It's that you'd basically see that, at the population level, there is a decrease of those outcomes.

DR. EL SAHLY: Dr. Messer?

DR. MESSER: I would follow up that observation, though, with the decrease that was seen was in the context of both preexisting immunity and a naive background. If your background is 100 percent naive, then you're asking an entirely different question.

So, the seroprevalence really does matter with regard to whether you're going to see an increase or

not in disease. You have to have a preponderance of seropositives that you vaccinate if you're going to see the effect that you're looking for. It does not appear to be protective against severe disease at all in naives.

DR. OFFIT: Right. So that gets to the question of how endemic it is in that region, right?

DR. MESSER: That's the issue. Yeah.

DR. EL SAHLY: And here's another question along the line of long-term. Would a decrease in the incidence of disease shift the age upward? In terms -- because we're looking for people to have been exposed, enough people have to be exposed. But are we talking here very long-term. Your immune people, now, are going to get older, right? Older than 9, probability of having been exposed.

DR. MONTO: Yeah, I think that's -- you'd have to model that, because it's pretty hard to judge on the basis of -- given the fact that this is not primary protection.

DR. MESSER: I think this depends, to a

certain degree -- and it's a question for the sponsor -- the degree of uptake that they are anticipating in the population that they are trying to vaccinate. If you vaccinate at a sufficient level to start to generate herd immunity, then I agree with your observation that you're actually going to be increasing the population of naives as you move further, deeper into your vaccine penetration in the population, which is creating sort of an alternate problem.

It's an interesting paradox. This is a vaccine that is actually dependent on the incidence of its disease in order to be further administered in a population. And there is no other precedent for that either, that I can think of. But it's a paradox that we should think about that, as you look for new vaccinees, you must be looking for new cases of dengue that have occurred in the background of your vaccinated population.

DR. KURILLA: But are you really going to increase the dengue-naive population? I mean, what --

DR. MESSER: Well, that -- yeah. So that really depends on the outcomes. It depends on the outcome of the vaccine campaign. If a vaccine campaign is really targeting individuals who personally want to reduce their risk of disease but represent a small portion of the population, you're unlikely to alter herd immunity. But if you alter the number of susceptibles dramatically by doing a blanket vaccine campaign, then you're taking a certain number of susceptibles out.

DR. KURILLA: But I -- no, I don't understand that because we're not preventing dengue infection in people. We're really just preventing serious sequela of the infection. And if there's a sylvatic component to this, then we may not be impacting the presence of dengue in the environment at all.

DR. MESSER: Your point's well taken. I'm using disease as a surrogate for transmissible viremia. There's probably a correlation between the two. As far as sylvatic dengue goes, that is an interesting side question to whether or not you have

sylvatic reservoirs that can reintroduce the vaccine into a population where there is endemic transmission that's been wiped out.

When you look at the phylogenies of dengue viruses worldwide, that appears to happen very, very infrequently. They really have developed to distinct genetic -- phylogenetic lineages between sylvatic and endemic. There isn't a whole lot of spillover. It's certainly a possibility, but it's not a typical path of reintroduction of dengue into susceptible populations in endemic areas.

DR. EL SAHLY: Dr. Bennink?

DR. BENNINK: Yeah. Do you consider additional booster shots or anything else that was out? Because it was 30 months, even in the seronegatives, from there. So, if you almost gave annual or something else, not that you want to do that for compliance and other things to get done. But, if you did that, would the titers stay such that you wouldn't get the effect?

DR. GURUNATHAN: I'm sorry. I lost a little

bit of the trail, so can you repeat? Oh, it was booster. Yeah. I'm sorry.

DR. BENNINK: Yeah. In essence, you're trying to make a seronegative like a seropositive because you boosted it enough times or anything else.

DR. GURUNATHAN: Yeah. The role of the booster is actually being evaluated in three studies. But an important point is that we're not really considering a booster as a rescue for seronegatives. That is because of the risk that was identified, and the recommendations by the program, Independent Data Monitoring Committee, that we no longer vaccinate seronegative individuals.

So, in seronegatives, we think we're not going to be able evaluate a role of booster as a rescue. The role in seropositives, whether it's needed and it will result in sustainable responses, is something that we will evaluate with the data that is being generated.

DR. BENNINK: So, you're really only looking at it in your studies from the seropositive

standpoint? Is that what you're saying?

DR. GURUNATHAN: Well, in two of the studies that we're -- around our way, there were individuals that were enrolled, whether they were seropositives or seronegatives. So, there are some analyses that can be done according to baseline dengue serostatus. One observation from those studies is that distant boosting -- now, this is about five years after the completion of the primary series -- does, at least, restores the antibody levels that are seen after dose 3.

