

**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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1 **CALL TO ORDER/INTRODUCTIONS**

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

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

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

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

1 Program in the United States.

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

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

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

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

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

1 -- or Medicaid, I should say, more specifically.

2 Thank you.

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

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

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

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

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

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

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

4 **DR. MONTTO:** Morning, I'm Arnold Monto,
5 Professor of Epidemiology at the University of
6 Michigan School of Public Health, interested in
7 infectious disease epidemiology.

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

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

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

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

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

8 **ADMIN ANNOUNCEMENTS, COI STATEMENT**

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

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

1 coordinating this meeting.

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

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

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

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

21 The Food and Drug Administration is convening

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

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

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

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

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

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

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

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

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

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

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

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

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

21 Dr. Anna Durbin, is a Professor in the

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

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

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

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

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

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

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

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

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

4 **INTRODUCTION/PRESENTATION OF QUESTIONS**

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

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

1 Presentations.

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

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

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

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

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

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

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

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

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

14 Dengvaxia is supplied as a vial of lyophilized
15 powder, which contains each of the four CYD virus
16 components, which are reconstituted at the time of use
17 with the accompanying vial of diluent, which is 0.4
18 percent sodium chloride. After reconstitution, each
19 0.5 milliliter dose of Dengvaxia contains 4.5 to 6.0
20 log 10 cell culture infectious dose 50 of each of the
21 different CYD viruses indicated here. Dengvaxia is

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

3 The sponsor submitted their biologics license
4 application with the following proposed indication.

5 Dengvaxia is a vaccine indicated for the prevention of
6 dengue disease, caused by dengue virus serotypes 1, 2,
7 3 and 4, in individuals 9 through 45 years of age,
8 with laboratory-confirmed previous dengue infection
9 and living in endemic areas. Previous dengue
10 infection can be accessed through a medical record of
11 a previous laboratory-confirmed dengue infection, or
12 through current serotesting.

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

21 Sanofi Pasteur submitted their BLA for

1 Dengvaxia on August 31 of last year. The clinical
2 package includes data from three randomized, placebo-
3 controlled, observer-blind clinical endpoint studies,
4 which evaluated the vaccine safety and the vaccine
5 efficacy in subjects 9 through 16 years of age. These
6 studies are CYD15, which enrolled subjects 9 through
7 16 years of age living in Latin America; that included
8 over 1300 subjects living in Puerto Rico. Study
9 CYD14, which enrolled subjects 2 through 14 years of
10 age living in Asia Pacific. And CYD23, which enrolled
11 subjects 4 through 11 years of age living in Thailand.

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

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

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

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

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

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

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

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

11 **CLINICAL CONSIDERATIONS OF DENGUE**

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

21 I'm going to discuss just a little bit about

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

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

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

21 Dengue can have a mortality rate that is very

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

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

1 classification system.

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

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

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

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

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

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

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

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

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

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

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

1 vascular leak syndrome.

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

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

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

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

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

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

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

8 You have to monitor the patient very carefully
9 for defervescence and warning signs, because this is
10 critical to recognizing progression of dengue into
11 vascular leak syndrome, or the critical phase.

12 Defervescence generally occurs on days three to eight
13 of illness, and it's defined when the body temperature
14 drops to less than 38 degrees Celsius and remains
15 below this level. Again, we say that because there
16 can be a saddle back fever where it may initially drop
17 below 38 degrees Celsius, but then go back up.

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

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

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

12 Generally, you develop a low white count about
13 24 hours before the platelet drop. I will say you can
14 see low white count and low platelet count, even in
15 people who do not progress to the critical phase.

16 It's very important to monitor pulse pressure, and
17 increasing hematocrit, as proxies for vascular leak.
18 And when you're on the wards in dengue endemic areas,
19 they go around and measure the hematocrit every few
20 hours, just with generally a capillary tube and a
21 microcentrifuge, just to monitor for signs of rising

1 hematocrit, which is indicative of a vascular leak
2 syndrome.

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

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

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

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

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

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

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

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

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

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

1 recover over several days to a week.

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

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

1 been hospitalized for several days.

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

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

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

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

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

1 petechiae to form in that area.

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

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

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

1 subcutaneous space, and form the bullae there.

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

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

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

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

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

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

21 The 1997 case definition really was helpful in

1 terms of classifying cases as dengue, dengue
2 hemorrhagic fever, or dengue shock syndrome. So from
3 an epidemiological standpoint, we were able to have a
4 better accounting of the severity of disease, with the
5 1997 case classification system. There were problems
6 with the 1997 case classification system, which I'll
7 go through, and which led to the 2009 reclassification
8 system. What's important to know about the WHO 1997
9 case definition for dengue, is that all four
10 components must be present to have a definition of
11 dengue hemorrhagic fever.

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

1 bleeding criteria.

2 You then had to have thrombocytopenia, or low
3 platelet count, which was defined as less than
4 100,000. And you had to have evidence of plasma
5 leakage due to increase vascular permeability. And
6 that was manifested by one or more of the following:
7 either a rise in hematocrit, of greater than or equal
8 to 20 percent above average for age, sex and
9 population. If you didn't have a baseline hematocrit
10 with which you could compare.

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

21 To meet the definition of dengue shock

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 20,000. And it's generally not recommended that
2 platelet infusions be given. It hasn't been shown
3 that they're all that effective. Of course, if
4 somebody is bleeding, then platelet transfusion may be
5 indicated. But in general, platelet transfusions
6 aren't given, even for people with very low platelet
7 count.

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

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

1 just a bit.

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

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

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

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

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

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

1 neutralize it, it won't inactivate the virus.

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

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

21 If treated properly, it can have a very low

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

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

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

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

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

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

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

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

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

12 But in other parts of Brazil, where more
13 recently you've had new serotypes come in, you'll see
14 severe disease or hospitalizations for severe disease,
15 in adults, young adults, even up into the 30s, 40s or
16 50s.

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

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

10 **DR. EL SAHLY:** Dr. Meissner.

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

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

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

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

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

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

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

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

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

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

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

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

11 **DR. EL SAHLY:** Dr. Follmann.

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

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

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

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

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

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

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

11 **DR. EL SAHLY:** Dr. Kurilla.

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

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

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

6 **DR. EL SAHLY:** Is it serotype specific?

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

10 **DR. EL SAHLY:** Dr. Bennink.

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

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

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

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

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

19 **DR. DURBIN:** Right.

20 **DR. EL SAHLY:** Any other questions? Okay.

21 Thank you so much.

1 **DR. DURBIN:** You're welcome.

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

7 **THE EPIDEMIOLOGY OF DENGUE**

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

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

21 So what is the global epidemiology of dengue

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

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

21 So infections can occur with any of the four

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

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

12 In terms of the clinical spectrum, about 25 to
13 35 percent of infections are symptomatic. And we
14 heard from Dr. Durbin, the classical symptoms that
15 include abrupt onset of fever, headache, retro-orbital
16 pain, and muscle and bone pain. That's why it's
17 called breakbone fever. And often there is a rash.
18 Of those symptomatic, between 10 to 20 percent are
19 hospitalized, and severe dengue happens in one to five
20 percent of symptomatics.

21 This is a study by Messina and co-authors that

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

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

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

21 This slide is to emphasize that dengue

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

8 The y-axis in the graph shows the proportions
9 seropositive, and you can see in the x-axis age. And
10 I want you to focus on the yellow line, that is 2004,
11 and the dark blue line, that is 2015. So while 50
12 percent of children were seropositive by age 4.5 in
13 2004, 50 percent seroprevalence is only reached by age
14 11, in the dark blue line, in 2015. So determination
15 of the optimal age to start vaccination needs to take
16 into consideration the changes in the force of
17 infection over time.

18 So we heard a lot about severe dengue from Dr.
19 Durbin, but I want to highlight that of the estimated
20 \$8.9 billion global financial burden of dengue, most
21 of this, \$5 billion, come from hospitalizations and

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

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

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

1 titers.

2 For dengue hemorrhagic fever and English shock
3 syndrome, they showed a hazard ratio of seven,
4 compared to having no previous dengue infection, that
5 is the dotted reference line. And the cumulative
6 hazard was 11 percent for that middle range antibody
7 that in this case is from 1:21 to 1:80, compared to
8 1.6 for dengue naïve children and 1.5 for children
9 with high titers. So having no antibodies, or a lot
10 of antibodies, is better than just having a little
11 bit.

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

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

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

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

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

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

13 31 companies have marketed 56 dengue IgG ELISA
14 tests, and at least seven rapid tests; but none of
15 these tests are approved for their use in the United
16 States. Performance is reported only among a subset,
17 among 14 tests, including 10 ELISAs and four rapid
18 tests. And the sensitivity ranges from 33 percent to
19 100 percent, and specificity from 92 to 100 percent.

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

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

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

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

1 cross-reactivity.

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

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

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

1 lower.

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

7 In a higher prevalence setting of 80 percent
8 seroprevalence that is presented here, the positive
9 predictive value is higher, 97 percent; and then only
10 3 percent of persons testing positive, would be
11 misclassifications, and would actually be false
12 positives.

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

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

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

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

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

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

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

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

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

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

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

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

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

8 For each of the territories, I'm going to
9 present the number of cases and the rates per 1,000
10 persons, for the most recent years when there was
11 transmission. So the most recent years when there was
12 transmission in Puerto Rico, is 2010, and 2013.
13 Passive surveillance data from Puerto Rico, from 2010
14 to 2013, shows that the highest number of cases, and
15 the highest rates are in the 10 to 14 age group, and
16 15 to 19 age group.

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

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

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

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

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

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

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

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

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

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

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

7 So the immunization registry covers both
8 children and adults, and it's pretty complete. About
9 70 percent of the private providers are reporting, and
10 this is increasing, and they have 100 percent coverage
11 of the VFC providers.

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

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

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

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

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

3 Again, this is data from passive surveillance
4 showing confirmed and probable cases in the upper
5 graph, and hospitalizations by age in the lower graph.
6 And you can see a pattern, similar to Puerto Rico,
7 with higher number of cases and rates among the 10 to
8 14, and 15 to 19 years of age.

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

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

1 Several counties in southern and central
2 Florida have reported locally acquired cases. In 2009
3 and 2010, nearly 90 cases were reported. And in 2013,
4 a locally acquired outbreak took place and there were
5 21 cases reported.

6 There was a serosurvey done in Martin County
7 in 2013, where they reported 2 percent being IgM or
8 PCR positive; and also the same year in Key West, with
9 4 percent IgM positive and 7 percent IgG positive.
10 And then after 2013, there have been just a handful of
11 locally acquired cases reported.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 there was also evidence of fluid overload.

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

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

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

21 **DR. EL SAHLY:** Dr. Kurilla.

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

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

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

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

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

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

4 **DR. EL SAHLY:** Dr. Levine.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

13 **DR. EL SAHLY:** Mr. Toubman.

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

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

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

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

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

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

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

21 And I just have to clarify that this is sort

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

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

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

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

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

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

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

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

3 **DR. EL SAHLY:** Dr. Fuhrman,

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

11 And so, we'd like to, you know, have the
12 vaccine rolled out in places that are very high
13 seroprevalence. But we're asked about putting it in
14 endemic areas, and so I was wondering if you or
15 someone had thoughts about what does endemic mean in
16 terms of seroprevalence? Would it mean between 50 and
17 100? Would it mean between 30 and 80, or 30 and 100?
18 So, to me the relevant issue seems seroprevalence, but
19 the charge is for endemic.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 group, despite the fact that it's sort of the 10 to
2 19, the ones with the highest numbers

3 **DR. EL SAHLY:** Dr. Bennink.

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

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

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

20 **DR. PAZ-BAILEY:** Yes.

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

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

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

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

1 challenge during the Zika epidemic.

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

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

20 **DR. EL SAHLY:** Dr. LeBlanc.

21 **DR. LEBLANC:** Just two comments with regards

1 to your question about seroprevalence and on a
2 countrywide level. It's my understanding -- tell me
3 if I'm getting this wrong -- that as of September
4 2018, when the World Health Organization SAGE
5 committee, considered the most recent data, they most
6 strongly recommended the laboratory confirmation of a
7 prior dengue infection should be the predicate upon
8 which this vaccine is given.

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

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

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

5 **DR. EL SAHLY:** Any additional comments or
6 questions to Dr. Paz-Bailey? Thank you, Dr.
7 Paz-Bailey. Thank you so much. Next, we will break
8 for let's say 10 minutes and reconvene at around
9 11:05. Thank you.

10

11

BREAK

12

SPONSOR PRESENTATION

13

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

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

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

4 Our proposed indication is for the prevention
5 of dengue disease caused by dengue virus serotypes 1,
6 2, 3, and 4 in individuals 9 through 45 years of age
7 with a laboratory-confirmed previous dengue infection
8 who are living in endemic areas. Previous infection
9 can be assessed through medical record of a previous
10 laboratory-confirmed infection or through current
11 serotesting. Dengvaxia is administered subcutaneously
12 in a three-dose schedule at six-month intervals.

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

21 Our immunogenicity studies support a level of

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

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

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

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

12 The Dengvaxia global clinical development
13 program was initiated in 2002. The program includes
14 26 completed clinical studies, with more than 41,000
15 subjects enrolled in 16 countries. The U.S. has been
16 part of all phases of our clinical program. This has
17 included Puerto Rico. More than 28,000 subjects have
18 received Dengvaxia in our clinical trials, with
19 approximately 21,000 subjects 9 through 45 years, the
20 age group specified in our proposed indication.
21 Dengvaxia is currently licensed in 19 countries and

1 the European Union.

