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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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116TH MEETING OF THE BLOOD PRODUCTS ADVISORY COMMITTEE

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December 1, 2017
8:00 a.m.

FDA White Oak Campus
Great Room, Building 31
10903 New Hampshire Avenue
Silver Spring, MD 20993

COMMITTEE MEMBERS:

CHRISTOPHER P. STOWELL, M.D., Ph.D.	Acting Chair
JUDITH BAKER, Dr.P.H., M.H.S.A.	Voting Member/ Consumer Representative
ALFRED DeMARIA, M.D.	Voting Member
MIGUEL ESCOBAR, M.D.	Voting Member
SUSAN F. LEITMAN, M.D.	Voting Member
ROGER LEWIS, M.D., Ph.D., FACEP	Voting Member
ROBERT J. REES, JR., M.H.A., MT(ASCP)	Voting Member
JACK STAPLETON, M.D.	Voting Member
KATHLEEN SULLIVAN, M.D., Ph.D.	Voting Member
JAMES R. ALLEN, M.D., M.P.H.	Temporary Voting Member
SRIDHAR V. BASAVARAJU, M.D., FACEP	Temporary Voting Member
ANDREI L. KINDZELSKI, M.D., Ph.D.	Temporary Voting Member
SUSAN STRAMER, Ph.D.	Industry Representative

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

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INDEX

INDEX

M E E T I N G

(8:05 a.m.)

LCDR EMERY: Good morning. I'm Bryan Emery. I'm the Designated Federal Official for today's meeting of the Blood Products Advisory Committee. Mrs. Joanne Lipkind and Mrs. Rosanna Harvey are the Committee Management Specialists, and they can assist you with any needs at the tables located in the hall.

I would like to welcome all of you to Day 2 of the 116th meeting of the Advisory Committee held in the FDA White Oak Great Room.

Dr. Christopher Stowell is the acting Blood Products Advisory Committee Chair. The CBER press media contact is Ms. Megan McSeveney, who is I think in the audience at this time. I don't see her, but that's who it is. Shaylah Burrill is the transcriptionist.

I would like to request that everyone please check your cell phones and pagers to make sure that they are turned off or in silent mode. Please also remember to speak directly into the microphone at all times, and please identify yourself. It is helpful for the public and people attending by webcast and the transcriber.

For the members around the table and the audience, coffee, drinks, and snacks are out the doors and to the right. There is a kiosk in the hall. Members' lunches will be brought to

the room in the back that we have reserved, at lunch time and right before break. And we have also -- and the restrooms are also out the doors to the right and at the end of the hall.

All committee topic and update discussion needs to be done in the public forum and not in groups during breaks. The FDA and the public needs your advice and expertise.

The public and industry must stay behind the stanchions and in the audience area. Please do not enter into the FDA or Blood Products Advisory Committee area. Please wait until the Open Public Hearing designated time to make any remarks using the center aisle microphone.

Now I would like to read into the public record the Conflict of Interest Statement for this meeting.

Good morning, everyone. I am Lieutenant Commander Bryan Emery, the Designated Federal Official for this Blood Products Advisory Committee meeting of the Center for Biologics Evaluation and Research, FDA, and I welcome you all to Day 2 of this 116th meeting of the Blood Products Advisory Committee, being convened by the Food and Drug Administration, December 1, 2017, under the authority of the Federal Advisory Committee Act of 1972.

This meeting is open to the public in its entirety, and all members and consultants are participating in person. At this meeting on December 1, 2017, in Open Session, Topic III, the Committee will discuss the strategies to reduce the risk of

transfusion-transmitted Zika virus. Following the Topic III, the Committee will hear two update presentations that have been determined to be non-particular matters on the following topics: (1) Transfusion-Transmission Infections Monitoring System and (2) FDA Summary of the Public Workshop on Tick-Borne Diseases and Blood Safety.

The following information on the status of the Advisory Committee's compliance with federal ethics 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. The Conflict of Interest Statement will be available for public viewing at the registration table.

With the exception of the Industry Representative, all participants of the Committee are either special government employees or regular federal government employees from other agencies and are subject to the federal conflict of interest laws and regulations.

Related to the discussion topics at this meeting, all members and consultants of this Committee have been screened for potential financial conflict of interest of their own, as well as those imputed to them, including those of their spouse and minor children and, for the purposes 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 primary

employment.

FDA has determined that all members of this Advisory Committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S. Code 208, Congress has also authorized FDA to grant waivers to special government employees and regular government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's service outweighs his or her potential financial conflict 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. Christopher Stowell is currently serving as the Acting Chairperson for this Committee meeting today. Dr. Stowell is an appointed special government employee, and he also serves as temporary voting member.

Dr. Judith Baker is currently serving as a voting member and the Consumer Representative for this meeting. She is employed by Western States Regional Hemophilia Network in policy. Dr. Baker is appointed as a special government employee and therefore is screened for her financial conflicts of interest and cleared prior to this participation.

Dr. Susan Stramer is currently serving as the Industry Representative to this Committee. Dr. Stramer serves as an Executive Science Officer at the American Red Cross and brings

her expertise in transfusion and cellular therapies to the Committee. Industry representatives are not special government employees and do not vote and do not participate in the closed sessions.

Dr. Carolyn Gould is an invited speaker for Topic III. Dr. Gould is a regular federal government employee who serves as the Medical Epidemiologist at the Centers for Disease Control and Prevention in Atlanta. She was screened and cleared for participation at this meeting.

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

FDA encourages all other participants to advise the Committee of any financial relationships that you may have with any firms, its products, and if known, its direct competitors.

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

and their exclusion will be noted for the record.

Additionally, I would like to provide the following specific guidance regarding this December 1 BPAC meeting.

Please note that Topic III of this meeting is determined to be a particular matter of general applicability and, as such, does not focus its discussion on any particular product but instead focuses on the classes of products under discussion. Presenters, speakers may provide data on products, if any, that will serve only as examples for the Committee to have a scientific discussion.

Please note that this BPAC meeting is not being convened to recommend any action against or approval for any specific product. This BPAC meeting is not being convened to make specific recommendations that may potentially impact any specific party or entity, individual, or firm in a unique way, and any discussion of individual products will only be to serve as an example of the product class.

This meeting of the BPAC does not involve the approval or disapproval, labeling requirements, postmarketing requirements, or related issues regarding the legal status of any specific products.

This concludes my reading of the Conflicts of Interest Statement for the public record. Now I would like to thank you all for your participation, and now I hand over the meeting to the Chair, Dr. Stowell.

DR. STOWELL: Thank you. Good morning, everybody, and welcome back for our second day of this 116th meeting. Brian described for you what's on our docket for today. And so with no further ado, let's go around and do some introductions. And if we could start with Dr. Kathleen Sullivan. Are you on the line?

DR. SULLIVAN: I am. My name is Kate Sullivan. I'm a pediatric immunologist at the Children's Hospital of Philadelphia.

DR. STOWELL: Thank you.

Doctor.

DR. STAPLETON: Jack Stapleton. I'm an infectious disease physician and Professor of Internal Medicine and Microbiology at the University of Iowa.

MR. REES: Robert Rees. I am the Manager for the New Jersey Department of Health Blood Bank Regulatory and Compliance Program.

DR. LEWIS: I'm Roger Lewis. I'm a Professor of Emergency Medicine at Harbor-UCLA Medical Center in Torrance, California.

DR. LEITMAN: I'm Susan Leitman, Director of the Medical Research Scholars Program at the NIH Clinical Center and formerly Head of the Blood Services Section at the Department of Transfusion Medicine at NIH.

DR. ESCOBAR: Miguel Escobar, Professor of Medicine and Pediatrics at the University of Texas, Hematology.

DR. DeMARIA: Al DeMaria. I'm the Medical Director and the State Epidemiologist in the Bureau of Infectious Disease and Laboratory Sciences at the Massachusetts Department of Public Health.

DR. BAKER: Judith Baker, Public Health Director, Center for Inherited Blood Disorders in Orange County and assistant professor at UCLA in Los Angeles.

LCDR EMERY: Lieutenant Commander Brian Emery. I'm the DFO for this meeting and for the Blood Products Advisory Committee.

DR. STOWELL: Christopher Stowell, Director of the Blood Transfusion Service at Massachusetts General Hospital and an Associate Professor of Pathology at Harvard Medical School.

DR. ALLEN: James Allen, retired public health service physician. I was at the Centers for Disease Control and the Office of the Assistant Secretary for Health for many years, back during the HIV, the beginning of the HIV/AIDS epidemic. Went on to a number of other positions, including state and local health departments. And I've retired after 17 years as a member of the Board of Trustees for Blood Systems International.

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

DR. KINDZELSKI: Andrei Kindzelski, Program Director, Blood Division, Heart, Lung and Blood Institute, NIH.

DR. STRAMER: Susan Stramer, Vice President, Scientific Affairs, American Red Cross, and Chair of AABB's Transfusion Transmissible Diseases Committee.

DR. STOWELL: Okay. Thank you. So our first topic relates to transfusion-transmitted Zika virus, and our first speaker is Dr. Anne Eder.

DR. EDER: Good morning. I'm Anne Eder. I'm Associate Deputy Director in the Division of Emerging and Transfusion Transmitted Diseases in the Office of Blood Research and Review at CBER. I'm going to introduce the first topic for discussion this morning, Strategies to Reduce the Risk of Zika Virus Transmission by Blood and Blood Products.

I'm going to say a few words about Zika virus, set the stage, briefly recount the events of 2016 and FDA's guidances, highlight data from individual donation nucleic acid testing using the two investigational tests to screen the blood supply, noting that the first blood donation screening test was licensed this past October.

I'll then introduce today's speakers, to provide updated data, to get the CDC surveillance data and medical epidemiology from the CDC, and more detailed data about the tests from the test developers. Then I'll return to discuss the considerations for blood safety and to frame the questions for the Committee.

