# FOOD AND DRUG ADMINISTRATION (FDA)
# Center for Biologics Evaluation and Research (CBER)
# 120th Meeting of the Blood Products Advisory Committee

## OPEN PUBLIC MEETING

## TOPIC I: Evaluating Strategies to Reduce the Risk of Zika Virus (ZIKV) Transmission by Blood and Blood Components

**FDA White Oak Campus**
**10903 New Hampshire Avenue**
**Great Room, Building 31**
**Silver Spring, MD 20903**

**March 20, 2019**

*This transcript appears as received from the commercial transcribing service after inclusion of minor corrections to typographical and factual errors as recommended by the DFO.*

# ATTENDEES

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| Richard M. Kaufman, M.D. | Brigham and Women's Hospital |
| Prabhakara Atreya, PhD | Food and Drug Administration (FDA) |
| Judith Baker, Dr.PH, MHSA | UCLA- Division of Pediatric Hematology/Oncology |
| Sridhar V. Basavaraju, M.D. | Centers for Disease Control & Prevention |
| Evan Bloch, M.D., M.S. | Johns Hopkins University School of Medicine |
| Barbara Bryant, M.D. | University of Texas Medical Branch |
| Meera B. Chitlur, M.D. | Wayne State University |
| Alfred DeMaria, M.D. | Bureau of Infectious Disease and Laboratory Science |
| Michael DeVan, M.D. | Walter Reed National Military Medical Center |
| Roger Lewis, M.D., Ph.D. | Harbor-UCLA Medical Center |
| Thomas Ortel, M.D., Ph.D. | Duke University Medical Center |
| Martin Schreiber, M.D. | Oregon Health & Sciences University |
| Amy Shapiro, M.D. | Indiana Hemophilia and Thrombosis Center |
| Jack Stapleton, M.D. | University of Iowa |
| Susan L. Stramer, Ph.D. | American Red Cross |
| F. Blaine Hollinger, M.D. | Baylor College of Medicine |
| Caren Chancey, Ph.D. | Office of Blood Research and Review, FDA |
| Marc Fischer, M.D. | Centers for Disease Control and Prevention |
| Sirjana Rajbhandary, M.P.H. | AABB |
| David Leiby, Ph.D. | Office of Blood Review and Research, FDA |

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| Andrei Kindzelski L., M.D., Ph.D. | National Institutes of Health |
| Tom Hardiman, M.D. | ROCHE |
| Jerry Holmberg, M.D. | GRIFOLS |
| Mike Busch, M.D. | VITALANT |

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## CALL TO ORDER/INTRODUCTIONS

**DR. KAUFMAN:** Hello. We're going to go ahead and get started. So, if I can ask everyone to take their seats. I really want to welcome everyone to what should be a very interesting couple of days. In particular, I want to welcome the members of BPAC as well as the speakers who will be presenting on the various topics that we will be talking about. I'd like to also welcome members of the general public and the audience who is joining us by webcast.

Just to get started, I want to point out that we have a couple of members of the committee that are calling in: so, Dr. Meera Chitlur and also Sue Stramer. And for everyone else that's here, I'd like to ask that the members please introduce themselves and give your institutional affiliation as well as your expertise. I'll start with Dr. Schreiber, please.

**DR. SCHREIBER:** Hi. I'm Marty Schreiber. I'm from Portland, Oregon. I work at Oregon Health and Science University, and I'm a general surgeon there. I

have a laboratory, and we are very interested in novel blood products. And I think that's why I'm sitting here today. Thank you.

**DR. BAKER:** Hi, Judith Baker from the Center for Inherited Blood Disorders in California, and UCLA, Peds Hematology. My background is in public health.

**DR. BLOCH:** I'm Evan Bloch. I'm Associate Director of Transfusion Medicine at Johns Hopkins.

**DR. STAPLETON:** Jack Stapleton. I'm a professor in internal medicine and microbiology at the University of Iowa. I'm an infectious disease physician who clinically does HIV and laboratory works on flaviviruses and HIV interactions.

**DR. DE MARIA:** Al DeMaria. I'm the medical and laboratory consultant with the Massachusetts Department of Health, and formally state epidemiologist and medical director at the Department of Public Health.

**DR. BRYANT:** I'm Barbara Bryant. I'm from the University of Texas Medical Branch in Galveston. I'm the medical director of the transfusion service.

**DR. HOLLINGER:** I'm Blaine Hollinger. I'm Professor of Medicine, Molecular Virology and Epidemiology at Baylor College of Medicine, mostly expertise in blood-borne pathogens, particularly hepatitis.

**DR. DEVAN:** Hi, I'm Mike DeVan. I'm the medical director for transfusion services at Walter Reed.

**DR. KINDZELSKI:** Hi. Andrei Kindzelski. Program director of blood division NHLBI NIH.

**DR. SHAPIRO:** I'm Amy Shapiro. I'm a pediatric hematologist from the Indiana Hemophilia and Thrombosis Center where I'm the medical director. My main interests are hemostasis and thrombosis and benign hematology.

**DR. ORTEL:** Tom Ortel from Duke. I'm chief of hematology there. My primary interests are in hemostasis and thrombosis.

**DR. LEWIS:** Roger Lewis. I'm the chair of Emergency Medicine at Harbor-UCLA Medical Center in Los Angeles, affiliated with UCLA. My primary academic

interest is in clinical emergency medicine and clinical trial design and statistics.

**DR. BASAVARAJU:** Sridhar Basavaraju, director of the CDC Office of Blood, Organ, and Other Tissue Safety.

**DR. KAUFMAN:** I'll be chairing the meeting. My name is Richard Kaufman. I'm the medical director for the Transfusion Service at the Brigham and Women's Hospital in Boston, and my specialty is transfusion medicine.

So, I'd like to ask Prabha to please read the Conflict of Interest statement.

**DR. P. ATREYA:** Before I do that, Dr. Chitlur, are you online? Are you available by phone? Can you introduce yourself. Okay. And Dr. Sue Stramer?

**DR. STRAMER:** Yes. Can you hear me?

**DR. P. ATREYA:** Yes. Can you introduce yourself, please?

**DR. STRAMER:** Certainly. My name is Susan Stramer. I'm the industry representative to the committee. My day job is Vice President of Scientific

Affairs at the American Red Cross, and my interests are infectious disease and testing.

**DR. P. ATREYA:** Excellent. Thank you. Good morning everyone. My name is Prabhakara Atreya and it is my pleasure to serve as the Designated Federal Officer for the 120th BPAC meeting. The committee management specialists for this meeting are Ms. Joanne Lipkind, Natalie Mitchell-Funderburk and Angelica Jones. They are outside at the registration table. And the committee management officer for this meeting is Ms. Marie Keller who assisted in the Conflict of Interest reading and also making travel and meeting arrangements.

On behalf of the FDA, the Center for Biologics Evaluation and Research, we would like to welcome everyone to this meeting. The meeting has three topics overall. We will complete topic one and two today and topic three tomorrow. Today's session topic one is open to the public in its entirety. The topic two has an open session followed by a closed session.

The meeting has been announced in the Federal

Register Notice on February 15, 2019. The press media representative of the FDA today is Paul Richards and also Ms. Megan McSeveney. I think Mr. Paul Richards is in the audience, if you can stand. So, if anybody has a question, you can contact him.

I would also like to remind everyone to please check your pagers and cell phones, and please make sure they that are turned off or on silent mode. Also, when you make your statement, please state your name first and then speak up so that the comments are accurately recorded by the transcriptionist. Our transcriptionist today is Linda Giles here. And also, now I'll proceed to read the Conflict of Interest statement.

**CONFLICT OF INTEREST STATEMENT**

The Food and Drug Administration is convening today, March 20, 2019, for the 120th meeting of the Blood Products Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972.

Dr. Richard Kaufman is serving as the chair of the meeting for all three topics covered between today and tomorrow.

Today, on March 20, 2019, for topic one BPAC will meet in open session to discuss the evaluation strategies to reduce the risk of Zika virus transmission by blood and blood components. This topic is determined to be a particular matter of general applicability. Presenters and speakers will likely provide data on various products or strategies that set only as examples for the committee to have a scientific discussion while considering various classes of products or strategies related to the topic.

This meeting is not being convened to recommend any action against or approval of any specific product or strategy or to make specific recommendations that may potentially impact any specific party, entity, or individual or form in a unique way.

Similarly, this meeting will not involve the approval or disapproval of labeling requirements, post-marketing requirements, or related issues regarding the legal status of any specific products. Any discussion of individual products will be only to serve as

examples of the product class.

In the afternoon for topic two, in the open session, the committee will hear overview presentations on the intramural laboratory research programs of the Laboratory of Biochemistry and Vascular Biology from the Division of Blood Components and Devices of Office of Blood Research and Review.

Per agency guidance, this session is determined to be a non-particular matter which will have no impact on outside financial interests. Hence, no affected firms were identified, and members were not screened for this topic. In the latter part of the afternoon, the meeting will be closed to permit discussions where disclosure would constitute a clearly unwarranted invasion of personal privacy under 5 U.S.C. 552(b)(c)(6).

With the exception of the industry representative, all participants of the committee around the table are either special government employees or regular government employees from the other agencies who are subjected to the federal

Conflict of Interest laws and regulations. The following information on the status of this advisory committee's compliance with the federal ethics and Conflict of Interest laws including, but not limited to, 18 U.S. Code 208 is being provided to participants at this meeting and to the public. This Conflict of Interest statement will also be available for public viewing at the registration table.

Related to the discussions at this meeting, all members and SGE consultants of this committee have been screened for their potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouse or minor children and, for the purpose of 18 U.S. Code 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents, and royalties, and their primary employment.

FDA has determined that all members of this advisory committee are in compliance with federal

ethics and Conflicts of Interest laws.

Under the 18 U.S. Code 208, Congress also has authorized the FDA to grant waivers to special government employees and regular government employees from other agencies who have financial conflicts of interest when it is determined that the agency's need for a particular individual's service as a subject matter expert outweighs the concern related to his or her potential financial conflicts of interest. However, based on today's agenda and all financial interests reported by members and consultants, no Conflict of Interest waivers were issued under 18 U.S. Code 208.

Dr. Sue Stramer is currently serving as the industry representative to this committee. Dr. Stramer is Vice President of Scientific Affairs at the American Red Cross. Industry representatives act on behalf of all regulated industry and bring general industry perspective to the committee. Industry representatives are not appointed as special government employees and they serve only as non-voting members of the committee.

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

Dr. Judith Baker is serving as the consumer representative of this committee. Consumer representatives are appointed special government employees and are screened and cleared prior to their participation in the meeting. They are voting members of the committee and, hence, they do have voting privileges and they do participate in the closed sessions if they are held.

Dr. Blaine Hollinger serves today as a temporary voting member for all topics of this meeting. He's a professor of medicine, molecular virology and epidemiology, as well as the director of Eugene Casey Hepatitis Research Center at Baylor College of Medicine. He brings his expertise with the bloodborne infectious diseases for the benefit of the committee discussions.

With regards to the external speakers, Dr. Marc Fischer is employed by CDC and serves as one of

the speakers for this meeting on the topic one. Dr. Fischer is a regular government employee and has been screened prior to his participation.

At this meeting, there may be other regulated industry speakers and outside organization speakers making presentations. These participants may have financial conflicts of interest associated with their employer and with other regulated firms. The FDA asks in the interest of fairness that they address any current or previous financial involvement with any firms whose products they may wish to comment upon. These individuals were not screened by the FDA for conflicts of interest.

FDA encourages all of the participants to advise the committee of any financial relationship that they may have with any firms, these products, and if known, any stated competitors.

We would like to remind members, consultants, and participants that if the discussions involve any of the products or firms not already on the agenda for which an FDA participant has a personal or imputed

financial interest, the participants need to inform the DFO and exclude themselves from such involvement and discussions. Their exclusion will be noted for the record.

This concludes my reading of the Conflicts of Interest statement for the public record.

At this time, I would like to hand over the meeting to our chair, Dr. Kaufman. Thank you, Dr. Kaufman.

**DR. KAUFMAN:** Thank you. So, we'll begin with topic one: Evaluation of Strategies to Reduce the Risk of Zika Virus Transmission by Blood and Blood Components. And at the conclusion of this session, the BPAC will be asked to vote on potential strategies for screening for Zika; namely continuing with the current approach of minipool or NAT testing of all units, ceasing all testing, or something in the middle.

So, I'd like to first introduce our first speaker, Dr. Caren Chancey from FDA. She'll be talking about the Evaluation of Strategies to Reduce the Risk of Zika Virus Transmission by Blood and Blood

Components.

Before you begin, Dr. Chitlur, are you able to see the slides?

**DR. CHITLUR:** Yes, I am. Thank you very much.

## EVALUATION OF STRATEGIES TO REDUCE THE RISK OF ZIKA VIRUS TRANSMISSION BY BLOOD AND BLOOD COMPONENTS

**DR. CHANCEY:** Okay, can everyone hear me? Okay. Thank you. My name is Caren Chancey. I'm a biologist with the Product Review Branch in the Division of Emerging and Transfusion Transmitted Diseases in OBRR. I'll be introducing our topic one today, which again is Evaluation of Strategies to Reduce the Risk of Zika Virus Transmission by Blood and Blood Components.

Our topic one issue for today is that the current FDA guidance issued in July 2018 recommends universal testing for U.S. blood donations by minipool nucleic acid testing, MP NAT, or individual donation nucleic acid testing, ID NAT, with triggering the ID

NAT when certain conditions are met, indicating risk of Zika transmission. However, the available information indicates a decline in Zika transmission in the U.S. and the Americas. Therefore, FDA is reevaluating its July 2018 recommendations on testing blood donations for Zika using MP or ID NAT.

For topic one, today, I will be presenting some background on the issue on Zika virus itself; on public health risks and U.S. blood safety concerns; and finally, a brief history of the screening of the U.S. blood supply for Zika. I'll then briefly outline the speakers for the rest of this topic. Then you'll hear from the FDA on consideration of blood safety options, questions for the committee, open public hearing, discussions, and voting.

Zika virus is an enveloped arthropod-borne virus, or arbovirus, with a single-stranded RNA genome. It is a member of the family Flaviviridae and the genus Flavivirus. As such, it is closely related to other transfusion-transmitted viruses, such as the dengue virus, West Nile virus, and yellow fever virus. Over

here on the right is a schematic of a cross-sectional and surface view of a representative flavivirus showing the protein envelope and genomic RNA.

Zika virus is transmitted primarily by Aedes mosquitoes. These are also the mosquitoes that transmit dengue, yellow fever, and chikungunya virus, which is an alphavirus. Zika is most commonly transmitted by Aedes aegypti. It was first identified in a rhesus monkey in the Zika forest of Uganda in 1947. The first human infections were reported from Nigeria in 1953.

The transmission routes for Zika virus or similar to those of other viruses for which humans are a reservoir host. Most commonly, Zika is transmitted between humans by the Aedes aegypti mosquito. Less commonly, it may also be transmitted from human to human during pregnancy from an infected mother to a fetus, between sexual partners, by blood transfusion, and rarely by laboratory transmission or other routes.

Although Zika virus was first identified over 70 years ago, it was not really considered a

significant public health risk until an outbreak in the Americas in 2015 and a similar outbreak in French Polynesia a few years earlier. At that time, the high potential for the Zika outbreak to spread to the United States was recognized due to an increase in travel-associated Zika virus cases due to U.S. travelers returning from Zika-affected areas, which are now greater in number and closer to the U.S. Also risk came from the presence of competent mosquito vectors throughout much of the United States.

Although Zika was originally considered to be relatively mild and self-limiting in healthy adults, as the outbreak progressed, significant potential morbidity of Zika was recognized, including congenital microcephaly in infants that were born to mothers that were infected with Zika during their pregnancy and also the neurological disease Guillain-Barré syndrome.

Sexual transmission was recognized for Zika virus and also it was thought likely and, as I will discuss further, was demonstrated that transfusion transmission also could occur for Zika virus.

Zika virus is believed to be a risk for a transfusion transmission first off because other flaviviruses such as West Nile and yellow fever are known to be transfusion transmitted, and dengue. Like those viruses, most, approximately 80 percent, of individuals remain asymptomatic and thus feel well enough to donate blood and would not be recognized by symptomatic screening.

The presence of virus in the blood may begin one to two days prior to symptom onset, if symptoms occur; and typically persists one to two weeks, although it may last longer in some individuals. And viral RNA can typically be detected for longer in whole blood or red blood cells relative to serum or plasma.

And what we know regarding Zika, specifically, is that in studies of the outbreaks in French Polynesia and the Americas it was shown that asymptomatic blood donors were Zika RNA positive at rates of 2.8 percent over the outbreak in French Polynesia and at peak rates in the Americas ranging from 1.8 to 3 percent. Three probable transfusion-transmitted cases were reported

from Brazil. And lastly, a retrospective study of the French Polynesian outbreak identified 30 Zika RNA reactive units that were transfused to 26 patients. However, in follow-up on the 12 patients for which information was available, none of them had Zika symptoms following transfusion.

So, FDA has issued guidance on Zika virus and transfusion transmission. The initial guidance was issued in February 2016, entitled Recommendations for Donor Screening, Deferral, and Product Management to Reduce the Risk of Transfusion Transmission of Zika Virus.

This guidance was revised twice: in August 2016 and then again in July 2018. And I would also like to note at this point that the guidance for blood screening is the only one under discussion today. There will be no changes to the tissue screening guidance at this time.