2 Shown here is the agenda for our presentation.

3 Next, Dr. Stephen Thomas will discuss the unmet

4 medical need for a dengue vaccine in the United

5 States. Dr. Sanjay Gurunathan will then present our

6 efficacy results. Dr. Cesar Mascareñas will present

7 our safety results. Dr. Corinne Jouquelet-Royer will

8 present our risk management plan. Dr Su-Peing Ng

9 will present the benefit-risk assessment and close our

10 presentation. And finally, Dr. Carlos DiazGranados

11 will moderate the Q&A session. Our external expert

12 has been compensated for his time and travel. We also

13 have a number of other experts here to answer your

14 questions. I will now turn the lectern over to Dr.

15 Stephen Thomas.

16 **DR. THOMAS:** Thank you, Dr. Greenberg. Good

17 morning. My name is Stephen Thomas, and I'm the Chief

18 of the Division of Infectious Diseases and a Professor

19 of Medicine and a Professor of Microbiology and

20 Immunology at the State University of New York,

21 Upstate Medical University. I have worked on dengue

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

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

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

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

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

13 Dengue infection can also disrupt the
14 coagulation system, resulting in significant bleeding.
15 If the intravascular volume is not properly
16 maintained, organ perfusion declines, and organ
17 dysfunction and failure can ensue, with the potential
18 for shock and death.

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

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

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

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

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

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

10 Moving on to the more specific impact of
11 antibody titers, in this graph, we see PRNT50 antibody
12 titers present before a second infection on the x-axis
13 and the probability of hospitalization on the y-axis.
14 As shown in the blue curve, there is a low risk of
15 hospitalization in those without any antibody,
16 depicted by the open circle, and an even lower risk in
17 people with high antibody titers, over 100. However,
18 as the curve shows, those with antibody titers between
19 1 and 100 experience a significantly higher risk of
20 hospitalization. Similar findings were seen in a
21 cohort in Latin America.

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

8 While other communicable diseases have seen
9 improvement in mortality over time, dengue has not.
10 This table, from the Global Burden of Disease study in
11 2017, shows that all age deaths from dengue increased
12 by 65 percent in the ten-year period from 2007 to
13 2017. When adjusted for age, the increase over the
14 same period was 40 percent. Additionally,
15 unrecognized deaths due to dengue may be common. In a
16 study from Puerto Rico, there was a two to three-fold
17 higher dengue mortality rate compared to previous
18 reports.

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

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

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

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

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

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

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

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

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

14 In addition to persistent endemic transmission in
15 Puerto Rico, indicated by the lighter bars, the
16 country has periodic epidemics, indicated by the
17 darker bars. This figure shows passively collected
18 suspected dengue cases reported in Puerto Rico from
19 1986 to 2013. The epidemic threshold is just below
20 10,000 cases per year.

21 Numerous factors contribute to these patterns,

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

21 This forest plot displays the relative risk of

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 *Medicine.*

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

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

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

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

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

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

16 We also showed vaccine efficacy against
17 symptomatic dengue for each of the four serotypes
18 during the active phase in seropositive subjects 9 to
19 16 years old. This complements the protection
20 observed against hospitalized dengue for each of the
21 four serotypes during the five to six years of

1 follow-up.

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

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

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

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

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

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

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

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

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

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

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

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

21 Thank you. Next, I will invite Dr. Cesar

1 Mascareñas to the lectern to review our safety
2 findings.

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

11 In our clinical development program, more than
12 27,000 subjects received at least one injection of
13 Dengvaxia. The majority came from the Phase 3 trials,
14 Studies 14 and 15, but the database also includes
15 subjects from other studies as well. Our full safety
16 analysis is composed of subjects in our targeted age
17 range, more than 19,000 subjects 9 to 17 years of age
18 and about 13,000 subjects 18 to 45 years of age.
19 Reactogenicity was evaluated in approximately 4,300
20 subjects, and more than 2,300 subjects in the safety
21 set were seropositive.

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

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

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

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

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

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

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

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

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

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

1 onset was compatible with the vaccine effect.

2 Importantly, no anaphylactic reactions were reported.

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

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

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

1 less than 1 percent.

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

9 The frequency of unsolicited adverse events was
10 also higher in Dengvaxia compared to control.
11 However, these medical conditions are commonly seen in
12 this population. They were mostly classified as Grade
13 1 or 2 and lasted between one and seven days.

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

1 investigator but not by the sponsor.

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

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

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

1 evaluated in more than 4,300 subjects.

2 The rates of some solicited symptoms were higher
3 in Dengvaxia than in placebo, with low rates of Grade
4 3 events overall. The majority of symptoms were mild
5 to moderate and transient. The rates of serious
6 adverse events and fatalities were low and similar in
7 both groups, and there was no cluster of events
8 identified. No related deaths were reported, and no
9 viscerotropic or neurotropic cases or severe immediate
10 anaphylactic reactions occurred. Allergic reactions
11 and anaphylaxis were considered a potential risk to be
12 monitored in any ongoing or future study and in our
13 post-marketing surveillance.

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

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

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

3 The safety profile of Dengvaxia has been closely
4 monitored during worldwide post-marketing experience.
5 Since Dengvaxia was first licensed in December 2015,
6 2.9 million doses were distributed, mostly in Brazil
7 and the Philippines where public programs were
8 conducted.

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

1 included in the Dengvaxia prosccribing information.

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

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

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

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

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

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

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

1 potential safety issues.

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

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

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

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

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

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

17 As part of our post-marketing plan, we have
18 conducted long-term safety follow-ups of CYD15 in
19 Puerto Rico, where 1,300 subjects included more than
20 800 on Dengvaxia, have been followed up for six years.

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

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

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

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

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

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

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

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

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

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

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

4 Dengvaxia has shown clear benefit. Vaccine
5 efficacy against symptomatic dengue was demonstrated
6 in 2- to 16-year-old individuals across two Phase 3
7 clinical studies. Dengvaxia also reduced the
8 occurrence of hospitalized dengue and clinically
9 severe dengue in both studies. In addition,
10 supplemental analyses by age and serostatus
11 demonstrated consistent vaccine efficacy against
12 symptomatic dengue in dengue seropositive individuals
13 9 to 16 years of age. Dengvaxia also demonstrated
14 clear protection against both hospitalized and severe
15 dengue in each of the Phase 3 studies over a five to
16 six-year period. This supports our proposed
17 indication of vaccination of seropositive individuals
18 nine years of age or older.

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

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

6 Next, we looked at how this benefit might
7 translate specifically in Puerto Rico. There are two
8 clear approved dengue diagnostic tests in Puerto Rico
9 that could be used to identify individuals with
10 laboratory-confirmed previous dengue infection. Using
11 the more conservative Biocan screening test, on the
12 next slides we show the results of one of the models
13 of the impact of screening and vaccination in Puerto
14 Rico. To approximate the epidemiology of dengue in
15 Puerto Rico, this model assumes two key parameters, 56
16 percent dengue seroprevalence in the entire 9- to
17 16-year-old population, which is what was observed in
18 the participants in Puerto Rico enrolled in Study 15
19 in 2011, 2012. Also, the incidence of severe dengue
20 in Study 15 extrapolated to Puerto Rico over a
21 five-year period. Without vaccination, we would

1 expect 79 severe dengue infections in the seronegative
2 population and 340 in the seropositive population.

3 With the screen-and-vaccinate approach, we could
4 expect, in the seronegative population, 0.9 percent to
5 be misclassified and vaccinated and 99 percent
6 correctly classified and, therefore, not vaccinated.

7 Over a five-year period, we would therefore expect
8 81 severe dengue infections in this population. In
9 the seropositive population, we could expect 66.1
10 percent to be correctly classified and vaccinated, and
11 33.9 percent to not be vaccinated due to false
12 negative results. Thus, over the same five-year
13 period, we could expect 147 severe dengue infections
14 in this population. The net result of a
15 screen-and-vaccinate strategy versus no vaccination
16 would be an overall reduction of 191 severe dengue
17 infections. This represents a 46 percent overall
18 reduction in severe dengue infections in the 9- to
19 16-year-old population in Puerto Rico over a period of
20 five years. The number of cases prevented is expected
21 to be higher if we use the ELISA with the higher test

1 sensitivity and when you include the adult population.

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

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

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

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

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

16 To conclude, the data demonstrate a positive
17 benefit risk profile for Dengvaxia in 9- to
18 45-year-old individuals living in endemic areas with
19 laboratory-confirmed previous dengue infection.

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

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

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

7 **DR. DIAZGRANADOS:** Thank you.

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

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

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

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

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

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

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

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

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

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

4 **DR. EL SAHLY:** Okay. Sure.

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

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

1 virus within a given serotype?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

21 We have done that in collaboration with

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

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

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

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

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

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

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

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

8 **DR. DIAZGRANADOS:** 17D.

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

12 **DR. DIAZGRANADOS:** Yes.

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

15 **DR. DIAZGRANADOS:** Yes.

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

17 **DR. EL SAHLY:** Dr. Edwards?

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

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

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

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

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

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

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

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

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

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

5 **DR. EL SAHLY:** Dr. Swamy?

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

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

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

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

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

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

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

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

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

1 3 studies, there was no restriction for that. The
2 study included individuals that had any type of
3 previous profile for dengue. So it included people
4 that were not exposed to dengue, people that were
5 exposed to dengue before, as well.

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

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

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

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

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

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

5 So they are available for use, currently, in
6 Puerto Rico in those laboratories for the evaluation
7 of previous exposure to dengue. And this is
8 evaluation and with it -- so this evaluation is
9 independent of the test manufacturers. We did this in
10 our global clinical immunology laboratory with samples
11 that we had extensively characterized. And that's the
12 basis for the performance characteristics of the tests
13 that we're reporting in there. So you can see that
14 the sample set is large. You have more than 250
15 samples assessing sensitivity, and you have more than
16 330 samples assessing specificity.

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

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

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

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

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

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

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

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

18 So I can tell you, the cross-reactivity of these
19 two tests on those 38 samples is that the first test
20 in there, the somatic ELISA, has a cross-reactivity of
21 13 percent. So 13 percent of those samples that are

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

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

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

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

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

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

1 individuals.

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

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

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

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

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

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

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

21 In another area of the world, where there was

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

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

7

8 **LUNCH BREAK**

9

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

16 **OPEN PUBLIC HEARING**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14 **MS. HUNTER-THOMAS:** Time.

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

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

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

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

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

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

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

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

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

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

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

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

1 tetraivalent vaccine.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

21 We can no longer argue whether there is

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 16-year-old subjects. CYD14 had the same design and
2 objectives and CYD15, but was conducted in 2 through
3 14-year-olds in five Asia-Pacific countries. And
4 CYD23 was a Phase 2 proof of concept study that was
5 conducted in 4 through 11-year-olds in Thailand.

6 A brief background now. The original clinical
7 development plan for this vaccine anticipated an
8 indication from 2 through 60 years of age. Therefore,
9 2 through 16-year-olds were included in the endpoint
10 studies.

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

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

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

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

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

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

16 The Hospital Phase, which could be
17 characterized as Hospital Phase year 1, if you look at
18 the bottom of the chart, where it says year 3 of the
19 study, that's year 1 of the Hospital Phase. Then year
20 2, then year 3, then year 4. During the Hospital
21 Phase, as originally planned, active case detection

1 for severe clinical and hospitalized dengue was
2 conducted.

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

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

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

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

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

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

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

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

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

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

21 Safety objectives, to describe rates of local

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

6 The case definitions that are relevant -- the
7 first thing I want to point out is, what is
8 virologically-confirmed dengue case. In CYD15 -- and
9 this is exactly the same for CYDB14 -- a case required
10 an acute febrile illness, temperature greater than or
11 equal to 38 degrees centigrade for at least 2 days;
12 and then, virological confirmation would be by dengue
13 RT-PCR and/or dengue NS1 ELISA antigen test. For
14 CYD23, the only difference was they had a different
15 fever criteria, and it was greater than or equal to
16 37.5 centigrade two times in one day, separated by at
17 least 4 hours. So, just a slightly different
18 threshold for fever triggering concern about a
19 clinical case of dengue.

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

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

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

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

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

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

1 So, the primary endpoint for trial CYD15,
2 which was the symptomatic virologically-confirmed
3 dengue case due to any serotype during that 12-month
4 interval, starting 28 days post-dose 3, by the per
5 protocol set for efficacy, and the point estimate was
6 60.8 with the confidence intervals that you can see.
7 This was 9 through 16-year-olds, so that entire age
8 range is in the requested indication. This is the per
9 protocol efficacy including dengue-immune and dengue
10 non-immune at baseline.

11 There was a secondary endpoint of cases in
12 dengue hemorrhagic fever post-dose 1 due to any dengue
13 serotype, and there were ten such cases in the placebo
14 group, one in the Dengvaxia group. The one case in
15 the Dengvaxia group was a Grade 2 dengue hemorrhagic
16 fever; and in the placebo group, there were two Grade
17 1s and eight Grade 2s. So, in this trial, there was
18 no Grade 3.

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

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

5 There is a range of point estimates of
6 efficacy by serotype that you can see on this slide.
7 In a very general way, it can be stated that serotypes
8 3 and 4 had a point estimate of vaccine efficacy that
9 was higher than 1 and 2. When data was analyzed in a
10 post-hoc analysis for vaccine efficacy against
11 symptomatic VCD, post-dose 3 due to any serotype, but
12 then analysis was done by dengue-immune status, these
13 are the results that you get.

14 So, for subjects who were dengue-immune at
15 baseline, which was defined by the PRNT-50 assay,
16 dilution of greater than 10, there was an 83.7 percent
17 point estimate. And for those dengue non-immune,
18 43.2.

19 There's one slide that I'm going to show on
20 the immunogenicity results from this Phase 3 study in
21 9 through 16-year-olds. You can see that the results

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

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

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

1 the antibody titer.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

16 So, study CYD23 was the Phase IIb study
17 conducted in Thailand as a "proof of concept" study,
18 and they enrolled 4,002 subjects. The study design
19 elements were essentially identical to that of 15 and
20 14, with the following differences. It was a Phase
21 IIb study. Subjects were 4 through 11 in this study.