Zika virus is an enveloped, single-stranded arbovirus in

the *Flaviviridae* family. It's a *Flavivirus*. It's closely related to dengue virus, West Nile virus, and yellow fever virus. It's transmitted by *Aedes* mosquitoes, which also transmit dengue and chikungunya viruses. Zika virus is most commonly transmitted by *Aedes aegypti*, and to a lesser extent, *Aedes albopictus*, both of which are present in the U.S. and its territories.

Zika was first identified in the rhesus monkey in the Zika Forest, Uganda in 1947, and it circulates in a jungle or sylvatic cycle among non-human primates. There was no indication that it caused human disease until the first three cases of human infection were described in Nigeria in 1953 as a mild febrile illness.

Then it seemed to fall silent for over 50 years, with occasional, about a dozen, about 13 or 14 cases of human infection during those 57 years. But in 2007, Zika was put on the map on the Yap Islands in Micronesia, where there were over 5,000 cases, or about 70% of the island's population.

And then it skipped over the Pacific, island hopping, most notably in 2013 in French Polynesia, where there were over 32,000 infections and where the association with neurologic complications of Zika virus infection, including Guillain-Barré, were first described. Then it landed in Brazil in about March of 2015 and caused the epidemic spreading in South America and Central America and points north.

The Zika virus transmission cycle in the urban cycle is shown on this slide, with *Aedes aegypti* mosquitoes, infected mosquitoes, transmitting to humans, transmitting to more mosquitoes and more humans. The *Aedes aegypti* mosquito can bite multiple humans in a single blood meal, is a daytime biter, and has an imperceptible bite.

But the unique aspects of Zika, of course, that raised public health concerns are the modes of transmission shown in the right panel: From the Brazil epidemic, the association with maternal infection causing intrauterine infection and causing severe, profound disruption of brain development and devastating congenital defects, including microcephaly; the first *Flavivirus* to be sexually transmitted from infected men or infected women to their sexual partners; and probable transmission from blood components from the Brazil outbreak; and rare cases of laboratory accidents in workers handling the virus.

So the features of Zika virus that pose a risk of transfusion-transmitted infections are summarized on this slide. Most individuals infected with Zika are asymptomatic. From the outbreak in French Polynesia that I mentioned, retrospective and some prospective testing demonstrated that about 3% of asymptomatic blood donors were Zika virus RNA positive.

Significant viremia can occur in those individuals who do

become symptomatic, in about the week prior to symptom onset, and persist for about 2 weeks in blood.

Their known transfusion-transmitted infection of other flaviviruses and the probable transfusion-transmitted Zika virus cases that were reported in the Brazil outbreak first appeared in media outlets. Four cases were described in the media, and now three have been published in peer-reviewed journals.

In retrospect, I have included the follow-up study from the French Polynesian outbreak, which looked at the 30 Zika virus RNA-reactive units that were transfused to 26 patients. There was follow-up reported on 12 patients, none of whom developed Zika virus symptoms after transfusion.

But in 2015, the heightened public health and blood safety concerns reflected the explosive Zika virus epidemic in the Americas in 2015; the large number of U.S. travelers returning from Zika virus affected areas -- in New York, an estimated hundred thousand travelers per month returning from Zika virus infected areas; the presence of competent mosquitoes in the U.S. -- I mentioned that the *Aedes aegypti* and *albopictus* are both present in the southern tier of the U.S. states and territories; the demonstrated sexual transmission and uncertainty regarding what contribution it would make, independent of mosquitoes' spread, to the epidemic; the three probable -- the probable cases of transfusion-transmitted that

were reported; and the significant potential morbidity of Zika virus infections, including congenital microcephaly and Guillain-Barré.

I'm going to build a timeline in 2016, from the end of 2015, when it really was a question of not if but when Zika would arrive in the U.S. and its territories -- and the first case was reported in Puerto Rico at the end of 2015 -- through the end of 2016, when universal individual donation nucleic acid testing was used to screen the entire U.S. blood supply.

So this was a remarkable 12 months. I'm only going to hit the highlights. In 15 minutes, I have to gloss over everything else. But this timeline recognizes the remarkable commitment, collaboration, and achievement among the industry, the test developers, and the blood collectors in 2016.

So from the time the first case was described in Puerto Rico in December 2015, followed soon thereafter by the first case in the U.S. Virgin Islands, and the first sexually transmitted case in the U.S., FDA released the first guidance in February of 2016.

The recommendations are summarized on this slide, but in short, the guidance had recommendations for areas without active transmission and areas with active transmission. The strategy in areas without active transmission was a risk-based strategy to educate donors and screen for travel and other risk factors. The donor educational material required -- educated

about Zika diagnosis, the signs and symptoms of Zika virus within 2 weeks after return from travel to affected areas, sexual contact with a man with Zika virus disease or travel and residence in areas with active transmission.

A question was added, and all donors were asked about travel or residence to areas with active Zika virus transmission, which rapidly changed during these months.

In areas with active transmission, however, FDA recommended that blood and blood components for transfusion should be obtained from areas of the U.S. without Zika virus or to use FDA-approved pathogen reduction technology, which in the U.S. is approved for platelets and plasma components but not red cells, or to test all donations with an investigational test and a licensed test when one becomes available, but to still defer if a donor reported a Zika virus diagnosis or symptoms or sexual contact. However, the travel deferrals and the deferral for travel-related sexual contact were removed for areas with active transmission.

So at the end of February, during the month of March, blood collections in Puerto Rico were discontinued, and blood was shipped to Puerto Rico from areas, from U.S. states that were not affected, with support from the federal government. Several millions of dollars, upwards of 20,000 units were sent during this period where collections in Puerto Rico were discontinued.

However, with the first IND in March, testing, using the investigational Zika NAT, began in Puerto Rico in April. The second IND was approved in May, and testing began in U.S. states in May, first in Texas.

In July, the first local case, mosquito-borne case of Zika was reported from Florida. And in August, FDA revised the guidance because of the rapidly expanding and evolving Zika epidemic. And it became clear that there was a significant lag time between recognition and confirmation of local mosquito-borne transmission, with rapidly changing information.

There was the logistic complexity and limited effectiveness of donor screening for risk factors when the risk could be present in an area long before it was recognized that the area was affected, especially with local transmission.

There was increasing concern about sexual transmission as a mode of spread of the epidemic, and as Zika countries were added as Zika risk areas, the potential effect of travel-based deferrals became a concern on its effect to the adequacy of the blood supply in some areas.

So in regulatory terminology, Zika became a relevant transfusion-transmitted infection because it had sufficient incidence and prevalence, which on August 16th, 2016, included over 8,000 locally acquired Zika virus cases in the U.S. territories, over 2,200 travel-associated cases in U.S. states, and 14 locally acquired mosquito-borne cases in Florida, with

many ongoing epidemiologic investigations of non-travel-related cases in Florida.

The revised recommendations are summarized on this slide. And there are a lot of words, but the bottom line is FDA moved from a risk-based approach to universal individual donation nucleic acid testing, using the investigational protocols, so that all donations -- with a phased implementation plan -- so that all donations collected in the U.S. and its territories would be tested by the investigational individual donation NAT, with immediate implementation if there was local transmission; implementation within 4 weeks in the 11 states and lower tier of the U.S. based on proximity to those states with local cases, the presence of mosquito vector, which I mentioned is in the lower southeastern and southern tier of U.S. states, and travel-associated cases, the large number of travel-associated cases, out of New York; with a 12-month implementation in all other states and territories.

So the blood supply had to be tested or pathogen reduced using the FDA-approved pathogen reduction device.

The donor deferral for a Zika diagnosis was kept. It was a 120-day deferral for a diagnosis, a positive test, or resolution of symptoms. But this guidance eliminated the sexual contact deferrals and the travel-related deferrals.

So immediate implementation occurred in the states that were affected by Zika, and by September 2016 in the 11 states

that were on the 4-week deadline. The first local case in Texas occurred in November of 2016, and by the end of the year, by the end of December 2016, the entire U.S. blood supply was screened with individual donation nucleic acid testing.

This is a snapshot of the symptomatic Zika virus disease cases reported to CDC's ArboNET surveillance system. The two maps show the difference in the number of cases, with many more cases in 2016 shown by the dark -- by the intensity of the shading, which has dropped off in 2017.

In 2016, in U.S. states, there were over 5,000 cases of Zika, over 4,800 cases from travelers, and 224 local mosquito-borne cases, with 218 cases in Florida and 6 cases in Texas. There were 46 sexually transmitted cases. In the U.S. territories, there were over 36,000 cases, and most were locally acquired.

In 2017, activity has dropped off, so that as of November 22nd, there have been 352 cases in U.S. states, two local transmissions, one in Florida, one in Texas, and three sexually transmitted cases. And there have been 584 cases in U.S. territories.

These are the symptomatic cases. The presumptive viral donors -- and there about a dozen of them in here, but these are the symptomatic clinical cases. The donation data, I'm going to highlight on the next slide. The experience with the Zika individual NAT testing under the INDs is summarized in

this slide and will be explained in much greater detail in the two talks that follow.

But in U.S. states, using the two investigational protocols, over 11 million donations were screened, and 398 were initially reactive, and 50 were confirmed positive. In Puerto Rico, over 111,000 donations were tested, with 369 initial reactive and 356 confirmed positives.

So with that introduction, I'll introduce the first speaker. I'll introduce the agenda for today, which is shown on this slide. And the first is an update of the current status of the Zika virus epidemic in the U.S. and its territories and future predictions. I'll introduce Carolyn Gould from the CDC. Then we'll have an update on Zika virus nucleic acid testing and blood donors. And I'll introduce Tony Hardiman from Roche Molecular Systems and Jeffrey Linnen from Grifols Diagnostic Solutions. And then I'll return to discuss the consideration for alternatives for blood donation testing and frame the questions for the Committee.

So with that, I'd like to introduce Dr. Carolyn Gould to talk about the medical epidemiology and the current status of Zika virus in the U.S. and its territories and abroad.

DR. GOULD: Thank you, Dr. Eder, and thank you for the opportunity to present today to you all.