In the initial guidance from February 2016, it was divided into areas with and without active Zika transmission. Areas with active Zika transmission were

directed to obtain blood and blood components from unaffected areas until pathogen reduction technology and/or testing for Zika became available. This affected Puerto Rico significantly. All blood components were obtained from the continental U.S. between March 5, 2016, and April 2, 2016, due to a significant Zika outbreak in Puerto Rico. At that point, Zika NAT was implemented under an investigational new drug protocol on April 3, 2016.

For areas without active Zika transmission, it was recommended that donors be screened by questionnaire and deferrals then be issued for known Zika infection or risk that was associated with travel to Zika-affected areas or sexual transmission.

After the first guidance was issued, a numberof significant pieces of knowledge were obtained. First and most importantly, two NAT-based assays for Zika virus were developed. And testing began under IND in April 2016 for Roche's assay and June 2016 for Grifols' assay.

The first reports of local mosquito-borne

transmission in the United States occurred in Florida during this time. And it was also noted that a significant lag time existed between the transmission themselves and recognition and confirmation of local mosquito-borne transmission.

Also over this time, concern increased about sexual transmission as a mode of spread of the epidemic because that really had not been previously recognized as a mode of spread for an arbovirus.

This increased the logistic complexity and challenges of donor screening for these risk factors, especially for local transmission, for questioning for domestic travel as opposed to travel outside the country. And ultimately, it was believed that there would be a potential effect of travel-based deferrals on the adequacy of the blood supply in some areas.

Therefore, in August 2016, FDA issued a revised guidance stating that all donations collected in the U.S. and its territories must be tested by investigational or licensed when available ID NAT or pathogen reduced using FDA approved PRT devices for

plasma or apheresis platelets.

ID NAT was phased in different areas of the United States based on risk through December 2016. Donor screening and deferral based on travel and sexual contact were discontinued, except that the deferral for recent history of confirmed Zika infection was maintained for 120 days after the positive viral test or resolution of symptoms, whichever was longer.

So, at the time of this guidance in 2016 -- I'm not going to discuss this extensively because you're going to hear more about it from the CDC, but a significant outbreak did occur in the U.S. territories and states. Over 5,000 cases in the U.S., most of which were from travelers, but 224 locally transmitted by mosquitoes. In the U.S. territory, over 36,000 cases, almost all of which were locally transmitted.

During this period, U.S. blood donations were being tested by Zika ID NAT under IND using two tests: the investigational cobas Zika test from Roche, which was licensed by the FDA on October 5, 2017; and then, at the time, investigational Procleix Zika assay from

Grifols, which was then licensed by the FDA on July 5, 2018.

In the U.S. states, over 11 million donations were tested with 398 initially reactive and 50 confirmed positive. In Puerto Rico, 111,842 donations were tested with 369 initially reactive, 356 of those were confirmed positive.

Again, just briefly, between 2017 and 2018, there was a significant drop-off in cases in both the U.S. states and the U.S. territories, and no local transmission observed in the United States in 2018.

So again, in the light of that information, we undertook reevaluating some risk in 2017 through 2018 overall with the decrease in Zika cases reported both in the U.S. and worldwide over those years. Therefore, FDA convened a meeting of the Blood Products Advisory Committee in December 2017. And they provided advice on screening blood donors for Zika.

First, the committee recommended that the incidence of Zika in the U.S. did not warrant continued universal testing by ID NAT; however, that blood

establishment should not stop testing donations for Zika in the U.S. and its territories. There were a number of options. The majority of the committee supported use of minipool NAT with a trigger to ID NAT.

Therefore, based on these recommendations, FDA issued a second revision of the guidance in July 2018, stating that all donations collected in the U.S. and its territories must be tested by either minipool NAT or ID NAT or pathogen reduced using an FDA approved PRT device for plasma or apheresis platelets.

ID NAT was recommended when certain conditions were met, indicating an increased risk of suspected mosquito-borne transmission in a defined geographic area. This was, if a Zika reactive donation was identified and local transmission was possible, based on the presence of transmitting mosquitoes, the trigger would be immediate.

If in prior areas of increased risk -- those in Florida and Texas -- there would be time allowed for an investigation if it was not in those areas. The trigger would also occur if the CDC announced an

increased risk in an area based on infections detected outside the blood donor population. In those cases, MP NAT may resume if the reactive donation was not due to local mosquito-borne transmission based on the investigation or if there are no cases in the area in 14 days and CDC removes any risk designation.

Since cases have continued to decline through 2018 and this year, FDA seeks advice from the committee on three proposed testing strategies to be presented today, which you will hear about in more detail later. Number one is no policy change, continue universal testing for Zika by minipool or ID NAT. Number two is regional testing for Zika with minipool or ID NAT with considerations for different regional options. Number three is to eliminate all testing for Zika virus.

You will be hearing more from speakers on today's topics from Marc Fischer from the CDC; Srijana Rajbhandary from the AABB; and finally, David Leiby from FDA will present the questions for the committee. Thank you.

**DR. KAUFMAN:** All right. Thank you. So, I

would next like to introduce Dr. Marc Fischer from CDC who will provide an update on the current status of the Zika virus epidemic.

**UPDATE ON THE CURRENT STATUS OF THE ZIKA EPIDEMIC**

**DR. FISCHER:** All right. Thank you. Good morning. I'm Dr. Marc Fischer from the CDC Arboviral Diseases Branch. We're based in Fort Collins, Colorado. It's a pleasure to be here this morning.

I'm going to skip the first two slides, as Dr. Chancey really covered them. The first slide is just a basic overview of Zika virus and its transmission. The second slide reviews the epidemiology that was already discussed as far as its identification and spread from 2007 to 2015.

I'll start here with Zika virus in the Americas. In 2015, as we already heard, the first locally acquired cases in the Americans were reported in Brazil. And then over the next two years, by the end of 2017, local mosquito-borne transmission had been reported in 48 countries or territories in the

Americas. As of today, the only countries in this region without reported local transmission are Bermuda, Canada, Chile, and Uruguay.

For the United States from 2007 to 2014, before the introduction into the Americas, there were 14 Zika virus disease cases identified all among U.S. travelers. Following the introduction and spread in the U.S. in the Americas, cases among travelers increase substantially. In 2016, there were large outbreaks in the three U.S. territories of Puerto Rico, U.S. Virgin Islands, and American Samoa. And then limited local mosquito-borne transmission was identified in the two states of Florida and Texas.

Okay, so this describes Zika virus surveillance activity in the U.S. Zika virus disease and Zika virus infection without disease, including positive blood donors, became a nationally notifiable condition in 2016. Cases and infections are reported to the CDC ArboNET system by all state and territorial health departments. That reporting is done according to standardized case definitions that have clinical

epidemiologic and laboratory criteria.

There are separate case definitions for congenital and non-congenital infections. Everything I'll present today is all for non-congenital infections and disease cases. When we report cases, we include both confirmed and probable cases in our reports and MMWR and on our web pages.

These are the case definitions for Zika virus disease cases, non-congenital. A confirmed case is a clinically compatible illness with laboratory evidence by Zika virus isolated in culture by viral antigen or positive RNA test, or serologically Zika IgM antibody with positive Zika neutralizing antibodies and negative neutralizing antibodies against dengue or, occasionally, other flaviviruses that are endemic to the region.

A probable case, as I'll include, is also a clinically compatible illness, but the laboratory evidence is just serologic: either an IgM antibody test with both positive Zika and dengue virus neutralizing antibodies; or Zika IgM with negative dengue virus IgM

and no neutralizing antibody testing performed.

In ArboNET, we also collect information on what we call presumptive viremic blood donors or viremic blood donors as I'll refer to them today. The definition we use in ArboNET that we asked state health departments to report is an initial reactive ID or minipool NAT result with confirmation by either a repeat Zika virus RNA by the same or an alternative NAT assay on the same or a follow-up sample; Zika IgM antibody with Zika neutralizing antibodies in the same or a follow-up sample; or Zika virus isolated or viral antigen detected in any specimen. So, this is a slightly different definition and is used by some of the blood services agencies as in AABB, and the counts as far as numbers of cases will not always match up exactly.

So, I'm going to start now by running through the data numbers of cases for Zika virus disease cases that have been reported to ArboNET from 2016 through 2018. So, this slide shows the numbers of both confirmed and probable cases reported to CDC by year

over the three-year period. And you see, as we've heard already, a dramatic decrease -- over 99 percent from the peak of 41,680 cases. This is reported for both states and territories. 2016 decreased to 1118 cases reported in 2017, and then 220 cases reported in 2018.

This slide for territories and states show the breakdown between those two. You could see that in 2016, 88 percent of the vast majority of the cases were reported from U.S. territories. This includes confirmed and probable cases and, again, excludes congenital disease and includes both travel-associated local acquired cases.

In 2017, of the 1,118 cases, now about 60 percent of them were reported from U.S. territories and 40 percent from states. And then in 2018, it was about two-thirds reported from the territories and 33 percent or 72 cases from the states.

When we look at just the cases reported from the territories, you could see that in all three years, 99 percent of them were attributed to local

mosquito-borne transmission. Obviously, there could be sexually transmitted cases included here; there's no way to separate those out. But basically, those people did not have a travel history. You could see also in the footnote that the vast majority of these cases were reported from Puerto Rico.

So, 97 percent of the cases across all three years from the territories were reported from Puerto Rico; 1,034 or 3 percent were reported from the U.S. Virgin Islands; and 131, less than 1 percent, were reported from American Samoa. There were a few travel-associated cases reported from Puerto Rico: 145 in 2016 and then one each in 2017 and 2018.

This is the same type of breakdown for cases reported from U.S. states, but you see really the flip of what we just saw. That is in the second row, you see the travel-associated cases, which was 95 to 100 percent of all the cases reported from U.S. states were travel associated, including all of the cases in 2018. I apologize. The columns are column headers are missing there, but they're same year '16, '17 and '18.

There were, as we heard, 231 locally transmitted cases reported across the 3 years: 224 cases in 2016 and 7 in 2018. Most of those, 95 percent, were reported from Florida and 11 cases or 5 percent from Texas.

And then the last row are other routes of transmission which include 52 sexually transmitted cases; 2 that were attributed to laboratory transmission; and 1 an unknown route, possible person-to-person transmission. There are no reported or identified cases of transfusion-transmitted transmission in the United States.

Focusing just on 2018 to get into an idea of where the activity remains, this shows the 73 travel-associated cases reported to ArboNET in 2018: 72 from U.S. states and 1 from Puerto Rico. So about three-quarters of the cases, the travelers had traveled within the Americas but outside the United States. The greatest proportion of those were to the Caribbean and most of those were to Cuba; 21 of those 27 were to Cuba. The 15 cases with travel to North America were

all to Mexico. And then there were a few cases to several countries in Central and South America. There are 12 cases -- this is a correction from your handout -- 12 cases who had traveled to Asia, parts of the Western Pacific. And then 8 cases that were travel associated, but we didn't have information on the specific country or region that they traveled to.

Now this is a busy slide. I'm going to walk you through it. These are the cases reported by state or territory of residents where the cases live, combining again both states and territories across the three years. And I think this is relevant to the discussion today.

So, each column shows the number of cases reported in that year. And I've chosen the sort of top seven jurisdictions that reported the most-number of cases in decreasing order. So, if you see in 2016, there were 41,680 cases reported overall to ArboNET: 85 percent of those were reported from Puerto Rico; and then 1,107 from Florida, which is 3 percent; 1,002 from New York; and so on down the line. As you move down to

New Jersey, there are then additional states and territories that reported additional cases, but they're all less than one percent of the total cases. If you add up these 7 jurisdictions, which are being considered for today's recommendations, they account for 95 percent of all the cases reported in 2016.

If you move over to 2017, it shows the same data for the 1,118 cases. Now, as the outbreak waned in Puerto Rico, you see it accounts for a much smaller proportion of the cases -- a little over half, 56 percent of all the cases -- and Florida accounted for 10 percent of the cases. This is both a combination of travel-associated and local transmission. And then you see the remaining jurisdictions down to New Jersey with one percent. If you add up those 7 jurisdictions -- the 2 territories and 5 states -- listed in 2017, they accounted for 85 percent of all the cases reported to ArboNET.

And then in 2018, of the 220 cases, you see a similar breakdown; Puerto Rico now accounted for two-thirds of the cases. You can see now California,

which is listed the fifth state down, accounted for 12 percent of the cases. So, there's a moving of the travel-associated risk, but these 7 jurisdictions combined still accounted for 92 percent of all the cases reported.

Then in the last column, I just show the population to give a sense of how much of the total U.S. population you'd be accounting for in these 7 jurisdictions, about 119 million, which is about a third of the total U.S. population considering these 7 jurisdictions.

I'm going to move on and do a similar run through for blood donor, viremic blood donor, data reported to ArboNET. So, the first slide shows the number of viremic blood donors reported to ArboNET: 363 in 2016. Again, you see a 99 percent decline over the next two years with 38 reported in 2017 and just 3 cases or 3 viremic blood donors reported to CDC in 2018.

This shows the breakdown between U.S. states and territories. So, in 2016, 90 percent of those

positive blood donors were reported from the territories, all from Puerto Rico; and 38, or 10 percent, were reported from various U.S. states. In 2017, there's sort of a flip of the viremic blood donors; and of the 38 cases, 32 or 84 percent were reported from U.S. states.

I will say that probably about half of those 32 cases are not actually confirmed, and were initial reactive NAT positive or NAT reactive but then were not confirmed but were by error remain within ArboNET and that will come in as an important distinction when we get to the by jurisdiction reporting that I'll go through. And then in 2018, there were only three viremic blood donors reported, all from U.S. states; no reactive donations reported from Puerto Rico or territories.

This is again the breakdown just for 2018 of just the three travel-associated cases, travel-associated viremic blood donors. One had traveled to the Caribbean again to Cuba, and two had traveled to Mexico.

This is the same slide that breaks down by jurisdiction the report to the viremic blood donors. So, in 2016, of the 363 positive or reactive blood donors, 325 or 90 percent were from Puerto Rico; 23 or 6 percent were from Florida; and after that, there's 1 percent or less from the remaining jurisdictions that I'm showing on the slide. And overall, that accounted for 358 of the 363 positive blood donors.

In 2017, again, there are 38 reactive blood donors reported to ArboNET and these 7 jurisdictions only account for 18, or less than half or about half, of those. However, of those 38, about half of those, as I said, appear to be an initial reactive positive that were not confirmed. And those cases were all from states other than are listed here. If you remove those 17 cases, in the end, these 7 jurisdictions are really 5 since New Jersey and U.S. Virgin Islands have zero reactive blood donors. These five jurisdictions would account for about 85 percent of the donors once we remove those cases that we don't believe are true confirmed viremic blood donors.

Then, in 2018, there are three viremic blood donors; two were reported from Florida. The third was reported from Minnesota and so is not listed on this table.

I'm going to move on now to broaden out the epidemiology and discuss the Americas at large, what has happened with the outbreak. So, this slide shows now what we call suspected and confirmed cases reported from countries in the Americas to PAHO. In this case, suspected would be a clinically compatible illness. And that definition may differ by country, with no laboratory confirmation performed, or they may even have negative laboratory testing but are still included in the numbers.

Confirmed has various types of laboratory evidence which would also differ by country. So, using that definition lumping everything together -- and I'll show the breakdown by suspected and confirmed on the next slide -- there were over 651,000 suspected and confirmed cases reported in the region in 2016 to PAHO. In 2017 there were 55,328. And by 2018 just over

28,000 or just under 29,000 cases. So, you see a sort of mirror of the same type of decline in cases from the region.

This shows a breakdown of those cases by year, by confirmed or suspected status, to give you a sense of how many of these have some laboratory evidence. So, you could see in 2016 and 2017, of all the cases reported, about a third -- 30 to 36 percent -- had some type of laboratory confirmation or were called laboratory confirmed.

There are some countries that will actually call a case confirmed without laboratory evidence if the patient has clinical findings consistent with Zika and has an epidemiologic link to another confirmed case. So, there are some cases, even in the confirmed category, that don't necessarily have positive laboratory testing.

Moving over to 2018, you'll see there's been a significant shift -- less surveillance, less testing performed. And of the 28,700 cases reported to PAHO, only 12 percent were reported as confirmed or had

laboratory testing performed.

Looking at a breakdown by sub-region within the Americas, I've broken Brazil out of South America just so you get a sense, because they by far have the greatest number of cases. And then the rest of the regions are South America, Central America, Caribbean, and North America. In North America, I've included Canada, the U.S., and Mexico. If you look at the web page that I have linked here, PAHO separates Mexico out from North America. So, you would need to add it back in to get the same numbers here.

So, in 2016, of the 651,000 cases, just under a half of them were just reported from Brazil alone. Another 160,000 from the remainder of South America, excluding Brazil, and 152,000 from the Caribbean.

In 2017, there's a similar breakdown. Brazil accounting for 31,700 of the 55,000 cases, followed now by the remainder of South America. And then the virus moved further north than they were more cases in Central America than the Caribbean.

And finally, in 2018, of the 28,700 cases

reported, 19,000 of those -- so still two-thirds of them -- were reported from Brazil; 14 percent from the remainder of South America; 13 percent from Central America; 4 percent from the Caribbean; and importantly, 860 or 3 percent from North America, really all of those being predominantly from Mexico. And I'll talk a little bit more about those.

This just shows you by region the differences in the testing patterns. So, of the 19,000 cases reported from Brazil, only 1400 or 7 percent of them are laboratory confirmed. So, these cases could be other things; dengue, even chikungunya, or other non-arboviral diseases. The remainder of South America did a little better with testing; about a third of those cases are confirmed.

And then in North America, Mexico, all of the cases, all 860 that are reported are laboratory confirmed. So overall for the region, 12 percent of all the cases that are reported in 2018 were confirmed.