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

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

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

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

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

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

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

1 2 randomized, placebo-controlled, observer-blind,
2 descriptive studies. One was in India; one was in
3 Singapore; one was in Vietnam. You can see the number
4 of subjects that were enrolled. And when there were
5 subjects, such as in Singapore and Vietnam, who were
6 less than 18, you can see how many adults were in each
7 study.

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

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

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

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

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

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

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

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

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

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

3 This just kind of summarizes it.

4 Descriptively, in studies CYD22 and 47, post-dose 3
5 GMTs among vaccinated dengue-immune adults 18 through
6 45 were similar to post-dose 3 GMTs of dengue-immune
7 vaccinated children 9 through 16 in the clinical
8 efficacy endpoint studies. These data are intended to
9 support effectiveness in dengue-immune persons 17
10 through 45.

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

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

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

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

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

18 Unsolicited adverse events within 28 days of
19 vaccination -- non-serious AEs were reported in about
20 46 and a half -- 46.6 percent of subjects in the
21 Dengvaxia group; 44 percent in the placebo group

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

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

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

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

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

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

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

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

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

1 that had a severe/hospitalized dengue.

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

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

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

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

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

12 Conversely, if subjects were dengue
13 seronegative at baseline or dengue non-immune, the
14 hazard ratio is essentially greater than 1, and it
15 depends on what study you're looking at, whether it's
16 14, 15, or all studies combined. But the point
17 estimate is basically right at 1 or above 1, and then
18 the confidence intervals go up to an upper level, as
19 you can see here.

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

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

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

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

1 clinical efficacy endpoint trials.

2 We have one brief slide on the
3 pharmacovigilance plan, simply to note that Sanofi
4 Pasteur submitted a Pharmacovigilance Plan to monitor
5 what are termed Important Identified Risks that could
6 be associated with Dengvaxia, and they cited allergic
7 reactions and severe/hospitalized dengue in
8 individuals not previously infected by the dengue
9 virus. Details of the PVP are still under discussion
10 between FDA and the applicant. So that's all we're
11 going to say.

12 Last two slides, summary of the immunogenicity
13 and safety -- just to recap on immunogenicity, the
14 specific threshold for neutralizing antibody titers
15 with which vaccine effectiveness could be predicted
16 reliably was not identified. There was no correlated
17 protection. However, there was a tendency towards
18 higher post-dose 3 neutralizing antibody titers in
19 non-cases compared to cases in CYD15 and 14.

20 Descriptively, the 28-day post-dose 3
21 neutralizing antibody titers that were observed in

1 subjects 18 through 45 in those three studies, but
2 particularly in 22 and 47 from India and Vietnam --
3 those titers were similar to the 28-day post-dose 3
4 neutralizing antibody titers in the subjects 9 through
5 16 in the clinical trials.

6 Just recapping what I said two minutes ago.
7 Safety -- again, the increased risk of hospitalized
8 VCD in Dengvaxia recipients who were seronegative at
9 baseline. Solicited local and systemic adverse
10 reactions were generally mild -- Grade 1 or 2 -- and
11 of short duration.

12 There was no substantial imbalance in severe
13 reactions between Dengvaxia and placebo. Overall,
14 SAEs -- excluding the hospitalized VCD -- and deaths
15 were reported in similar proportions of subjects in
16 the Dengvaxia and placebo groups. There were no
17 deaths in any of these studies that were found to be
18 attributable to the vaccine product. And
19 viscerotropic and neurotropic disease entities were
20 clearly defined and were clearly looked for in the
21 first six months' safety follow-up, and there's no

1 case of either in any of the three trials.

2 This is the final slide. It's the summary of
3 the efficacy results. You see study 15, the primary
4 endpoint, its vaccine efficacy estimate, and the
5 confidence intervals. Study 14, full age range, 2 to
6 14, a little bit lower efficacy estimate, pretty
7 similar confidence intervals. CYD23, as pointed out,
8 if you look at the full age range and their primary
9 endpoint, lower vaccine efficacy estimate, lower bound
10 less than zero. And then, if you look at three
11 post-hoc analyses and focus in on the 9 and above --
12 for CYD23, 9 to 11 -- all subjects, you get an
13 efficacy estimate of 70.1 with those confidence
14 intervals.

15 Then, if you look at seropositives instead of
16 the whole group, CYD15, point estimate of 83.7 in
17 those seropositive 9 through 16-year-olds. And in
18 CYD14, if you look at the 9 through 14-year-olds,
19 seropositive point estimate of 79.2.

20 Thank you for your patience. I'll take any
21 questions anybody might have.

1 **COMMITTEE DISCUSSION/RECOMMENDATIONS/VOTE**

2 **DR. EL SAHLY:** Thank you, Dr. LeBlanc. I
3 would begin by asking, regarding the test that was
4 used to characterize individuals as seropositives, is
5 the NS1 ELISA an antibody ELISA? And is this test
6 available for use? And how does it perform in
7 post-Zika era?

8 **DR. LEBLANC:** Oh, those are good questions.
9 Yeah. I would let the applicant address how it's
10 available for use. I'll let them address how it
11 performs in a post-Zika era. I'm going to let him
12 address both of them.

13 **DR. GURUNATHAN:** So the dengue NS1 ELISA test
14 that was used for the case-cohort analysis is -- I'd
15 say that was specifically used for the purposes of
16 addressing a research question. And it's not
17 available for use in the field.

18 The influence of Zika on the test was
19 evaluated based on a few samples, but the important
20 point is that, for the purpose of the study that was
21 done, which was to characterize the baseline of the

1 individuals in the studies, at a time when the sample
2 was available, which was the month 13 sample, Zika had
3 not occurred in the Americas yet.

4 So, for the purposes of addressing the
5 research question at hand, the assay was not
6 influenced by Zika, because Zika was not in the
7 Americas at that time.

8 **DR. EL SAHLY:** Dr. Kurilla.

9 **DR. KURILLA:** Does that NS1 test distinguish
10 dengue subtypes? The serotypes?

11 **DR. GURUNATHAN:** No.

12 **DR. KURILLA:** So, do you have any evidence,
13 even if it's limited to animal model -- evidence of
14 the vaccine efficacy after two or more dengue
15 infections, particularly heterotypic dengue
16 infections?

17 **DR. GURUNATHAN:** Yes. We actually did some of
18 those analyses at the request of the European
19 Medicines Agency. For doing that, we utilized the
20 PRNT90 assay to classify individuals in the immune
21 subsets in the studies as monotypic, meaning that they

1 only had immunity to one dengue serotype, or
2 multitypic, meaning that they have immunity to two or
3 more dengue serotypes.

4 The data is summarized to -- see if it's going
5 up or not on this screen. Okay. So, this is the
6 summary of the data. And here we have information for
7 the immunogenicity subsets for the two studies pulled
8 and for the age group 2 to 16 years of age. What you
9 have in the top of the slide is the data for
10 symptomatic dengue over a period of zero to 25 months
11 post-vaccination, expresses vaccine efficacy. And at
12 the bottom, you have the information for hospitalized
13 dengue.

14 First, if you concentrate on the right side of
15 the slide, the placebo data, what you can see there is
16 that the individuals that are classified as monotypic
17 have a higher risk of symptomatic dengue compared to
18 the multitypics, and also a higher risk of
19 hospitalized dengue compared to the multitypics. So,
20 that information is consistent with the dengue
21 paradigm that you have a much higher risk of

1 symptomatic dengue and more severe forms of dengue if
2 you have a single previous dengue infection.

3 So then we can take a look at the left side of
4 this slide and the estimates of vaccine efficacy and
5 relative risk. What you can see is that, for
6 monotypic immunes, the vaccine efficacy is close to 80
7 percent and significant. And the protection or risk
8 reduction against hospitalized dengue is around the
9 same range. Also, it's statistically significant for
10 the subgroup of people that are classified of
11 multitypic.

12 What is interesting is that you also see
13 protection for the two outcomes of both symptomatic
14 dengue at the top and hospitalized dengue at the
15 bottom. So, the vaccine is providing benefits to the
16 group that needs the benefit the most, which are the
17 monotypic immunes. But the people that have been
18 exposed to two or more dengue serotypes before also
19 start to benefit from the vaccine.

20 **DR. LEBLANC:** What I would just add to that,
21 and it's a basic perspective, I think it's important

1 to keep in mind what these studies were powered for.
2 They were powered for efficacy against any serotype.
3 That was the main thing. Even going to
4 serotype-specific efficacy, you're getting into
5 smaller numbers. Getting into the type of question
6 you asked, which I think is immunologically very
7 important, but you have very few data points. So, I
8 would just question that that type of data needs to be
9 interpreted consciously.

10 **DR. EL SAHLY:** Would the Singapore volunteers
11 -- would they have been classified as immune?

12 **DR. LEBLANC:** The only subjects whose data
13 were presented in that table, they were all immune.
14 There were non-immune people in each one of those
15 studies; but the comparisons were GMTs post-dose 3
16 between adults and adolescents who were immune at
17 baseline.

18 If you remember the data from the CYD15 and
19 the immunogenicity subset, if you're non-immune at
20 baseline, you don't get much of a titer post-dose 3.
21 So, the comparison was in dengue-immune adults,

1 dengue-immune adolescents. And the people from
2 Singapore were immune at baseline by that greater than
3 10 threshold, but their pre-injection titers were
4 quite a bit lower than --

5 **DR. EL SAHLY:** So I'm trying to put this into
6 context of the bridging data, meaning the Singapore
7 volunteers post-dose 3, their titers were way lower
8 than what we observed in CYD14, 15 and the two other
9 adult studies.

10 **DR. LEBLANC:** Correct.

11 **DR. EL SAHLY:** So I'm wondering about why
12 different and how do we put this in the context of the
13 bridging data?

14 **DR. LEBLANC:** The only explanation I have for
15 you as to why the data from Singapore is different is
16 that they start at a different level. Their
17 pre-injection titers were substantially lower.
18 There's some thinking that that relates to lower
19 overall levels of endemicity in Singapore.

20 **DR. EL SAHLY:** But they're still considered
21 immune. We should have given them the vaccine.

1 **DR. LEBLANC:** Yeah, but that doesn't mean that
2 they're necessarily immune and protected from getting
3 dengue. There's a difference. The immune definition
4 is a function of the PRNT50 assay.

5 **DR. EL SAHLY:** Exactly.

6 **DR. LEBLANC:** And that lower threshold's
7 pretty low. But it's a legitimate concern.

8 **DR. FINK:** So I'll jump in and clarify that,
9 for purposes of the descriptive comparison between
10 adults in the immunogenicity study and the pediatric
11 subjects in the efficacy studies, we considered that
12 the two studies done at sites where there was known to
13 be an overall higher level of endemicity would be the
14 most appropriate comparisons; apples to apples
15 comparisons for looking at the immune post-dose 3 GMTs
16 in adults versus those in the children in those
17 studies that were also conducted in highly endemic
18 areas.

19 **DR. KURILLA:** Are you suggesting, then, that
20 people living in endemic areas are being constantly
21 boosted by repeated mosquito bites even though they're

1 immune and that's what's keeping their titers higher?

2 **DR. LEBLANC:** There is some evidence that
3 suggests that, if you look at the immunogenicity table
4 for CYD15 and you look at subjects who didn't get
5 Dengvaxia and they got placebo, and you look at their
6 post-dose 3, year 1, their titers keep going up. They
7 didn't get the vaccine. And we know that there's
8 repetitive exposure and that they could be getting
9 boosting. So, yes, there's the assumption that their
10 titers are being maintained or even rising a little
11 bit as a function of ongoing dengue exposure.

12 **DR. EL SAHLY:** Okay. Dr. Bennink?

13 **DR. BENNINK:** Yeah. Part of the issue is that
14 these are averages anyways, as you say, when they're
15 not in the endemic area. It's an average of everyone
16 that you have in the thing. What would be nice,
17 really, is if we had the individual data, particularly
18 the data for people that had a problem after the
19 vaccine. Was that monovalent or was there nothing?
20 What really came out of the vaccination after you had
21 that and then there was a failure? And that's much

1 more difficult to get a --

2 **DR. EL SAHLY:** Okay. Dr. Edwards?

3 **DR. EDWARDS:** So do you think that Puerto Rico
4 is more Singapore-like or more Thailand-like? And if
5 we're going to try and make a bridge, then I think
6 it's really important because the efficacy data are in
7 seropositives who have much higher titers. So, how do
8 we interpret what you show us for Singapore?

9 **DR. MONTO:** And is it regions in Puerto Rico
10 that are more Singapore-like?

11 **DR. LEBLANC:** So, if you look at the baseline
12 epidemiology, Puerto Rico's pretty much midway between
13 Singapore and Vietnam and India. So, Puerto Rico in 9
14 to 16-year-olds, for the most recent data prior to the
15 studies, was about 56 percent seropositive in the 9 to
16 16-year-old. It was on the low end for those five
17 studies that were in South America. Brazil, I think,
18 was maybe the highest; Brazil or Columbia. I can't
19 remember the numbers exactly. But they were, like, 70
20 to 80 percent. So, that does vary. But Puerto Rico
21 is mid-50 percent.

1 **DR. EDWARDS:** But we're used to seeing
2 serology in populations that we're going to use the
3 vaccine in and we're used to seeing serology that we
4 can kind of go back to what the efficacy is. And I'm
5 very uncomfortable with the Singapore serology because
6 you say that efficacy is based on the height of the
7 titer, and these titers aren't very high. In fact,
8 these titers are pretty much the same as the
9 seronegative kids that got vaccinated.

10 **DR. GRUBER:** So can I -- I'm sorry. This
11 is --

12 **DR. EL SAHLY:** Dr. Gruber?