My name is Carolyn Gould. I'm a medical epidemiologist in the Division of Vector-Borne Diseases at the Centers for

Disease Control and Prevention, and I'll just be giving an update on the epidemiology of Zika virus today.

So Dr. Eder reviewed some of this, so I will try to go pretty quickly, but just to review, Zika virus is an RNA *Flavivirus* that's related to other flaviviruses, dengue, yellow fever, Japanese encephalitis, and West Nile virus. It's transmitted primarily by the *Aedes*, subgenus *Stegomyia*, species mosquitoes, and it typically causes an asymptomatic infection or a mild febrile illness. And the recent outbreaks have identified new modes of transmission as well as clinical manifestations.

So in terms of the clinical course and outcomes, most infections are asymptomatic. The clinical illness is usually mild, characterized by fever, rash, joint pain, or conjunctivitis. Symptoms last several days to a week. And severe disease requiring hospitalization is very rare. Fatalities are rare but have been reported.

In terms of the newly identified clinical manifestations, these include fetal loss, congenital defects including microcephaly and other abnormalities, Guillain-Barré syndrome and other neurologic syndromes, and thrombocytopenia or low platelets.

In terms of the Guillain-Barré syndrome, this was first described in the French Polynesia outbreak in 2013 to 2014, and as of March 9th, 23 countries and territories have reported

Guillain-Barré syndrome potentially associated with Zika virus infection, meaning they either have an increase in cases of Guillain-Barré syndrome concomitant with a Zika outbreak, or they identified cases of Guillain-Barré that have a confirmed preceding Zika virus infection.

As of November 8th, there have been 16 Guillain-Barré syndrome cases reported from U.S. states associated with Zika virus and 53 from Puerto Rico.

In terms of the estimated risk of Guillain-Barré syndrome associated with Zika virus infection, the estimate has ranged between 1.1 to 2.6 cases per 10,000 Zika virus infections, and that's based on cumulative data from multiple countries.

The outcomes and increased risk in older adults appears to be similar to Guillain-Barré syndrome associated with other causes, although there are still follow-up studies ongoing to look at the outcome in Guillain-Barré cases associated with Zika virus infection.

The non-mosquito-borne modes of transmission that have been identified, as Dr. Eder reviewed, are for documented -- documented transmission include intrauterine infection, intrapartum from a viremic mother to the newborn, sexual transmission, laboratory exposure, and probable blood transfusion. Possible modes of transmission include organ or tissue transplantation, breast milk, and other body fluids.

So I'm just going to review some of the data on Zika virus

sexual transmission. This was identified in sexual partners with discordant travel history, so partners that lived in areas that didn't have endemic Zika virus going on, endemic transmission occurring, where one of the partners traveled to an area with Zika virus transmission and returned and infected the partner.

This was first reported in 2011, in a returning traveler from Senegal who transmitted it to his spouse. And that actually occurred in 2008 but was reported in 2011.

And in 2016, sexual transmission cases were reported from 12 countries, and this included 46 cases in the U.S. Most reported cases result from men who are symptomatic, transmitting it to their female or in one case a male partner. There has been one report of transmission from a woman to a man and two reports of transmission from asymptomatic men.

So the data of Zika virus persistence in semen and vaginal fluids, there's been accumulating data, but there's still -- we have a lot to learn. Zika virus RNA has been detected in semen up to about 6 months after illness onset; however, that seems to be the exception, that length of time.

There was a recent study that was published, out of Puerto Rico, that found that the median duration of RNA positivity in semen was about a month, and 95% of men cleared the RNA from their semen after 3 months. There have been case reports of longer RNA duration. For vaginal fluid, RNA has been detected

up to 2 weeks after illness onset.

Zika virus has been cultured from semen up to 69 days after illness onset; however, again, that seems to be an exception to what's typically found in most of the reported literature. The success of culture of Zika virus in semen really hasn't gone beyond 30 days in most cases.

The sexual transmission duration, in terms of when the partner was symptomatic and when the partner became infected, that's been reported up to about 41 days after illness onset. However, most of the reported cases, the transmission occurred within a few days of the partner's symptom onset.

So the data in a lot of the case reports may not reflect the true incidence or the risk of transmission, and we still have a lot to learn.

In terms of the impact of sexual transmission, we don't know the exact incidence, the duration, or risk factors for sexual transmission at this time. There have been several modeling studies, trying to determine the impact of sexual transmission. And one study from Brazil suggested that the increase in disease in women was in due in part to the sexual transmission. But another model looked at the impact of sexual transmission in an endemic area and found it was not a significant factor in driving the outbreak.

I think the general thought is that the R-nought number for sexual transmission is less than 1. So if you don't have

an area of mosquito transmission, if you're not in an area where there's mosquito-borne transmission, that sexual transmission, in and of itself, is not enough to sustain an outbreak.

And the impact of sexual transmission in areas with mosquito-borne transmission has been estimated in modeling studies to be between 3% and about 20%. So it's still a pretty big unknown. There have been two cohort studies in the U.S. that have looked at duration and frequency of Zika virus RNA and live virus in semen, one of which I just referred to, the Puerto Rico data that was published in the *New England Journal of Medicine* and another study that is soon to be published.

And Dr. Eder already reviewed some of the transmission data, the transfusion transmission data for Zika virus. In the French Polynesian outbreak, about 3% of blood donors were positive. And for the units that were transfused, there were no symptomatic infections reported among 12 recipients that were investigated.

And then in 2016, there were three reported cases of transfusion-transmitted Zika virus infections from platelets, and none of the recipients developed symptoms of Zika virus disease. Between April and December of 2016, a routine screening in Puerto Rico identified Zika virus RNA in about 0.6% of the blood donations.

So going back to reviewing the epidemiology and where we

are in the epidemic now, as you heard just now, Zika virus was first isolated from a sentinel rhesus macaque that was placed in the Zika virus -- or Zika Forest in Uganda during a yellow fever study in 1947.

Prior to 2007, there were only sporadic cases of human disease reported from Africa and Southeast Asia. And then there was the first reported outbreak of human disease in 2007 on Yap, the state of Yap and the Federated States of Micronesia, and then the outbreak beginning in 2013 in French Polynesia and other Pacific islands.

In the Americas, the first locally acquired cases were identified in May of 2015 in Brazil, and as of August 2017, local mosquito-borne transmission had been reported in 48 countries and territories in the Americas. The only countries that have not reported local transmission are Bermuda, Canada, Chile, and Uruguay. Easter Island, which is a territory of Chile, did have cases prior to 2015 but nothing on the Chile mainland.

These are data reported to PAHO from the regions of the Americas between 2015 and 2017. So you can see that there were over 800,000 cases reported to PAHO, Pan American Health Organization, from the various 48 countries in the Americas. Just note that most of these cases are suspect. Only less than a third of cases were actually laboratory confirmed, just so you're aware.

So most of the cases were reported, or almost half of them were reported by Brazil, followed by Colombia, Venezuela, and Puerto Rico.

And this is just a pie chart showing the regions of the Americas. And the South American region reported the most cases, followed by the Caribbean, Central America, and North America.

This is an epi curve, showing the data from the Americas as of August 12th. So the green curve is South America, and orange is Caribbean, and blue is Central America. So you can see the numbers dropped dramatically in 2017, but there have been continued cases in multiple countries and some countries that had more cases in 2017 than in 2016 and pockets of transmission in certain countries.

So these are data looking specifically at 2017. So as of November 9th, 45 of the 52 countries in the Americas continued to report Zika virus disease cases in 2017. And this is just a selected list of countries that reported more cases in 2017 than in 2015 and 2016. Just note again that for the data reported to PAHO, most of the cases are suspected and not laboratory confirmed. And just another caveat is that they're generally reported by report date as opposed to onset date, so some of these cases may have occurred in 2016 but just were reported in 2017.

But you can see the list of countries that have reported

the majority of their cases in 2017. Peru stands out, Curacao, Bolivia, and Bahamas, and Cuba, which many of the travel-related cases we are seeing, Cuba stands out as being a travel location that has been more common in 2017, in addition to Central American countries.

This is the epi curve for Peru. So you can see that Peru reported more cases in 2017 than previously. And these are the numbers for 2017 in Central America. Central America reported over 1,700 cases in the month of October of 2017. And Costa Rica, in particular, and Panama have ongoing transmission. And again, just the same caveats that these are cases reported by report date as opposed to onset date, so we don't know exactly when they occurred, and they're not all laboratory confirmed.

Mexico, which I believe reports only laboratory confirmed cases, this is the epi curve for Mexico. And you can see, there's been a slight increase in cases beginning in epi week 16, which is in April of 2017. And there's particular concern about continued transmission in Mexico and including in the states along the border, the Mexican states along the border. So that's an area that people are watching closely.

In the U.S., prior to the outbreak occurring, there were only 14 disease cases identified in U.S. travelers. And then this, of course, increased substantially following the outbreak in the Americas. In 2016 there was limited local mosquito-borne transmission in Florida and Texas and then also outbreaks

in three U.S. territories, Puerto Rico, U.S. Virgin Islands, and American Samoa.

These are the ArboNET numbers for laboratory-confirmed Zika virus disease cases reported to ArboNET, which is the nationally notifiable reporting system for arboviral diseases. In 2016 there were over 4,800 cases among travelers, compared to 344 so far in 2017. There were 224 locally acquired cases in 2016 versus 2 so far reported in 2017.

And then other routes, as Dr. Eder showed, there were 46 cases of sexual transmission in 2016 and 1 case of laboratory transmission and 1 case reported as an unknown route, and then 3 cases of sexual transmission in 2017. This is the epi curve for 2016 and 2017 data for the U.S. states.

And these are the states of residence of reported Zika virus cases for 2016 and 2017. So you can see the four states that had the highest number of cases included Florida, New York, California, and Texas. And there were cases, a substantial number of cases reported from the mid-Atlantic states as well, New Jersey, Pennsylvania, and Maryland, and then Massachusetts.

This doesn't necessarily reflect incidence data if you look at it using population denominators, but these are the numbers of cases reported. And you can see, they've all gone down markedly in 2017 but are still occurring. And this is -- these are the maps that Dr. Eder showed, looking at 2016 versus

2017.