And then finally for the region, this shows the breakdown of suspected and confirmed cases by

country in decreasing order of incidents. So again, at the top of the list is Brazil with a total of 19,020 cases. Of those, 1379 were confirmed or 7 percent, and Brazil has a population of over 210 million. Then you could see the other countries that account for the remainder of the 28,000 or so cases reported in 2018 and the proportion of them in the second column that are confirmed.

So only 5 percent of the cases reported from Guatemala were confirmed but a third of the cases reported from Bolivia; all of the cases from Mexico; and 71 percent of the cases from Columbia. And then you can see the fifth row down, Cuba had 873 cases, although they don't report any data on laboratory evidence. But as I mentioned, that's where most of the travel-associated cases to the Caribbean have now been reported from in 2018.

This shows the epi curve by week, just to demonstrate that most of the cases reported in 2018 from the Americas were reported in the first half of the year, or at least there was a declining incidence

over the year by week.

There are a couple important exceptions, and Mexico is the one that I want to touch on. So, in 2018, as I mentioned, there are 860 all laboratory-confirmed cases were reported from Mexico. The map shows the states in Mexico that are depicted on the table. And you could see most of these cases are being reported or were reported from the north and north and west part of the state, which is a different area than Mexico had cases in previously.

And Sonora, Sinaloa, and Baja California, which are those three northwestern most states, including Sonora, which borders Arizona, about half of all those cases that were reported from those states were reported just in November and December of 2018. So, they had cases really later in the year and fairly recently, just as recent as three or four months ago.

Finally, I'm going to end with just a quick discussion about the outbreak in India that occurred last year. So historically, during the initial outbreak in 2016 that occurred in the Americas, there

were a small number of cases that were reported by the Indian Ministry of Health. There were five cases reported from Gujarat state between 2016 and just one case reported from Tamil Nadu state.

In addition, there's a study which is cited at the bottom that did some retrospective testing for Zika from specimens that were submitted for testing for other etiologies. And they identified retrospectively one additional case of Zika virus from Rajasthan state that occurred in 2016.

However, then in 2018, in Rajasthan state shown on the map on your right, which borders Pakistan up in the northwest part of India. They reported a case with onset in September of 2018, subsequently did some very active surveillance to identify cases, and identified a total of 159 cases: all with some laboratory evidence of infection, most PCR confirmed between September and October in 2018. The focus of the outbreak was in Jaipur, the capital city of Rajasthan state, which is shown on the map.

They then subsequently identified additional

cases in Madhya Pradesh, which is the state just to the southeast, shown in sort of a light green on the map. And overall, they identified about 130 cases from that state that were reported mostly in November of 2018.

Since that time, the ministry of health has reported that both outbreaks have subsided. They've stopped reporting new cases; although, it's sort of difficult to get additional information that's publicly available. This is all through reports, some press releases, or direct communications with the ministry of health.

So, in summary, large outbreaks of Zika virus peaked in 2016 and then substantially decreased in 2017. There had been lower levels of transmission that have continued in focal areas in some countries in 2018, of some importance includes Mexico and bordering areas of the southwestern United States. The U.S. territories have markedly decreased incidents in 2017 and '18. Although, sporadic infections have still been reported.

I will say most of the cases that are still

being reported from Puerto Rico are all only serologically confirmed. And it's possible those represent previous infections with persistence of IgM or cross-reactivity due to dengue or other flaviviruses. We've only had one PCR confirmed case from Puerto Rico in 2018 and two PCR confirmed cases from U.S.V.I. in 2018, and both of those occurred in January. So, there's really been very little evidence of circulating virus in Puerto Rico or U.S. Virgin Islands in 2018, and none thus far in 2019.

And then the incidence in disease risk among U.S. travelers has basically followed the epidemiology of the outbreaks in the Americas with marked declines in travel-associated cases after 2016, very few in 2018, and only that limited local transmission that we discussed in Florida and Texas in 2016 and '17. And I think I will stop there. Thank you very much.

**DR. KAUFMAN:** All right. Well, thanks very much. So, I'd like to ask the committee if there are any questions for the previous two speakers actually.

**DR. SCHREIBER:** Marty Schreiber from Portland.

Do you have any information on reported morbidity associated with transfusions that were given to patients?

**DR. FISCHER:** In the U.S.?

**DR. SCHREIBER:** Anywhere, any association with transfusions received and Zika contracted, and what the morbidity was associated with that.

**DR. FISCHER:** So, in the U.S., there have been no identified transfusion-transmitted cases, so no morbidity, no infections. There have been the cases that were referred to in the previous talk that have been published from Brazil with, as far as I know, no significant morbidity reported associated with those.

**DR. SCHREIBER:** So, in patients who aren't -- so my understanding is that the pregnant patients are the ones -- that the fetus is at greatest risk. Is that correct?

**DR. FISCHER:** Right. So, the risk -- clearly the greatest risk of Zika virus is in congenital infection and the congenital microcephaly and other birth defects that can result from it. So, the

greatest risk would be to infecting a pregnant woman and having the risk of congenital infection and those outcomes.

There is a risk of Guillain-Barré syndrome, as well, in people without any comorbidities; although the rate overall is relatively low, but it is certainly associated.

There have been a number of reports of not transfusion-associated disease, but there were reports of Zika virus infection, wild type infection, through mosquito. In immunocompromised populations, it's a fairly limited case series, some HIV infected, some transplant recipients. And there does not seem to be increased morbidity in those populations with wild type Zika virus, although it's a very limited number of reports.

**DR. HOLLINGER:** Ah, yes. Thank you for the information. We have to, of course, understand that testing was being done at the time and no transfusions could have been due to the testing. You mentioned there were three viremic cases in the U.S. states and

territories in 2018.

**DR. FISCHER:** Right.

**DR. HOLLINGER:** Did they have antibody? Did they have IgM antibodies, neutralizing antibodies, that fell into where these window period viremic cases?

**DR. FISCHER:** So, I don't have the specific data on the three cases; but in order to meet the case definition, if they were reported, according to it -- I'd have to look up those three specific cases. They would need to have positive NAT, NPR ID NAT, depending on when they were identified, and then have some type of confirmatory testing which would be a repeat NAT and/or serologic testing that was performed.

So, in all likelihood, those three cases did have some confirmatory neutralizing antibody testing or a second NAT, but I don't know off the top of my head for those three.

**DR. HOLLINGER:** But the important thing would be whether they had an antibody also?

**DR. FISCHER:** Correct. I mean, they --

**DR. HOLLINGER:** Okay.

**DR. KAUFMAN:** So, I was wondering if you could comment on what sort of the predictions or expectations are for India? And are there other parts of the world where there's not been an obvious clinical outbreak where the mosquito's present and there's concern for a future outbreak?

**DR. FISCHER:** Sure, I mean the presumption is that Zika virus is transmitted throughout most of the same areas of the world that dengue is transmitted. It has been identified in most of those areas. Many other countries in Southeast Asia have identified cases or even outbreaks: Cambodia, Vietnam, etc. in Southeast Asia and other parts of Asia.

Africa, also, we know the virus is transmitted and circulates. It's unclear whether it's the same, so there are different genotypes of Zika virus. There has been some data reported that different genotypes may have different risks for the congenital disease outcome.

And because of lack of really surveillance and testing, we don't know how frequent the transmission

is. We don't know if transmission may occur, where it occurs more in childhood, it's more frequent. And then so people of childbearing age are not susceptible or at risk for infection.

But the presumption is that Zika virus circulates throughout the tropics and subtropics and all the same places you would see dengue. And going forward, we will probably continue to see sporadic infections, endemic disease reported with occasional outbreaks.

As far as what's currently in India, I certainly would expect to see more outbreaks and disease in India. But currently, the outbreak that was reported in '18, again, appears to be over.

**DR. KAUFMAN:** Dr. DeMaria.

**DR. DE MARIA:** Considering what is known about what has been seen in the United States, is there an estimate of what the overlap is with malaria and deferral of donation on the basis of malaria and eliminating people who may have been exposed to Zika?

**DR. FISCHER:** That's a very good question. I

don't think I can answer that question. I don't know Sri or maybe -- can you answer that question? I don't -- so I can't answer that question. I think there must be overlap certainly with regard to travel relationships, but somebody else can probably answer that question better than me.

**DR. EDER:** Anne Eder, Office of Blood at CBER. So, generally, those deferral areas do not overlap. There is some overlap, but in general, they were in addition to in the Americas when the Americas were a deferral.

**DR. FISCHER:** Thank you.

**DR. KAUFMAN:** Dr. Basavaraju.

**DR. BASAVARAJU:** So, I had a question about the numbers that you showed from PAHO for 2018 and the fact that there's less testing. So, is the fact that there's fewer cases that are being reported just an effect of less testing, or do you think there's actually fewer cases?

**DR. FISCHER:** I think there's actually fewer cases. I mean, all of the evidence certainly points

that there's a dramatic decrease in disease and infections identified, including in 2017 when the amount of testing was the same. But I do think there probably is decreased testing and decreased surveillance as well. But I don't think that accounts for the entire pattern. And I think that's why you see similar patterns across the region in the U.S., when you look at blood donors, when you look at disease cases, some of which are independent of surveillance effort and testing efforts like screening of blood donors. You see all the same things. So, while I think there is some change in surveillance activity, I think we've seen a true decline in disease and infections from 2018 to '16.

**DR. BASAVARAJU:** So, if there was a resurgence of the epidemic in parts of the Americas, how quickly do you think that would be recognized?

**DR. FISCHER:** That's a good question. I mean, dengue is circulating right now in the Caribbean. There have been outbreaks in Jamaica and some other islands. We're expecting that there will be activity

in Puerto Rico. It's been remarkably quiet for several years with outbreaks in Puerto Rico. So, I think there will be some time period where things may be thought of or considered to be dengue before Zika is recognized.

However, there has been a shift in the sense that a trioplex assay, molecular assays are much more available now. And many more countries have the availability and capacity to do that testing. The trioplex essay, which most countries are using, test simultaneously for Zika, dengue, and chikungunya.

So, at least when patients present acutely within the first week or so of illness, there will be a recognition of the disease even if they're considering it to be dengue based on the clinical presentation. So, I think we will recognize it when it occurs, but I can't tell you how long that will take and how large the outbreak would need to be for us to know that it's occurring.

**DR. KINDZELSKI:** Ah, yes. Andrei Kindzelski. Do you have data from the European Union, for example, on the incidents and potential decline in the numbers

of Zika probably related to traveling infection there; and also what kind of approach the European Union is using to test for Zika in relationship to blood donation?

**DR. FISCHER:** A good question. I'm sorry, I can't completely answer it. So, the European CDC posts similar information, usually in periodic reports, as I've shown there for PAHO and for the United States.

All the cases reported in Europe have been travel associated. There was no local transmission, as far as I'm aware, recognized at any point in Europe itself. They were in territories of European countries. And they also have seen a dramatic decline, but I don't know the exact numbers over this period of time in travel-associated cases. I do not know what their approach is to blood donor screening. I'm sorry.

**DR. KAUFMAN:** Please, go ahead. Dr. Schreiber, please.

**DR. SCHREIBER:** Sorry. Second question. I know in the case of dengue fever the initial exposure can result in a febrile illness with a rash, but a

second exposure could be fatal in a patient that's been pre-exposed. Is the same true in Zika?

**DR. FISCHER:** No, as far as we know. I mean, there's been a fair bit of work. I mean, for Zika there's only one serotype unlike dengue, so even though there are multiple genotypes, there's only a single virus serotype. So, when you are infected, you're believed to be protected long term perhaps for life from that virus. And we believe there's cross-protection across the genotype. So, even if you're infected with the Asian genotype, you're probably protected against African.

For dengue, obviously, there are four actual distinct virus serotypes, and secondary infection can cause antibody-enhanced worsening of the disease. There has been speculation as to whether that can occur across flaviviruses; so, whether previous flavivirus infection, dengue, can worsen Zika or vice versa. There have been a number of in vitro models that have suggested it could. Although, in almost any in vitro model, you can demonstrate that.

In non-human primate models and other modeling efforts, so far there has been no evidence that there's any increased severity of disease with a Zika virus infection that if previously a person had dengue or vice versa. Although, there have been very few situations to date where you've seen thus far dengue following Zika.

There was an outbreak in American Samoa that occurred. That's the largest. And if we see it in the Caribbean, now dengue, this will be the first time we'll have extensive experience with dengue after Zika. But so far, there does not appear to be any worsening of the disease in a secondary flavivirus infection with Zika.

**DR. KAUFMAN:** Dr. Hollinger.

**DR. HOLLINGER:** I just want to go back just a minute to the India thing, since there's so much travel between the U.S. and India. Do you know what lineage the virus has been in Rajasthan and so on?

The African virus has not been associated with many outbreaks. And it was really only until it

changed a little bit to the Asian, supposedly to the Asian, lineage that there was this huge global outbreak. So, do you know what the Indian virus is?

**DR. FISCHER:** I believe it's the Asian strain, but I'm not sure.

**DR. HOLLINGER:** Okay.

**DR. FISCHER:** You're correct that there's been speculation that, again, the congenital disease is primarily linked to or associated with the Asian virus. There's been at least one study that suggests that they've found where that link is, but I'm not sure that's completely established at this point, whether there's a true difference and that the congenital effects have been associated just with the Asian virus.

But so far, the outbreak in the Americas was due to that. And that's when the congenital disease was first recognized. Same thing in French Polynesia where Guillain-Barré syndrome and then congenital microcephaly was first identified. That was associated with the Asian strain as well.

**DR. KAUFMAN:** For regions where there have

been really big outbreaks -- Polynesia, Brazil -- do you have a sense of what proportion of the general population has serologic immunity?

**DR. FISCHER:** Yeah, that's a difficult to assess because of the cross-reactivity of flaviviruses and routine serologic testing with most assays, IgG, or even neutralization testing. There's a significant cross-reactivity.

But based on blood donor surveillance data and some other studies that have been done, there's an estimate that about 30 percent of the population, at least in Puerto Rico, was probably infected and would now be immune.

In Brazil, I think it's spottier because the outbreak was much more focal in areas. The northeast part of the country had much higher incidence of disease. There was much less than the west. And then the virus spread in the second year down more to the southeast. So, I think it would depend on what part of the country you're talking about. But there was probably a similar type of sera prevalence numbers in

certainly the northeast, maybe higher in Brazil.

So, I think 30 percent would be a good estimate, but it's going to vary very much based on the area and place you're talking about.

**DR. CHITLUR:** Dr. Kaufman?

**DR. KAUFMAN:** Yes, Dr. Chitlur.

**DR. CHITLUR:** Thank you, Dr. Kaufman. I'm sorry. I didn't introduce myself earlier. I'm Meera Chitlur. I'm a pediatric hematologist at Wayne State University and Children's Hospital in Michigan. I'm a special government employee for the FDA on this committee. Thank you for having me today.

My question was are the clinical manifestations of Zika virus infection different in immunocompromised individuals compared to otherwise immune competent people? Is there any different risk for this population?

**DR. FISCHER:** Thank you. So, as I mentioned, there's a limited amount of data on immunocompromised patients. It mostly comes from Brazil. And based on the published data, in limited numbers of patients,

there does not appear to be a significant difference or increased severity in immunocompromised patients infected with Zika virus compared to non-immunocompromised patients.

**DR. KAUFMAN:** Dr. Shapiro.

**DR. SHAPIRO:** Along the same lines, is there information from Brazil about infection in patients with hemoglobinopathies, such a sickle cell in terms of any other sequelae besides the acute infection?

**DR. FISCHER:** Not that I'm aware of. I believe there was one of the first case reports of severe disease. I think it was from Brazil. It was in a patient, I believe, with sickle cell and had a severe outcome, had kind of like a chest type of syndrome as you may see with other infections. But that's the only report that I can remember. I'm not aware of any case series or studies done or other data reported in that population that I can think of.

**DR. KAUFMAN:** Okay. So, if there are no other questions from the committee. Thank you very much.

I'd like to introduce our next speaker Ms.

Srijana Rajbhandary from AABB.

**AABB ZIKV BIOVIGILANCE NETWORK**

**DR. RAJBHANDARY:** Good morning, everyone. And I would like to thank FDA for this opportunity. I'm Srijana Rajbhandary from AABB and I'll be speaking on the AABB Zika Virus Biovigilance Network.

I have no conflicts of interest to disclose. And before I go ahead with my formal presentation, I'd like to talk briefly about what AABB is. AABB is an international nonprofit association representing individuals and institutions involved in the field of transfusion medicine and cellular therapies.

AABB membership includes physicians, nurses, scientists, researchers, administrators, medical technologists, and other health providers. AABB membership is located in more than 80 countries and we also accredited institutions in over 50 countries.

Moving ahead with the objectives of my presentation, as requested by FDA, I'll be providing an overview of the AABB Zika Virus Biovigilance Network and also present data that has been voluntarily

reported to the AABB Zika Virus Biovigilance Network.

Going ahead with the program overview, this is the landing page of our platform which is available publicly and can be found under the tab of Research AABB Hemovigilance. We provide a publicly available map which maps the reactive/not reactive donations reported to our platform. And we also have the password protected site for collection of data, as well as reports to our users.

The AABB's Zika Virus Biovigilance Program is a collaboration between AABB and U.S. blood collection establishments. It was initiated in 2016 in response to the FDA's first guidance on Zika virus released in February 2016.

It was modeled after AABB's previous work in West Nile Virus Biovigilance Network. The current platform contains collection and reporting of data for donation with reactive Zika virus NAT results and also maps these data to U.S. geographical locations. We deployed the enhanced Zika reporting platform in December 2018 to support the revised guidance issued by

the FDA in July 2018.