13 **DR. GRUBER:** Yes. I actually, at this point,
14 would actually ask and invite Sanofi Pasteur to
15 comment on this. This is a complex subject and topic
16 and I think they need to give the sponsor a chance to
17 comment.

18 **DR. GURUNATHAN:** Thank you, Dr. Gruber. Yes,
19 for understanding study CYD28, it is also important to
20 understand a couple of things. Of course, the level
21 of endemicity in Singapore was much lower than the

1 level of endemicity in the other adult studies that
2 were shown and in study CYD14 and CYD15.

3 So, to understand the possible implications of
4 that, I think we have to take a look at the baseline
5 and what is affecting the baseline. The baseline PRNT
6 antibody titers are affected by the magnitude of
7 previous exposure to dengue. So, with higher level of
8 exposures, you are expected to have higher baseline
9 PRNT50 antibody titers. That's the first point.

10 The second point is that there is a clear
11 relationship between the pre-vaccination antibody
12 titers in seropositive individuals and the post-dose 3
13 antibody titers in individuals; so that if you want to
14 compare the post-dose 3 antibody titers, you have to
15 account somehow for baseline or for magnitude of
16 exposure.

17 We have tried to do some analysis that adjusts
18 for baseline to compare the studies. So, first, let
19 me just show the relationship I was mentioning about
20 baseline and post-dose 3 that's represented by the
21 figure that you see on the screen right now.

1 Now, the second point, which was described by
2 Dr. LeBlanc, is that the antibody titers in CYD28 were
3 much lower a baseline than the antibody titers in, for
4 instance, CYD14 studies age 9 to 14, where efficacy
5 was demonstrated. So, that is illustrated in the
6 slides that we are projecting right now on the screen.
7 This is specifically for people that are seropositive.
8 So, we think the -- you know, not all the
9 seropositives are the same. We think the
10 seropositives -- the antibody titers for the adults in
11 CYD28 were much lower than the antibody titers in 9 to
12 14-year-olds in CYD14.

13 So then what we did, in collaboration with the
14 University of Washington, was to adjust for baseline.
15 And those analyses that adjusts for baseline, what we
16 have is -- in the slides presented here, is that the
17 differences that we're largely seeing in analyses that
18 were unadjusted are low.

19 Once you adjust for baseline, you see that the
20 bars are relatively similar for all the other
21 serotypes. And for the average titer records of the

1 four serotypes, they're also very similar with the
2 ratio for the average titer that is very close to one
3 between the studies -- 28 adults, 18 to 45 years of
4 age, and adolescents or children 9 to 14 years of age
5 in study CYD14 where efficacy was illustrated.

6 So, a large part of the difference is
7 explained by the differences in baseline between the
8 different individuals, even after classifying them as
9 seropositive. We did a similar analysis trying to
10 adjust for magnitude of exposure as well, looking at
11 only individuals that were positive for a single
12 serotype, using the PRNT90 assay. And the findings
13 are consistent with what I've just shown.

14 So, this slide is only showing individuals
15 that were characterized as monotypic by PRNT90. And
16 again, you see that the bars are relatively consistent
17 between the adult population in CYD28 and the
18 children, 9 to 14-years-old in CYD14, where efficacy
19 was demonstrated.

20 When you look at the average titer for the
21 four serotypes, the bars are very similar, also

1 reflected in the ratios between the studies being very
2 close to one. So, our interpretation is that the data
3 is the way it is when it's unadjusted because the
4 baseline is completely different.

5 **DR. LEBLANC:** Dr. Edwards, if I may, there's
6 another point -- two more points, actually, I want to
7 make. And I'm not trying to convince you on
8 something; I appreciate your skepticism. You
9 referenced seroprevalence rate in Puerto Rico, and
10 we're talking about 9 through 16-year-old with the 54,
11 56 percent, and seroprevalence rate in Singapore and
12 that was 18 to 45. If you remember the slides that
13 were shown about the epi, basically every decade you
14 go up in age in a dengue-endemic area, you're going to
15 have a higher seroprevalence in your 20-year-olds,
16 your 30-year-olds, your 40-year-olds.

17 So, I can't give you the estimate of
18 seroprevalence in the blended age range, 18 to 45 in
19 Puerto Rico. Maybe the applicant would have that
20 number. But it's not going to be 56 percent. It's
21 going to be higher than that. A little bit, perhaps,

1 closer -- maybe not as high as what you're going to
2 have from Vietnam and India. So that was point one.

3 And I understand that immunogenicity data in
4 adults in Puerto Rico indicated adult age range would
5 be desirable. I understand that. Another discussion
6 that we've tried to have, because we grapple with
7 these things, is we tried to look at what we call the
8 biological plausibility of there being protection in
9 18 to 45-year-olds. Just totally set aside any
10 immunogenicity data at all. Look at the disease.

11 Is there anything about dengue disease that
12 says to us it's significantly different in 18 to 45
13 than it is from 9 to 16? Or is there anything we know
14 about the immunology that would suggest that immune
15 responses in adults who are dengue-immune at baseline
16 would be different in a substantial way from
17 adolescents? I'm just kind of making an argument.
18 I'm not saying that --

19 **DR. EDWARDS:** I guess I'm used to seeing data
20 rather than hypothesizing whether there could be a
21 difference. And the numbers of people in the 18 to

1 45, I think, was quite small. It was less than 50.

2 **DR. LEBLANC:** It is. It is small.

3 **DR. EDWARDS:** Less than 50 people in that
4 slide. That's not usually what we see.

5 **DR. LEBLANC:** Yes ma'am. Right.

6 **DR. EL SAHLY:** Dr. Wharton?

7 **DR. WHARTON:** Yeah, I was just trying to jump
8 in on this discussion about the adult data, just with
9 the either question or observation that there were no
10 adults in the safe group -- or there were no adults
11 from whom we've seen data from, the Western
12 hemisphere, and that's not what I'm used to seeing.

13 **DR. EL SAHLY:** All right. First, Mr. Toubman,
14 then --

15 **MR. TOUBMAN:** Thank you. I, first, have a
16 question for Dr. LeBlanc. It's going back to the
17 number 23 study. I appreciate that you included all
18 three effectiveness studies. The applicant did not.
19 They excluded C23.

20 My question -- this -- I have questions for
21 you. I also have some questions for either of you.

1 But this question is about when the chair asked why it
2 was excluded, the answer was, oh, well, they just, for
3 brevity, they just exclude one of the three studies;
4 and we were told that that study was consistent with
5 the other two.

6 And I'm looking at their own presentation, the
7 206-page briefing document where they say that the
8 primary estimate of VE at 30 percent was lower than
9 anticipated and did not reach levels of statistical
10 significance since the lower bound of the 95 percent
11 CI was less than zero.

12 So, in their document, they seem to be saying,
13 no, it didn't confirm. And I understood you to be
14 saying you agreed with what they said in the
15 documents, most of what they said today, which is that
16 the C23 did not confirm effectiveness. I just want to
17 know if that's -- is that your understanding as well?
18 My first question.

19 **DR. LEBLANC:** CYD23 did not meet their
20 prespecified criteria for success in efficacy.

21 **MR. TOUBMAN:** Thank you. And then my other

1 questions, which could be for either, and this is
2 concerning -- I mean, this is, I think -- one of the
3 nubs of it is -- and we can take what WHO says, which
4 is in their September position paper, that countries
5 should consider introduction of the dengue vaccine
6 only if the vaccination of seronegative persons can be
7 avoided. So I think everybody seems to be in
8 agreement on that.

9 So, I have real practical questions about how
10 that would be done, the testing. Again, I don't know
11 who can answer these questions, but the questions are,
12 first of all, is there a test that's actually
13 available? Because we're being asked to approve this
14 thing when the test may not be available.

15 Second, if there is a test, does it require a
16 patient to come in twice? Meaning, they come in, they
17 get blood drawn, it gets sent out to a lab, that takes
18 several days, and the person has to come back. I
19 represent low-income folks in an urban area, and
20 according to providers in the clinics, it's hard to
21 get people to come in. People in rural areas, it's a

1 bigger deal. So, I'd like to know -- that's my second
2 question -- if they do have to come in twice. And
3 this is all about concerns of compliance.

4 So, the third question is, if that's going to
5 be required in order to even know whether the person
6 can get the vaccine, are there any examples anywhere
7 where a vaccine has been approved with the condition
8 that the person has to be tested first which will
9 require them to come in twice? Has that ever been
10 done, to know whether it's even feasible?

11 And then the last question is this. I heard a
12 reference to a rapid test or something. Is that, in
13 any way, feasible in the near future such as, perhaps,
14 this thing could -- just throwing it out, this thing
15 could be approved subject to such a rapid testing
16 available? I don't know if that's realistic at all.
17 You can answer any or all those questions.

18 **DR. LEBLANC:** You've got four questions. I
19 think Dr. Gruber is going to answer that for you.

20 **MR. TOUBMAN:** Okay.

21 **DR. GRUBER:** Yeah. Go ahead.

1 **DR. FINK:** All right. So let me try to
2 address all of your questions. First of all, we don't
3 have a prior example of a vaccine that has been
4 indicated for use contingent upon a test prior to
5 vaccination. So, this, if approved, would be the
6 first example of that.

7 We did have extensive discussion within the
8 agency, both during the review of this application and
9 even before receipt of the application, about the
10 consequences and the practical issues of the
11 requirement for a diagnostic test to identify
12 individuals who would be indicated for the vaccine,
13 especially considering the current state of available
14 tests in areas where the vaccine would likely to be
15 used.

16 There were a number of factors that we
17 considered. First of all, as is mentioned in the
18 proposed indication, laboratory-confirmed prior dengue
19 infection could be documented either by current
20 sero-testing, which is what you're talking about, or
21 through the medical record. So, there may be

1 opportunity to use the vaccine in individuals who have
2 documented laboratory-confirmed dengue infection by
3 history. And you heard a little bit from Gabriela
4 Paz-Bailey this morning about the systems that are in
5 place in Puerto Rico that might enable that type of
6 paradigm.

7 The second factor that we considered is that,
8 while the options for current sero-testing are
9 currently limited today, there are ongoing efforts to
10 develop new tests, so availability of such tests may
11 change over time. The performance of such tests,
12 specifically the positive predicted value, may change
13 over time.

14 So, given that, we are charged with assessing
15 the safety and the effectiveness of the vaccine for
16 the intended indication, which is for use in
17 individuals living in endemic areas with
18 laboratory-confirmed prior dengue infection, and we
19 were asking for your advice or your opinion on whether
20 the data presented today do support the safety and
21 effectiveness.

1 But if we can conclude that the data do
2 support the safety and the effectiveness for that
3 indication, then it might be left up to public health
4 authorities and recommending bodies, such as the ACIP,
5 to determine, under the current conditions or under
6 future conditions, whether the vaccine should or
7 should not be used. So, that was another
8 consideration.

9 Finally, you heard a little bit from the
10 applicant about benefit and risk considerations given
11 the performance characteristics of currently available
12 tests. We also considered these, including
13 considerations where we took a more conservative
14 approach to what the positive predicted value might
15 be. And we considered that, even if currently
16 available tests were used to identify individuals who
17 are indicated for vaccination and even if the positive
18 predicted value was not 100 percent, that the benefits
19 might still outweigh the risks of the vaccine. So
20 these were the discussions that we had.

21 **MR. TOUBMAN:** I appreciate that. I guess that

1 I'm particularly worried that there is no examples of
2 this ever, and that you're putting physicians in a
3 situation where they're now going to have access to
4 this wonderful opportunity to prevent some of the
5 horrible things we've heard about, and the fact that
6 there's this two-visit requirement and this testing
7 that it might -- people will slip through the cracks,
8 is what I'm worried about.

9 I understand what you're saying is you
10 analyzed the possibilities that even if that weren't
11 really in place, maybe the cost benefit analysis
12 warrants, but given the other things I've heard, I'm
13 not sure about that.

14 **DR. EL SAHLY:** Okay. Dr. Follmann, then
15 Marion.

16 **DR. FOLLMANN:** Yeah, my question is more for
17 Dr. Edwards, I guess. I wanted to -- and then maybe
18 have a question for the sponsor. But I think -- was
19 your concern that Puerto Rico might have -- well, had
20 seropositives but their titers might be kind of low,
21 and you're worried about the vaccine efficacy as a

1 function of titer even in the seropositives?

2 **DR. EDWARDS:** Yes.

3 **DR. FOLLMANN:** So I was wondering if the
4 sponsor had done such an analysis where you take
5 seropositives, and amongst seropositives, you look at
6 those with very high titers, medium titers, and low
7 titers, all positive, and look at vaccine efficacy for
8 those two or three groups. And if you see similar
9 VEs, I think that would allay Kathy's concern.

10 **DR. GURUNATHAN:** So, in Puerto Rico
11 specifically, as Puerto Rico was one of the countries
12 included in the study CYD15, we do have data specific
13 for Puerto Rico that we can show in seropositive
14 individuals and the indicated age population. That's
15 one point that we don't have for the adult region, but
16 for Puerto Rico, we do have specifically data in these
17 children.

18 So, this is the summary of the data for you,
19 specific for Puerto Rico, and putting it into context
20 with the overall study CYD15. These are seropositive
21 individuals based on the case-cohort analysis from

1 Puerto Rico. You can see that the vaccine efficacy
2 from month zero to month 25 estimated is 91 percent,
3 which is generally consistent with a high efficacy
4 observed in the overall CYD15 study. But the
5 relationship between vaccine efficacy and PRNT titer
6 after 3 doses -- I'm sorry?

7 **DR. FOLLMANN:** I think the issue was at
8 baseline.

9 **DR. GURUNATHAN:** So baseline and antibodies
10 and efficacy?

11 **DR. FOLLMANN:** Yes.