So the cases that are travel associated are still widely dispersed, but you can see by the lighter colors that there are many fewer cases in 2017 versus 2016.

And then these are the presumptive viremic blood donors reported to ArboNET by U.S. states as of November 15th, by state. And according to our reporting instructions, these are supposed to be confirmed cases. So they're cases that initially were not reactive and then were, had additional laboratory confirmation. I can't guarantee that all of these cases were confirmed, but that's the way they're supposed to be reported.

And so you can see that there were 37 PVDs, or presumptive viremic donors, reported to ArboNET in 2016, and 15 cases reported in 2017. Florida still had the most cases, compared to last year, followed by California. Alabama had three cases reported this year. Texas had a case. And then there are single cases reported from multiple other states, including New York, Pennsylvania, West Virginia, this year. Last year there were single cases from other states, including Arizona, Iowa, Massachusetts, and Nevada.

And as far as the travel locations -- so these were -- the 2017 cases were all travel associated. We have the location for six of them. We're hoping to get the other nine that are currently unknown. But the six cases that we know about

traveled to Mexico, the Caribbean, and Central America.

These are the data for the U.S. territories. So you can see that most were locally acquired. There were over 36,000 cases that were reported in 2016. And these are laboratory-confirmed cases. And then in 2017, it's down to 584 cases.

Oh, and just to note that sexually transmitted cases are not reported for U.S. territories because it's not possible to distinguish between sexual transmission and a mosquito-borne transmission in endemic areas.

And this is the epi curve for the U.S. territories. You can see the scale is much higher than for the U.S. states, and you can't see the numbers for 2017 because of the scale, but you can see that most of the cases occurred in August, and then there was a pretty rapid drop-off.

And these are the particular territories that reported. Most of the cases came from Puerto Rico followed by the U.S. Virgin Islands. You can see the numbers going down in 2017.

For American Samoa, we believe that transmission was actually interrupted in 2016, probably in the summer or fall of 2016, but the reason they continue to have cases reported in 2017 is they've had an ongoing dengue outbreak since November of 2016. And with the serologic testing, there is a great deal of cross-reactivity between Zika and dengue virus, and in addition to IgM persistence, the antibodies, IgM antibodies persist after Zika infection. So we don't believe that the

cases actually reported in 2017 represent acute Zika virus disease, but they were reported that way.

And then these are the presumptive viremic donors reported by Puerto Rico for 2016. There were 322 and then 6 in 2017 thus far.

So, in summary, there were large outbreaks in the Americas that peaked in 2016, with substantially decreased activity in 2017. However, there are smaller outbreaks and continued transmission in some countries and in some focal areas of countries. Some of them that stand out are Peru, countries in Central America, and Cuba.

There is an increased incidence in disease risk among U.S. travelers that has followed the epidemiology of the outbreaks in the Americas. And for the U.S. territories, the incidence has markedly decreased, but sporadic infections are still being reported.

So looking at the Zika dynamics in 2017 and beyond, we can look at evidence from Zika as well as chikungunya and dengue, which are other arboviruses transmitted by *Aedes* mosquitoes, to try to understand what is occurring this year and what might occur in the future.

These are the chikungunya data, the travel-associated data for chikungunya. So after the initial outbreaks that occurred in 2014, the numbers among travelers have really dropped substantially. I'll show you the 2017 data as well, but there

have been 88 cases reported for 2017 so far. So you can see that the numbers have been dropping off, similar to what is occurring with Zika virus.

The seasonality of Zika virus mirrors what has occurred with chikungunya, so these are combined years. But looking at the months of disease onset for travel-associated cases, most of them occur in late summer. And so there is a similar seasonal pattern there.

And then for the local transmission cases for U.S. states, these are the data for dengue and chikungunya and Zika thus far. And although arbovirus introduction continues to happen, local transmission has been limited. We do think that because there's more awareness and testing for Zika, that the numbers for Zika might be higher than for dengue and chikungunya moving forward. But you can see the local transmission for chikungunya has been very limited and has dropped substantially for Zika.

And these are the data for chikungunya from the CDC website. So these are data reported to ArboNET. So starting in 2014, you can see there were over 2,700 travel-associated cases in the States, there were over 4,700 cases in the territories, and there were 12 local transmission cases in the U.S. states. Actually, it was just Florida. There were 12 cases in Florida in 2014, and then in 2015, there was one case in Texas.

And you can see that the numbers drop, start to drop for the travel-associated cases and the cases in the territories, and then 2016 continues to drop. There have been no local cases of chikungunya over the past 2 years, and the numbers have dropped substantially. But you can see, looking at the maps, that the travel-associated cases are pretty well dispersed throughout the United States.

So for future predictions, we believe that in Puerto Rico and other dengue endemic areas, that herd immunity will likely reduce transmission of Zika virus in the near future, as it already has, but not eliminate it.

For U.S. travelers, the risk will continue to decrease and show some seasonality, similar to chikungunya. In the U.S. states, limited local transmission may occur, with sporadic cases or clusters. And we think that improved surveillance and testing practices in the U.S. may lead to higher case numbers for Zika compared to what we've seen for dengue and chikungunya.

These are just sort of statistical numbers looking at the disease incidence on the positive predictive value and the false positive rate with any diagnostic assay. Just as a reminder that as we've seen what's been happening with the Zika virus epidemic, and we've been thinking about our testing recommendations, we've spent a lot of time discussing the positive predictive value of the test as disease incidence

really declines pretty dramatically.

And you can see, just from this table, that as disease incidence decreases below 1%, your positive predictive value drops dramatically, and most of the positives you find end up being false positives. Over 90% are going to be false positives.

So that has really influenced recent updates to clinical testing guidance because of the concern about giving people, particularly pregnant women, misinformation, false positive tests. And then there's also a problem that we've been discussing, with the IgM antibody persisting, which we know from other *Flavivirus* data that IgM can persist sometimes for years.

And so when you have a positive IgM result, it's very difficult to determine the timing of infection. And that also has a lot of impact on pregnant women who are tested because it's hard to determine, if they're IgM positive, the infection actually occurred during the pregnancy or prior to the pregnancy.

So for those reasons, our testing guidance has been modified. It was modified over the summer. For non-pregnant patients who are symptomatic, the testing guidance really didn't change. We still recommend NAT testing on serum and urine collected within 14 days of symptom onset. If the serum is collected more than 14 days after symptom onset, it's

recommended to perform IgM and then the neutralizing antibody testing if the IgM is positive.

For pregnant women with possible exposure during the current pregnancy, the testing has been pulled back to some degree, with an emphasis more on doing concurrent NAT and IgM testing, given the difficulty in interpreting the IgM results. So for symptomatic pregnant women or women who have evidence of congenital infection on prenatal ultrasound, it's recommended to do concurrent NAT and IgM testing.

And then for asymptomatic pregnant women, it's only recommended to test those women who have ongoing mosquito-borne exposure, and that testing is recommended through doing NAT testing as opposed to IgM testing three times during the pregnancy.

And then for women who travel who remain asymptomatic, routine testing is no longer recommended because of the problem with the low pretest probability and high rate of false positive results. But we do have language in the guidance about this decision being a shared decision between the patient and the provider, whether to test.

So I just wanted to put that out there for you so you're aware of the current testing guidance as it may impact our surveillance data and our understanding of the current epidemiology.

So that's all I have. Thank you.

DR. STOWELL: Thank you. I believe our next speaker is going to be Anthony Hardiman from Roche.

MR. HARDIMAN: Good morning. My name's Tony Hardiman. I'm the Life Cycle Leader for Roche Molecular Systems. I'm working on blood screening molecular tests.

I'd like to thank the FDA and the BPAC committee for allowing us to present the information here today on the clinical trial associated with the Roche cobas Zika test. I'd also like to thank the collaborators throughout the blood industry and especially the principal investigators that allowed us to consolidate all this data and bring the data to you here today.

To start with, in terms of disclosures, I am an employee and shareholder of Roche Molecular Systems, as well as the data you will see presented here today from Puerto Rico during 2016 was supported by a grant from BARDA, and all of that data has been reviewed and cleared by BARDA for presenting today.

So a little bit of background, and some of this has been covered already, but the key for us was, as we looked back to the beginning of 2016, following discussions with both the CDC and the FDA, we entered into a very rapid development for the cobas Zika test, really to try and fight the then starting outbreak in Puerto Rico, and allow us to bring a test forward ready to be utilized under clinical trial, to test the donations, which at that point were stopped in Puerto Rico, and

allow us to start those testing at the beginning of April in 2016 and resume the blood supply locally collected in Puerto Rico.

All of that testing at that point, and currently to date, has all been done under individual donor tests to allow for the maximum sensitivity and detection possible with the Zika virus.

As we moved on from there, we expanded the clinical trial to start in the southern states of the U.S. in late spring, as many of the blood centers started to gain concern around the potential for both travel and also local infections with Zika.

As you know, at that point, as we moved into August, the FDA decided to change its guidance, and we worked actively with all of the Roche sites to bring the test up under the IND so that all of the sites were ready and started testing under individual donor testing in November 2016.

As we move forward in this presentation, I'm now going to take you through the data we generated from those 13 testing sites, and split the data later on to look at both Puerto Rico as the outbreak and obviously the extensive number of positive donations that come from there, and then secondly, the U.S. states where we also see continued positive donations being detected through 2016 but also through 2017.

As we look at the map on the left, you will see the location of the 13 testing sites that performed the Roche Zika test. And in those 13 sites we also tested not just the

donations from Puerto Rico but also from various military sites as well, to give us a total of 4.45 million donations that were tested throughout the period of this clinical trial, starting in April 2016, through to the beginning of October this year, when as was stated earlier, the test was licensed and is now in routine use.

Of those 4.45 million donations, there was just short of 112,000 donations from Puerto Rico. And if we look at the confirmed number of positive donations in both of those populations, you will see 356 positive donations from Puerto Rico and 29 positive donations from the U.S. states. And as we move forward, I will split those out and talk about those donations in a bit more detail.