For some serotypes, it increases the antibody levels beyond those seen after the third dose in seronegatives. Much more than that, we cannot say. The study that is evaluating more approximate boosting, which is evaluating boosting at 1 and 2 years, is not going to be able to address the question in seronegatives.

DR. EL SAHLY: Dr. Meissner.

DR. MEISSNER: Thank you. I'd like to go back to the question regarding herd immunity, because I

have been thinking about that in -- I know we're not supposed -- today, we're not going to consider cost effectiveness or qualities. But certainly, herd immunity would be an important consideration when we do get to the point of thinking about custom -- and I had -- my own mind comes to the conclusion that there would not be any herd immunity.

So, I just want to make sure that -- I wasn't quite sure, with that discussion, if everyone agreed. This is not going to reduce the circulation of this virus in the population, number one.

Then, the second point that I want to -- as follow-up to another question that was discussed early, is, it seems to me that on balance this vaccine will reduce the number of severe cases of dengue. But there will be some cases that will probably occur as a result of the vaccine. On balance, there will be fewer cases, but there will still be some. And I don't -- that's a principle of vaccinology that I don't think we've ever gone there before. I'm uncomfortable about that, I must say.

DR. EL SAHLY: Okay. Dr. Messer?

DR. MESSER: I wanted to go back to the boosting question if that's all right. I appreciate that it's being evaluated. I'm curious about what endpoints are being looked at to establish whether or not you need a boost. Is it loss of antibody titer? Is it loss of evident protection in a sentinel cohort? How is it that you're establishing the need for a boost?

DR. GURUNATHAN: Again, the need of a boost in seropositives is not clear. The data that we have when we look at it by time period, perhaps we can show --

DR. MESSER: Figure 30 from your briefing manual.

DR. GURUNATHAN: Yes, I think it's the same one. Yeah. Okay. What this figure shows is data by time period. What you see here is that there is protection maintained throughout the study at different periods of time or windows. But you also see that there is some level of protection decay from

the Active Phase to the rest of the study. The rest of the estimates are consistent overall.

The one thing that is perhaps not captured within this light is the effect that is expected on the unvaccinated population used as a comparator group. Because what is happening in the people that are unvaccinated is that they get progressively exposed to dengue, right? So, the gap in the difference of the protective responses between the vaccine and the control group is expected to diminish over time as the control group gets more and more exposed to vaccination.

So, two factors possibly at play here. One is the decreasing antibody responses that you've seen after the third dose of the vaccine, so that is one factor. The other one is the fact that the control group is acquiring more protective antibodies over time. So, the complement to this figure here is the figure on kinetics of antibody responses.

DR. MESSER: So, before we look at this figure, just with regard to that observation, I agree.

But when you look at your control ends and your dengue ends, the control ends over the last three periods after the Active Phase remain essentially unchanged. But the dengue ends are going up. So, you're actually -- beyond, you're forcing more cases in your Dengvaxia group without much of a change in the control group, where your background immunity doesn't seem to have changed as much in the control group.

DR. GURUNATHAN: Well, the epidemic is not dystopic from year to year. So, I'm not sure that one can look at the incidence in one year and compare to the previous year and expect that they would be identical. All right. So that's one point.

The other point I wanted to make was on the antibody titers pattern, because that is a measure of what are the changes in protective immunity. We can summarize it here with this figure that you have to maybe know the patterns before. There is an increase of the titers from a prevaccination level to post-dose 3, where you can see the peak. Then, there is some level of antibody decay at one and two years, and

after that, the antibody titers tend to remain relatively plateau or stable.

In comparison, what you can see in the control group is that, over time, they start acquiring a higher level of antibodies as expected with exposures to dengue and other flaviviruses over time.

DR. MESSER: Could it be that your year 3 and 4 Dengvaxia group was being boosted by the same virus that boosted the population in your placebo control arm, and that's why you don't see decay?

DR. GURUNATHAN: It could be. We cannot distinguish that. It's a possibility.

DR. EL SAHLY: Dr. Kurilla?

DR. KURILLA: Yeah. So it's pretty clear that you started this program with the expectation of a primary prevention vaccine in seronegatives naive, dengue-naive, which is why you've started with the younger age group. But I'm wondering about what are your long-term plans in terms of older age groups, particularly in light of -- you showed the multitypic efficacy.

And I understand that's a post-hoc analysis and it really wasn't adequately powered, but I was more concerned that two or more dengue infections were going to show no vaccine efficacy at all rather than actually more, but recognizing that some is better than nothing. So, what about the over 45 group? Are you pursuing that in terms of eventual -- for licensure?