12 **DR. GURUNATHAN:** Yes. So can I invite Dr.
13 Laurent Chambonneau to address that question?

14 **DR. CHAMBONNEAU:** Good afternoon. My name is
15 Laurent Chambonneau. I'm a lead statistician in
16 biostatistics of our department in Sanofi Pasteur. We
17 do have a V curve actually taken into account for
18 baseline. I do have one. Here we are.

19 So, as you can see, actually, the baseline of
20 which titer is a modifier of vaccine efficacy, not as
21 strong as post-dose 3, of course, but still, a

1 modifier of vaccine efficacy.

2 **DR. FOLLMANN:** And just for my reference, what
3 would be -- these are all seropositives, so what would
4 be the cut-off be for seropositivity?

5 **DR. CHAMBONNEAU:** Greater than 10. The limit
6 of quantification was 10 for PRNT.

7 **DR. FOLLMANN:** Okay.

8 **DR. EDWARDS:** It looks like the efficacy is
9 lower for lower pre-titers.

10 **DR. EL SAHLY:** Dr. Gruber?

11 **DR. GRUBER:** Yeah, I just wanted to come back
12 for a moment, again, to discuss the availability of a
13 rapid diagnostic test that can be used at point of
14 care and provides rapid results and is of sufficient
15 specificity and sensitivity. We had actually -- and I
16 would like to, again, call upon Sanofi Pasteur to
17 perhaps provide the committee here with additional
18 information. Because we've had a couple of meetings
19 with the applicant to discuss efforts made to really
20 develop such tests in the not-too-distant future. Can
21 I invite Sanofi to provide this information and

1 summarize the discussions that we've had?

2 **DR. GURUNATHAN:** Yes, Dr. Savarino can expand
3 on that, I think.

4 **DR. SAVARINO:** I'm Stephen Savarino. I'm in
5 Translational Sciences and Biomarkers at Sanofi
6 Pasteur. As you've seen today, we've evaluated the
7 tests that are available in Puerto Rico. We've also
8 done evaluation of the tests that are available in
9 other parts of the world. Similarly to the tests in
10 Puerto Rico, we find that the specificity in detecting
11 prior dengue infection is relatively high -- very high
12 for all these tests, so we think that's a good
13 starting point.

14 We have, as a company, made a commitment to
15 develop or codevelop a test that's for this specific
16 intended use of determining prior dengue infection.
17 We are in the process of developing a partnership to
18 do that. And our commitment is to -- our expectation
19 is to bring that test forward by late 2020 to FDA
20 registration.

21 As was pointed out earlier, the tests that are

1 available in Puerto Rico to the issue of visits, these
2 are available in a laboratory setting, not at point of
3 care. The intent is to develop the point of care test
4 that could be used in a single visit in the right
5 situation.

6 **DR. EH SAHLY:** Dr. Myron Levine.

7 **DR. LEVINE:** Okay. I had a few more questions
8 on the rapid diagnostic test as well, but I'd like to
9 get there with my understanding of what I've heard
10 today and what I've read today, and all the
11 information that we have as a background to grappling
12 with the questions to the answer.

13 So, for Americans and a dengue vaccine, one
14 might think of two major possible uses. One would be
15 a traveler, and the other would be those parts of the
16 U.S. population, such as in Puerto Rico and American
17 Samoa, where there is an endemic disease.

18 This particular vaccine, from all I've heard,
19 we've read, and what we're grappling with in terms of
20 finding the seronegatives, this is obviously not a
21 vaccine a traveler would take. But there is American

1 population that's at risk. Of that American
2 population, from what I think I heard this morning
3 from the presentation, is that the overwhelming burden
4 of endemic dengue is in Puerto Rico. And within
5 Puerto Rico, we saw one map today where there are
6 different relative burdens in different states or
7 regions of the island.

8 So, one would think, if the public health
9 authorities in Puerto Rico want vaccine to help
10 grapple with their problem, one would think that they
11 might start looking at their really high burden areas.
12 And they're going to have to grapple with how they
13 identify the folks who are seronegative. The
14 seropositives, they're going to get vaccine. And one
15 would see what would happen in the context of this
16 piece of the American population that's at risk. For
17 the seronegatives, there has to be a good test, and
18 I'll get to that in a moment.

19 In terms of how to use a non-point of care
20 test, if it's a really good test -- if -- looking at
21 the one, I don't know exactly what these numbers mean

1 for the Simetics dengue IgG test, but it claims 100
2 percent sensitivity with the way you all have tested
3 it with whatever the sera are. To me, 100 percent, 99
4 percent, really high in this context means the ability
5 of a test to detect a true seronegative. And that's
6 what you want, a test with a very high specificity to
7 find the person who is truly antibody negative and,
8 therefore, possibly at risk of getting this vaccine
9 and being in an endemic area.

10 One would also like to have high sensitivity
11 so that you don't miss people who are seropositive and
12 would gain benefit from the test, because efficacy
13 data and seropositives are clearly in the positive
14 area.

15 So, one way, just sitting here today, that I
16 could think one could do this with a test where you
17 have to get blood, bring it to a lab, have it done
18 under clear conditions, see who does and who doesn't
19 have a positive test, and then go back and vaccinate
20 for the school-age population, in much of Latin
21 America, school-based immunization is very, very, very

1 common, much more so than in the U.S.A.

2 If the Puerto Rican public health authorities
3 wanted to do this, this is one possibility. It's a
4 captive population. That doesn't help the
5 clinic-based. It doesn't -- that's still cumbersome.
6 And I was wondering whether the folks from Sanofi or
7 others around the table have thought of ways to get at
8 the clinic-based. It may be that that will have to
9 wait for a true point of care test. But at least,
10 seems to me, for school-age, it's a captive population
11 and that's a possibility.

12 I think that testing people with a reliable
13 test beforehand is very important in relation to the
14 use of this vaccine, and I think that Puerto Rico's
15 the big burden. If there are some folks from public
16 health in Puerto Rico here could comment on that, or
17 if CDC can comment for Puerto Rico, that might be
18 helpful.

19 **DR. EL SAHLY:** Anyone can comment on that. I
20 must say, though, you're also asking the schools to do
21 diagnostics then vaccinate. So, how -- it's also

1 unchartered territory there.

2 **DR. LEVINE:** Well, send other -- I have lots
3 of experience with school-based immunization with
4 trials that led to FDA licensure of a live oral
5 typhoid vaccine that was outside usual immunization
6 regimens because it required multiple doses with a
7 short interval between doses. And the only way that
8 one could get at the highest risk population was to do
9 school-based immunization. Those trials were done in
10 Santiago, Chile. Chile has a long tradition of
11 school-based immunization.

12 It may be that, in Puerto Rico, that's totally
13 incompatible. It may be that because of the results
14 of the hurricane that schools are destroyed. I don't
15 know the local suit, but the Puertorriqueños do.
16 School-based immunization works and it can be done,
17 but it requires that the equivalent of a ministry of
18 education and ministry of health have to get together
19 and agree. You have to put aside a day for testing or
20 half a day. You have to put aside a day for
21 immunization. But I think it's feasible.

1 **DR. EL SAHLY:** Dr. Kurilla?

2 **DR. KURILLA:** Yeah. So I'm struggling with
3 the restriction in the labeling to endemic regions. I
4 think this has some particular issues going forward
5 because if, in fact, other parts of the United States
6 -- Florida, around the Texas area -- I think that,
7 first of all, calling somebody endemic, it's a little
8 subjective.

9 To me, it's kind of a squishy definition and
10 there's probably going to be a preference by a lot of
11 communities to avoid being labeled endemic. But it's
12 particularly frustrating in light of the benefit risk
13 analysis that was done which would seem, to me, that
14 if you can define the parameters of testing
15 sensitivity and specificity, and you know your
16 seroprevalence data, you can do a risk benefit
17 analysis for a region without having to wait for it to
18 be declared endemic and it might be more flexible,
19 particularly, in areas.

20 It may be, going forward, that we will see
21 outbreaks such as occur with many of the flavies

1 (phonetic) in other parts of the world where they come
2 and go. So, we may have a bad year and we might see a
3 lot of dengue in a particular region. And by the time
4 the decision is made to actually do something, it will
5 be over and it won't come back for a few years. So,
6 we may miss opportunities in order to actually
7 implement something that may actually have quite
8 substantial benefits to communities.

9 **DR. EL SAHLY:** And Dr. Messer?

10 **DR. MESSER:** Yeah. I just also want to offer
11 a counterpoint interpretation of that, which is that,
12 if the goal of vaccination is to drive down disease
13 transmission and overall burden of disease, an
14 effective vaccine actually stands, again, under the
15 language of the question that we're looking at,
16 turning an endemic region into a non-endemic region.
17 And then how do you approach interpreting your
18 vaccination going forward? It can work in both
19 directions.

20 **DR. EL SAHLY:** Any additional questions or
21 comments? Dr. Edwards.

1 **DR. EDWARDS:** Do we have any serologic data
2 from Puerto Rico? I know it was only, like, 6 percent
3 or 10 percent of the study. But do we have any
4 serologic data from Puerto Rico from the studies that
5 were done?

6 **DR. GURUNATHAN:** We do have the data from
7 Puerto Rico. This is the summary of the data for
8 Puerto Rico. What you see here is the average titer
9 across the four dengue serotypes in Puerto Rico, so
10 these are seropositive. Of course, in the study,
11 everybody was 9 years and above. And you can see the
12 titers throughout the study. Starting with the
13 prevaccination titers and what the kinetics of the
14 antibody responses were over time, also compared to
15 the right side with the antibodies that were in the
16 control group.

17 **DR. EDWARDS:** Do you have a geometric titer or
18 the main titer? About 600, is that right?

19 **DR. GURUNATHAN:** The dot is the average titer
20 across the four serotypes. So, for example,
21 pre-vaccination, we don't have exactly a number in

1 this light, but you see that it's somewhere in between
2 probably 100 and 150, and then that goes up to
3 approximately 400 to 500. It has, then, a period of
4 some decay from the picked titer, post-dose 3, and
5 then maintains levels of antibodies after the year 2.

6 **DR. LEBLANC:** Is that the data that you were
7 looking for, Dr. Edwards? Or were you looking for
8 some other kind?

9 **DR. EDWARDS:** Oh, I think that's helpful to
10 know what the titers are in that population and kind
11 of put it into context of the other titers that we're
12 seeing.

13 **DR. EL SAHLY:** Okay. Dr. Monto?

14 **DR. MONTO:** Could I ask what the plans for
15 marketing this vaccine are? Are there any plans to
16 market the vaccine in the continental U.S. plus
17 Hawaii, or is this all going to be in Puerto Rico,
18 American Samoa, Virgin Islands?

19 **DR. GURUNATHAN:** For distribution of the
20 vaccine, the target at the moment is dengue-endemic
21 areas as defined by the U.S. CDC. So, the

1 distribution is going to be linked to that designation
2 as a measure to support, actually, appropriate use of
3 the vaccine. But, of course, if the dengue
4 epidemiology evolves, then that will also evolve. And
5 if some areas in Florida or Southern Texas would be
6 designated as dengue-endemic, then, of course, they
7 would become target for distribution as well.

8 **DR. EL SAHLY:** Okay. Dr. Offit?

9 **DR. OFFIT:** Let me ask this question. Let's
10 suppose, worst case scenario, that we introduce this
11 vaccine, say, with Puerto Rico, and people just decide
12 to use it off-label. They just gave the vaccine
13 without knowing the serological status of the person
14 who was getting vaccinated. Would you increase the
15 incidence of dengue shock syndrome and hemorrhagic
16 fever? Would that increase that incidence or not?
17 And does it depend on how endemic the virus is in a
18 given region? Whoever can answer that question.

19 **DR. GURUNATHAN:** Well, it depends on what's
20 the target population. If you're thinking about the
21 balance between those that are benefited by the

1 protection of the vaccine and those that are put at
2 risk while being seronegatives and vaccinated --

3 **DR. OFFIT:** Say you immunize all 9 to
4 14-year-olds. Period. You don't know their
5 serological status. You're just immunizing them all.
6 What would happen in the instance of dengue shock
7 syndrome, dengue hemorrhage fever?

8 **DR. GURUNATHAN:** It decreases. That's
9 basically what they've seen when you do the analysis,
10 regardless of serostatus. It's that you'd basically
11 see that, at the population level, there is a decrease
12 of those outcomes.

13 **DR. EL SAHLY:** Dr. Messer?

14 **DR. MESSER:** I would follow up that
15 observation, though, with the decrease that was seen
16 was in the context of both preexisting immunity and a
17 naive background. If your background is 100 percent
18 naive, then you're asking an entirely different
19 question.

20 So, the seroprevalence really does matter with
21 regard to whether you're going to see an increase or

1 not in disease. You have to have a preponderance of
2 seropositives that you vaccinate if you're going to
3 see the effect that you're looking for. It does not
4 appear to be protective against severe disease at all
5 in naives.

6 **DR. OFFIT:** Right. So that gets to the
7 question of how endemic it is in that region, right?

8 **DR. MESSER:** That's the issue. Yeah.

9 **DR. EL SAHLY:** And here's another question
10 along the line of long-term. Would a decrease in the
11 incidence of disease shift the age upward? In terms
12 -- because we're looking for people to have been
13 exposed, enough people have to be exposed. But are we
14 talking here very long-term. Your immune people, now,
15 are going to get older, right? Older than 9,
16 probability of having been exposed.

17 **DR. MONTO:** Yeah, I think that's -- you'd have
18 to model that, because it's pretty hard to judge on
19 the basis of -- given the fact that this is not
20 primary protection.