Important to note at the bottom here that the assay was submitted in April of 2017 for BLA licensure, and that licensure was achieved on October the 5th this year. All 12 of the 13 sites are now up and running routinely on the licensed assay, which has been now running for the last couple of weeks.

So as we move from there to look at the performance characteristics of the test, first of all, the actual clinical protocol or clinical study was really designed firstly to look at the specificity of the cobas Zika test, and really that's best defined in the low prevalence area of the U.S. states.

As you look here over the full period of the clinical trial, there were 4.34 million donations that were tested, and

there were only 71 indexed reactive donations that were not confirmed.

That gives us an overall specificity for the test of 99.998%, which we're very pleased of because obviously that in itself allows us the opportunity to not waste blood donations and keep the valuable safe blood supply going in the U.S.

Moving down there to start looking now at the reactive donations that were detected during the clinical trial, this is the confirmation algorithm that was utilized. And as you will see, first of all, on the left-hand side, the index donation was repeated twice in the cobas Zika test, followed the same day by a simulated pool of six tests. And we'll present some of that pool data later on. And then at Blood Systems Research Institute, an alternate NAT test and two serology tests for IgM and IgG were performed.

Important to note here that the alternate NAT test was significantly less sensitive, approximately 40 times less sensitive than the screening test, but nevertheless a very good confirmatory test for this.

Following on from there, all of the donors that were initially reactive were enrolled into follow-up. The vast majority complied with that, and we gained follow-up sample in the first 2 weeks and then a subsequent sample between 2 and 8 weeks after that. And you will see there the follow-up tests that were performed on those samples, to look at some

progression of the disease in those donors.

So now moving into -- and I'm going to talk first about Puerto Rico and the reactive donors from Puerto Rico. As you look -- and we talked -- we, in this clinical trial, pooled 112,000 approximately donations. There were 369 initial reactive cobas Zika tests, of which 356 confirmed by the prior algorithm, giving us a confirmation rate of 96.5%.

Most of those were confirmed on the index donation, as you see here, of 347, but 9 of them were not confirmed on the index donation but confirmed on follow-up, to give us that complete number of 356.

As we look at the distribution of those positives, and this follows very much the last presentation, you will see here the peak detection in blood donors in Puerto Rico was in July at 1.27%, and that declined over the coming months in 2016. I think, of note here, it's important to see that during 2017, there were still nine positive donations that have been detected from Puerto Rico, the last of which was at the end of May in 2017.

I think it's also important to note that on those index donations, there was a simulated mini-pool of six, performed on all of those positive donations, and you will see here that only 70.5% of those positive donations were detected in mini-pool.

As we move on now to look at the lower prevalence, in the

U.S. states, you will see at the top an overall confirmed positive rate significantly lower than Puerto Rico, at 0.0007%, and this is as of the end of the clinical trial on October the 7th.

In the 4.34 million donations that were tested, there were 100 initial reactives, of which 29 confirmed as true positives, 28 of those on the index donation and one on the follow-up donation, once again using the prior confirmation algorithm that was described.

Looking at the distribution of those positive samples, you will see here the peak was in September, at 0.006%, which is a couple of months later than we saw in Puerto Rico. Of note here also is that in 2017, we have seen nine positive donations in the U.S. states, of which the last one was actually a couple of days before the end of the clinical trial cutoff, which was on October the 4th, as our last positive donation that was collected.

If we look at the simulated pool testing here in this population, you will see that on those initial positive donations, we only detected 9, 39.3% in mini-pools of 6.

Let's drill further into the 29 positive donations from the U.S. states. This gives you a picture of the follow-up markers and testing that was done on the confirmatory algorithm, and I think of note here, it's important to say that 13 of these 29 confirmed positives were repeat reactive on the

index donation, and the following 16 that were not repeat reactive were IgM positive. So using those two markers in particular, as well as the others that you can see on here, you see that there were 29 confirmed positives in the U.S. states.

Drilling into those 29 to where they were actually collected, you will see, as was mentioned a little while ago, the vast proportion were in Florida; 24 of 29 were from Florida. But interestingly, we did detect two from Texas, one from Pennsylvania, one from Tennessee, and one from Iowa.

As you will also see that in 2017, four of the nine that have been positive donations were from outside of the Florida state: two in Texas, one in Pennsylvania, and also one from Tennessee.

As we move onto the risk factors associated with these 29, 23 of the 29 were travel associated. Of that 23, 6 of those were combined travel and sexual contact with a partner that had traveled, as well as 4 of the 29 that were neither travel or sexual contact risk related.

As we move down into the identification of where that travel occurred, you will see obviously some very similar countries here to what was just presented. Obviously, the larger number was from Puerto Rico. I was surprised that 4 of the 29 were from Cuba, but that does seem -- as we just saw an increasing number coming out from Cuba and travel to Cuba, as well as the fact that three of these were from domestic travel

in the U.S. to Florida.

And also our latest donation, and two in total were from Mexico. And there seems to be significant heightened concern around donations coming from Mexico, as was stated, across the border states, and obviously, one of those, which was our last donation in October, was detected from Mexico travel.

So now looking and narrowing the data -- and positive predictive values was talked about just now for diagnostic tests. As we narrow down the data to the data that was submitted for our BLA licensure of the test, you will see here positive predictive values calculated for both the outbreak in Puerto Rico plus also the lower prevalence in the U.S.

I think, for Puerto Rico, not surprisingly, the positive predictive value was extremely high at 96.2%, and for the U.S. states, it was still extremely high, at 60.9%. Very much the rationale behind this is that when you look to the bottom here, the clinical sensitivity claim established for this assay was 100%. And obviously, with a highly sensitive and highly specific test for cobas -- or for Zika, you will actually get these higher positive predictive values, even in generally negative populations.

As we look now at that same population, and transferring that same number of positive confirmed donations from the prior chart and our submission for the licensure, you will see here, assessing mini-pool reactivity and the viability of doing mini-

pool testing shows that in the Puerto Rico, large number of Puerto Rico samples during the outbreak, only 214 of the 275 positive donations were detected by mini-pool testing on that initial reactive sample, which equates to 77.8%.

In the lower prevalence U.S. states, only 6 of the 14 positive donations were detected in mini-pools of 6, giving us only a 42.9% detection rate by mini-pool testing. This really is not surprising when you do the further analysis that BSRI did on the samples, and looking at viral concentrations, that the vast proportion of these were low viral concentrations and therefore were below the limit of detection of the assay when looked at in a pool of six setting but were clearly detected and confirmed in individual donor testing.

So with that, I'd like to bring it to a point of conclusion, firstly for Puerto Rico and then for the U.S. states.

For Puerto Rico, summing up, the clinical trial tested 112,000 approximately blood donors, of which 356 were confirmed positive for Zika virus. The peak incidence of detection in Puerto Rico was in July 2016 at 1.27%. But it's important to note that during 2017 there have still been nine positive donations that have been detected and interdicted in Puerto Rico, the last of which was at the end of May 2017.

Utilizing mini-pool assessment on those positive donations, only 70.5% were detected in mini-pools of six, and

the vast majority that were tested were low viral concentrations that were not detected in mini-pools.

And also, a big shout-out here to the CDC, the local health departments, and also the FDA for the great collaboration on Puerto Rico and the work that was done to really help keep that blood supply going and safe in Puerto Rico. And I think that was an extremely important thing, not just to us but to the environment and to what happened in Puerto Rico.

From the U.S. states, we tested here 4.34 million donations; 29 confirmed Zika virus positive donations were removed from the blood supply. Of those 29 donations, only 39% were detected by mini-pool testing. For the donors that were confirmed positive by Zika virus, it's clear that 85.2% of these had recent travel to Zika active areas, and importantly 13% was domestic travel and not just international.

I think it's also important to note that the Zika reactive donations have continued in the U.S. through 2017 -- nine year-to-date. And of those nine donations, three positive donations have occurred in the last 3 months of this clinical trial, one in August, one in September, and the last one in October, as we continue to see positive donations in the U.S.

I think, with that, I'd like to say thank you very much and also highlight the commitment of Roche Diagnostics to continue to work with the FDA and this Committee to implement

any of the recommendations that come out of today's discussions, and we thank you all for your attention.

DR. STOWELL: Thank you, Mr. Hardiman.

Our next speaker is Jeffrey Linnen from Grifols Diagnostics.

DR. LINNEN: First, I'd like to thank the FDA and the Committee for the opportunity to give this update. I'll be talking about the investigational Procleix Zika virus assay. This is from Grifols Diagnostic Solution. So I'm Vice President, Product Development at Grifols Diagnostic Solution in San Diego.

Before I get started, I have a number of disclaimers, disclosures. So as I mentioned, I'm an employee of Grifols and a stockholder in Grifols. This assay is still investigational, so it's considered under development. The performance characteristics have not been established, although the data has been submitted to the FDA and is under review.

So this assay is not available for commercial sale in the U.S. but is available under an investigational new drug protocol, actually two protocols. The assay is CE marked, though, and so it's available for sale in regions that recognize the CE mark.

And then at the bottom of the slide I have a similar statement, similar to the one Tony had, because this project was partially funded by BARDA. BARDA is the Biomedical

Advanced Research and Development Authority. And that's part of HHS. And so this presentation has been reviewed by BARDA.

Okay. I'd just like to briefly let you know what I'm going to talk about. So I'm going to give some background and an overview of the assay. I'd like to give you an idea of how sensitive the assay is in terms of analytical sensitivity. Then I'll talk about two clinical studies, reproducibility and specificity, and then in the rest of the talk, I'll cover the ongoing testing under the IND protocols.

So here's the background on the assay. So the Procleix Zika virus assay runs on the Panther system. It's a qualitative transcription-mediated amplification assay. And this assay amplifies two regions of the Zika virus genome, and I'll just talk a little bit more about that on another slide.

The testing for our assay became available in the U.S. on June 17th when the IND became effective. And there's actually two protocols, roughly dividing the testing in half, for different organizations in the U.S.