Moving ahead with the program timeline, soon after FDA released the February 2016 FDA guidance, AABB worked together with its transfusion-transmitted disease committee, the AABB TTD Committee, to come up with the AABB's Zika Virus Biovigilance Network platform in August 2016. The first reported case, which happens to be a confirmed positive, was reported with the donation date of August 16, 2016.

After FDA released the revised guidance in July 2018, the core team of AABB again came together with the AABB TTD Committee to deploy the enhanced platform to include recommendations that were put into the revised FDA guidance and allow minipooled reactive donations resolved through ID NAT. In the screenshot below, I show the collection form for version one, which lasted from August 2016 to December 2018 and which was focused on the IND tests at that time. And we have a current version. For more information, please visit our site.

I'll go through the process of reporting and

how we map and how we give alerts to our subscribers. When a reactive ID NAT from a donor is reported by a blood center, it is reported to our platform within 24 hours. And with the initial record into our system, our map and the report get automatically updated. We sent a first alert email to our email subscribers. Blood centers and testing labs are requested to do further investigation on the exposure status and a confirmatory test within 24 hours. And they can go back to our platform to update their record.

Once a record is updated with exposure status or/and confirmatory test result, the map gets auto updated and so does the report; but the second updated email alert goes out to our subscribers only when our exposure status is updated.

Moving ahead with the summary data, in this graph I represent the initial reactive donation in blue line, and confirmed positives that had been reported to our platform since its initiation in red line. Of note is the fact that we analyze the level of participation during the IND phase, and it was established that

around 84 percent of confirmed positives reported to the NAT developers were also reported to AABB.

We can see that the initial reactive donation had been reported to our platform through 2016 -- August 2016 throughout 2018 -- with peaks in fall months. However, the confirmed positives dropped down significantly after 2017 with the last confirmed positive being reported in the month of March 2018. And the last reported initial reactive to our platform was in February 2019. We can also see the margin of difference between the initial reactive and confirmed positive as apparent in this graph.

Here I show the confirmed positive cases by date of collection and the last confirmed positive that was reported to our platform was on March 16, 2018. There were 27 confirmed positives reported in 2016, from August 2016 to December 2016. Seventeen confirmed positive in 2017 and only two confirmed positive in 2018.

Moving ahead with the positive predictive value, the positive predictive value as reported to our

platform and taking data from 2017 to 2018 comes up to be 2.36 with 19 confirmed positive for the total of 805 initial reactive ZIKV NAT results.

When we look at the ZIKV confirmed positives by state, we find that the maximum number of cases were reported from donations made in the state of Florida, followed by the state of California, the state of Texas, and the state of New York.

Going ahead with the exposure status among confirmed positives, we find that around 63 percent, which is 29 confirmed positives, were reported to have no alternate exposure through travel or sexual contact, followed by 14 such cases with a significant travel history, 2 cases with current sexual contact history, and 1 case with dual exposure of significant travel and sexual contact.

Here I present the locations that were reported by donors with significant travel history and those who had confirmed positives. We find that the highest number of cases were reported from travelers who went to Mexico. The last confirmed positive being

associated with travel was with a donation date of December 28, 2017, with the travel history to Mexico.

Other epidemic areas that were reported by these confirmed positive cases are mentioned in the slide at the bottom.

When we go and look at the cases confirmed positive that had no alternate exposure by travel or sexual exposure, we find that the highest number of cases -- around 19 -- 19 cases were reported from a donation in the state of Florida. The last confirmed positive being on March 16, 2018, from a donation in Miami, Florida. And the second following Florida is the state of California.

Here I would like to mention the fact that some of our blood centers and testing labs reported back to us saying that the donors were not available for further investigation, and therefore, they were put under the “no alternate exposure” category.

In summary, AABB Zika Virus Biovigilance Network has been utilized by blood centers and testing labs to voluntarily report initial NAT as well as

confirmed positives for Zika. There have been 880 initial reactive donations with 46 confirmed positives. I would like to mention the fact that -- I forgot to mention earlier that currently there are 896 initial reactives that are reported to our platform. However, in preparation of this presentation, I determined that 16 of those cases were reported by the blood center as well as testing labs and were deemed duplicates. So, they were removed for the purposes of analysis for this presentation.

The positive predictive value of NAT tests is 2.36, taking the data years 2017 and 2018. The last reactive donation reported to the platform was on February 4, 2019. The last confirmed positive reported to the platform was on March 16, 2018. And the last confirmed positive with exposure due to travel was associated with travel to Mexico in December 2017. The last confirmed positive reported in March 2018 was in Florida with no exposure to travel and sexual contact.

I'd like to thank AABB Transfusion Transmitted Disease Committee and especially Dr. Sue Stramer, Dr.

Lou Katz, and Dr. Steven Kleinman for helping me to prepare these slides. And my special thanks go to my AABB colleagues Jackie Thomas and Sharon Carayiannis. Thank you.

**DR. KAUFMAN:** All right, thank you very much. Actually, if you wouldn't mind staying there, I'd like to ask if the committee has any questions for this speaker and then we'll plan on taking a 15-minute break after that. Any questions?

I actually have one. Can you comment on what approximate fraction of donor centers report into your system? And sort of what number or proportion of U.S. donations would be covered by the system?

**DR. RAJBHANDARY:** We actually have 22 independent blood centers reporting and one big centralized testing lab reporting to our platform. AABB's membership, we estimate that it is spread almost hundred percent to the blood centers in the U.S.

And going back to the data for blood centers, when I was preparing this presentation, I found that the centralized testing lab was, in fact, reporting for

almost 22 other blood centers. So more than 50 blood centers are reported, and we believe almost 90 percent of the blood donations in the U.S. are covered by our platform.

**DR. KAUFMAN:** Dr. Hollinger?

**DR. HOLLINGER:** Can you tell us what the lag time is or has been on the biovigilance? After it's reported to the AABB within the 24 hours, how long does it take then to get the investigation and then the report back for the confirmatory test results?

**DR. RAJBHANDARY:** We recommend 24 hours, but the nice thing about our platform is reporting organizations can go back to their report anytime and update their record. I have seen around two days of turnover for reporting the exposure status. But for confirmatory, I have not tracked down, but I can definitely look into that.

**DR. HOLLINGER:** I'm sorry. So, once it's reported in 24 hours, then how long does it take? What is the lag time? With the reporting in the past, there must be some information regarding how long it takes to

get it back to the confirmatory tests and everything.

**DR. RAJBHANDARY:** We don't collect that data, but we recommend coming back within 24 hours. But in the new platform, we have made the confirmatory test an optional section. But we don't really track how long the blood center takes to report the confirmatory results.

**DR. KAUFMAN:** Any questions from Dr. Stramer or Chitlur?

**DR. CHITLUR:** No.

**DR. STRAMER:** I can just add some information to the questions that Blaine has. Confirmatory testing is variable depending on the testing laboratory that's used. But AABB does encourage all blood centers to confirm once a reactive entry has been made. So those data should be available. Again, it's highly variable. With the initial investigation, it's supposed to be completed within 24 hours for the purposes of understanding when we should trigger or not.

**DR. KAUFMAN:** All right. Thank you. Sorry. Dr. Lewis.

**DR. LEWIS:** So, this is a general question about epidemiologic surveillance. I'm actually not sure which speaker it should be directed towards. So, my question is unrelated to blood donations or blood banking, what is our infrastructure with respect to epidemiologic surveillance in the population in general? Are there any systems in place to detect asymptomatic sera conversions or infections in the population in general? And this would apply to U.S. states and territories.

**DR. KAUFMAN:** Dr. Fischer.

**DR. FISCHER:** Mark Fischer from CDC. So, both disease cases, symptomatic disease cases and symptomatic infections related to blood donation or otherwise, are nationally notifiable conditions. So, the Council of State and Territorial Epidemiologists along with CDC made those nationally notifiable conditions in June of 2016.

So, they are reportable conditions. Laboratories with positives are required to report them to health departments, and all state and territorial

health departments report cases that they're aware of to CDC, but it is a passive reporting system. There's not active surveillance that's identifying these cases.

**DR. LEWIS:** So, just to clarify, the question was for, I guess, serologic surveillance unrelated to blood donation. For example, I can picture a system, perhaps just in my imagination, in which random samples of blood that are used for routine clinical care -- blood glucose measurements, hemoglobin, A1C measurements in diabetics, and at public clinics -- are tested to see whether or not there's sera conversion or evidence of infection. And what I'm understanding is there is no such system in place in the U.S. or its territories for Zika virus. Is that correct?

**DR. FISCHER:** So, there's not a system to routinely screen other blood specimens that are collected for clinical purposes other than blood donations. However, if somebody -- a physician or health care provider -- chooses to test a patient -- and this includes, for example, many asymptomatic pregnant women who have no symptoms of disease, may not

even have an epidemiological exposure. If they get tested and are positive, they will be reported into the system. First from the laboratory result and then from the state health department will report it. So, if the testing is performed, it will be captured. But there is no other system to routinely screen clinical patients or blood products other than in the blood donation system.

**DR. LEWIS:** So, it relies on clinical suspicion?

**DR. FISCHER:** Correct.

**DR. LEWIS:** Okay.

**DR. CHITLUR:** Hi, this is Meera Chitlur. Can ask a question?

**DR. KAUFMAN:** Yes, please.

**DR. CHITLUR:** In continuation with the conversation that has just taking place, so if a person donated blood, say two weeks ago, and then developed some kind of viral illness, goes in to see the physician, is diagnosed with Zika virus, how does -- and I'm sure the CDC gets that information. But is

there any way to -- is that information backtracked to the donation site to say that this patient has now developed an infection?

**DR. FISCHER:** So, there are two parts to that question. CDC would learn about that patient if they had a laboratory test done and it tested positive for Zika. That would be reported to their state or local health department. That would be investigated and then reported to CDC. Or if the health care provider, even if a test wasn't done, reported the case to the health department, then eventually after investigation, confirmation will be reported to CDC.

The follow-up of that patient, just because they were a blood donor and had donated two weeks earlier, is separate from CDC surveillance; and that really could be better answered by someone from the blood services agency as to what follow-up there is for blood donations.

**DR. STRAMER:** This is Sue Stramer. I don't know if you can hear me.

**DR. KAUFMAN:** Yes, go ahead, Sue.

**DR. STRAMER:** Let me respond. Blood donors are encouraged to report post donation information if they were diagnosed for any specific agent for which blood donation screening occurs. Typically, this is required during the time where products are still within our control, so we can take actions on those components. But if a donor has a confirmed infectious disease, even within two weeks, the expectation, either from the donor or the donor's physician or even from the state public health department, is that that will find its way back to the blood center.

**DR. KAUFMAN:** Thank you. Sorry. Dr. Baker.

**DR. BAKER:** Thank you. Judith Baker. So, following up on this thread, so if a woman gives birth to a child with microcephaly, what might be some systems in place to investigate that in the U.S., currently, that might trace it back to a blood donation?

**DR. FISCHER:** So first, I'll talk about the first part. The tracing back to a blood donation is a separate issue. The first part would be, again, there

needs to be -- there are two ways that the birth could be associated back to a Zika virus infection. The first would be, at the time of birth, somebody -- a health care provider -- recognizes microcephaly. The mother maybe had an exposure and performs testing. Although, I will say testing for congenital Zika virus infection is difficult, and we don't know the optimal way to do that. But that will be the first way it'd be identified.

The second is during the outbreak, there were two registries that were established in the United States, one for U.S. states and one for Puerto Rico, where any pregnant woman who was identified as being infected during her pregnancy was reported into the registry. And then those babies were followed, or the births were followed to outcome. That has since stopped. But during the peak of the outbreak through 2016 and into 2017, the birth might be identified that way, whether the baby had a normal birth and outcome or not.

The linking it back to a possible blood

donation would be difficult to do. I mean, there's a pretty extensive investigation that would be done about why the mother was tested, if she was identified through the registry, and how she was exposed. And we would get information potentially about blood donation there. It would be a harder case if the baby is first identified at the time of birth. Somebody would have to really be thinking along those lines as to what type of exposure might this mother have had as much as eight months ago.

**DR. HOLLINGER:** I don't know whether you're the person to ask or not or really maybe Sue. The specificity of this test is really low. And I understand the difference between when you have a low-risk population versus a high-risk population. For example, Puerto Rico, it was very high. Here, it's very low -- 2.5 percent.

My question is, is this peculiar to just this test or is the percentage the same for HPV, HIV, HCV, West Nile, the other things which have NAT testing in the blood banks as well, in terms of specificity?

**DR. STRAMER:** Blaine, this is Susan. I'll answer the question. Both West Nile and Zika have extraordinarily high specificity. The positive predictive value is low, but the specificity for both of the FDA licensed Zika tests is 99.996 to 99.997 percent. So, extraordinarily good specificity, meaning we have few initial reactives. However, of the initial reactives that we have as shown in the line chart that was shown by AABB, the delta between the blue line, the initial reactive, and the red line is tremendous. And that's why we have a low positive predictive value.

This is not unusual for blood donation screening tests, but Zika happens to be one of the agents because of the absence of true positives with the lowest positive predictive value currently. HPV would be one with the highest positive predictive value.

**DR. HOLLINGER:** Thank you and I stand corrected about the specificity. Sorry.

**DR. KAUFMAN:** Okay, any other questions from the committee? All right. Well, why don't we take a

break. We'll reconvene at 10:30. Thank you.

**BREAK**

**DR. KAUFMAN:** Okay, thank you. So, I'd like to welcome Dr. David Leiby. Okay. Leiby. He works at OBRR of FDA. And he's going to discuss Current Considerations for Reducing the Risk of Transfusion-Transmitted Zika Virus.

## CURRENT CONSIDERATIONS FOR REDUCING THE RISK OF TRANSFUSION-TRANSMITTED ZIKV

**DR. LEIBY:** Thank you. As already stated, I am David Leiby and I'm chief of the Product Review Branch here in CBER. I'll be talking about Current Considerations for Reducing the Risk of Transfusion-Transmitted Zika.

Specifically, we'll be exploring alternatives to universal testing for Zika virus in the U.S. As you've already heard earlier, available information indicates a decline of Zika virus in the U.S. and the Americas. Thus, FDA is reevaluating its July 2018 recommendations on testing blood donations for Zika using minipool or ID NAT. Therefore, FDA seeks advice

from the committee on the following three testing strategies, and you saw these briefly earlier. The options are: Option one, no policy change; continue universal testing for Zika virus by minipool or ID NAT. Regional testing for Zika virus with minipool or ID NAT; and then we'll talk about some considerations for these regional options and will also entertain others.

**DR. KAUFMAN:** Sorry. I would just like to ask if those who are calling in if you could please mute your phones. We're getting a little feedback here. Thank you.

**DR. LEIBY:** Okay. Then the final option which we'll talk about is to eliminate all testing for Zika virus. Apparently, I have an echo. Okay. Along with the three options I presented, there are also certain caveats that go along with these. First of all, FDA is not proposing pre-donation assessment for Zika virus risk factors, and this includes exposure through travel or sexual contact.

In part, this is because most infected persons and their sexual partners are asymptomatic and unaware

that they are infected. Also, as the outbreak in the Americas has waned, many countries no longer perform active Zika virus surveillance. Keep in mind that FDA approved pathogen reduction technologies remain an alternative to testing when used with apheresis platelets and plasma.

Now there are three proposed strategies that have inherent pros and cons, and I'll go through each of those at this time.

First, option one: No policy change. As you recall, this is to continue universal minipool or ID NAT testing of blood collections for Zika virus. The advantage of this approach is that it provides nationwide coverage against all modes of Zika virus transmission. This includes local vector-borne, sexually transmitted, and travel-related cases. In contrast, this would still require, though, maintaining a resource-intensive approach in the face of diminishing resources.

Option two: Regional minipool or ID NAT. This would involve discontinued testing in most states

but maintain regional testing for Zika virus using minipool or ID NAT in at-risk states and territories. I will present a few considerations, and they'll actually be open for discussion later amongst the committee.

One consideration is to continue testing in Florida, Texas, Puerto Rico, and the U.S. Virgin Islands where documented local mosquito-borne Zika virus transmission has --

**DR. CHITLUR:** Hi. I'm so sorry. This is Meera Chitlur. We are not able to hear anything.

**DR. LEIBY:** The second option, and this is cumulative, would be to test in California and New York where the mosquito vectors are present. These states accounted for a significant proportion of Zika reactive donations from travelers returning from Zika-affected countries during the 2016 outbreak.

Additionally, for consideration is Hawaii and other U.S. territories where the mosquito vectors are present and documented transmissions of other Aedes-borne arboviruses -- in particular, dengue virus

and chikungunya virus -- have occurred.

For option two, again, regional minipool or ID NAT, there are several pros and cons. The advantages of option two is that it reduces the volume of testing and alleviates burden in states with low or absent risk of mosquito-borne Zika virus transmission.

It also continues testing in areas of highest risk of Zika virus cases from local mosquito-borne Zika virus transmission and with high numbers of returning travelers. And lastly, this approach would maintain a capability to rapidly respond to reemergence of Zika virus in U.S. states and local outbreaks.

In contrast, this option would maintain a regionally resource-intensive approach on the blood system for testing donations for Zika in the face of significantly diminished risk. This approach will also not detect an outbreak if one occurs in states that are not testing and will not detect Zika virus infections among returning travelers or sexual contacts in states that are not testing.

The third option for consideration today is to

eliminate all Zika virus testing. This would eliminate all testing pending another outbreak in the United States.