21 **DR. MESSER:** I think this depends, to a

1 certain degree -- and it's a question for the sponsor
2 -- the degree of uptake that they are anticipating in
3 the population that they are trying to vaccinate. If
4 you vaccinate at a sufficient level to start to
5 generate herd immunity, then I agree with your
6 observation that you're actually going to be
7 increasing the population of naives as you move
8 further, deeper into your vaccine penetration in the
9 population, which is creating sort of an alternate
10 problem.

11 It's an interesting paradox. This is a
12 vaccine that is actually dependent on the incidence of
13 its disease in order to be further administered in a
14 population. And there is no other precedent for that
15 either, that I can think of. But it's a paradox that
16 we should think about that, as you look for new
17 vaccinees, you must be looking for new cases of dengue
18 that have occurred in the background of your
19 vaccinated population.

20 **DR. KURILLA:** But are you really going to
21 increase the dengue-naive population? I mean, what --

1 **DR. MESSER:** Well, that -- yeah. So that
2 really depends on the outcomes. It depends on the
3 outcome of the vaccine campaign. If a vaccine
4 campaign is really targeting individuals who
5 personally want to reduce their risk of disease but
6 represent a small portion of the population, you're
7 unlikely to alter herd immunity. But if you alter the
8 number of susceptibles dramatically by doing a blanket
9 vaccine campaign, then you're taking a certain number
10 of susceptibles out.

11 **DR. KURILLA:** But I -- no, I don't understand
12 that because we're not preventing dengue infection in
13 people. We're really just preventing serious sequela
14 of the infection. And if there's a sylvatic component
15 to this, then we may not be impacting the presence of
16 dengue in the environment at all.

17 **DR. MESSER:** Your point's well taken. I'm
18 using disease as a surrogate for transmissible
19 viremia. There's probably a correlation between the
20 two. As far as sylvatic dengue goes, that is an
21 interesting side question to whether or not you have

1 sylvatic reservoirs that can reintroduce the vaccine
2 into a population where there is endemic transmission
3 that's been wiped out.

4 When you look at the phylogenies of dengue
5 viruses worldwide, that appears to happen very, very
6 infrequently. They really have developed to distinct
7 genetic -- phylogenetic lineages between sylvatic and
8 endemic. There isn't a whole lot of spillover. It's
9 certainly a possibility, but it's not a typical path
10 of reintroduction of dengue into susceptible
11 populations in endemic areas.

12 **DR. EL SAHLY:** Dr. Bennink?

13 **DR. BENNINK:** Yeah. Do you consider
14 additional booster shots or anything else that was
15 out? Because it was 30 months, even in the
16 seronegatives, from there. So, if you almost gave
17 annual or something else, not that you want to do that
18 for compliance and other things to get done. But, if
19 you did that, would the titers stay such that you
20 wouldn't get the effect?

21 **DR. GURUNATHAN:** I'm sorry. I lost a little

1 bit of the trail, so can you repeat? Oh, it was
2 booster. Yeah. I'm sorry.

3 **DR. BENNINK:** Yeah. In essence, you're trying
4 to make a seronegative like a seropositive because you
5 boosted it enough times or anything else.

6 **DR. GURUNATHAN:** Yeah. The role of the
7 booster is actually being evaluated in three studies.
8 But an important point is that we're not really
9 considering a booster as a rescue for seronegatives.
10 That is because of the risk that was identified, and
11 the recommendations by the program, Independent Data
12 Monitoring Committee, that we no longer vaccinate
13 seronegative individuals.

14 So, in seronegatives, we think we're not going
15 to be able evaluate a role of booster as a rescue.
16 The role in seropositives, whether it's needed and it
17 will result in sustainable responses, is something
18 that we will evaluate with the data that is being
19 generated.

20 **DR. BENNINK:** So, you're really only looking
21 at it in your studies from the seropositive

1 standpoint? Is that what you're saying?

2 **DR. GURUNATHAN:** Well, in two of the studies
3 that we're -- around our way, there were individuals
4 that were enrolled, whether they were seropositives or
5 seronegatives. So, there are some analyses that can
6 be done according to baseline dengue serostatus. One
7 observation from those studies is that distant
8 boosting -- now, this is about five years after the
9 completion of the primary series -- does, at least,
10 restores the antibody levels that are seen after dose
11 3.

12 For some serotypes, it increases the antibody
13 levels beyond those seen after the third dose in
14 seronegatives. Much more than that, we cannot say.
15 The study that is evaluating more approximate
16 boosting, which is evaluating boosting at 1 and 2
17 years, is not going to be able to address the question
18 in seronegatives.

19 **DR. EL SAHLY:** Dr. Meissner.

20 **DR. MEISSNER:** Thank you. I'd like to go back
21 to the question regarding herd immunity, because I

1 have been thinking about that in -- I know we're not
2 supposed -- today, we're not going to consider cost
3 effectiveness or qualities. But certainly, herd
4 immunity would be an important consideration when we
5 do get to the point of thinking about custom -- and I
6 had -- my own mind comes to the conclusion that there
7 would not be any herd immunity.

8 So, I just want to make sure that -- I wasn't
9 quite sure, with that discussion, if everyone agreed.
10 This is not going to reduce the circulation of this
11 virus in the population, number one.

12 Then, the second point that I want to -- as
13 follow-up to another question that was discussed
14 early, is, it seems to me that on balance this vaccine
15 will reduce the number of severe cases of dengue. But
16 there will be some cases that will probably occur as a
17 result of the vaccine. On balance, there will be
18 fewer cases, but there will still be some. And I
19 don't -- that's a principle of vaccinology that I
20 don't think we've ever gone there before. I'm
21 uncomfortable about that, I must say.

1 **DR. EL SAHLY:** Okay. Dr. Messer?

2 **DR. MESSER:** I wanted to go back to the
3 boosting question if that's all right. I appreciate
4 that it's being evaluated. I'm curious about what
5 endpoints are being looked at to establish whether or
6 not you need a boost. Is it loss of antibody titer?
7 Is it loss of evident protection in a sentinel cohort?
8 How is it that you're establishing the need for a
9 boost?

10 **DR. GURUNATHAN:** Again, the need of a boost in
11 seropositives is not clear. The data that we have
12 when we look at it by time period, perhaps we can
13 show --

14 **DR. MESSER:** Figure 30 from your briefing
15 manual.

16 **DR. GURUNATHAN:** Yes, I think it's the same
17 one. Yeah. Okay. What this figure shows is data by
18 time period. What you see here is that there is
19 protection maintained throughout the study at
20 different periods of time or windows. But you also
21 see that there is some level of protection decay from

1 the Active Phase to the rest of the study. The rest
2 of the estimates are consistent overall.

3 The one thing that is perhaps not captured
4 within this light is the effect that is expected on
5 the unvaccinated population used as a comparator
6 group. Because what is happening in the people that
7 are unvaccinated is that they get progressively
8 exposed to dengue, right? So, the gap in the
9 difference of the protective responses between the
10 vaccine and the control group is expected to diminish
11 over time as the control group gets more and more
12 exposed to vaccination.

13 So, two factors possibly at play here. One is
14 the decreasing antibody responses that you've seen
15 after the third dose of the vaccine, so that is one
16 factor. The other one is the fact that the control
17 group is acquiring more protective antibodies over
18 time. So, the complement to this figure here is the
19 figure on kinetics of antibody responses.

20 **DR. MESSER:** So, before we look at this
21 figure, just with regard to that observation, I agree.

1 But when you look at your control ends and your dengue
2 ends, the control ends over the last three periods
3 after the Active Phase remain essentially unchanged.
4 But the dengue ends are going up. So, you're actually
5 -- beyond, you're forcing more cases in your Dengvaxia
6 group without much of a change in the control group,
7 where your background immunity doesn't seem to have
8 changed as much in the control group.

9 **DR. GURUNATHAN:** Well, the epidemic is not
10 dystopic from year to year. So, I'm not sure that one
11 can look at the incidence in one year and compare to
12 the previous year and expect that they would be
13 identical. All right. So that's one point.

14 The other point I wanted to make was on the
15 antibody titers pattern, because that is a measure of
16 what are the changes in protective immunity. We can
17 summarize it here with this figure that you have to
18 maybe know the patterns before. There is an increase
19 of the titers from a prevaccination level to post-dose
20 3, where you can see the peak. Then, there is some
21 level of antibody decay at one and two years, and

1 after that, the antibody titers tend to remain
2 relatively plateau or stable.

3 In comparison, what you can see in the control
4 group is that, over time, they start acquiring a
5 higher level of antibodies as expected with exposures
6 to dengue and other flaviviruses over time.

7 **DR. MESSER:** Could it be that your year 3 and
8 4 Dengvaxia group was being boosted by the same virus
9 that boosted the population in your placebo control
10 arm, and that's why you don't see decay?

11 **DR. GURUNATHAN:** It could be. We cannot
12 distinguish that. It's a possibility.

13 **DR. EL SAHLY:** Dr. Kurilla?

14 **DR. KURILLA:** Yeah. So it's pretty clear that
15 you started this program with the expectation of a
16 primary prevention vaccine in seronegatives naive,
17 dengue-naive, which is why you've started with the
18 younger age group. But I'm wondering about what are
19 your long-term plans in terms of older age groups,
20 particularly in light of -- you showed the multitypic
21 efficacy.

1 And I understand that's a post-hoc analysis
2 and it really wasn't adequately powered, but I was
3 more concerned that two or more dengue infections were
4 going to show no vaccine efficacy at all rather than
5 actually more, but recognizing that some is better
6 than nothing. So, what about the over 45 group? Are
7 you pursuing that in terms of eventual -- for
8 licensure?

9 **DR. GURUNATHAN:** So, as I mentioned, we are
10 currently generating data on that age bracket. There
11 are two studies that are ongoing that include that age
12 bracket. They are including dengue-endemic areas, so
13 we expect to have a majority of seropositive
14 individuals from those studies in that age group.

15 In total, what we're expecting is to
16 supplement what we already have with about between 300
17 and 400 subjects exposed to the vaccine in that age
18 group, and we'll see what the data indicates to see if
19 it's potentially supportive to going up in the age of
20 indication.

21 **DR. EH SAHLY:** Dr. Wharton.

1 **DR. WHARTON:** How long is the extended
2 surveillance section of the study going to continue?
3 It was indicated on the figure as going through year
4 6, but is the plan to continue it beyond that?

5 **DR. GURUNATHAN:** No, there's a total of six
6 years. So, those studies have finished a follow-up
7 right now.

8 **DR. EL SAHLY:** Oh, so these remain under
9 analysis right now? Year 5 and 6.

10 **DR. GURUNATHAN:** So the integrated analyses
11 for those, according to serostatus, is being completed
12 at the moment. And we're expecting to send those
13 analyses to use of the incoming weeks and months.

14 **DR. EL SAHLY:** These data are of quite
15 interest, given the waning efficacy over years 2, 3, 4
16 that you showed in a couple of slides before.

17 **DR. GURUNATHAN:** We have actually some of the
18 data with the final data. And first, before showing
19 something that we have not submitted to the U.S. FDA,
20 I want to say that what was included in the analyses
21 that you saw which also was included in the file

1 before the analyses that we presented by serostatus,
2 included the vast majority of the data for severe and
3 hospitalized dengue.

4 So, that's -- to be precise, now that we know
5 the number of events that we had through the duration
6 of the studies, we can say that what was included in
7 the file corresponded to 96 percent of the total data.
8 And without maybe having to show specific data, I can
9 tell you that the information, the data, is not
10 measurably changed with the final information.

11 **DR. EL SAHLY:** And if there are no additional
12 questions, we will go around the table and ask for
13 final thoughts, beginning with Dr. Nolte.

14 **DR. NOLTE:** I don't have any other comments.

15 **DR. EL SAHLY:** Dr. Follmann?

16 **DR. FOLLMANN:** Final thoughts and then we'll
17 vote, I guess. Okay. So, for me the big issue is
18 this sort of risk benefit thing that was shown, I
19 think, pretty well on the sponsor's slide, C0108,
20 which showed they would prevent 193 cases of severe
21 dengue, right? So this slide -- this is sort of how I

1 think about bringing it all home and bringing it all
2 together on how we make a decision, but this is just a
3 very precise number.

4 I was curious about how robust this is to
5 different scenarios, like less seroprevalence; maybe
6 the test isn't as good; maybe when you go to the
7 hospital records, they're not so accurate because it
8 was an old test or someone wrote it down wrong; or I
9 don't know what else.

10 So, this is a very compelling case here, but I
11 wonder about sensitivity analyses. And I think the
12 sponsor mentioned that, in response to Dr. Offit's
13 question, that even if they just gave everyone in
14 Puerto Rico the vaccine, there would be a net benefit.
15 So, that's some comfort.

16 Then, I think the FDA also mentioned that --
17 they had Dr. Fink mention this, that they had done
18 what I would call sensitivity analysis and risk
19 benefit analysis. It seemed like you were suggesting,
20 Dr. Fink, that they gave you some comfort. Under
21 different scenarios, you felt there was sort of a

1 robust benefit. So, I also did a little calculation
2 myself, looking at 33 percent seroprevalence in here
3 instead of 50 or 56 -- whatever it was. And all of
4 these things are suggesting to me that there's still a
5 pretty big benefit under -- I don't want to say worst
6 case, but kind of a bad case scenario.

7 This is what's the main thing driving me.
8 This is the main thing I'm thinking about. A minor
9 comment had to do with something that Dr. Kurilla sort
10 of brought up which has to do with bridging,
11 ultimately, so I think they bridge to the older people
12 based on antibody alone, thinking -- but the older
13 people are going to have had more dengue exposures.
14 So, maybe the vaccine efficacy won't be as strong in
15 the older people as it was in the younger people.
16 Even if they have the same antibody titer, maybe the
17 old guys had another one or two infections, so the
18 vaccines won't work as well.

19 That just is another uncertainty about the
20 extrapolation going on. I don't know if they could
21 look at that as well. So, you know, I have an opinion

1 and I think additional sensitivity analyses of this
2 type, to make sure it's really solid, would be helpful
3 later.