The testing started out rather slowly, looking at pools of 16 donations in some individual donor nucleic acid testing, or ID NAT. So as you've heard, all of the testing now, based on the August 2016 guidance, is by ID NAT. The IND was amended in February of this year to include plasma and serum specimens from living donors of human cells, tissues, and cellular tissue-based products.

The testing has included donors from all 50 states, but I have to mention, only a small number of donations from the U.S. territories have been tested. And the other thing I want to point out is the testing covered -- our IND protocols did not cover most of Florida, so at least the time for the data that I am going to report.

And it was December of 2016 when the assay was CE marked. This same assay was granted an emergency use authorization by the FDA on the same date that the IND opened. This assay had to be validated in a slightly different way. It was reviewed by a different branch of the FDA. And it's marketed by Hologic, which was the company I worked with prior to joining Grifols, and it has the name Aptima Zika virus assay. But the chemistry is the same.

Just very briefly, I mentioned this assay targets two regions of the Zika virus genome. This is what's shown here schematically. And the reason we did this was to mitigate the risk of false negative results that could arise from mutations in one of the two regions. It also, to some degree, enhances the sensitivity of very low levels, because this assay has two reactions occurring simultaneously for the two regions, plus an internal control is amplified at the same time.

So how sensitive is the assay? We looked at analytical sensitivity a number of ways. What's shown here are studies where we looked at both plasma and serum, using the WHO

standard, which was developed during the course of the outbreaks, and is now available to compare the sensitivity of different assays.

What's shown on the left is sensitivity in plasma, in the right, in serum. Down below is the probit analysis resulting from the experiment. So those graphs show percent reactivity at different copy levels. Ninety replicates were tested at each of the copy levels. A regression analysis was performed.

And if you look in the table, you can see both the 50% and 95% detections for the two matrices. The 50% levels of detection were identical, based on the probit analysis, 0.6 IU/mL, and the 95% detection levels were about 3 for plasma and around 2 for serum. And if you look at the data in the graphs, you can see the performance is similar, and that does not represent a statistically significant difference when the regression analyses are compared.

So what I just showed you was international units per mL. A lot of people have no idea really what that means, so we looked at copies, by performing a similar limited detection experiment with an in vitro synthesized transcript. Whereas the WHO corresponds to an Asian strain, this transcript that we constructed corresponds to an African strain of the Zika virus.

You can see here now that the data are in copies per mL. The 50% detection in this experiment, which included a large number of replicates at each level, for the levels 30 copies

and below, there are actually 216 replicates. So each one of those bars represents 216 reactions.

So the 50% level of detection by probit was predicted to be 3 copies; in the 95% detection level, around 12 copies. And you can see what corresponds to basically the confidence intervals on the right.

Now I'd like to talk about a couple of the clinical studies. This shows the preliminary clinical reproducibility. It was evaluated at three U.S. sites. And this was to support the package insert's claims. So these data are under review with the FDA.

The study included four panel members, and they're shown here: a negative; what we considered low positive, which was a little bit less than 12 copies per mL; moderate positive, around 24 copies per mL; and the high positive, around 60 copies.

Now, I'm not going to go through all the numbers. What we look for in a study like this is to be assured that the largest source of variation does not become between or is not due to the instrument, the operator, the lots, or factors like that. What we hope to always see in this kind of experiment is that the largest of source of variation comes within the run or the random error of the assay.

And that's what we saw in this experiment. The intra-run or within-run variability was the largest source of

variability. In overall, the variability was low, ranging from, at the lowest copy levels, around 21½ percent and around 5 percent at the higher copy level.

Now, before I get into the clinical specificity, I wanted to talk about the algorithm for confirming an initially reactive result. So there were two protocols, as I mentioned. And I'll point out on this slide a little bit how they differed.

So every initially reactive donation was tested either two times or three times, depending on the protocol. The samples were shipped to one of two reference labs, either to the Blood Systems Research Institute or the Wadsworth Center in New York, which is part of the New York State public health.

There, additional NAT testing was performed, with PCR test. And similar to what Tony mentioned, both of these tests are considerably less sensitive than the screening assay, the Procleix assay, greater than a log less sensitive.

Two types of NAT were performed, one either PCR or TMA on red blood cells, or in a few cases, whole blood, and PCR on plasma. The presence of IgM was determined using a CDC MAC-ELISA. If IgM was positive, one of two different kinds of neutralizing tests, either a plaque reduction neutralization assay or viral particle neutralization assay, was used to confirm that result.

So, just basically, the thing you have to remember, the

results were not confirmed by repeat reactivity of the Procleix test. There had to be reactivity in an alternative NAT, or confirmation by IgM, either at the index or from a follow-up donation.

The data that I'm going to show here is a subset of all the data that was generated. What is shown here is what we have generated, the data that we used to support the package insert claim for specificity, which is under review at the FDA. It was generated from 12 U.S. sites. A total of 1.6 million donations, more than 1.6 million donations were included for this study, and that included over 1.2 million individual donations and over 24,000 pools of 16 donations, which then represented almost 400,000 donations that were tested in pools.

The study duration for the subset of the data ran from June of 2016 through the end of 2016, December 31st. Three reagent master lots were used. And the other thing to point out is a result was considered unknown if not confirmed at index and the donor did not participate in follow-up, regardless of repeat reactivity in the Procleix test.

You can see the data in the table below. For the more than 24,000 pools tested, there were no true positives. There were unknown results and no false positives. So the overall specificity for pool testing was a hundred percent.

For individual donations, for the greater than -- more than 1.2 million tested, there were a total of 12 true

positives. Eleven fell in the category of unknown, and there were 17 false positives. The overall specificity for individual donations for the study was 99.999%. I have a hard time with too many 9s. I think I got that right.

The other thing that I want to point out is that in this study there were two confirmed positive donations that were considered window period, so were IgM negative at index but showed seroconversion in a follow-up donation.

Now, moving to the summary of the ongoing testing under IND, so this covers all of the investigational test results through November 18th of this year. With this test, over 9.2 million donations have been screened, and that includes the 24,000 pools of 16 donations that were screened in the beginning of the study. So this is the entire dataset, including the subset that was used for the specificity analysis.

These data covered eight reagent master kit lots, and it included 12 testing sites under the two protocols. The table shows the data. I will just skip to the bottom row, where it says Total Donations. So over 9.2 million tested. There were 376 initially reactive, 25 confirmed positive, and 146 were in the category of unknown.

And in this case, it includes the ones where the donors were not confirmed at index and did not participate in follow-up but also results that are still pending. There were

a total of 205 false positives. So the estimated specificity for the ongoing study is 99.998%. And you can see the confidence in it because the numbers are so large. The confidence intervals are pretty narrow for these data.

There's one donor that was not included as a confirmed positive but was an interesting case that came out of the testing in the American Red Cross organization. This was a donor that received an experimental Zika virus vaccine and was reactive four times in the Procleix assay, so reliably detected at index but was not considered positive based on the protocol's confirmation algorithm.

The donor participated in follow-up, and there was no reactivity in any tests after that. So it's a very interesting case. And Dr. Stramer probably has more details on it because this person, on the day they received the vaccine, decided to donate platelets. We were able to detect the -- I don't know if it was attenuated or result -- we were able to detect the nucleic acid from the vaccine apparently.

So for the total confirmed positive donations, there were 25, and the rate overall is 1 per 370,000 donations.

Now I'd like to, on this slide, summarize the confirmation testing for these 25 confirmed positive donations. If you look at the last row, labeled Table, you see the 25. I want to make a number of points here.

The rate of repeat reactivity in these donations were

relatively low. What's shown in that column is the number and the percentage of donations, so the number out of the 25 that showed repeat reactivity in the assay. So only 9 out of 25 showed some level of repeat reactivity, only 36%.

And this is not too surprising, considering where we were screening. Most of the confirmed positive donors -- and I'll show some information on this later -- came from travel-related cases. So these were not -- these were infections -- we were not catching them in the earliest stages. They had traveled and then come back to the U.S. and donated.

So you'll see also here that the confirmatory rate for the alternative NAT was even lower. Only 4 out of 25 were confirmed by the alternative NAT, which as I mentioned, both assays were less sensitive than the screening assay, so only 16%.

However, 19 out of 25 were confirmed by the presence of IgM, or 76%. What's interesting, and I'll show some more detailed data on this, and you might hear more about this in the public session, 88% or 22 out of 25 were confirmed by performing NAT, either PCR or TMA, on red blood cells.

There were a total of four window period cases for -- these four window period cases, we required that seroconversion was demonstrated. So that gives you an idea of the overall results from the confirmatory testing.

When did we see these confirmed positive donations? This

is the data by month, and you can see that the peak occurred in January of 2017. And the outbreak may roughly correspond to the level of the outbreaks where people were traveling.

The other thing that's important to point out here is the last confirmed positive was in October, mid-October of 2017, and this was a donor that traveled to Mexico, resided in California and traveled to Mexico. So we do expect to see cases as we move on.

Now, where did these donors live? The confirmed positive donors are mapped by donor residence zip codes, shown here. And you can see that there might be a pretty rough correspondence with the population of the states. You can see the largest number of confirmed positives, nine, resided in California, then followed by New York and Texas, which each had four. A total of nine U.S. states had confirmed positive donors.

What were the risk factors for these confirmed positive donors? So this again is all of the data through November 11th. The largest number were travel cases. And you can see the countries shown there, where the donors traveled previous to donating blood.

We were conservative in categorizing these because it's difficult, with sexual contact, to know for certain whether it was sexual contact or a different risk. We put one in the category of sexual contact, and that donor came from

California. Three were put in the category of probable local transmission, and those two were from Miami, and the other one was from Brownsville, Texas.

And unfortunately six were either there was no risk noted or the risk was unknown, and those were from California and New York. So, definitely, travel to areas with active mosquito-borne transmission was the most common risk factor.

Now I'd like to go back to the issue of detection in red blood cells. What I'm showing here is one of the longer cases of viral persistence in a blood donor. This donor, if you look at the first line labeled Index, was reactive in the screening test, reliably, so initially reactive, and then reactive in all three replicates tested; was equivocal, meaning that not all of the replicates were reactive, for the alternative NAT run at the New York State public health lab, the Wadsworth Center, and was detected at a lower rate in red blood cells at index.