DR. GURUNATHAN: So, as I mentioned, we are currently generating data on that age bracket. There are two studies that are ongoing that include that age bracket. They are including dengue-endemic areas, so we expect to have a majority of seropositive individuals from those studies in that age group.

In total, what we're expecting is to supplement what we already have with about between 300 and 400 subjects exposed to the vaccine in that age group, and we'll see what the data indicates to see if it's potentially supportive to going up in the age of indication.

DR. EH SAHLY: Dr. Wharton.

DR. WHARTON: How long is the extended surveillance section of the study going to continue? It was indicated on the figure as going through year 6, but is the plan to continue it beyond that?

DR. GURUNATHAN: No, there's a total of six years. So, those studies have finished a follow-up right now.

DR. EL SAHLY: Oh, so these remain under analysis right now? Year 5 and 6.

DR. GURUNATHAN: So the integrated analyses for those, according to serostatus, is being completed at the moment. And we're expecting to send those analyses to use of the incoming weeks and months.

DR. EL SAHLY: These data are of quite interest, given the waning efficacy over years 2, 3, 4 that you showed in a couple of slides before.

DR. GURUNATHAN: We have actually some of the data with the final data. And first, before showing something that we have not submitted to the U.S. FDA, I want to say that what was included in the analyses that you saw which also was included in the file

before the analyses that we presented by serostatus, included the vast majority of the data for severe and hospitalized dengue.

So, that's -- to be precise, now that we know the number of events that we had through the duration of the studies, we can say that what was included in the file corresponded to 96 percent of the total data. And without maybe having to show specific data, I can tell you that the information, the data, is not measurably changed with the final information.

DR. EL SAHLY: And if there are no additional questions, we will go around the table and ask for final thoughts, beginning with Dr. Nolte.

DR. NOLTE: I don't have any other comments.

DR. EL SAHLY: Dr. Follmann?

DR. FOLLMANN: Final thoughts and then we'll vote, I guess. Okay. So, for me the big issue is this sort of risk benefit thing that was shown, I think, pretty well on the sponsor's slide, CO108, which showed they would prevent 193 cases of severe dengue, right? So this slide -- this is sort of how I

think about bringing it all home and bringing it all together on how we make a decision, but this is just a very precise number.

I was curious about how robust this is to different scenarios, like less seroprevalence; maybe the test isn't as good; maybe when you go to the hospital records, they're not so accurate because it was an old test or someone wrote it down wrong; or I don't know what else.

So, this is a very compelling case here, but I wonder about sensitivity analyses. And I think the sponsor mentioned that, in response to Dr. Offit's question, that even if they just gave everyone in Puerto Rico the vaccine, there would be a net benefit. So, that's some comfort.

Then, I think the FDA also mentioned that -- they had Dr. Fink mention this, that they had done what I would call sensitivity analysis and risk benefit analysis. It seemed like you were suggesting, Dr. Fink, that they gave you some comfort. Under different scenarios, you felt there was sort of a

robust benefit. So, I also did a little calculation myself, looking at 33 percent seroprevalence in here instead of 50 or 56 -- whatever it was. And all of these things are suggesting to me that there's still a pretty big benefit under -- I don't want to say worst case, but kind of a bad case scenario.

This is what's the main thing driving me. This is the main thing I'm thinking about. A minor comment had to do with something that Dr. Kurilla sort of brought up which has to do with bridging, ultimately, so I think they bridge to the older people based on antibody alone, thinking -- but the older people are going to have had more dengue exposures. So, maybe the vaccine efficacy won't be as strong in the older people as it was in the younger people. Even if they have the same antibody titer, maybe the old guys had another one or two infections, so the vaccines won't work as well.

That just is another uncertainty about the extrapolation going on. I don't know if they could look at that as well. So, you know, I have an opinion

and I think additional sensitivity analyses of this type, to make sure it's really solid, would be helpful later.

DR. EL SAHLY: Thank you. Mr. Toubman?

MR. TOUBMAN: Yes, thanks. Again, understand that I don't understand this stuff nearly as much as everybody else in the room. But I have significant concerns that when the question was put to the applicant on would -- if you don't screen at all and just do it, will you reduce disease? The answer is yes.

Well, that's coming from a company that really wants to see this thing approved. It's the same company that did not include the C23 study. And then, when asked about it, gave an answer that wasn't accurate.