The clear advantage of this approach is that it provides relief from Zika virus testing when Zika virus risk is substantially reduced or absent. It also increases the availability of resources for other blood safety initiatives.

However, this approach will reduce preparedness against possible resurgence of the Zika virus epidemic. And lastly, this approach will not prevent transfusion transmission of Zika virus and poses risk of Zika virus complications among at-risk patients -- in particular, pregnant women.

So, we will pose three questions for the committee, and after the open public hearing, I believe, the committee will discuss these three questions and then eventually come back to these to vote on them. But I'll just review the three questions at this time, and each question will be voted on.

The first question is: At this time do the

available data support continuing universal testing for Zika virus using minipool or ID NAT as recommended in the July 2018 final guidance? So, in other words, no policy changes at this time. This was option one.

The second question: Do the available data support a regional testing option strategy for Zika virus using minipool or ID NAT in at-risk U.S. states and territories? During the discussion, we can discuss the various options for regional testing.

And lastly, question three: Do the available data to support the elimination of all testing for Zika virus without reintroduction of donor screening for risk factors -- in particular, travel -- in areas with no risk of Zika virus infection pending another outbreak in the United States? This, of course, is option three. Thank you.

**DR. KAUFMAN:** Thank you. Are there any questions from the committee for Dr. Leiby? Dr. Bryant.

**DR. BRYANT:** On both option two and three, there's a comment about reduced preparedness against

the possible resurgence and delay in being able to rapidly respond to reemergence. What would we be looking at if we had a reemergence and we were not currently testing? What type of delay would be expected?

**DR. LEIBY:** That's probably a question better answered by the blood centers, I believe, how quickly they could ramp up testing.

**DR. KAUFMAN:** Dr. Shapiro.

**DR. SHAPIRO:** Is there another possibility of testing units for individuals at higher risk of sequelae from transmission; for example, any pregnant woman who received a transfusion, and testing those units?

**DR. LEIBY:** I think that's certainly a possibility; but I think, in general, keeping dual inventories of products is not popular among the blood centers. But they can speak to that as well.

**DR. KAUFMAN:** Yeah, I think that's right. I think, in general, it's logistically challenging, for example, to identify specific patients that might be at

particular risk for babesia, for example, we worry more about asplenic patients getting infectious units. But in fact, people that have had transfusion-transmitted babesia have kind of run the full gamut of patients that get transfused.

And so, I think, in general, both at the blood center level and at the hospital transfusion service level, the preferred approach is to kind of handle the safety at the level of the blood rather than worry about, well, this blood is safe except for this particular patient, that sort of thing. Dr. Ortel.

**DR. ORTEL:** So, if we went with one of the strategies that potentially decreased testing, would there be some type of metric potentially attached to the CDC so that if there was a bump in reported infections that that would lead to a reevaluation? Or is there a way to link it so that if there is a change in apparent infection rate in the U.S. that that would have this be reexplored?

**DR. KAUFMAN:** I don't know. That might be a question for Dr. Fischer. I would say that one of the

inherent challenges with this is that part of the surveillance itself is screening the blood supply. So, you won't find things that you're not testing for. So, you would be more reliant on other surveillance.

**DR. SCHREIBER:** Marty Schreiber. I'd like to lend support to Dr. Shapiro's idea, because I actually thought the same thing. I mean, when you look at these options, option number one, we're going to test everyone, spend millions of dollars when there's only a very select group that's at risk. Option two, even within those -- those are big states California, Texas, Florida -- millions of people live in those states. But if there's only a very specific sensitive population, why not focus on that population? Then option number three, don't test anyone. Well, pregnant women are at risk.

It seems to me that you would isolate this down to maybe option number three, but the sensitive population. It makes the most sense that -- what we've heard earlier today was that if infected blood is given to a non-sensitive population, it has essentially no

morbidity. So, it doesn't make sense to test blood going to those patients. I think Dr. Shapiro's idea makes a lot of sense.

**DR. KAUFMAN:** Dr. Fischer.

**DR. FISCHER:** So, with regard to the question about surveillance, certainly having blood screening as an alternative surveillance mechanism is useful because it's unbiased. It tests everybody, but it's not a primary mechanism that we use as surveillance. It's certainly not sensitive to -- there's not a high enough population of blood donors that are being tested. So, it's nice as an additional system, but it's not a primary mechanism for surveillance.

As far as linking restarting screening to indicators that we would have, I think that could be done. I think the biggest issue is going to be that what's going to happen is you'll see increases in travel-associated cases, because there's more likely to be outbreaks in other areas. And those are going to be sporadic throughout the country. Although, just based on population where those people live and where they're

traveling from, you are going to see more cases in certain states, which I was trying to show in my slides. But it's less likely we're going to see local transmission and outbreaks.

When that does occur, if it happened again in Puerto Rico or U.S. Virgin Islands or Florida, that would be, I think, easier to respond to. I don't know how long it would take to get there, but that would be easier to respond to and reinstated in that area.

But I don't know what you would do if you had a large outbreak outside of the United States. Most of the cases and risk to the blood was from sporadic cases of travelers going to other areas. That would be more difficult to respond to, I think. Would you reactivate it across the country or just in those areas sort of, I guess, like what you're proposing in choice two right now.

**DR. KAUFMAN:** Dr. Bloch.

**DR. BLOCH:** Evan Bloch. So just getting back to the selective inventory, I'm not sure how that would actually work, because I think the only (inaudible)

where we maintain a dual inventory is with CMV, which arguably you have parallel leukoreduction which impacts that. But because antenatal transfusion is so rare, I'm not sure how you would actually implement that.

I think that there's actually no data on rates of antenatal transfusion. And just, conceptually, if the patients, fetuses, which are most at risk, are going to be in the first trimester when really you won't see any transfusion outside of an abortion spectrum or ectopic pregnancy. So, the risk is really probably later on in pregnancy and is really a difficult thing to implement.

**DR. SHAPIRO:** Except maybe in higher risk groups, such as sickle cell, women who are pregnant might be at a higher risk of transfusion.

**DR. BLOCH:** Sure, but the catch is that, I think, that when the transfusion is actually happening, I think would be later in pregnancy where it's hard to say what the actual risk of transfusion-transmitted Zika is. But it would be more likely to be in your second and third trimester when at least organogenesis

has -- most of it's taken place.

**DR. SHAPIRO:** I would say that's not exactly true in sickle cell disease. Some of these people are transfusion dependent.

**DR. KAUFMAN:** Dr. DeMaria. Sorry. Go ahead, Sue.

**DR. STRAMER:** I just wanted to respond and support what you said. Most hospitals do not want and are very adamant against carrying a dual inventory, whether it's for babesia or CMV, and it's something we are trying to reduce or eliminate. It's very difficult to know who's pregnant, who's not pregnant, even though this would reduce testing significantly.

But let me talk about not testing, and the question was asked about the time for ramp-up. So, the FDA released guidance in July 2016 for universal ID NAT and it took the blood establishment six months to ramp up. So that may be a question. But that was when the vendors were making tests and all they had to do was increase testing volumes.

If we totally eliminate testing, then we're

dependent for the manufacturers then to reinitiate manufacture of tests. So that timeline from six months -- I mean, theoretically could be longer, but the timeline is unknown. But without any testing, I would think it would be really short. And recognize, too, with minipool NAT, the way we do it now if there are local outbreaks, we would initiate individual donation testing to increase the sensitivity of testing.

**DR. KAUFMAN:** Thank you. Go ahead.

**DR. DEMARIA:** Al DeMaria. I just think that you'd have to consider a situation where a woman would need a transfusion during pregnancy, which is, except for sickle and a few other things, is probably a rare occurrence; and then just happens to get that one in a hundred thousand units, even at the height, that would have been putting them at risk. And then what we know about the risk during pregnancy, I'd still be worried. But it looks like maybe five to ten percent risk of a serious outcome in the baby. So, when you sort of multiply all of those risks, it comes out to be extremely low.

**DR. KAUFMAN:** Go ahead, Marty.

**DR. SCHREIBER:** So, along those lines, why couldn't you -- instead of having a dual blood supply, why couldn't you screen units of blood designated to go to pregnant women at the time that those units are designated to go? And if that unit is positive for Zika, you don't give it to her. It's going to be an extremely rare event, but if that unit is negative, which is a 99.9 percent likelihood that it will be negative, you don't give that unit to her.

**DR. KAUFMAN:** Oh, well, any unit that's positive for any infectious marker's not transfused. So those are all discarded.

**DR. SCHREIBER:** Right. But what I'm saying is that you would only test the ones designated for pregnant women. So, you wouldn't test for Zika virus unless the unit is designated to go to a pregnant woman.

**DR. KAUFMAN:** Oh yeah. So, the way that the blood enters the hospital inventory is first the donor undergoes the usual screening questions, donates the

unit; and then, at the time of donation, samples are collected. The samples are then tested by the blood center or at a central testing facility.

So, in our case, for example, we have a hospital-based blood donor center. We send testing off to a central testing facility and usually get results back, both for the serologic screening tests and for the nucleic acid tests, within about 36 hours, something like that. Before those tests come back, the units are not entered into inventory. So, that is, they cannot be labeled or given to any patients until the results come back.

**DR. SCHREIBER:** So, it's not possible for a hospital that's giving a blood transfusion to test at the time the transfusion is ordered?

**DR. KAUFMAN:** It is not. The only exception -- I mean, sort of the only test that can sort of be contemplated in the setting of a unit that's already in inventory has to do with bacterial testing for platelets. Other than that, all the testing is completed and resulted and found to be negative before

the unit can be made available for patients.

And again, just to talk about the dual inventory part, not only is it logistically complicated -- not impossible, but very, very hard for hospitals to maintain, kind of – frankly, even CMV tested, CMV not tested. My own hospital uses leuko-reduced blood as equivalent for CMV safe to avoid that issue. And frankly, we also -– this is not done everywhere -- we support a large cancer center. We actually universally irradiate cellular products, again, for this idea of not having kind of boutique style. We have different sort of inventories.

But, in addition to the logistics, it's very hard to even run into situations, okay, if we sequester a set of O negative units, and we're going to save these for just in case a pregnant woman needed to be transfused, now our inventory is limited. And now somebody's bleeding, and they really need O negative units. So those kinds of practical things come up frequently, making it very hard to say we're going to have kind of special units for certain patients.

There are some different sorts of cases. We're talking about sickle cell disease where you might have, for example, genotypically negative or extended matched units specific for our population. But when it comes to infectious disease screening, it's definitely not something that would be easy or popular to do. I don't know if anyone else wants to comment on that.

Oh, sorry. Dr. Lewis.

**DR. LEWIS:** So, I have a comment about the way the question has been framed. It seems to me that there's two different -- qualitatively different types of vulnerabilities that we're trying to address. So, one is the vulnerability to the blood supply and potential recipients of blood products based on the current epidemiology of the tail end of a waning epidemic.

And I think it would probably be a pretty easy question for the committee and for the agency if we actually had some way of having a crystal ball and knowing that the current trend was likely to continue.

That's actually not the question. I think the

question is, what is the optimal strategy, given that we have no idea if that tail is going to continue in the current trend for years or decades; or if a year from now or three years from now or six years from now, when clinicians have largely forgotten about this disease, and therefore don't send tests for clinical suspicion because we have no suspicion, if we're at the beginning of an uptick.

I think it's the incredible uncertainty in the likelihood that in each year from now we're going to be at the beginning of a new epidemic that makes the question really difficult.

It seems to me that, given the agency's ability to revisit these questions at periodic intervals, we're going to know more about the global epidemiology of this disease in two years than we know now, and in four years than we do two years from now; and that maybe the committee ought to be thinking about what is the right strategy for the next two years, with an underlying assumption that this is a question that can be brought back as we learn more about how this

disease behaves? Because, you know, 10 years from now, we knew nothing about it, essentially.

**DR. KAUFMAN:** No, I mean, I think that's a really good point. In preparing for this meeting, one of the things that I learned is there has not been a second wave identified yet. It doesn't mean it won't happen someday, somewhere. But in outbreaks in Yap, in Polynesia, in Brazil, in other places, this virus seems to kind of explode in a population and then it sharply declines. That's what's been seen everywhere so far. And that's what we know.

There's a little bit of weirdness to that, too. We heard from Dr. Fischer that maybe it seems like about 30 percent of the population has antibodies, roughly, maybe. And what does that mean? Like is that -- I don't know. It seems low to me to have a kind of a herd immunity, but maybe it's not. I don't know.

But I do think you're right; I think we have to evaluate with the knowledge that we have now and think about what realistically might happen. That has to weigh into kind of how we think about what to do.

**DR. LEWIS:** But to rephrase, just ever so slightly, I actually think that the tremendous volume of information that was presented about history up to March of 2019, it actually, I think, is not the point. The point is that we have experience with, essentially, one epidemic, and we're trying to extrapolate from that the likelihood of a second epidemic. That's a virtually impossible problem, at least from a statistical point of view.

**DR. KAUFMAN:** Dr. Basa- -- sorry. Is that Sue?

**DR. STRAMER:** Yes. I just wanted to add to Dr. Lewis's comments. In trying to gather industry opinion, I mean, we share the concerns raised by Dr. Lewis, that it may be premature to come up with a definite strategy for the future because we don't understand what will happen. We are in a stable phase right now with minipool NAT. Although it's costly, it is far less burdensome than we had with individual donation NAT, and many of the cons that were presented go away. So, one position that industry has is that we

should wait at least another year, continue with what we're doing, and then revisit it based on additional knowledge that we gain in at least a year.

**DR. KAUFMAN:** Thank you. Dr. Basavaraju.

**DR. BASAVARAJU:** I just wanted to also point out that the virus is not gone. There're still tens of thousands of cases in the Western Hemisphere, at least that we know of, based on limited testing. There're presumably hundreds of thousands, if not more, of people who are returning from these areas to the United States.

I think when people -- pregnant women or potentially pregnant women or soon to become pregnant women -- can get transfused for non-pregnancy related issues. And I think it would be at times -- at least when people are being emergently transfused, it's impossible to know if they're pregnant or not. So, it seems that there's still a risk if testing was to be discontinued.

**DR. KAUFMAN:** Dr. Baker.

**DR. BAKER:** Judith Baker, so in looking at

option two, which asks for supporting, quote, "a regional testing option," is there flexibility to even consider more than one regional testing option? Does the FDA have that as an option?

**UNIDENTIFIED MALE:** Yes, we can actually consider other options than those three presented or some mix of those, but we're flexible.

**DR. DEMARIA:** The question I have about regional testing is that when you present this to the public, anybody from anywhere can travel anywhere and get Zika. So, there's a fairness issue, in terms of just testing where you think the risk is the highest. If we're really going to have sort of a zero-risk approach, then regional testing may reduce that risk to close to zero. But somebody in the middle of America may have a baby affected by Zika.

So, I think that becomes problematic when trying to explain regional testing. It came up with babesia too. Regional testing to the general public, because they're taking a zero-risk approach and they're saying, well, you know, my neighbor could have traveled

and then they had a tick and something -- you know, they donated blood and I got babesiosis because you didn't test in Iowa.

So, you know, I think that's another consideration when considering regional testing, especially if it's something that has such a low risk of actually happening and a relatively low consequence risk.

Because, I think, ultimately with Zika, I'm not sure we would be testing every donor in the United States if babies were not severely affected. Because the approach to Zika changed immediately. And I'm not saying that was inappropriate, but I think that's the context of why we're testing. We're not testing because Zika is bad in general. We're testing because Zika is bad in particular.

**DR. KINDZELSKI:** Andrei Kindzelski. To continue what you just mentioned, I think it would be interesting to know, what is the status of development of a rapid Zika testing assay that potentially could be implemented in the hospitals for very specific type of

patients? And also, another thing is, to what degree pathogen inactivation can help with Zika?

**DR. KAUFMAN:** So, in response to the second question, I think the Zika virus like other flaviviruses is easily killed by pathogen reduction and the FDA's basically already decided that that can be used as an alternative to screening. With respect to the first question, I'm not sure that's within the scope of today's talk. It would not be something that would affect testing of donated blood specifically. Sorry. Dr. Ortel.

**DR. ORTEL:** Tom Ortel. Can I just clarify on number three? It states that support the elimination of all testing for Zika without reintroduction of donor screening for risk factors, for example, travel in areas with no risk. Is there an option that it could be that you would reintroduce testing for high risk for people who travel to high-risk areas? In other words, kind of following up on Dr. DeMaria's question about instead of being regional, should we target people who may have placed themselves at a higher risk to be

exposed?

**DR. HOLLINGER:** Yeah, along those same lines too and I think it's a good question. Is the 30-day travel deferral to certain regions still in existence and utilized? I'm always in favor of a 30-day travel deferral for everything, for any travel outside the contiguous United States because I think so many of the infections that we're concerned about have a short viremic stage. It would not be a bad policy that anybody that travels would not donate for 30 days, which would eliminate, I think, a lot of things.

And that comes back to the other question is, if we still have the 30-day travel deferral, what is it based on? What triggers it? That's the question I'd like to get an answer to if I could. Anybody in the blood banking?

**DR. STRAMER:** Blaine, this is Sue Stramer. We don't have a 30-day travel deferral. Several years back when chikungunya emerged, we did a pilot looking at either a 14- or 28-day deferral, but that was just a pilot and that's not national policy.

**DR. HOLLINGER:** And what is the problem with that? With that policy?

**DR. STRAMER:** Whether there's a problem or not, it's nothing that has been vetted by the industry or implemented. It's not to say we couldn't do that; it's just something that involves a lot of stakeholder review and determination if that's what we want to do. It's not an FDA requirement done voluntarily. We, the blood industry, have not done that. The only travel deferral we have is for malaria.