4 **DR. EL SAHLY:** Thank you. Mr. Toubman?

5 **MR. TOUBMAN:** Yes, thanks. Again, understand
6 that I don't understand this stuff nearly as much as
7 everybody else in the room. But I have significant
8 concerns that when the question was put to the
9 applicant on would -- if you don't screen at all and
10 just do it, will you reduce disease? The answer is
11 yes.

12 Well, that's coming from a company that really
13 wants to see this thing approved. It's the same
14 company that did not include the C23 study. And then,
15 when asked about it, gave an answer that wasn't
16 accurate.

17 Obviously, they have an interest in pushing
18 this. I think Dr. Messer dug down into that and said,
19 well, no, actually, it depends. That's an answer that
20 might make sense; but if you have a very high naive
21 population, then it may not be true. Since I don't

1 understand this stuff, I look at other people and what
2 WHO said beside the thing I quoted before. They said,
3 "Only if prevaccination screening is not feasible,
4 vaccination without individual screening could be
5 considered in carefully selected areas with recent
6 documentation of seroprevalence rates of at least 80
7 percent by the age of 9 years."

8 And Puerto Rico -- it sounds like we've been
9 hearing, like, low 50s. So, even by the WHO
10 standards, you would not even consider doing this
11 without the screening. So, to me, that's critical.
12 It has to be done, though I just think this should be
13 rejected unless there's really strong testing
14 available.

15 I understand that the slide 107, 108 -- I
16 agree with this nice slide that said, well, here's the
17 benefit even if you don't screen. But this is
18 premised upon 100 percent sensitivity. And they
19 acknowledge that it was before the Zika situation
20 developed, and that reduces those figures. So,
21 there's problems with the test.

1 The thing I'm focusing most on, though, is how
2 practical is the test? I appreciate Dr. Levine's
3 creative suggestions about school-based testing and
4 all that. But he asked, does anybody have any
5 thoughts of that from Puerto Rico? And I believe
6 there are several people here from Puerto Rico.
7 Nobody volunteered to say, oh, yeah, we're all set to
8 do that; we're great; great shape; things are great
9 economically here; we can just do it. That's not
10 realistic.

11 So, I would like to propose, frankly -- and
12 this has happened before at one of these meetings is,
13 you know, there's the question and we're given only
14 two choices, yes or no. But we can suggest something
15 in between. And I would like to suggest, in light of
16 the very helpful answer that Dr. Gruber obtained from
17 the applicant that they are working on developing a
18 rapid test for the end of 2020, as I heard it, which
19 is really good news, I would like to propose that we
20 alter the first question, inserting the phrase
21 same-day or point of service laboratory-confirmed.

1 I would like to see that, because I just don't
2 trust that this test is going to be done. Under the
3 current conditions, particularly in Puerto Rico, I
4 don't think it's going to be done. Therefore, given
5 that we're way below 80 percent by the WHO
6 recommendation, where you wouldn't consider applying
7 this vaccine without the testing, I think we would
8 want to see that kind of protection. Thank you.

9 **DR. EL SAHLY:** Thank you, Mr. Toubman. Dr.
10 Munoz-Jordan?

11 **DR. MUNOZ-JORDAN:** You have asked a few times
12 about our opinion from Puerto Rico. We are from CDC,
13 and we're not from the Department of Health and we
14 don't know -- I mean, Puerto Ricans have been with
15 considerable infrastructure clinical laboratories
16 everywhere; there's schools everywhere. So, these
17 kinds of things could occur. It's not out of the
18 picture, but I don't know what the plans are in terms
19 of the health authorities in Puerto Rico. And that's
20 the comment I have about that.

21 In terms of my concerns, I do not see a clear

1 strategy yet devised by the company, in terms of what
2 is the testing strategy for implementation in Puerto
3 Rico? Is it going to be laboratory-based? My
4 impression, in Puerto Rico, is that clinical
5 practitioners cannot run rapid pace in their offices.
6 Rapid paces have to be run in a clinical laboratory
7 setting.

8 So, my impression is that they will attempt to
9 do that in a clinical laboratory setting. But it is
10 not clear to me what is the test. What is the study
11 that they plan to do? And with that being so crucial,
12 I agree that that is a concern that I have.

13 **DR. EL SAHLY:** Dr. Messer?

14 **DR. MESSER:** Yeah. So I'd like to preface my
15 comments by saying -- acknowledging the really
16 heartfelt testimony by the public about how incredibly
17 unpleasant dengue is, and about the incredible need
18 and desire there is for a vaccine in an endemic area,
19 and the incredible amount of work that's gone into
20 developing this vaccine. With regard to the
21 questions, I have a couple of lingering thoughts that

1 I think I'll just share now.

2 Question number one, are the available data
3 adequate to support the effectiveness of Dengvaxia for
4 preventing dengue disease? I think there are a lot of
5 data to show that their vaccine is effective in
6 seropositive vaccinees aged 9 to 45. I don't actually
7 take much issue with that. I would make one
8 observation about the available data though. This is
9 a retrospective analysis of a vaccine trial that was
10 designed to test a different question.

11 Many times, we have been burned in medical
12 field by applying retrospective analyses of data and
13 making prospective assumptions about whether or not
14 that retrospective analysis really reflects what a
15 prospective study that did sero-testing before
16 vaccinating subjects in endemic areas would provide in
17 terms of protection. And that's not what's provided
18 here. That is a standard that we typically look to.

19 So, really, to ask the question of
20 effectiveness, you would really have to do what's
21 proposed here which is to sero-survey subjects,

1 vaccinate them with a test, and see how many misses
2 you have and how many people get sick as a result of
3 your misses. I don't know that that is necessarily
4 something that we can solve; but it is, I think, a
5 shortcoming of the available data.

6 My second question regards boosting and the
7 necessity for boosting. The available data show
8 through year 4, maybe 5, there is efficacy. The
9 durability of that efficacy beyond that time point
10 isn't really established, and I think that boosting
11 and the need for a booster should be formally
12 assessed, frankly. And some endpoints that say
13 whether or not it needs to be done could probably be
14 defined. It doesn't necessarily have to be a barrier
15 today, but it's something that I think is a concern.

16 Then, the final question I have already was a
17 little bit addressed by Dr. Munoz-Jordan. The
18 available data supporting the safety really depends on
19 the specificity and sensitivity of the assay with a
20 background seroprevalence that makes that assay a
21 good, safe assay for identifying people who are going

1 to be properly vaccinated and for identifying people
2 who would be at risk.

3 I think, at the moment, there is a lot of
4 equipoise about the efficacy of the serologic study in
5 Puerto Rico in the context of the recent Zika outbreak
6 and whether or not those tests are capable of really
7 making that delineation in a safe manner. So, I would
8 echo some of the other concerns that you've heard.

9 **DR. EL SAHLY:** Thank you.

10 **DR. EDWARDS:** Well, I still continue to be
11 concerned about the bridging data and whether the
12 bridging data are adequate to assess and to compare,
13 serologically, the efficacy studies. I don't think
14 we've seen the granularity of that data, and the
15 extent of that data makes me very uncomfortable to say
16 that I can say that we've adequately addressed that.
17 I also have concerns about the safety.

18 And I think that, if we use a commercially
19 available test that says the patient is seropositive
20 and have sera before that, and then an adverse outcome
21 occurs and, really, the patient gets a false positive

1 serology that we contribute to disease and there's a
2 severe outcome. I think that there is a lot to be
3 said for the damage that does, in terms of vaccine
4 safety. So, I don't think we have a test that won't
5 allow us to adequately say whether they're
6 seropositive that will be able to be used in the
7 field.

8 **DR. EL SAHLY:** Thank you. Dr. Beckham?

9 **DR. BECKHAM:** I would reiterate what everyone
10 said about the diagnostic testing today. I don't
11 believe we have a test available to allow us to
12 determine whether or not this would be safe in the
13 field. In the light of that, I have serious concerns.

14 **DR. EL SAHLY:** Thank you. Dr. Wharton?

15 **DR. WHARTON:** I am impressed with the disease
16 burden in the population that's under discussion in 9
17 to 45-year-olds and the health system impact that
18 potentially could be prevented by a vaccine. I think
19 there is an opportunity for prevention. And I think
20 the data for the populations that were actually
21 studied in the efficacy studies, it's compelling that

1 the vaccine does prevent these severe outcomes in
2 these seropositive people.

3 Others have already commented on the
4 limitations of available laboratory tests, and I think
5 the really significant operational challenge is about
6 routinely having to do a serologic assay prior to
7 vaccination. It's just, operationally, a really
8 difficult thing to do.

9 I'm also concerned about making a decision on
10 use of a vaccine among adults in Puerto Rico based on
11 data -- somewhat sparse data, actually -- from India
12 and Vietnam. I could understand if it was another
13 country in the region, but it's not. And it's not
14 that I've got a high expectation it would be
15 different. But to not have anything for a decision
16 like this just really -- I'm really uncomfortable with
17 that.

18 **DR. EL SAHLY:** Thank you. Dr. Swamy?

19 **DR. SWAMY:** Yeah. So I think I'm somewhat
20 similar to things that have been said, but I struggle
21 with the fact that it's not dissimilar when we think

1 about a screening test. We don't go out and screen
2 people for something we don't have a treatment for.
3 So, now we're sort of looking to approve a treatment
4 that we don't have validation -- that we have a screen
5 for that we can use. It seems a little backwards.

6 The other fact is that, generally speaking,
7 when we go to disseminate something based on clinical
8 trials, we do it similarly to the eligibility criteria
9 of the trial. And we're being asked to approve
10 something that's based on things that were not used in
11 the trials.

12 There was not a screening and then treatment
13 modality in the trials. So, I'm not disputing the
14 data and that there certainly appears to be benefit in
15 those who are seropositive, but those were
16 subpopulations of the larger population.

17 I think, from the safety perspective, we're
18 looking at thousands upon thousands of individuals who
19 got the vaccine. But now, we're taking that
20 subpopulation of people to, then, treat. So, those
21 are my concerns.

1 **DR. EL SAHLY:** Thank you. Dr. Bennink?

2 **DR. BENNINK:** Yeah. I don't have a lot to
3 add, I would say, in terms of what has already been
4 said. I think if I was focusing a little bit on
5 something, again, I would say something about the
6 boosting because of the drop-off, to some extent, of
7 even the ones.

8 But even whether it could help in the case for
9 the -- if there was testing or something and the
10 seronegatives somehow got vaccinated, whether that
11 actually would make a difference. And then you
12 wouldn't have those negativities that you see
13 otherwise. So, I think there's lots of reasons here
14 at that.

15 **DR. EL SAHLY:** Thank you. Dr. Kurilla?

16 **DR. KURILLA:** Yeah. Two points. I think it
17 needs to be recognized that we're really talking about
18 a very novel application of vaccine technology that
19 really hasn't gotten a lot of attention, and that is
20 not trying to prevent disease in a naive population
21 but actually treating people who have already been

1 infected, and not in a therapeutic sense but in
2 another manner of preventing downstream potential
3 disease. It's true that the original development and
4 design of the studies was not really done that way.
5 It was really what came out of the data. So, I think
6 we need to be a little cautious.

7 Because, while it's certainly breaking new
8 ground and potentially offers a lot of applications in
9 potentially other disease areas -- whether this can be
10 expanded even beyond just limited to dengue serotypes
11 but potentially maybe even other types of flavies and
12 a lot of other related viral families -- there's a lot
13 of potential here. But I think we need to be a little
14 cautious.

15 The second point is in line with what a lot of
16 other people have said, is I think that the
17 diagnostics are really absolutely critical here. And
18 I think it is incumbent to really define not just
19 what's out there already, but really to define what
20 the sort of minimum sensitivity and specificity
21 combined with the available seroprevalence data that

1 would really allow public health officials, in
2 general, to make a decision as to whether this is a
3 vaccine they want to implement in their region, as to
4 whether it's going to have an overall effect on the
5 population.

6 **DR. EL SAHLY:** Thank you. Dr. Levine?

7 **DR. LEVINE:** I agree with a number of the
8 points colleagues have made around the table. Looking
9 at the specific question that we grapple with, on the
10 age range, I am also sensitive to the point that Kathy
11 Edwards made about the serological bridge and the
12 leap. And since there are some other -- I think
13 limiting the initial use approved target for this
14 vaccine to the school-age group, I think, is the way
15 to go and not depend upon the bridge because there's
16 so many questions on the serology.

17 In terms of the safety profile for a
18 population with a known endemic burden, I am convinced
19 that where there's a fair amount of disease where they
20 tested the vaccine -- that's where you go to test the
21 efficacy of a vaccine -- clearly, it brought down

1 disease and it was, then, dissected, such that it
2 worked better in people who were seropositive. But
3 not only did it not work as well in the seronegative,
4 there was a safety signal, such that we wanted to
5 identify those people.

6 I know the WHO grappled with this and there's
7 a great editorial in the New England Journal by Lisa
8 Rosenthal called "Trolleyology and the Dengue Vaccine
9 Dilemma." If anybody hasn't read it, you should read
10 it. It's great. Basically, what it gets at, if I can
11 take 15 seconds, if a trolley --

12 **DR. EL SAHLY:** Thirty. Thirty seconds.

13 **DR. LEVINE:** Okay. If a trolley is moving
14 towards a group of four or five people and is going to
15 hit them, and there's a split in the tracks, and
16 there's one person standing along the other track, and
17 there is a bystander looking at this and has the
18 chance to pull a switch that would change the train,
19 what is the ethical thing to do?

20 Do you save the four people but essentially
21 kill the single person? That's kind of the dilemma

1 that we deal with, is getting the public health
2 benefit without harming. And that's where the test
3 comes in. I think the test is so important.