Obviously, they have an interest in pushing this. I think Dr. Messer dug down into that and said, well, no, actually, it depends. That's an answer that might make sense; but if you have a very high naive population, then it may not be true. Since I don't

understand this stuff, I look at other people and what WHO said beside the thing I quoted before. They said, "Only if prevaccination screening is not feasible, vaccination without individual screening could be considered in carefully selected areas with recent documentation of seroprevalence rates of at least 80 percent by the age of 9 years."

And Puerto Rico -- it sounds like we've been hearing, like, low 50s. So, even by the WHO standards, you would not even consider doing this without the screening. So, to me, that's critical. It has to be done, though I just think this should be rejected unless there's really strong testing available.

I understand that the slide 107, 108 -- I agree with this nice slide that said, well, here's the benefit even if you don't screen. But this is premised upon 100 percent sensitivity. And they acknowledge that it was before the Zika situation developed, and that reduces those figures. So, there's problems with the test.

The thing I'm focusing most on, though, is how practical is the test? I appreciate Dr. Levine's creative suggestions about school-based testing and all that. But he asked, does anybody have any thoughts of that from Puerto Rico? And I believe there are several people here from Puerto Rico. Nobody volunteered to say, oh, yeah, we're all set to do that; we're great; great shape; things are great economically here; we can just do it. That's not realistic.

So, I would like to propose, frankly -- and this has happened before at one of these meetings is, you know, there's the question and we're given only two choices, yes or no. But we can suggest something in between. And I would like to suggest, in light of the very helpful answer that Dr. Gruber obtained from the applicant that they are working on developing a rapid test for the end of 2020, as I heard it, which is really good news, I would like to propose that we alter the first question, inserting the phrase same-day or point of service laboratory-confirmed.

I would like to see that, because I just don't trust that this test is going to be done. Under the current conditions, particularly in Puerto Rico, I don't think it's going to be done. Therefore, given that we're way below 80 percent by the WHO recommendation, where you wouldn't consider applying this vaccine without the testing, I think we would want to see that kind of protection. Thank you.

DR. EL SAHLY: Thank you, Mr. Toubman. Dr. Munoz-Jordan?

DR. MUNOZ-JORDAN: You have asked a few times about our opinion from Puerto Rico. We are from CDC, and we're not from the Department of Health and we don't know -- I mean, Puerto Ricans have been with considerable infrastructure clinical laboratories everywhere; there's schools everywhere. So, these kinds of things could occur. It's not out of the picture, but I don't know what the plans are in terms of the health authorities in Puerto Rico. And that's the comment I have about that.

In terms of my concerns, I do not see a clear

strategy yet devised by the company, in terms of what is the testing strategy for implementation in Puerto Rico? Is it going to be laboratory-based? My impression, in Puerto Rico, is that clinical practitioners cannot run rapid pace in their offices. Rapid paces have to be run in a clinical laboratory setting.

So, my impression is that they will attempt to do that in a clinical laboratory setting. But it is not clear to me what is the test. What is the study that they plan to do? And with that being so crucial, I agree that that is a concern that I have.

DR. EL SAHLY: Dr. Messer?

DR. MESSER: Yeah. So I'd like to preface my comments by saying -- acknowledging the really heartfelt testimony by the public about how incredibly unpleasant dengue is, and about the incredible need and desire there is for a vaccine in an endemic area, and the incredible amount of work that's gone into developing this vaccine. With regard to the questions, I have a couple of lingering thoughts that

I think I'll just share now.

Question number one, are the available data adequate to support the effectiveness of Dengvaxia for preventing dengue disease? I think there are a lot of data to show that their vaccine is effective in seropositive vaccinees aged 9 to 45. I don't actually take much issue with that. I would make one observation about the available data though. This is a retrospective analysis of a vaccine trial that was designed to test a different question.

Many times, we have been burned in medical field by applying retrospective analyses of data and making prospective assumptions about whether or not that retrospective analysis really reflects what a prospective study that did sero-testing before vaccinating subjects in endemic areas would provide in terms of protection. And that's not what's provided here. That is a standard that we typically look to.

So, really, to ask the question of effectiveness, you would really have to do what's proposed here which is to sero-survey subjects,

vaccinate them with a test, and see how many misses you have and how many people get sick as a result of your misses. I don't know that that is necessarily something that we can solve; but it is, I think, a shortcoming of the available data.

My second question regards boosting and the necessity for boosting. The available data show through year 4, maybe 5, there is efficacy. The durability of that efficacy beyond that time point isn't really established, and I think that boosting and the need for a booster should be formally assessed, frankly. And some endpoints that say whether or not it needs to be done could probably be defined. It doesn't necessarily have to be a barrier today, but it's something that I think is a concern.