**DR. KAUFMAN:** My understanding is that, for example, in Canada, there are travel risk questions around Zika, but they do no testing. There's no Aedes aegypti mosquitoes in that area. There are no cases and so on.

My understanding also is that the FDA is relatively uninterested in travel questions as a deferral strategy for Zika specifically. Maybe someone from FDA would like to comment on that.

I think one of the issues is that 80 percent of people who get infected are asymptomatic. Where

Zika is and isn't is always changing on the maps. And so, I think, at least for this meeting, that was not -- that a travel deferral was not going to be kind of a major focus. I don't know if someone from FDA wants to comment on that point. Dr. DeVan.

**DR. DEVAN:** Dr. DeVan from Walter Reed. Two things. The experience with the Armed Services Blood Program is that travel questionnaires are difficult. People forget where they've been, and they forget when they've been. So, putting a time on it would be difficult. And even asking people to remember locations is difficult, especially with something with a vector that may not respect boundaries. I think it would be very difficult.

The second point, to follow on what was said about pathogen reduction, I think that's a good option, but it doesn't affect all products. It would only be good for the plasma and platelet products.

**DR. KAUFMAN:** Okay. So, I'd like just to keep things moving along. There will be an hour for the committee to continue, basically, trying to figure this

out. But prior to that, I'd like to start the open public hearing.

**OPEN PUBLIC HEARING**

So, I've been asked to read this statement. Welcome to the open public hearing session. Please state your name and your affiliation if relevant to this meeting. Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session at the advisory committee meetings, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, as you begin, to state if you have any financial interests relevant to this meeting, such as a financial relationship with any company or group that may be affected by the topic of this meeting.

If you do not have any such interest also, FDA encourages you to state that for the record. If you

choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking and you may still give your comments.

So, I'd first like to introduce Tony Hardiman from Roche.

**MR. HARDIMAN:** Thank you. Tony Hardiman. I'm the vice president of blood screening for Roche Diagnostics. I am a shareholder in Roche at this time.

I'd like to start by saying thank you to the FDA and also the Blood Products Advisory Committee for giving us this opportunity to make a statement and give some feedback on behalf of Roche Diagnostics, who is a manufacturer and supplier of the Zika test to the blood industry in the U.S. and also to other industries -- blood services around the world.

Our history of working with the FDA and the blood industry on focused collaborations has been well established. If we look back in 2015 with the potential outbreak of chikungunya, we immediately invested and went into a development of a test and an

IND with chikungunya and has been highlighted here today with Zika.

In late '15-16, we went forward and moved with a Zika development at the same time. As the Zika outbreaks spread to Puerto Rico in early 2016, as you heard this morning, we were asked by the FDA to prioritize the development and deployment of a Zika screening test to protect the blood supply for the Puerto Rico community and patients in general.

Roche, upon this interaction with the FDA and the blood community, immediately prioritized the rapid development of a Zika test with an extremely accelerated 10-week timeline. And for us, it involved a very significant investment in people, time, and resources.

On April 2, testing was initiated under an investigational new drug application, as you heard earlier, to screen blood unit sourced locally in Puerto Rico. This allowed the blood supply that was stopped from being taken locally to be reinitiated in Puerto Rico and ensure a safe blood supply, as we all want.

Following guidance from the FDA, we deployed the tests fully to all Roche platform users in the United States and submitted this to the FDA for licensure in 2017. This was licensed six months later.

The Zika story, as you are aware, continued through 2018. In fact, here as you know, in late 2017, the Blood Products Advisory Committee decided to recommend that all donations were screened by minipool versus IDT in the initial case. Again, Roche rapidly ensured that the minipool protocol for the Zika test was developed, submitted, and ultimately implemented as rapidly as possible within weeks of that notification from this committee; and ultimately, on guidance from the FDA, was brought into use in the blood centers.

Now, as we look at today and the BPAC answers to the questions that have been posed, I would like to highlight the challenges and significant changes in testing practices and processes will bring from a manufacturer's perspective. Ultimately, we believe this could have, from our view, a significant impact on blood safety.

Now the cobas Zika test performed on the cobas 6800/8800 system is fully licensed, as we just said. The product is now produced under a full, good manufacturing process quality system. And for us, if that volume is decreased, product availability and the safety stock that we hold for the blood services in the U.S. will need to be reduced.

Obviously, as one of the options, if testing is stopped, then during that period of time, we will need to suspend production of the test. Now, different to what we saw under an IND, the fact that this test is produced under a full GMP quality system, it will take us at least three to four months to restart production of that test and, thereby, allow the test to be utilized in the U.S.

Now, we, of course, will work with the blood testing centers to implement and support whatever recommendation comes out from this committee and ultimately is put into guidance via the FDA. But I really would like you to be aware of the supply chain considerations and issues that I've already mentioned.

Roche has and will continue to invest significantly in blood safety. Just as today, we have an active surveillance program ongoing that is designed to detect new and emerging agents worldwide in order to develop tests as needed to protect the blood supply. But obviously, any collaboration requires commitment from all parties concerned to allow us to continue that research.

Over the past several years, Roche has received FDA approval for novel NAT testing platforms such as the cobas 6800/8800 system, and a growing portfolio of assays specifically to meet the needs of the blood industry. Now, I really hope we can continue to expand that, based on commitments as we move forward.

So, for us, Roche requests that this committee clearly demonstrates its continued commitment in blood safety for the United States such that Roche Diagnostics and other manufacturers can continue to invest in novel products as we continue to focus on global surveillance and detect emerging infections that

can threaten our blood supply.

Finally, on behalf of Roche Diagnostics, I would like to reinforce our commitment to the blood industry and to blood safety. Our goal is to be your partner in fighting back against the risk of any and all emerging infections by providing proven, robust technology for the testing of blood and blood products. Thank you very much for your time.

**DR. KAUFMAN:** Thank you. I would like to invite Jerry Holmberg from Grifols.

**DR. HOLMBERG:** Thank you. My name is Jerry Holmberg. I'm senior director of Strategic Scientific Innovation at Grifols Diagnostic Solutions.

Grifols is a global healthcare company with more than 75 years of history of advancing patient care. The company strives to meet the needs of the patient through our four divisions: diagnostic, bioscience, hospital, and bio-supply.

Our diagnostic division offers a comprehensive transfusion medicine portfolio designed to support transfusion safety with nucleic acid testing,

capability, and immunohematology solutions from donation through transfusion. Grifols' bioscience division produces lifesaving plasma derivative medicines to treat a variety of rare, chronic, and often life-threatening diseases. And the hospital division offers specialized products and services to enhance the quality, safety, and efficiency of hospital pharmacies including sterile compounding processes.

Grifols applauds the FDA for seeking the advisory committee's recommendation to appropriate strategies to reduce the risk of Zika virus transmission by blood and blood components.

Effective transfusion disease response is a critical component of the public health infrastructure. Management of the blood supply requires robust strategies to promote stewardship of this public good. The development and implementation of these strategies should take into account diverse stakeholders' perspectives, including blood collection facilities, providers, suppliers, and recipients of blood and blood products.

From a supplier's perspective, effective infectious disease response requires predictability. As a developer and manufacturer of nucleic acid blood screening assay, Grifols supports the 2016 recommendation of the Advisory Committee on Blood and Tissue Safety and Availability, particularly their recommendation to reduce regulatory uncertainty with respect to innovation and to encourage investment in their development and implementation.

Grifols relies on a predictable regulatory policy approach when making investment decisions, including determining which infectious disease targets are appropriate for the development of a new blood screening assay.

Today, the committee is considering three different testing strategies to reduce the risk of Zika virus transmission by blood and blood products. Grifols would like to share our perspective on these strategies and how they may impact a potential resurgence of Zika virus.

The first option of no policy change would

ensure the most robust response to a potential resurgence of the Zika virus. While there has not been a confirmed Zika positive donation since March 2018, continuing with the current approach to testing is the lowest risk option because every blood donation would continue to be screened.

Universal screening supports surveillance and early identification of new potential outbreaks, enabling the mobilization of multiple tubes to prevent further spread of the virus, including vector control strategies.

The universal testing mandate was a critical part of the successful response to the Zika virus in 2016, maintaining universal donor would support a strong defense to the risk of a new outbreak of Zika.

The second option of discontinuing testing in most states but maintain it in certain states presents some challenges to preparedness. The highly mobile nature of the public makes it difficult to know if a donor has been exposed to the Zika virus if the donor is donating in a state outside the mandated geographic

screening area. This is particularly true because the FDA is not recommending a pre-donation assessment for Zika risk factors, such as possible exposure through travel or sexual contact.

Because most infected individuals are asymptomatic, relying on other pre-donation assessments such as questions regarding wellness, are unlikely to filter out donors who have been exposed to Zika. Furthermore, it is challenging to predict when Zika may reemerge as a major threat to the blood supply.

While there has been a decline of identified cases of Zika over the last two years, an article published in *Nature Microbiology* this month concluded that the global population at risk from malaria or from mosquito-borne diseases will likely continue to expand as mosquitoes migrate to new geographical regions. The authors relied on a statistical model to predict the future geographic distribution of Aedes aegypti and Aedes albopictus mosquitoes and found that by 2050, 49 percent of the world's population will be at risk of an arbovirus transmission.

Finally, the third potential strategy of eliminating all testing presents the most difficult to preparedness from a supplier's perspective. If the FDA eliminates the Zika testing mandate, the demand for Zika nucleic acid assays is likely to drop significantly.

Any uncertainty in the potential demand for Zika assay will impact the ability to supply assays to the marketplace. The manufacture and distribution of assays are complex and cannot be easily turned on and off. It may be very challenging for manufacturers to accommodate a "just in case" or "just in time" inventory of blood screening assays.

Due to shelf life limitations and operational challenges, Grifols may be unable to maintain a significant number of assays on hand to aid in response to a reemergence of the Zika virus. Additionally, manufacturers may cease production if there is an uncertain demand for screening assays.

If new outbreaks emerge, it would take significant resources and time to deliver the assay.

In order to redeploy the assay, manufacturers would need to allot time to restart production; obtain FDA lot release; to obtain, retrain customers; and possibly for customers to validate the assays in their laboratory. We estimate that the reactivation process could take three months or greater from the time of notification of a need of the assay when the assay may be ready to be deployed. The time involved to restart manufacture is a vulnerability in Zika virus response.

Again, Grifols applauds FDA's openness to address these important issues by seeking recommendations from the advisory committee. We encourage the committee to consider the impact of any changes to the Zika screening recommendation on all stakeholders, including blood collection, facilities, providers, suppliers, and recipients of blood products.

We thank you for the opportunity to comment today. And please consider Grifols a resource as you continue to discuss these important issues. Thank you.

**DR. KAUFMAN:** Thank you. Our next speaker will be Kate Fry from America's Blood Centers. Okay.

Mike Busch.

**DR. BUSCH:** Thank you. I wanted to present a broader context for this discussion and then some specific data, some of it addressing some of the questions of the committee. So, this is really my life. I started doing blood bank research in 1982 and you can see the dramatic reduction in established pathogens -- HIV, hep C, hep B -- but across the top, you can see that virtually every year for the past 20 years, we've responded to an emerging infectious threat.

Some of these have been clear pathogens for which we've introduced testing or other technologies. Others are true human pathogens but are not transmitted or don't cause significant disease and others were false alarms, the most recent big example XMRV, but just to illustrate that this is an ongoing process. The next slide, please.

It just shows a WHO map from last year of the number of emerging and reemerging infectious diseases around the globe. I think we're all aware of this.

This just increases with expanded virus discovery, global warming, etc.

The next slide focuses in on the arboviruses -- human arboviruses -- and shows the regions of the world and particularly the Americas, where we now have all three Zika, dengue, and chikungunya circulating simultaneously at substantial but unpredictable rates year to year. In the little box to the left, you can see the Caribbean islands, including Puerto Rico, which has again all three viruses and an early evidence of a new dengue outbreak this year.

I just want to point out that the contribution of the blood screening field to enhance diagnostics is actually substantial and I'll come back to that. Many of the tests that we've helped develop through our needs for very sensitive molecular serologic tests have been brought to bear on epidemic surveillance and response. And this is a very recent report in *BMJ* on the importance of having good diagnostics for epidemic response.

I'm not going to go through any of this in

detail due to lack of time. But it's clear that we need to synergize the blood screening needs for diagnostic assays with broader public health needs in order to be ready and responsive to pandemics. Next slide.

I just want to mention that while we're talking about scaling back testing, there's actually a huge expanded focus now on epidemiology to respond to emerging arboviruses and infectious diseases. After the pandemic of Zika recently and the continued reemergence of Ebola, there've been a number of initiatives; this one funded through the United Kingdom to respond with very focused networks to proactively identify and understand the epidemiology, understand the pathophysiology, clinical consequences of arboviruses throughout Brazil.

The next slide is an initiative just announced by NIAID to establish emerging infectious disease research centers throughout the high-risk regions of the Americas and Africa and Southeast Asia, recognizing the dramatic gaps that we've had in research

infrastructure to detect and rapidly respond to emerging pathogens, and particularly, RNA viral pathogens, such as these arboviruses.

So, we are intending to respond to this network with a collaboration of Brazilian sites throughout the country that are part of the REDS-III network along with Puerto Rico in order to contribute the blood screening environment along with clinical case surveillance in response to -- to be proactive in responding to these not only known but unknown flaviviruses and other arboviruses.

So, moving on to just a little bit of data. So, we've conducted two large studies that have, I think, informed prior committees' deliberations. One was focused on the outbreak in Puerto Rico. We're in collaboration with Roche.

We screened the population there through our testing division and identified 339 infected donors. A large proportion of those donors were enrolled into a follow-up study where samples were obtained two to eight weeks later, and I'll show a little bit of that

data and how that's relevant to understanding the magnitude of infection in Puerto Rico.

And then a second study where 53 infected donors were enrolled into longitudinal follow-up for a year and extensive data on persistence of the virus and blood compartments and serologic patterns et cetera have been generated that, again, I'll show you are relevant to the question of the magnitude of infection in Puerto Rico.

So, the next slide just summarizes the methodology that was used. This was modeling done by Brad Biggerstaff at CDC, where we used the doubling time of Zika from infected macaques to estimate dates of infection of the donors in Puerto Rico detected in the pre-IgM phase. And then based on the follow-up data from the IND trial, we could establish the duration of NAT reactivity that is detectable by the very sensitive blood screening assay; in this case, the Roche assay. And then those data were further modeled to estimate the infection rate that occurred within the general population of Puerto Rico.

The next slide just points to the persistence of the viral RNA. So it, on average, last 11.6 days from initial detectability to clearance of that plasma viremia; and about seven and a half of those days are sera negative and therefore highly at risk for transmitting.

Using that 11.6 days in the NAT yield data through the course of the epidemic, on the next slide, Brad Biggerstaff was able to model the number of infections in the Puerto Rican population and the proportion of the Puerto Rican population that was infected during that very large outbreak. As you can see, at the bottom, we estimate that 21.6 percent of the Puerto Rican population was infected during that very large 2016 outbreak.

Now in the next slide, you can see the antibody patterns over time. These were tests that were selected after extensive assessment of a large number of different antibody tests, many of which have very nonspecific reactivity as a consequence of prior dengue infection. But, in particular, these tests from

Nirmidas, from Bio-Techne, and are tested at U.C. Berkeley called the blocking of antibody assays showed very specific reactivity to Zika, not impacted by preexisting dengue reactivity.

But you can see that the antibodies wane over time. In particular, on the lower right are the neutralizing antibody titers in these 53 donors followed for a year. And you can see how those antibodies wane over time, raising concerns over susceptibility of even previously infected people to reinfection.

Now the next slide shows an important study that we recently completed where we took 500 samples from early 2015. This was actually a post-chikungunya outbreak sample set that's been previously published, and then samples from the very first week when we started screening in Puerto Rico in April of 2016, and then at three sequential time points through the rest of the epidemic and just after the epidemic, and then a year later. And these samples, 500 at each time point, were tested by the very specific Bio-Techne NS1 antigen

IgG assay.

The next slide shows the results of that testing. You can see that those samples from March 2015 were virtually completely negative for Zika IgG. By the time we started screening in April the first week of testing, already four percent of the Puerto Rican population had sera converted to Zika.

So, by the time that first three months from the warning signal to the availability of the test was turned on, we already had four percent of the donor pool infected, which means that proportion of people had gone through acute viremia. And were Puerto Rican blood still being collected during that period, those units would have been transfused and likely transmitted.

In March of 2017, you can see that the peak rate was 23 percent. So that's very consistent with what we projected based on the NAT yield data of the population being infected. So that means three-quarters of the Puerto Rican population is still Zika naive.

In the samples collected a year later, April '18, you can see how the overall rate of reactivity had dropped to 16 percent and the overall reactivity levels began to be much lower. This is indicative of waning antibodies, as I showed in the prior study.

So, it points out that you can't rely on a sera survey done years after an outbreak to estimate what proportion of the population was infected and raises the concern that the waning immunity may signal a potential for reinfection, which has been well documented for chikungunya and all four dengue virus sequences.

Next slide, wrapping up here. Just to point out the registry under NHLBI sponsorship has executed surveillance studies within Brazil, including both molecular surveillance and sera surveillance across these four hemo centers shown as stars in the upper right corner. And what we've done is to track the rates of Zika, CHIK, and dengue by saving minipools.

They were routinely processed for screening for HIV, HPV, and HCV. And minipools of '18 were

constructed from all four hemo centers over a period of now three years and they were tested with a research-use only triplex assay, in this case developed by Grifols. This is essentially a blood screening technology assay that was optimized, in part, for purposes of this study.