Only two out of seven of the replicates tested by the research TMA assay were reactive, so about 30%. And there was no reactivity for IgM, so this was a window period case.

You can see then, if you look at that column that is labeled Grifols RBC Research TMA Assay, there was -- well, there was repeat reactivity on the first follow-up visit with the screening assay, but you can see that the virus was reliably detected with a large number of replicates in red blood cells in most of the cases where we had the data, all the

way through, if you follow down to say -- we started to see lower levels of detection in red blood cells at -- see Follow-Up 17, and that continued for several follow-up visits.

There was then no reactivity. And then the last follow-up, Follow-Up 22, one out of six replicates was reactive in red blood cells.

So there really is a question -- so obviously, this is probably a great aid in diagnosis of an infection. We really are not certain whether there would be any infectivity in these donations where the virus is only detected in red cells. And you may hear more about that later today.

So, with that, I'd like to get into the conclusions. Just to recap, that we have a pretty good idea about the analytical sensitivity. We've tested it a number of different ways, plasma and serum. The detection of the WHO standard in those two matrices was similar, 2 to 3 IU/mL. With respect to copies, the sensitivity we saw with our transcript was about 12 copies at 95%.

The assay was reproducible at low copy levels, and intra-run variability was the largest contributor to the overall variability. We've screened 9.2 million donations under the IND. Twenty-five confirmed positive donations, or 1 out of 370 donations have been identified. And as I mentioned, the majority had a history of travel to areas with local Zika virus transmission. And we are still seeing positive

donations. The latest was in October.

Overall specificity for the entire IND testing is 99.998%. And the last data I showed was Zika virus that was detected for up to 154 days by follow-up testing of red blood cell samples in a research TMA assay.

Now I'd like -- there are a lot of people to acknowledge. First, I'd like to acknowledge the principal investigators, the American Red Cross, Blood Assurance, Creative Test Solutions, Interstate Blood Bank, Inova Blood Donor Services, Labs, Inc., MD Anderson, Oklahoma Blood Institute, Rhode Island Blood Center. All performed -- I'm grateful for the work that was done under the IND protocols.

I'd like to acknowledge the reference labs, both Blood Systems Research Institute, the Wadsworth Center.

And then the people from Grifols, I'd just like to mention a couple of people by name: Kui Gao, who was the technical lead for the development of the assay, and Alanna Janssen, who was the technical lead for the verification and validation under the BARDA contract. The key person from Clinical Affairs for this project was Alanna Menez, and then in Regulatory, Petra Pavlickova and Katerina Capkova were the two main contributors in that department for this project.

And then again, just to remind you, this was funded in part by BARDA.

So with that, that concludes my presentation. And thank

you for your attention.

DR. STOWELL: Thank you very much. Anne Eder will be coming back to the podium to recap and also to review the questions that are going to be posed to the Committee.

DR. EDER: All right. I want to thank our speakers. Now I'm going to present the considerations for blood safety, as we look at the options to screen the blood supply. I'm going to talk through the options and then pose the questions, but these are what we're putting to the Committee today. There are five options or alternatives.

The first is no policy change, continue universal ID NAT to screen blood donations.

Number 2, regional use of individual NAT in at-risk states, and mini-pool NAT or MP NAT testing in all other states with trigger criteria. This option I'll refer to as the combination ID/mini-pool NAT.

Number 3, test all donors by ID NAT in areas with active mosquito-borne infection when there is activity, but when there isn't, and in all other areas, selectively test at-risk donors by individual donation NAT based on donor screening questions for Zika risk factors. This is a screen-and-test strategy.

Number 4, maintain a Zika-negative or selective inventory of blood components in transfusion services to provide for at-risk patients, such as pregnant women or intrauterine transfusion or infants.

Or 5, eliminate all blood safeguards for Zika virus pending another significant outbreak in the United States or its territories.

We'd like the Committee to consider each option and discuss pros and cons. I'm going to talk through an example of what might be discussed as advantages and disadvantages.

So if we have no policy change and continue universal ID NAT testing of blood donations but reassess the policy periodically, this will provide nationwide monitoring of blood donors with asymptomatic infection resulting from all modes of transmission, mosquito-borne, sexually transmitted, and travel-related cases.

A disadvantage, of course, is that it maintains a resource-intensive approach, placing burden on the blood system in the face of significantly diminished risk.

A regional ID NAT combined with mini-pool NAT strategy is shown on this slide. This involves continuing ID NAT year-round in the shaded states and Puerto Rico and U.S. territories, because they historically have had cases of Zika virus, dengue, and chik for Florida, Texas, Hawaii, and U.S. territories; or they have the documented or possible presence of the vector, *Aedes aegypti*, which will add Georgia, New Mexico, Arizona, California, South Carolina, Alabama, Mississippi, and Louisiana; and states with a high number of travelers to Zika virus areas and the highest number of Zika

virus disease cases from travel that was shown on the CDC ArboNET surveillance data, and this would add New York.

So individual donation NAT in the shaded states and U.S. territories, but in all other states, substitute mini-pool NAT instead of ID NAT year-round, with consideration for the criteria that would be used to switch from mini-pool NAT to individual NAT.

And these are some criteria that the Committee could discuss. The trigger could be based on a defined number of presumptive viremic donors in a 7-day rolling period based on results of mini-pool NAT in a defined geographic collection area, and/or a defined threshold of symptomatic clinical cases reported by national surveillance in a defined geographic area, which would require also defining a time period or other trigger criteria that the Committee discusses.

The next option is regional use -- I'm sorry. The pros and cons of this combined strategy of ID NAT and mini-pool NAT are shown on this slide.

In the pro column, it would reduce the volume of testing but continue testing in areas with the highest risk with the most sensitive test, ID NAT, while decreasing the resources needed in the areas of lower risk. It offers a likelihood of detecting most of the travel-associated symptomatic cases in the U.S., and it maintains a capability to rapidly respond to local outbreaks or changing epidemiology.

Disadvantages would mean maintaining testing of blood in the areas of the U.S. where there are no reported cases of Zika virus. You heard from the presentations that mini-pool NAT is less sensitive than individual donation NAT. Criteria for switching from mini-pool NAT to individual donation NAT are complex and might be error prone. And although it's less resource-intensive, it still burdens the blood system in the face of significantly diminished risk.

The next option is a combination of screening and testing. This would still require to test donors by ID NAT in areas when there is active mosquito-borne infection, but in other areas, to allow selective testing of at-risk donors by individual donation NAT based on donor screening questions for Zika virus risk factors.

So performing ID NAT on all collections in areas if there is active mosquito-borne Zika virus transmission in the state; perform ID NAT in other states based on the donors' responses to questions about travel to Zika virus countries, using the CDC maps, and areas within the U.S., questioning about sexual partners with a Zika virus diagnosis or with a history of recent travel to areas with active transmission of Zika virus; and to trigger ID NAT selectively in areas with a large number of reported travel-associated or sexually transmitted Zika virus cases.

The pros and cons, some of the pros and cons of this

option are shown on this slide. In the advantage column, it would reduce the volume of testing but maintain testing in areas of highest potential risk with the most sensitive test while decreasing the resources needed in areas of lower risk.

Disadvantages include all the complexities of triggering screening based on -- triggering testing based on a response to a question, when the questionnaire is nonspecific, insensitive, and error prone compared to individual donation NAT or mini-pool NAT; the geographic-based criteria to identify at-risk donors are problematic and may not be effective given the delays, the lags between identifying an area of risk and asking questions about it; the Zika travel risk is also different from malaria-related risk in that the Zika risk countries are defined -- CDC defines Zika risk on a countrywide level.

So in other words, all of Mexico, any travel anywhere in Mexico is considered, would be considered a Zika risk, whereas malaria travel focuses in on areas within countries, which decreases the number, by a lot, of donors that are deferred. So with the high numbers of travelers, this might actually not decrease -- you're still doing a significant amount of testing, and you also have to have a way to reliably trigger testing based on the response to a question. It also will become complicated if there is domestic travel risk within the U.S. in the event of resurgence of local transmission.

Option 4 is a transfusion practice related option, to

provide Zika virus individual donation NAT negative blood components only for certain clinical indications, such as pregnant women, intrauterine transfusion, or infants.

In the pro column, it would reduce testing burden, and it would direct Zika virus tested blood components to identified at-risk recipients.

Disadvantage of this approach would include all the complexities of managing a dual inventory; the potential for ordering and release errors, the inability to identify all patients at risk; it might compromise the ability to scale up testing rapidly if needed; the undefined risk of Zika virus infection in several populations, including immunocompromised and transplant patients; and the potential for sexual transmission to a pregnant woman if her partner receives an untested Zika virus unit.

Option 5, the last option for consideration, is to eliminate all Zika virus safeguards. So eliminate donation testing for Zika virus without reintroduction of donor screening for risk factors pending another significant outbreak in the United States or its territories.

Advantages would include providing relief from Zika virus testing when Zika virus risk is substantially reduced, and it would increase the availability of resources for other blood safety initiatives presumably.

In the disadvantage column, it would not prevent

transfusion transmission of Zika, and it would pose risk of Zika virus complications among at-risk patients. It also reduces preparedness against possible resurgence of the Zika virus epidemic.

Now I'm going to walk you through the questions, so stay with me on this. I'm going to walk you through the questions and how we would like to ask the Committee to consider them. So I'll take you through the questions, through these options.

And presumably, if you vote yes on an option, since these are mutually exclusive, we assume that you'll vote no on the other options. If it doesn't work out that way, that's fine, but you're going to vote on every question. But we want you to consider, you know, we'll be looking at the yes votes to see which approach is favored by the Committee as we walk through these.

If you do vote yes, however, we don't want you to check out or start checking your phone. We want you to continue to comment in the discussion on the pros and cons so we can gauge the responses to these options. Okay.