Then, the final question I have already was a little bit addressed by Dr. Munoz-Jordan. The available data supporting the safety really depends on the specificity and sensitivity of the assay with a background seroprevalence that makes that assay a good, safe assay for identifying people who are going

to be properly vaccinated and for identifying people who would be at risk.

I think, at the moment, there is a lot of equipoise about the efficacy of the serologic study in Puerto Rico in the context of the recent Zika outbreak and whether or not those tests are capable of really making that delineation in a safe manner. So, I would echo some of the other concerns that you've heard.

DR. EL SAHLY: Thank you.

DR. EDWARDS: Well, I still continue to be concerned about the bridging data and whether the bridging data are adequate to assess and to compare, serologically, the efficacy studies. I don't think we've seen the granularity of that data, and the extent of that data makes me very uncomfortable to say that I can say that we've adequately addressed that. I also have concerns about the safety.

And I think that, if we use a commercially available test that says the patient is seropositive and have sera before that, and then an adverse outcome occurs and, really, the patient gets a false positive

serology that we contribute to disease and there's a severe outcome. I think that there is a lot to be said for the damage that does, in terms of vaccine safety. So, I don't think we have a test that won't allow us to adequately say whether they're seropositive that will be able to be used in the field.

DR. EL SAHLY: Thank you. Dr. Beckham?

DR. BECKHAM: I would reiterate what everyone said about the diagnostic testing today. I don't believe we have a test available to allow us to determine whether or not this would be safe in the field. In the light of that, I have serious concerns.

DR. EL SAHLY: Thank you. Dr. Wharton?

DR. WHARTON: I am impressed with the disease burden in the population that's under discussion in 9 to 45-year-olds and the health system impact that potentially could be prevented by a vaccine. I think there is an opportunity for prevention. And I think the data for the populations that were actually studied in the efficacy studies, it's compelling that

the vaccine does prevent these severe outcomes in these seropositive people.

Others have already commented on the limitations of available laboratory tests, and I think the really significant operational challenge is about routinely having to do a serologic assay prior to vaccination. It's just, operationally, a really difficult thing to do.

I'm also concerned about making a decision on use of a vaccine among adults in Puerto Rico based on data -- somewhat sparse data, actually -- from India and Vietnam. I could understand if it was another country in the region, but it's not. And it's not that I've got a high expectation it would be different. But to not have anything for a decision like this just really -- I'm really uncomfortable with that.

DR. EL SAHLY: Thank you. Dr. Swamy?

DR. SWAMY: Yeah. So I think I'm somewhat similar to things that have been said, but I struggle with the fact that it's not dissimilar when we think

about a screening test. We don't go out and screen people for something we don't have a treatment for. So, now we're sort of looking to approve a treatment that we don't have validation -- that we have a screen for that we can use. It seems a little backwards.

The other fact is that, generally speaking, when we go to disseminate something based on clinical trials, we do it similarly to the eligibility criteria of the trial. And we're being asked to approve something that's based on things that were not used in the trials.

There was not a screening and then treatment modality in the trials. So, I'm not disputing the data and that there certainly appears to be benefit in those who are seropositive, but those were subpopulations of the larger population.

I think, from the safety perspective, we're looking at thousands upon thousands of individuals who got the vaccine. But now, we're taking that subpopulation of people to, then, treat. So, those are my concerns.

DR. EL SAHLY: Thank you. Dr. Bennink?

DR. BENNINK: Yeah. I don't have a lot to add, I would say, in terms of what has already been said. I think if I was focusing a little bit on something, again, I would say something about the boosting because of the drop-off, to some extent, of even the ones.

But even whether it could help in the case for the -- if there was testing or something and the seronegatives somehow got vaccinated, whether that actually would make a difference. And then you wouldn't have those negativities that you see otherwise. So, I think there's lots of reasons here at that.

DR. EL SAHLY: Thank you. Dr. Kurilla?

DR. KURILLA: Yeah. Two points. I think it needs to be recognized that we're really talking about a very novel application of vaccine technology that really hasn't gotten a lot of attention, and that is not trying to prevent disease in a naive population but actually treating people who have already been

infected, and not in a therapeutic sense but in another manner of preventing downstream potential disease. It's true that the original development and design of the studies was not really done that way. It was really what came out of the data. So, I think we need to be a little cautious.

Because, while it's certainly breaking new ground and potentially offers a lot of applications in potentially other disease areas -- whether this can be expanded even beyond just limited to dengue serotypes but potentially maybe even other types of flavies and a lot of other related viral families -- there's a lot of potential here. But I think we need to be a little cautious.