On the next slide, you can see that the -- oops. Sorry. This is just an analytic data on those panels on that assay comparing on the left the triplex assay with a single Zika assay showing that these assays are exquisitely sensitive, as we know. At the very bottom, you can see the 50 percent limits of detection of both the Zika component of the triplex and the Zika assay is approximately 1.5 copies per mL.

In contrast, the CDC assays are a lot less sensitive; the boxed component here, the high input CDC trioplex assay, which is rarely performed outside of the CDC reference lab, the low input assays which are broadly used are even substantially less sensitive.

So, on the next slide, you can see that the surveillance in Brazil has documented fluctuating but

significant rates of viremia for all three viruses across the four hemo centers, which are part of this network, approaching half a percent of donations being viremic based on the pool surveillance study.

The next slide just shows that as we expand in REDS-IV, which is launching soon in Brazil, we're going to add two additional hemo centers, one in the Amazon region and one in a very rural region of Sao Paulo state. So, this surveillance using minipool testing will continue for the next five-plus years.

Next slide, finally, just showing some data that speaks back to my earlier point that this is comparing the sensitivity of detection of these three viruses by the ArboPlex test that was built as a prototype for a blood screening assay, compared to the CDC trioplex assay. And what this is demonstrating -- this a head-to-head blinded comparison of the two different technologies on clinical samples. So, this was a thousand patients presenting with dengue-like syndromes.

What you can see is overall 40 percent of

these patients had one of these three viruses. There were no cases that were detected by the CDC trioplex that were not detected by the Grifols ArboPlex, but the Grifols ArboPlex assay increased detection by a substantial proportion, detecting 50 percent more dengue infections, 40 percent more Zika infections, and 20 percent more chikungunya infections.

So just speaking back to the point that we really need these highly sensitive blood screening technologies which are not available outside of the diagnostic. And that other diagnostic settings are from CDC, not only for blood safety surveillance and response, but also to make these tests available for broader clinical utilization. I think that's it. Thank you.

**DR. KAUFMAN:** Thank you. So, Michael, I wanted to ask are you going to present for Brian Custer?

**DR. BUSCH:** I was asked to just make a brief statement to alert the committee to the statement that was distributed for Brian and Alton Russell. Just to

mention that this relates to a recently published study titled Screening of the Blood Supply for Zika Virus in the 50 U.S. States and Puerto Rico: A Cost-Effectiveness Analysis.

It includes additional findings regarding the estimated health consequences of transfusion-transmitted Zika that were just as important as the cost-effectiveness ratios that were the primary focus of the paper. And that study touches on the topics this committee has been discussing, particularly with respect to the rates of detection or Zika in the blood supply and the impact of regional testing on minipool and ID NAT.

So, I just wanted to alert the committee to that statement and happy to address any questions on behalf of Brian and Alton.

**DR. KAUFMAN:** Thank you. So, at this time, I want to ask if there's anyone else from the public that would like to make a comment? All right. Thank you.

So, we'll have the open committee discussion now. Thank you. Okay. Well, Dr. DeMaria, would you

like to get the ball rolling?

**OPEN COMMITTEE DISCUSSION AND VOTE**

**DR. DEMARIA:** I think I sort of moved back and forth during this whole discussion, because I really hear -- everything we do in preventive medicine, public health, is based on a concept that it should be cost effective; that cost effective is important, and that that should be applied to our decision making.

So, in the past 25 years or so, observing the blood collection and transfusion world as sort of an outsider, it's a different world in terms of risk perception and risk aversion. Understandably, because I also work with the public a lot, understandably the public wants to have a totally safe blood supply, and I want to have a totally safe blood supply. But adding testing and never changing it, despite a change in conditions is not really looking at any kind of cost-effectiveness analysis.

So, I was happy for this discussion, because I wanted to sort of rigorously think about the

possibility of taking something out of the testing mix. Could we get to that point with Zika? And if nothing changed, then I think we're at that point; but we can't say that nothing will change in the near future.

I think it's hard to, within the context of the specific questions, but then maybe it's premature to eliminate all testing for Zika. And maybe it makes sense to do the minipools for another few years as other testing options might come up in the future and as pathogen reduction technologies improve. So, I have to think about how I'm going to vote.

**DR. KAUFMAN:** Thank you. I think this is a really complicated question. And to your point, and something that the members of the committee who are not transfusion medicine specialists in their regular jobs may not realize that the FDA really has not -- once a test goes in place, it tends to stay.

So, for example, we're still testing all donations for syphilis. It's not clear that there's any real value now for doing that. One test that was implemented and then taken out was P24 testing for HIV

when nucleic acid testing became available. The NAT testing has a shorter window period, so it really completely obviated the need for that test because it was better and more sensitive.

But other than that, there's been really no testing that's been put in and then taken out. And so there's -- I don't know -- there's probably good and bad to that. Testing was put in for, for example, non-A, non-B hepatitis before anyone knew what that was. Hepatitis B core testing was put in. There's now specific testing for hepatitis C virus, which we now know that was what that was. The hep B core testing has remained because it seems to potentially have a little bit of yield for hep B, but it's not used at all for hep C. So, anyway, this would be a little bit of a break in tradition if we -- that is, if the FDA -- if we and the FDA decided to make a change.

Again, to your point, I think the primary goal is to protect the safety of the blood supply, to protect our patients. Having said that, if there's truly no yield from a test, then it really, I think

does need to be questioned in the current era where there really are limited resources. If we put a lot of resources into one safety initiative, then it means something else is not getting resources. So anyway, other comments? Marty.

**DR. SCHREIBER:** So, this is a question for the epidemiologists. I don't think we addressed this yet. But is it not likely that there will be future epidemics at any time, potentially this year, next year, the following year? Can anyone comment on epidemiologically what we're looking at for the future? Maybe Captain Fischer?

**DR. FISCHER:** I think as, Dr. Lewis brought up, it's difficult to predict. I think we're unlikely to see an event like we saw in 2016 when the virus was introduced into a completely susceptible population. But I think we're going to continue to see certainly sporadic disease and then outbreaks that will be more focal and probably lower level. And they'll pop up in different areas. I wouldn't want to predict beyond that.

**DR. STAPLETON:** So I, like you, Dr. Kaufman, I went back and looked at the Easter Island outbreaks; and that was 10 to 12 years ago, and there doesn't seem to be this second wave phenomenon that everyone worries about.

So, my initial feeling was that we haven't seen transfusion-associated disease. But again, the risk aversion nature of what we're trying to do, to protect the blood supply, means you have to be really careful. And I think the new outbreak in India raises concerns because of the size of the population and the potential for spread. So, I've also struggled with this, as well; but I think I'm leaning like Al, that given the need to be risk averse, we may need a few more years before we can change that.

**DR. KAUFMAN:** No, and I think that's an interesting point. We don't know what's going to happen in India, for example, and other parts of the world. One of the things that Dr. DeMaria had mentioned before had to do with the initial rollout of nucleic acid testing for this across the country, when

really the local transmission risk in the continental United States seemed to be restricted to Florida, basically Texas, parts of the Gulf Coast.

But one of the arguments that was made for testing in Iowa, Montana, places where there wasn't going to be any local transmission, was that: One, there seems to be some, not a lot, some sexual transmission possible. And another is the travel. And that is a real challenge.

It is striking that, basically, even though the absolute numbers are quite low, for the U.S., it's almost all travel. Not all. There was a little bit of local transmission. And then for Puerto Rico, it was basically all local with a tiny bit of travel. So, anyway, that does need to be considered.

On the other hand, the absolute risk -- so if you were to collect a unit in Montana, say, the risk of that being a Zika infectious unit -- let's say you weren't doing any screening -- would really approach zero, even with a travel risk. And even for a while, it was possible to -- for example, in Puerto Rico, they

had the option of doing that as a reduction or you could get blood products from the mainland without testing. Sorry. Dr. Hollinger.

**DR. HOLLINGER:** Yeah, so I'll put on one of my other hats. When I was at the CDC many years ago, I was in the arbovirus infections unit, subsequently, as the assistant chief of that unit; so, I've sort of maintained an interest in these diseases all along.

But one of the issues is that, as you mentioned, looking at the United States particularly, taking Puerto Rico out of the picture for a minute, is that almost all the cases, or most of the cases we see, are travel related, with just a few locally acquired infections, mostly in Florida, as it was for chikungunya, as it was for dengue, and so on, and then some in Texas where I'm from.

So, we haven't seen much. And I've always felt -- this is the way it is. If you understand mosquitoes and particularly the Aedes mosquito, that it doesn't travel very far, it stays within close confines and so on, that was not going to be a real issue. It's

never really gotten into the stages where we have major outbreaks.

So now you have Zika with a very little locally acquired disease, mostly travel deferral. Which is why I mentioned, and the slide which Mike Busch put up about all these different diseases around. If you look at most of those diseases, again, they all have a very short viremic period and that travel deferral is a good thing for us to think about. It may not be for this meeting, but it certainly, as a universal requirement, might be very good in times of eliminating these diseases; particularly Zika, in which most of it is travel-acquired. So, for me, I'm very much toward option three or option two here.

I'm very empathetic with the companies that have spoken here, particularly Roche, Grifols, and so on, because they have come through and produced these at a time when we really needed it to have produced these excellent tests in a fairly short period of time. But we sometimes have to set that aside because that's a commercial issue. It's a cost issue. And again, the

costs of doing these tests are relatively expensive, adding to the cost of blood in this country. And we need to, I think, think of that.

Again, going back to my question, the question doesn't cost anything, but doing testing does. It doesn't mean you're going to pick up everybody and, as Michael said, you might not remember if you traveled there. That's why I take my wife with me when I go donate blood, so she can tell me if I have been out of the country 30 days ago.

But, other than that, I do think that it is -- sometimes you have to decide. And I think you brought it up very well, is whether we have to continue on with all these tests when we don't seem to have an issue there. And so maybe the best approach would be a regional approach and one could actually just do it in Florida. They seem to be the sentinel animal.

I remember with, and again, in arboviruses, St. Louis encephalitis, for example, we had sentinel chickens out to determine. Now, in many cases, there's a lot of surveillance for mosquitoes and so on. It's

still the travel-associated cases or travel-acquired cases that are going to be an issue. But you can determine, and there are surveillance going on in mosquitoes, to determine when they are infected. And that usually occurs several months before transmissions.

This is something and one could just do it in one or two states, which particularly Florida would be sort of the sentinel animal, if you will, in determining whether there are cases coming in and where that's a real big issue. And then decide what you're going to do after that. So that's sort of where my take on it is right now.

**DR. KAUFMAN:** Dr. Shapiro.

**DR. SHAPIRO:** How much does this test add to a unit of blood? What's the actual cost?

**DR. KAUFMAN:** I don't know. Dr. Bloch, do you want to comment on this?

**DR. BLOCH:** It's about $7 to $10. I don't know the most up-to-date; but at least in the publications, it's been about $7 to $10.

**DR. KAUFMAN:** And there have been different ways to look at this. Let me first say I'm not an economist at all. One of the ways that people have looked at this question of cost-effectiveness has to do with how many quality adjusted life years do you save by doing testing, with the idea that something that cost like fifty or a hundred thousand dollars per quality is cost effective. That would be like a stem cell transplant or heart surgery.

The testing that we do for blood is extraordinarily sensitive and specific, and the costs are way out of proportion to other things in medicine. So, HIV NAT, for example, is a million dollars per quality or $10 million per quality, something like that. And for Zika quite a bit more than that, actually. So anyway, that's what we can say.

Now there's a couple different ways of looking at that. One is well, blood, in a sense, can be thought of as qualitatively different. That is the view of the public is -- and it's not something that can be so easily quantitated. There's an emotion about

it, that you want to be confident that when you get a unit of blood that it's going to be safe and will be helpful and not harmful and that sort of thing. So, there's been a willingness for society to pay more for this. But that's sort of what we're talking about. I'm sorry. Dr. Lewis? No.

**DR. DEMARIA:** The question about regional testing came up particularly with the babesiosis. It really brought home the fact that small differences in blood product prices can drive the market, and that healthcare delivery systems will look for the least expensive source of blood. And that's a reality. It raises all kinds of issues when you talk about adding a little bit of expense in one part of the country versus another. So, I think that's real. It's unfortunate, but it's real.

The other thing is that I was involved in a public engagement discussion about babesiosis, testing for babesia. It was interesting to me that after extensive discussion, and I alluded to this before, that people do not feel it's fair to test in one part

of the country and not in another part of the country if there's any chance that the risk could exist in that other part of the country.

And we were talking about babesiosis -- a very small risk that someone outside of the endemic area would just happen to have babesia swimming around in their blood at the time they donated. But that was enough to make the almost unanimous decision at this public engagement group that either we should test everywhere, or we should test nowhere. It was that decisive.

**DR. KAUFMAN:** Yeah, I mean so there was a large risk-based decision-making exercise that went on about this. I think there was -- everyone, again, was trying to do, okay, what would be the most logical approach for something like babesia which is in the northeast and the upper Midwest and that's about it -- New York, New Jersey.

And so the blood collectors would say, well, that's fine. We won't collect any blood in New England. Well, you know, collect more in the Midwest,

that sort of thing. It was going to sort of change how blood was collected, and this issue still hasn't really been resolved.

Sorry. Why don't we start with Sue Stramer and then Dr. Lewis and then Dr. Basavaraju. Sue, go ahead.

**DR. STRAMER:** I didn't have any comments to make right now, but as long as you called on me; to respond to Dr. DeMaria's and your comments about the risk-based decision making on babesia, that really isn't the topic for today. I understand why Al brought it up regarding public perception. But the overall group decision for risk-based decision making for babesia was regional testing and that's been published.

But to go to the issue of the day, which is Zika, as I mentioned earlier, there is no consensus opinion from industry. We feel that there are a lot of pros and cons to each of the three strategies that FDA proposed.

But just to give some examples; some imported Zika cases still occur in Florida. In 2018 there have

been 103, eight in 2019. So, we still see cases in the United States.

We need additional time to determine if a regional testing model versus the total elimination of testing is the way to go. As I mentioned, there is no consensus as of yet. Minipool NAT has been stable to date. In one additional year or so, minipool NAT should provide adequate data for further discussions of a future direction. And as mentioned by our test manufacturers, an abrupt elimination of testing would be problematic if we ever wanted to bring up testing again. And it really sends a mixed message to the manufacturers who work tirelessly to bring us testing as a priority and then we implement testing, and then we automatically or abruptly dismiss it. So, I think it would be hard for them to remain our partners without more serious discussion of this topic.

**DR. KAUFMAN:** Thank you. Dr. Lewis.

**DR. LEWIS:** So, two comments. One has to do with the flexibility of responsiveness of our regulatory approach to blood safety. I heard comments

earlier supporting and applauding the re-evaluation of the need for the test and the changing epidemiology. I think the chairman made the point that we tend to add things. We tend not to take them away, even when the original motivation for adding them may have waned.

I think that it is internally inconsistent, as just a decision approach to risk mitigation, if we consider one type of variability, like the changing epidemiology of the epidemic over time, and not another variability, which is the risk associated with geographic location.

So, with respect to the prior speakers, I don't think it's rational for us to arbitrarily say we'll ignore risk and changes in risk in one dimension, but not another. So, if we're going to consider that the epidemiology and the epidemic is changing, and if the actual quantitative risk is changing, we should be willing to consider different strategies based on the region in which the blood is donated or other characteristics that we can objectively use to estimate risk.

That's one comment. A different comment has to do with quantification of risk. And I was, in my mind, trying to think about the risk of the no testing strategy even in an area in which the prevalence of the virus in the donating population might be nearing a percent. I'm going through the risk that they donate during the viremic period that it's transmitted that a woman relatively early on in pregnancy -- I'm being intentionally vague in that-- receives a blood transfusion.

I realize there are high-risk populations. I work in a county trauma center. We frequently find ourselves giving blood to women who we subsequently find out were pregnant, a surprise to us and often to the patient. But that's not a common event as compared to all women who are pregnant and deliver.

Significant congenital abnormalities are a not uncommon event. And I'm wondering if anybody has actually calculated the marginal increase in risk in this strategy compared to just the risk of having a baby and the risks that are associated with congenital

anomalies that we see.

I'm trying to quantify the marginal risk associated with a no testing strategy in an absolute sense. And I'm struggling with it because I don't have all the numbers on the top my head.

**DR. KAUFMAN:** Yeah, I don't know that I can give you precise numbers. There was a little bit of information in the packet something like relatively few -- let's say, I don't know, 5 per 10,000 something like that is something like a typical rate of microcephaly seen. So, something in that ballpark, something in the range of 1 out of 1000 or 1 out of the 10,000 babies, but ballpark, is what sort of the expected background is.

**DR. LEWIS:** Yeah. The key number I had trouble figuring out where we would find is the fraction of all women who are transfused in other than the peripartum period. And I think that's a key piece of information that would be useful to know.

**DR. BASAVARAJU:** Actually, I had two like technical questions, I guess, logistic questions for

FDA. So, the first is when the committee is considering the changes to the screening strategy, my understanding is that we have to consider the scientific and technical merits of screening, but the cost of the screening should not figure into that. Is that correct? Yeah.

So, the second question then for FDA is if the committee was to vote that screening could be done regionally, could we leave the regional strategy itself up to FDA to determine based on -- so like for now, it could be certain states then add certain states later, remove certain states later? And so the committee would just vote, screening everywhere, screening nowhere, screening in some places?

**DR. VERDUN:** Yes, that's fine. You can consider a regional testing option and leave the specifics to FDA as an option as well.