4 I can't grapple successfully with the Zika.
5 But take the Zika away, and what I've seen about one
6 of these tests says that a test is possible. And to
7 me, to have the opportunity to look at this vaccine in
8 the school-age group, post-licensure, and to learn and
9 gain, to get the answer rather than to assume or guess
10 or model informally, I think, is a way to go.
11 Ultimately, one would want a really good test.

12 I can't technically speak to the Zika, just
13 looking at what was tested here. So, to me, it's all
14 about the test. Maybe we need some more information.
15 And the other point is limited to the school-age kids,
16 and then I think we should look post-licensure. We
17 learn so much post-licensure with those caveats.

18 **DR. EL SAHLY:** Thank you. Dr. Meissner?

19 **DR. MEISSNER:** Thank you. The first point is
20 that I thought the presentations this afternoon were
21 terrific, by the sponsor. And I appreciate all the

1 effort that's gone into this. I think, as has been
2 said, the burden of disease is quite real and there is
3 a lot of suffering from dengue, and this vaccine
4 offers an opportunity to reduce much of that illness.
5 And I think that's what we all want. The problem, I
6 guess, that I'm wrestling with is one of the
7 principles of administering vaccines is that everybody
8 has an opportunity to benefit.

9 But, with this and from the data that's been
10 presented by the sponsor, there will be, clearly, a
11 reduction in the amount of disease. But there will
12 also be a few cases that can be traced back to the
13 vaccine. And I'm uncomfortable with that. I think
14 that even when there is a good test, there is still
15 going to be errors in testing. And there is with
16 every test. It will be misinterpreted or there will
17 be problems.

18 So, this vaccine may result in an undesirable
19 outcome. And I don't -- on balance, it will be
20 wonderful. But I worry about the situation where
21 there is going to be complications from the vaccine

1 itself.

2 **DR. EL SAHLY:** Okay. Thank you. Dr. Monto?

3 **DR. MONTO:** When you come next to last,
4 there's very little to say that hasn't been said
5 before. So, I'm just going to focus, first, on my
6 shared discomfort about the bridging data. Because I
7 thought more data could be given to us. I'm not so
8 concerned about the region of the world but the
9 numbers, which were relatively small. I'm just going
10 to focus on the questions.

11 And I hate to hear that we're going to kick
12 the can down the road in terms of the implementation
13 of the program; but if we look at the question we are
14 asked, it says, "Living in endemic areas and
15 laboratory-confirmed previous dengue." I'm willing to
16 vote on that, assuming that we can confirm dengue with
17 a test, which is going to be at least reasonably
18 sensitive and specific.

19 I hate to take tests that are being advertised
20 with certain sensitivity and specificity data without
21 getting independent confirmation. So, I think we need

1 to look at the question we're being asked.

2 **DR. EL SAHLY:** Okay. Thank you. Dr. Offit?

3 **DR. OFFIT:** So we have a disease that we know,
4 as expressed by the people who came up to the
5 microphone, that is common, that is associated with --
6 at least, in endemic areas, is associated with
7 suffering and hospitalization and death. We have,
8 clearly, in hand, a technology that can prevent that
9 if used the right way. So, that becomes the question,
10 if used the right way. But what's incumbent upon us
11 now is to be able to make sure that we select away
12 from a seronegative population.

13 Now, I've seen one case of dengue in my life.
14 It came up from Puerto Rico. It took me a little
15 while to figure it out. I think that physicians in
16 Puerto Rico would've had far less trouble figuring out
17 than I did. I mean, they're used to seeing this. So,
18 in terms of who's been clearly symptomatically
19 infected in the past, they'll know.

20 So then the question becomes someone who is
21 asymptotically or less symptomatically infected, and

1 now we rely on a serological test, which are not
2 perfect. They have -- their specificity and
3 sensitivity's only so good. But still, you're largely
4 going to select that for a population that likely has
5 been infected before.

6 So, do I think, when balanced, this will do
7 far more good than harm? Yes. And unlike -- I mean,
8 it's not like we haven't, in the past, used vaccines
9 in this country which have been harmful.

10 In the oral polio vaccine, it was known to be
11 a cause of vaccine-associated paralytic polio for
12 decades. And we continue to use it in this country,
13 even though it caused six to eight cases of vaccine-
14 associated paralysis every year until we finally got
15 away from that in the late 90s, early 2000s.

16 And there was another option there, which was
17 the inactivated vaccine. But here, you have the
18 option, actually, of just making sure that someone has
19 been previously infected, either clinically or
20 serologically.

21 So, therefore, it becomes incumbent upon us to

1 do everything that we can do when we introduce these
2 vaccines into regions not only like Puerto Rico, but
3 presumably, there's an interest in going to Vietnam
4 and India and Singapore, et cetera, to make sure that
5 it's very clear what the purpose of this is, which is
6 we have to use it the right way.

7 So, I think instead of backing away because
8 it's difficult to use it the right way, I think we
9 should just be -- double our energies to make sure it
10 is used the right way. So, that's how I see it.
11 Thanks.

12 **DR. EL SAHLY:** Thank you. In light of the
13 discussions of today, I'm considering the questions
14 that we are asked. There are concerns that were
15 already voiced, namely the absence of a reliable test
16 for use right now. Right after we vote, we cannot
17 recommend a test or tell the doctors, "Go use that
18 test," given that the seropositivity was imputed. And
19 I meant to ask that question, but there were so many
20 bright questions being asked, I probably ran out of
21 time.

1 The seropositivity was imputed 13 months after
2 dose 1 without -- and we were not given data on what
3 was going on with the circulation of dengue in those
4 13 months and in that particular region. Then, the
5 absence of a correlative protection, we were asked to
6 bridge data to adults based on really small numbers.

7 So, all of the above are causes for concern
8 regarding this particular vaccine and the content of
9 the questions being asked.

10 Dr. Gruber, do you have any final comments or
11 instructions?

12 **DR. GRUBER:** Well, we appreciate the lively
13 discussion and suffice it to say we had a lot of very
14 similar discussions internally. So, we understand
15 that this has been a very difficult and complex topic
16 that we brought before you. I think what we want to
17 do, and I just had some initial exchanges to my
18 colleagues, I don't know where they arrived at. I'm
19 going to have to verify before I suggest a path
20 forward here. Okay?

21 **DR. EL SAHLY:** Sure. Thank you.

1 **MR. TOUBMAN:** In the meantime, can I ask a
2 question about the questions?

3 **DR. EL SAHLY:** Wait until she comments.

4 **MR. TOUBMAN:** Okay. Thank you.

5 **DR. GRUBER:** Thank you. That's what I
6 thought. I think what we'd like for the committee to
7 do is really vote on question one the way it is
8 currently phrased. And depending on the outcome, we
9 may have another question that we actually prepared in
10 anticipation of these discussions.

11 **DR. EL SAHLY:** Okay. Can you put the question
12 on the screen please? To read the question: Are the
13 available data adequate to support the effectiveness
14 of Dengvaxia for the prevention of dengue disease
15 caused by dengue virus serotypes 1, 2, 3, and 4 in
16 persons 9 through 45 years of age with lab-confirmed
17 previous dengue infection and living in endemic areas?
18 Please vote on your microphone yes, no, or abstain.

19 **MR. TOUBMAN:** Excuse me, can I ask a question?
20 The question I had, it was premised upon the comment
21 by the fourth person -- the last public speaker who

1 raised a concern that adverse events did not include
2 getting sick from dengue. And I don't know if that's
3 accurate. I think I've seen it different ways.

4 But in terms of the questions, when we're
5 talking about the clear -- it's confirmed for sure
6 that there are some people who have adverse events in
7 terms of hospitalization and severe disease. Is that
8 affecting effectiveness or is that safety? That's my
9 -- I just wasn't sure which way it was.

10 **DR. EL SAHLY:** The way it was presented today,
11 hospitalization and virologically-confirmed disease,
12 that's relating to effectiveness. Hospitalization
13 from dengue, confirmed disease from dengue.

14 **MR. TOUBMAN:** And including from the vaccine
15 as well? It factors in people who seem to have gotten
16 it -- or increased risk of it because of exposure to
17 the vaccine.

18 **DR. EL SAHLY:** Well, that probably is safety,
19 but most of the data presented was on effectiveness
20 today.

21 **MR. TOUBMAN:** Okay.

1 **DR. EL SAHLY:** Can you please go and vote?

2 **DR. GRUBER:** Can I comment? I'm sorry.

3 Before everybody votes.

4 **DR. EL SAHLY:** Yes. Go ahead.

5 **DR. GRUBER:** I think the concern expressed by
6 Mr. Toubman -- we would like to really have this
7 addressed under question two, because there we're
8 asking specifically about the safety of the vaccine.
9 And what we have to really keep in mind there is this
10 clearly identified safety signal that was observed
11 when seronegative individuals received the vaccine.

12 And in that regard, I've asked can we get a
13 vote on question one? And then we would adjust
14 potentially. But I think -- in light of this comment
15 just made, I think we would like to hear your votes on
16 questions one and two as currently phrased before we
17 continue.

18 **DR. EL SAHLY:** Okay. I probably misunderstood
19 your question as what was presented. Okay.

20 **MS. HUNTER-THOMAS:** Did everyone vote on
21 question one?

1 **DR. EL SAHLY:** Okay. The votes are in. One
2 more. Someone didn't vote. Yes, please.

3 **MS. HUNTER-THOMAS:** So, it was a total of 14
4 votes. 6 indicated yes to question number one, that
5 we have 1 abstained, and we have 7 no's. So, now
6 we're going to read the results individually.

7 Dr. El Sahly, no. Dr. Swami, no. Dr.
8 Wharton, no. Dr. Beckham, no. Dr. Edwards, no. Dr.
9 Messer, yes. Mr. Toubman, yes. Dr. Follmann, yes.
10 Dr. Kurilla, no. Dr. Levine, no. Dr. Meissner, yes.
11 Dr. Monto, yes. And Dr. Offit, yes. Bennink is the
12 abstained. Thank you.

13 So, now, do we go to question number two as
14 Dr. Gruber --

15 **DR. EL SAHLY:** Going to question number two:
16 Are the available data adequate to support the safety
17 of Dengvaxia when administered to persons 9 through 45
18 years of age with lab-confirmed previous dengue
19 infection and living in endemic areas? Please vote
20 yes, no, or abstain. Are all the votes in?

21 **MS. HUNTER-THOMAS:** So we have a total of 14

1 that have voted; 7 voted yes, zero abstains, and 7
2 no's. So we'll read the results individually.

3 Dr. El Sahly was a yes. Dr. Swami, no.
4 Wharton, no. Beckham, no. Edwards, no. Messer, no.
5 Toubman, no. Follmann, yes. Bennink, yes. Kurilla,
6 yes. Levine, yes. Meissner, yes. Monto, no. Offit,
7 yes. Thank you.

8 **DR. EL SAHLY:** Dr. Gruber, additional
9 questions or instructions?

10 **DR. GRUBER:** Yeah. We have to throw up the
11 additional questions that we have prepared. And I
12 don't know if this can be transmitted from -- can we
13 hook up your computer? Give us a minute, okay?
14 Because we need to display it.

15 **DR. EL SAHLY:** Okay. Here's question three.
16 Are the available data adequate to support the
17 effectiveness of Dengvaxia for the prevention of
18 dengue disease caused by dengue virus serotypes 1, 2,
19 3, and 4 in persons 9 to less than 17 years of age
20 with lab-confirmed previous dengue infection and
21 living in endemic areas? Please vote yes or no.

1 **MS. HUNTER-THOMAS:** Okay. So we have a total
2 of 14 votes. 13 indicated yes, zero abstains, and 1
3 no. So, we'll read the votes results individually.

4 The one no is Dr. El Sahly. Dr. Swami is yes.
5 Wharton, yes. Beckham, yes. Edwards, yes. Messer,
6 yes. Toubman, yes. Follmann, yes. Bennink, yes.
7 Kurilla, yes. Levine, yes. Meissner, yes. Monto,
8 yes. And Offit, yes. Thank you.

9 **DR. EL SAHLY:** Okay. Well, thank you all for
10 this very lively and engaging --

11 **MS. HUNTER-THOMAS:** Oh. Oh, there's another
12 question. Sorry.

13 **DR. EL SAHLY:** Okay. You said -- I thought
14 one question. Okay.

15 **DR. GRUBER:** I'm sorry. That was -- but in
16 light of the vote, we had these two additional
17 questions.

18 **DR. EL SAHLY:** Two additional. Okay.

19 **DR. GRUBER:** Yes. Sorry.

20 **DR. EL SAHLY:** Are the available data adequate
21 to support the safety of Dengvaxia when administered

1 to persons 9 through less than 17 years of age with
2 lab-confirmed previous dengue infection and living in
3 endemic areas?

4 **MS. HUNTER-THOMAS:** Okay. We have 14 votes
5 submitted and we'll read -- it's a total of 10 yes,
6 zero abstained, and 4 no. Now, I'll read the results
7 individually.

8 Dr. El Sahly, yes. Swami, yes. Wharton, yes.
9 Beckham, no. Edwards, no. Messer, no. Toubman, no.
10 Follmann, yes. Bennink, yes. Kurilla, yes. Levine,
11 yes. Meissner, yes. Monto, yes. Offit, yes. Thank
12 you.

13 **DR. EL SAHLY:** Any additional questions or
14 instructions from Dr. Gruber?

15 **DR. GRUBER:** No. I thank the committee for
16 the additional votes and, again, appreciate how
17 difficult the discussion was. We hope we can move
18 forward now with our review and the discussions with
19 the applicant. Thank you.

20 **DR. EL SAHLY:** Thank you to all.

21 **MS. HUNTER-THOMAS:** This meeting is now

1 adjourned. Thank you all. Have a great evening.

2 **OPEN MEETING ADJOURNED**