The second point is in line with what a lot of other people have said, is I think that the diagnostics are really absolutely critical here. And I think it is incumbent to really define not just what's out there already, but really to define what the sort of minimum sensitivity and specificity combined with the available seroprevalence data that

would really allow public health officials, in general, to make a decision as to whether this is a vaccine they want to implement in their region, as to whether it's going to have an overall effect on the population.

DR. EL SAHLY: Thank you. Dr. Levine?

DR. LEVINE: I agree with a number of the points colleagues have made around the table. Looking at the specific question that we grapple with, on the age range, I am also sensitive to the point that Kathy Edwards made about the serological bridge and the leap. And since there are some other -- I think limiting the initial use approved target for this vaccine to the school-age group, I think, is the way to go and not depend upon the bridge because there's so many questions on the serology.

In terms of the safety profile for a population with a known endemic burden, I am convinced that where there's a fair amount of disease where they tested the vaccine -- that's where you go to test the efficacy of a vaccine -- clearly, it brought down

disease and it was, then, dissected, such that it worked better in people who were seropositive. But not only did it not work as well in the seronegative, there was a safety signal, such that we wanted to identify those people.

I know the WHO grappled with this and there's a great editorial in the New England Journal by Lisa Rosenthal called "Trolleyology and the Dengue Vaccine Dilemma." If anybody hasn't read it, you should read it. It's great. Basically, what it gets at, if I can take 15 seconds, if a trolley --

DR. EL SAHLY: Thirty. Thirty seconds.

DR. LEVINE: Okay. If a trolley is moving towards a group of four or five people and is going to hit them, and there's a split in the tracks, and there's one person standing along the other track, and there is a bystander looking at this and has the chance to pull a switch that would change the train, what is the ethical thing to do?

Do you save the four people but essentially kill the single person? That's kind of the dilemma

that we deal with, is getting the public health benefit without harming. And that's where the test comes in. I think the test is so important.

I can't grapple successfully with the Zika. But take the Zika away, and what I've seen about one of these tests says that a test is possible. And to me, to have the opportunity to look at this vaccine in the school-age group, post-licensure, and to learn and gain, to get the answer rather than to assume or guess or model informally, I think, is a way to go. Ultimately, one would want a really good test.

I can't technically speak to the Zika, just looking at what was tested here. So, to me, it's all about the test. Maybe we need some more information. And the other point is limited to the school-age kids, and then I think we should look post-licensure. We learn so much post-licensure with those caveats.

DR. EL SAHLY: Thank you. Dr. Meissner?

DR. MEISSNER: Thank you. The first point is that I thought the presentations this afternoon were terrific, by the sponsor. And I appreciate all the

effort that's gone into this. I think, as has been said, the burden of disease is quite real and there is a lot of suffering from dengue, and this vaccine offers an opportunity to reduce much of that illness. And I think that's what we all want. The problem, I guess, that I'm wrestling with is one of the principles of administering vaccines is that everybody has an opportunity to benefit.

But, with this and from the data that's been presented by the sponsor, there will be, clearly, a reduction in the amount of disease. But there will also be a few cases that can be traced back to the vaccine. And I'm uncomfortable with that. I think that even when there is a good test, there is still going to be errors in testing. And there is with every test. It will be misinterpreted or there will be problems.

So, this vaccine may result in an undesirable outcome. And I don't -- on balance, it will be wonderful. But I worry about the situation where there is going to be complications from the vaccine

itself.

DR. EL SAHLY: Okay. Thank you. Dr. Monto?

DR. MONTO: When you come next to last, there's very little to say that hasn't been said before. So, I'm just going to focus, first, on my shared discomfort about the bridging data. Because I thought more data could be given to us. I'm not so concerned about the region of the world but the numbers, which were relatively small. I'm just going to focus on the questions.

And I hate to hear that we're going to kick the can down the road in terms of the implementation of the program; but if we look at the question we are asked, it says, "Living in endemic areas and laboratory-confirmed previous dengue." I'm willing to vote on that, assuming that we can confirm dengue with a test, which is going to be at least reasonably sensitive and specific.

I hate to take tests that are being advertised with certain sensitivity and specificity data without getting independent confirmation. So, I think we need

to look at the question we're being asked.

DR. EL SAHLY: Okay. Thank you. Dr. Offit?

DR. OFFIT: So we have a disease that we know, as expressed by the people who came up to the microphone, that is common, that is associated with -- at least, in endemic areas, is associated with suffering and hospitalization and death. We have, clearly, in hand, a technology that can prevent that if used the right way. So, that becomes the question, if used the right way. But what's incumbent upon us now is to be able to make sure that we select away from a seronegative population.