**DR. STAPLETON:** And so, given that you'd be testing fewer units if you adapted a regional policy, technically you'd be increasing your predictive value of the tests as well. Correct?

**DR. KAUFMAN:** Yeah.

**DR. CHITLUR:** Hi, this is Meera Chitlur.

**DR. KAUFMAN:** Yes, please, go ahead.

**DR. CHITLUR:** My question was actually exactly what the previous speaker had brought up regarding, I think, a couple things. One is that the Indian outbreak occurred very recently. And travel is so common and so easy and it's still a significant risk. So, is it too early for us to consider discontinuing, like many of the speakers so far have mentioned? And I think the economic and health care costs of caring for a child or a baby with microcephaly and developmental issues for the rest of their life really have to play a role in the decision that we make.

**DR. KAUFMAN:** No, I think that's -- thank you -- I think that's a fair point. You know, as has been mentioned, most people that get Zika are completely asymptomatic. There have been some cases of Guillain-Barré that have been associated, but it's really the risk to the fetus that drives the entire kind of thinking around the discussion.

**DR. CHITLUR:** And I think, coming from -- as a hemophilia treater, this sort of is similar to me to the history that we've had. I know it's not exactly the same. I know it's kind of different, but in some ways, it is similar. The risks are associated with transfusions with blood products that are considered to be safe by the public and are not paying enough attention maybe to this should not bring us back to where we were with the hemophilia population in the past.

**DR. KAUFMAN:** So okay. I'll just be the devil's advocate a little bit. So, they've been no -- we learned that there have been zero confirmed positives from blood donors for the past year. Would anyone be comfortable with just stopping screening all donors? Dr. DeMaria.

**DR. DEMARIA:** I thought it would be, because it seemed to me that what we did know about Zika suggested that whatever happens, and it may happen again but was totally unpredictable. But I think that totally unpredictable now makes me think that we should

continue until we're sure that the risk is gone.

And if we go to a regional -- you know, Massachusetts wasn't on the list of states that had a higher risk, yet we had two confirmed positive donors. And part of that is yeah, California, New York, Florida are on the list, but those are also the states have large numbers of people traveling. We have a smaller number of people traveling in Massachusetts, but that doesn't mean proportionately that we might not have as significant a risk as many people.

Because what's different with Zika from West Nile is that West Nile, there was a risk across the whole country. And it was the birds who are presenting the risk, not the people traveling. So, I think this is a different circumstance.

I don't think we have parts of this country, even in Texas and Florida, that are really at the same level of risk as where Zika has occurred elsewhere, because people -- lifestyles are different, screens are different, the air conditioning is different.

So, you know that, again, to me speaks against

having a regional approach because I think it's the same as saying stop doing it. We don't know what's going to happen with people traveling. We don't know the relative risk of traveling to India, if it becomes widespread in India, is for states that aren't Florida, Texas, and California.

**DR. KAUFMAN:** Thanks. Dr. Shapiro.

**DR. SHAPIRO:** I think one of the things that concerns me about stopping testing is not just the issues related to how frequent do you find positives, but the lack of surveillance that would then occur. There's no organized surveillance in this country for looking at recipients of blood products or individuals in particular endemic areas.

So how are we to know what might happen? We can look at past data, but you're talking about an infectious disease that you really have very little control over whether it recurs or not.

**DR. KAUFMAN:** Dr. Bloch and then Dr. Hollinger.

**DR. BLOCH:** So, I actually completely agree;

but just to play devil's advocate, you know, is that the role of the blood collection agencies to be conducting public health surveillance? So, it's kind of a different role. So, I absolutely think it's an incredible resource for surveillance, but it's not primarily what they're supposed to be doing.

**DR. SHAPIRO:** I agree with you. It's not their role, but you're charging for a product that you're giving to a patient, and the patient has a sense of safety. I'm sorry, what Dr. Chitlur said, I don't think HIV is the same thing. No, I agree with you, Meera. I'm supporting you. I think there are lessons learned there, and I think surveillance of some sort -- it may not be your role, but if that's the only method we have so far that's set up, then I think that's where it falls.

**DR. BLOCH:** But then why aren't we testing for other agents?

**DR. SHAPIRO:** For example?

**DR. BLOCH:** For anything. You know, dengue, chikungunya. There's a whole -- one could screen for

the whole gamut of agents. So, like I'm torn because I do absolutely agree with you that it is an incredible resource for that. But is the question, is testing protecting, offering some sort of benefits to recipients? By our doing surveillance is not necessarily impacting those recipients. Indirectly, it might.

**DR. SHAPIRO:** I think it might, because --

**DR. STRAMER:** Can I --

**DR. KAUFMAN:** Yes, Sue, go ahead.

**DR. STRAMER:** Sorry. It's hard because I'm not there when I can speak in turn. But anyway, to support Dr. Bloch's statements, although blood donation screening is used in many degrees to monitor surveillance of infectious disease agents in the United States.

I mean, their justification to maintain Zika blood donation screening because it's useful for surveillance is not a good argument; or it's not, I should say, a valid argument. I mean, we're not reimbursed for this activity. It costs the blood

organizations millions of dollars.

So, although, we as an industry do not support discontinuation of testing now. It's really not for the purposes of ongoing surveillance, but it's for the purposes of the unknown and to take time to develop what the best strategy long term is.

**DR. SHAPIRO:** And to determine that, you need surveillance.

**DR. STRAMER:** Without question, but I mean it's the default to have the blood centers do it. It's difficult because, if you calculate $7 to $10 a unit to transfuse, we are paying for that. It's not a U.S. public health service activity, which it should be.

But I mean, I understand where the rubber meets the road. I mean, we are doing the testing. And we're the only ones who will monitor infection in asymptomatic individuals. I get that. It's just problematic because that's not our primary job and that's not how we recover our costs.

**DR. KAUFMAN:** Dr. Hollinger.

**DR. HOLLINGER:** Well, a couple of things.

Mike Busch mentioned before that they're doing some surveillance studies down in Brazil and other areas, which I think will be very important since they're about half -- they're the summer when we're the winter and so on. So that's important.

I think I'd like to just briefly read into the record a little bit about what Brian Custer said in the thing that was passed out to us. So, I want to just be sure it gets in. Mike sort of passed over it, but he's one of the authors of a paper that came out in the *Annals of Internal Medicine* in January of this year.

But they looked at some of the strategies and one of the things, if we just look at option two. In option two he says, "Targeted screening was far more efficient than universal testing," when they looked at those at that particular option.

And then he looked at like topic three and he states, "We estimated that the harms that would have resulted if no testing had been in place for Zika during the period of our analysis would have resulted in several transfusion-transmitted Zika infections: 242

in Puerto Rico, 45 in the 50 states. Most of them, however, would have been asymptomatic."

He said, "We estimate that serious sequela would have been very unlikely. It is easier to conceptualize the likelihood of these events as following: If Zika activity had remained at the level observing in our period of analysis year over year, we would expect the transfusion-transmitted Zika to cause one Guillain-Barré syndrome case in Puerto Rico every 16 years, one Guillain-Barré syndrome case in the 50 states every 84 years, one congenital Zika syndrome case in Puerto Rico every 33 years, and one congenital Zika syndrome case in the 50 states every 176 years. Because Zika activity has decreased dramatically since the period of our analysis, the risk of these serious adverse events today is essentially zero."

**DR. BASAVARAJU:** Yeah, I think that you have to be careful when we read this and kind of take it for what it is. You know, a lot of this is just based on the inputs into the model, so if you have a growing epidemic somewhere, it's not recognized. You have a

lot of return travelers. I think, you could -- you know that's one issue. So, I think that there could be more than what is being estimated here.

The other issue is let's say theoretically that's true that, there is one congenital Zika case every whatever how many years. I think the optics of that would be really poor if that one case occurred next week after you discontinued screening.

So, I think there's ongoing transmission in the Western Hemisphere. There are large numbers of return travelers from the Western Hemisphere, other elsewhere in the Western Hemisphere. And you have a mechanism in place right now to identify those people who -- and, you know, the fact that it hasn't happened in a few months or whatever doesn't mean it's not going to happen anytime really.

**DR. KAUFMAN:** Let's have Dr. Schreiber and then Dr. Stapleton.

**DR. SCHREIBER:** So, I agree with those statements, and I would add unless I have this wrong, I'm less worried about Texas and Florida and

California. I'm more worried about the naive populations that have never been -- had any exposure in the rest of those surrounding states who are actually potentially at greater risk for an epidemic because they've never been exposed to the virus.

So, this regional approach, focusing on states where disease has occurred, makes absolutely no sense to me because I'm more worried about the states where there has been no exposure. To me, there's no reason why this disease would happen in Texas but would not happen in a place like Louisiana or other parts of the South or other areas near California.

So, we've been told that the risk of epidemic is real. If that epidemic occurs, it'll most likely occur an area where the people are naive to the virus. The effects of this disease are devastating in the fetuses of pregnant women. I feel -- that's how I feel about it.

**DR. KAUFMAN:** Thank you. Dr. Stapleton.

**DR. STAPLETON:** Thanks. Dr. Schreiber gave me a couple more things to mention. When I first saw this

topic I thought, oh, it's time to stop this because I think Zika is going to be like SARS, and it's gone. And hopefully in two years that I'll feel that I was right in my initial assessment. But I think the fact that there are ongoing infections in the Western Hemisphere and a new epidemic last fall in India, that we've been told is under control but that doesn't reassure me yet. So, what we need, as somebody mentioned, is a crystal ball; and I don't think I feel confident we have one.

I want to also mention about surveillance; there's intense surveillance of mosquitoes, and that's being done. And also in Central America and South America there are many studies looking at surveillance of febrile illness similar to this and trying to sort out with this. So, I feel a little less worried about losing the blood supply which is, as the surveillance has told us, that there isn't anything to worry about. I think we're more likely to pick it up quicker through mosquito and endemic area surveillance and regions that are at higher risk than Texas and yet have not had much

disease yet.

And then finally about seroprotection, I think that's an open question. To my knowledge, the incidence of antibody prevalence in any of the United States, outside of the territories, is not reassuring that we're not all at risk for that.

**DR. HOLLINGER:** Let's talk a little bit about seroprevalence in the waning of the antibody. We know that most diseases, if you follow them, I can tell you for hepatitis B and C and so on, you see them over time. We looked at them 25 years or 30 years later, and their antibodies are gone but they don't get the disease. There are great memory B cells still present. There are good responses immediately to infection. So, I'm not sure that I'm concerned about that in that area.

**DR. STAPLETON:** Not so much loss of antibody and being susceptible. I think yellow fever shows that. But I think the idea that, right as of now, nowhere in the U.S. has significant seroprevalence exposure to Zika so that we are a susceptible

population.

**DR. KAUFMAN:** I think that's true, although, the vectors -- well, supposedly, the Aedes aegypti mosquito can be as far north as here, maybe a little farther. But it seems like the -- well, as Dr. Hollinger mentioned, it doesn't fly so well. And I think they don't go more than a mile from where they were born kind of thing. It's not like the birds in the case of West Nile. But for whatever reason we've just not seen anything so far outside of these tiny little pockets in the very Deep South. I'm sorry. Go ahead.

**DR. DEMARIA:** And I think the other aspect of this is you have to have infected humans to have a reservoir for the virus. So, the force of infectivity also depends on how many people in that population are infected and can infect mosquitoes who can then pass the infection.

And that would presume that you're in a circumstance where you would have enough people around to sustain transmission. Even in the parts of the

country where Aedes aegypti occurs and where people might be susceptible, you'd also have to have widespread transmission to have widespread transmission.

**DR. HOLLINGER:** Yeah, I think it's important also to point out that the albopictus which has moved up -- I don't know if -- I don't think there's any Aedes in Iowa, Jack.

**DR. STAPLETON:** Northern Missouri.

**DR. HOLLINGER:** But certainly, the albopictus vectorially is not a very efficient transmitter of this disease. It's not true for dengue and a few others, but --

**DR. KAUFMAN:** All right. So, does the group feel like -- I'll ask for any remaining comments and then we're going to need to vote. So, but go ahead, Dr. Bloch.

**DR. BLOCH:** Sorry. Are they not two different problems? Because there's no doubt that it's highly prevalent and extrapolating from other arboviruses, the chances are that it probably will resurge at some

point. There will be ongoing outbreaks. But the question is more about risk to transfusion recipients, which is not really being demonstrated. So, it seems to me two different issues.

**DR. KAUFMAN:** So, there is another part. So, we think about risk of infection from -- so first, what's the risk of an infectious unit being donated and getting into the blood supply? And then what is the risk of a recipient getting that infectious unit? But that's right. I mean, the fact is no one's gotten sick from Zika from a transfusion to date that we know of.

The best-case reports came from Brazil. There were a few patients who got platelet transfusions and perhaps, not surprisingly, since most of the people get infected by the mosquito are asymptomatic, but we have not seen disease. But that does kind of factor into the risk calculations. I'm sure that was part of the thinking of that model that Brian Custer came up with. What's the real thing we're trying to prevent? This is different than getting an HIV-infected unit, for example, but anyway.

Dr. Lewis.

**DR. LEWIS:** So, there is a study of blood transfusion during pregnancy that separates out the transfusion rate in the different periods of pregnancy and states that from the period of 2001 to 2010 that the transfusion rate across pregnancy including the delivery period was 1.4 percent. And of that, 91 percent occurred during the birth admission. So that leaves 9 percent, so about 0.13 percent of women received transfusion during pregnancy, not during delivery. And I'm just making the assumption that by delivery, it's too late for there to be damage. So, I think that gives us some quantification of the risk. So, between 1 in 500 and 1 in 1,000 women in earlier pregnancy will be transfused, if I did the math right.

**DR. KAUFMAN:** I think, like with CMV, I think the biggest worry is about kind of the first trimester, but there's -- I think the data are clear, but there seems to be some risk later in pregnancy as well, maybe even into the early third trimester. But I think most of the risk is thought to be early.

All right. So, we're going to ask everyone to vote. So, we're going to vote by using these buttons that are on the microphones in front of you. I believe this is not a secret ballot. It's a simultaneous ballot, but I think everyone's votes will be read aloud.

So, first question: At this time do the available data support continuing universal testing for Zika using minipool or ID NAT as recommended in the July 2018 final guidance? That is no policy change at this time, option one. So, everyone please vote for yes, no, or abstain.

Everybody vote? Okay. And, Meera, can I ask you to announce your vote, please?

**DR. CHITLUR:** Hi. I'm sorry. Can you say that again?

**DR. KAUFMAN:** Yes. I need to ask if you can announce your vote for question one.

**DR. CHITLUR:** For question one, I would like testing to continue as is.

**DR. KAUFMAN:** Okay. Thank you.

**DR. P. ATREYA:** Okay. So, I'm going to read out the votes. Eleven yes, four nos. And then, Nick, if you can display, I can read them aloud.

Okay, I'll start from Dr. Hollinger said no; Dr. DeVan, yes; Dr. Kindzelski, yes; Dr. Shapiro, yes; Dr. Ortel, yes; Dr. Lewis, no; Dr. Basavaraju, no; and Dr. Stramer is not a non-voting member. Dr. Kaufman, yes; Dr. Chitlur, yes; Dr. Schreiber, yes; Dr. Baker, yes; Dr. Bloch, no; Dr. Stapleton, yes; Dr. DeMaria, yes; Dr. Bryant, yes. So, it's 11 out of 16 [sic] yes and 4 nos.

**DR. KAUFMAN:** Okay, so second question: Do the available data support a regional testing option strategy for Zika virus using minipool or individual donation NAT in at-risk U.S. states and territories? Option two.

And, Meera, can you announce your vote, please?

**DR. CHITLUR:** My vote is no.

**DR. P. ATREYA:** Total votes are 15 and six yeses, nine nos, and zero abstain. For the public

record, I will read it aloud. Dr. Hollinger said yes; Dr. DeVan said no; Dr. Kindzelski said no; Dr. Shapiro said no; Dr. Ortel said no; Dr. Lewis said yes; Dr. Basavaraju said yes; Dr. Kaufman said no; Dr. Chitlur said no; Dr. Schreiber said no; Dr. Baker said yes; Dr. Bloch said yes; Dr. Stapleton said yes; Dr. DeMaria said no; and Dr. Bryant said no. Thank you.

**DR. KAUFMAN:** So, question two: Florida, Texas, Puerto Rico. So, this would be various regional options. Do you support doing regional testing in Florida, Texas, and Puerto Rico, the U.S. Virgin Islands where documented local mosquito-borne Zika virus transmission has occurred? And (b) California, New York where the mosquito vectors are present. And hang on one second, please.

We'll move to question three. Do the available data support the elimination of all testing for Zika virus without reintroduction of donor screening for risk factors -- for example, travel -- in areas with no risk of Zika virus infection pending another outbreak in United States? Option three.

**DR. KAUFMAN:** Dr. Chitlur?

**DR. CHITLUR:** My vote is no.

**DR. P. ATREYA:** Okay, for the public record, the total votes are 15. Fourteen no and one yes and zero abstain.

Okay. For the record, Dr. Hollinger said yes; Dr. DeVan said no; Dr. Kindzelski said no; Dr. Shapiro said no; Dr. Ortel said no; Dr. Lewis said no; Dr. Basavaraju said no; Dr. Kaufman said no; Dr. Chitlur said no; Dr. Schreiber said no; Dr. Baker said no; Dr. Bloch said no; Dr. Stapleton said no; Dr. DeMaria said no; and Dr. Bryant said no. Thank you.

**OPEN SESSISON TOPIC I ADJOURNED**