Now, I've seen one case of dengue in my life. It came up from Puerto Rico. It took me a little while to figure it out. I think that physicians in Puerto Rico would've had far less trouble figuring out than I did. I mean, they're used to seeing this. So, in terms of who's been clearly symptomatically infected in the past, they'll know.

So then the question becomes someone who is asymptomatically or less symptomatically infected, and

now we rely on a serological test, which are not perfect. They have -- their specificity and sensitivity's only so good. But still, you're largely going to select that for a population that likely has been infected before.

So, do I think, when balanced, this will do far more good than harm? Yes. And unlike -- I mean, it's not like we haven't, in the past, used vaccines in this country which have been harmful.

In the oral polio vaccine, it was known to be a cause of vaccine-associated paralytic polio for decades. And we continue to use it in this country, even though it caused six to eight cases of vaccine-associated paralysis every year until we finally got away from that in the late 90s, early 2000s.

And there was another option there, which was the inactivated vaccine. But here, you have the option, actually, of just making sure that someone has been previously infected, either clinically or serologically.

So, therefore, it becomes incumbent upon us to

do everything that we can do when we introduce these vaccines into regions not only like Puerto Rico, but presumably, there's an interest in going to Vietnam and India and Singapore, et cetera, to make sure that it's very clear what the purpose of this is, which is we have to use it the right way.

So, I think instead of backing away because it's difficult to use it the right way, I think we should just be -- double our energies to make sure it is used the right way. So, that's how I see it. Thanks.

DR. EL SAHLY: Thank you. In light of the discussions of today, I'm considering the questions that we are asked. There are concerns that were already voiced, namely the absence of a reliable test for use right now. Right after we vote, we cannot recommend a test or tell the doctors, "Go use that test," given that the seropositivity was imputed. And I meant to ask that question, but there were so many bright questions being asked, I probably ran out of time.

The seropositivity was imputed 13 months after dose 1 without -- and we were not given data on what was going on with the circulation of dengue in those 13 months and in that particular region. Then, the absence of a correlative protection, we were asked to bridge data to adults based on really small numbers.

So, all of the above are causes for concern regarding this particular vaccine and the content of the questions being asked.

Dr. Gruber, do you have any final comments or instructions?

DR. GRUBER: Well, we appreciate the lively discussion and suffice it to say we had a lot of very similar discussions internally. So, we understand that this has been a very difficult and complex topic that we brought before you. I think what we want to do, and I just had some initial exchanges to my colleagues, I don't know where they arrived at. I'm going to have to verify before I suggest a path forward here. Okay?

DR. EL SAHLY: Sure. Thank you.

MR. TOUBMAN: In the meantime, can I ask a question about the questions?

DR. EL SAHLY: Wait until she comments.

MR. TOUBMAN: Okay. Thank you.

DR. GRUBER: Thank you. That's what I thought. I think what we'd like for the committee to do is really vote on question one the way it is currently phrased. And depending on the outcome, we may have another question that we actually prepared in anticipation of these discussions.

DR. EL SAHLY: Okay. Can you put the question on the screen please? To read the question: Are the available data adequate to support the effectiveness of Dengvaxia for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3, and 4 in persons 9 through 45 years of age with lab-confirmed previous dengue infection and living in endemic areas? Please vote on your microphone yes, no, or abstain.

MR. TOUBMAN: Excuse me, can I ask a question? The question I had, it was premised upon the comment by the fourth person -- the last public speaker who

raised a concern that adverse events did not include getting sick from dengue. And I don't know if that's accurate. I think I've seen it different ways.

But in terms of the questions, when we're talking about the clear -- it's confirmed for sure that there are some people who have adverse events in terms of hospitalization and severe disease. Is that affecting effectiveness or is that safety? That's my -- I just wasn't sure which way it was.

DR. EL SAHLY: The way it was presented today, hospitalization and virologically-confirmed disease, that's relating to effectiveness. Hospitalization from dengue, confirmed disease from dengue.

MR. TOUBMAN: And including from the vaccine as well? It factors in people who seem to have gotten it -- or increased risk of it because of exposure to the vaccine.

DR. EL SAHLY: Well, that probably is safety, but most of the data presented was on effectiveness today.

MR. TOUBMAN: Okay.

DR. EL SAHLY: Can you please go and vote?

DR. GRUBER: Can I comment? I'm sorry. Before everybody votes.

DR. EL SAHLY: Yes. Go ahead.

DR. GRUBER: I think the concern expressed by Mr. Toubman -- we would like to really have this addressed under question two, because there we're asking specifically about the safety of the vaccine. And what we have to really keep in mind there is this clearly identified safety signal that was observed when seronegative individuals received the vaccine.

And in that regard, I've asked can we get a vote on question one? And then we would adjust potentially. But I think -- in light of this comment just made, I think we would like to hear your votes on questions one and two as currently phrased before we continue.

DR. EL SAHLY: Okay. I probably misunderstood your question as what was presented. Okay.

MS. HUNTER-THOMAS: Did everyone vote on question one?

DR. EL SAHLY: Okay. The votes are in. One more. Someone didn't vote. Yes, please.

MS. HUNTER-THOMAS: So, it was a total of 14 votes. 6 indicated yes to question number one, that we have 1 abstained, and we have 7 no's. So, now we're going to read the results individually.

Dr. El Sahly, no. Dr. Swami, no. Dr. Wharton, no. Dr. Beckham, no. Dr. Edwards, no. Dr. Messer, yes. Mr. Toubman, yes. Dr. Follmann, yes. Dr. Kurilla, no. Dr. Levine, no. Dr. Meissner, yes. Dr. Monto, yes. And Dr. Offit, yes. Bennink is the abstained. Thank you.

So, now, do we go to question number two as Dr. Gruber --

DR. EL SAHLY: Going to question number two: Are the available data adequate to support the safety of Dengvaxia when administered to persons 9 through 45 years of age with lab-confirmed previous dengue infection and living in endemic areas? Please vote yes, no, or abstain. Are all the votes in?

MS. HUNTER-THOMAS: So we have a total of 14

that have voted; 7 voted yes, zero abstains, and 7 no's. So we'll read the results individually.

Dr. El Sahly was a yes. Dr. Swami, no. Wharton, no. Beckham, no. Edwards, no. Messer, no. Toubman, no. Follmann, yes. Bennink, yes. Kurilla, yes. Levine, yes. Meissner, yes. Monto, no. Offit, yes. Thank you.

DR. EL SAHLY: Dr. Gruber, additional questions or instructions?

DR. GRUBER: Yeah. We have to throw up the additional questions that we have prepared. And I don't know if this can be transmitted from -- can we hook up your computer? Give us a minute, okay? Because we need to display it.

DR. EL SAHLY: Okay. Here's question three. Are the available data adequate to support the effectiveness of Dengvaxia for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3, and 4 in persons 9 to less than 17 years of age with lab-confirmed previous dengue infection and living in endemic areas? Please vote yes or no.

MS. HUNTER-THOMAS: Okay. So we have a total of 14 votes. 13 indicated yes, zero abstains, and 1 no. So, we'll read the votes results individually.

The one no is Dr. El Sahly. Dr. Swami is yes. Wharton, yes. Beckham, yes. Edwards, yes. Messer, yes. Toubman, yes. Follmann, yes. Bennink, yes. Kurilla, yes. Levine, yes. Meissner, yes. Monto, yes. And Offit, yes. Thank you.

DR. EL SAHLY: Okay. Well, thank you all for this very lively and engaging --

MS. HUNTER-THOMAS: Oh. Oh, there's another question. Sorry.

DR. EL SAHLY: Okay. You said -- I thought one question. Okay.

DR. GRUBER: I'm sorry. That was -- but in light of the vote, we had these two additional questions.

DR. EL SAHLY: Two additional. Okay.

DR. GRUBER: Yes. Sorry.

DR. EL SAHLY: Are the available data adequate to support the safety of Dengvaxia when administered

to persons 9 through less than 17 years of age with lab-confirmed previous dengue infection and living in endemic areas?

MS. HUNTER-THOMAS: Okay. We have 14 votes submitted and we'll read -- it's a total of 10 yes, zero abstained, and 4 no. Now, I'll read the results individually.

Dr. El Sahly, yes. Swami, yes. Wharton, yes. Beckham, no. Edwards, no. Messer, no. Toubman, no. Follmann, yes. Bennink, yes. Kurilla, yes. Levine, yes. Meissner, yes. Monto, yes. Offit, yes. Thank you.

DR. EL SAHLY: Any additional questions or instructions from Dr. Gruber?

DR. GRUBER: No. I thank the committee for the additional votes and, again, appreciate how difficult the discussion was. We hope we can move forward now with our review and the discussions with the applicant. Thank you.

DR. EL SAHLY: Thank you to all.

MS. HUNTER-THOMAS: This meeting is now

adjourned. Thank you all. Have a great evening.

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