So, option 1, we're going to mix up the order a bit, and take the last option first. The question number 1 is, at this time, at this time, do the available scientific data on the course of the Zika virus epidemic justify the elimination of all blood safeguards for Zika virus pending another significant outbreak in the U.S. its territories?

Again, we ask you to vote yes or no, and then we'll go on to the next question, which is diametrically opposed, should we continue with the current policy, which is universal ID NAT on the entire blood supply?

Question 2, do the available scientific data on the course of the Zika virus epidemic identify a risk to the blood supply that justifies continuing universal ID NAT?

Okay. If you've still voted no, we'll consider the third option, to vote yes or no, comment if you voted yes on another option.

Question 3, do the available scientific data on the risk of transfusion-transmitted Zika virus support the regional use of ID NAT in at-risk states and territories combined with the use of mini-pool NAT in all other states? The ID/mini-pool, individual/mini-pool strategy. And with this strategy, we're asking for discussion among the Committee of what criteria would be used, or could be used, to switch from mini-pool NAT to individual donation NAT within a defined geographic area or state considering these factors or others to trigger mini-pool.

All right, and then we'll go on. If you've still voted no, no, no, no, no, you have a couple more options. We ask that you continue to participate in the discussion if you've voted yes.

This is the testing based on responses to a screening question. So would selective ID NAT performed based on the

donors' responses to questions about, one, travel to Zika endemic or epidemic countries; two, sexual contact with partners diagnosed with Zika virus; and/or three, sexual contact with partners having travel risk for Zika virus, provide an adequate and appropriate safeguard against transfusion transmission of Zika virus?

If you've voted no, we're still waiting to hear from you -- and this is the selective inventory or transfusion practice option. Would the option to provide individual donation NAT-negative blood components to selected patients based on clinical indications, for example, to pregnant women, for intrauterine transfusion or to infants, and Zika virus untested blood components for all other transfusion recipients provide an adequate and appropriate safeguard against transfusion transmission of Zika virus?

And if you've still not voted yes on any of those, we ask that you provide any additional comments to consider testing donations using ID NAT or mini-pool NAT.

So here's our road map. Let's go.

DR. STOWELL: Okay. Thank you. We have some time for some questions from the -- of the speakers. Any questions from the Committee?

Dr. Basavaraju.

DR. BASAVARAJU: So I had a question for Dr. Linnen from Grifols, about slides 10 and 11, where the 16-sample pool data

is presented. So there's 24,000 pools of 16 donations where there was zero true positives, zero false positives. But the question that I had is were all of these also tested individually?

And the individual donations that were true positive, were those tested in simulated mini-pools? And the question would be the same for slide 11.

DR. LINNEN: Okay. Now that I found where I need to talk -- okay. So you wanted to know -- I'm looking at slide 11, which you want to know if the pooled donations were also tested individually, and the answer is no. Those were tested at the beginning of the study, so they were only tested in pools.

DR. BASAVARAJU: And then were the individuals that were detected, were they tested in simulated pools? Same question for slide 10.

DR. LINNEN: Okay. So the total screened were not tested in pools, but the confirmed positives, a subset of those were tested. You know, as I mentioned on the slide, that -- so if you go to the next slide, and the next one after that, a number of the -- most of the confirmed positives were not detected in multiple replicates of the assay individually. So those were not tested in pools. They would not be detected in pools.

The thing that I didn't point out during the presentation is that the window period cases are actually, in this study,

tended to be high titer samples that could be detected in pools. So those were the ones that were NAT-positive and IgM-negative. This tended to be higher copy -- I think has -- is probably related to the replication time of the virus, that it's less likely to find an antibody-negative sample that is at a low titer, based on the replication of the virus.

DR. BASAVARAJU: So I guess I'm wondering, of the ones that were tested individually, positive, what proportion of those would be detected in a pool?

DR. LINNEN: I don't have the exact number for that, but it's probably going to be around 20% of those. And we think, you know, as I mentioned during the presentation, the reason why that rate of detection is low is because these are not -- in most cases, these are not recent infections. As you look at the column that shows IgM reactivity, about 76% of these had already seroconverted because the vast majority of these were travel cases, people that were infected, some time went by, and then they donated.

DR. STRAMER: Can I help answer that? Just to clarify, when you look at pool reactivity, you really have to look at it in two domains, and this is what we've learned for West Nile and now we've learned for Zika. Most of the donations, as have been presented by both speakers from industry, are tail-end infections, where travelers have returned to the United States, waited some period of time, weeks to months, and then donated

blood.

So those are all IgM-positive, very low level detected on the licensed tests -- or the investigational tests, not detected by alternate NAT. So we have that one group of remote prior infections.

Then we have a group of active infections, which include the window period donations that are IgM-negative. So the most logical way to look at pool reactivity is to divide them into IgM-negative versus IgM-positive. The IgM-positives will not be detected in pools.

One can even ask why they need to be detected individually. These represent low-level infections. We don't know if they're infectious versus the window period donors that are, in the absence of any antibody, high titer, repeatedly reactive and pool reactive. So hopefully that's helpful.

DR. STAPLETON: Yeah, for Dr. Linnen, on the RBC-positive samples, did you look at regions -- I guess, because you characterized that virus further -- either by looking at other genome regions, next-gen sequencing or infectivity?

DR. LINNEN: No. We haven't done that.

DR. STAPLETON: Do you have an idea of the viral load on those from the red cell preparations?

DR. LINNEN: They're still low. They're in the hundred -- they tend to be in the hundreds. I don't have the data here. Maybe Dr. Busch has some of that data. Maybe he'll talk about

that in the public hearing.

DR. STAPLETON: Okay. Because clearly, if there's infectious virus in the red cells, if you're giving a 500 mL transfusion, there's going to be a significant amount of viral RNA present.

DR. LINNEN: Yeah. Right now, my presentation really doesn't address this. Maybe that'll be addressed later, but there is neutralizing antibody in these cases. The ability to detect the virus in red cells increases after seroconversion.

DR. LEWIS: So I think my question is related to the points that were just made about the over-simplification that's associated with simply counting all positives as if all positives are the same. And I think of it in terms of spectrum bias. And the goal here is not, in my view, to prevent any viral RNA ever getting into a recipient. It's to prevent adverse effects in a recipient, whether it's clinical disease, impact on an unborn child, etc.

And so what I was struck by was a lack of data on the relationship between viral concentrations and the risk of inducing an adverse effect, you know, actually transmitting an infection.

So I guess my question -- and this could be for multiple speakers, but for the speaker from the CDC, do we actually know anything about the viral titer in the transfusions that caused -- that were infectious, clinically infectious, and do

we actually have any data that suggests that for those donations that are detectable reliably by mini-pool but not by ID NAT, that any of those have ever transmitted disease?

DR. GOULD: Thank you. I'm not aware of any data that is available, at least in humans, looking at the correlation between viral load and clinical disease or adverse outcomes. Nor do -- I don't believe there's any human data about the infectiousness of specimens that are IgM-positive versus IgM-negative. There may be animal models or data that are somewhat informative, so thank you.

DR. NAKHASI: My name is Hira Nakhasi, FDA. I think Mike, which his presentation, he may have some data on the use of some of the samples in animal model to show the infected. Maybe that will answer your question.

DR. BUSCH: Yeah. So I'll present, during the Open Public Hearing, a fairly detailed analysis of the longitudinal characterization of infection in donors on follow-up, will include infectivity data.

In terms of the infectivity of what are termed tail-end, very low-level viremic seropositive units, there's very limited data so far. There's a series of studies in progress that will include inoculations in the macaques that will directly answer that question.

I'll comment that even mosquito acquisition, if you take macaques and infect them and then feed mosquitoes on the

macaques through the course of acute infection, there's actually a very transient period during high-titer acute infection pre-seroconversion that you can even transmit from a human to a mosquito.

So these very high-level viremias that we see, even preceding seroconversion neutralizing antibodies, there's only a very brief period of that that is sufficient titer that you actually can transmit to mosquitoes. Of course, it's very small volume compared to a blood transfusion, but you'll see a lot of data in about 45 minutes on these issues.

DR. STOWELL: Thank you, Dr. Mike Busch. And --

DR. LEWIS: That must be very reassuring for pregnant mosquitoes.

I had a question, I think best for Dr. Gould, and this has to do with what kind of surveillance of mosquito pools is being done in the United States for Zika? Is this being done anywhere routinely?

DR. GOULD: Yes. It varies by state, so states are doing mosquito surveillance and reporting those to ArboNET, but it's not uniform, national reporting. It's state by state.

DR. LEWIS: Do we know if the states which have had endogenous autochthonous Zika, are they screening pools there or any of the states which have had a high prevalence of travelers with Zika that's being done in those places?

DR. GOULD: That's my understanding, that, in particular,

the states that have had local transmission have done mosquito screening. And that data has been -- I'm not aware of any positive mosquito pools that have been identified recently. But again, it varies by state, and the data are not necessarily complete representative of all areas in the states.

DR. STOWELL: Dr. Escobar.

DR. ESCOBAR: I've got two questions for Dr. Gould. I guess, based on what we know so far with the Zika virus, do you think the behavior is going to be very similar to other viral, you know, epidemics that we've had, like the dengue or the West Nile, where you have that peak and it disappears and then you have sporadic cases?

That's one, and the second question is, the few donations or the few products that have been transfused to individuals and those products were infected, my understanding is they were completely asymptomatic, those patients, but we don't know if they later got pregnant or not, or do we have that information?

DR. GOULD: Right. So for the second question, from the literature, the cases that have been reported in the literature, those cases were reported to not have developed symptoms of Zika virus disease, as you said. I'm not aware of any follow-up that was done. It's not in the papers, about pregnancies or anything like that. Many of the transfusion recipients were quite ill and older patients.

For the first question, we've looked at data on

arboviruses that have similar epidemiology, same vector, so in particular, chikungunya and dengue virus. And as I showed in a presentation I gave for chikungunya, there are a lot of parallels with what we've seen with Zika so far, so in terms of the initial outbreak causing a larger number of travel-associated cases and a large number of cases in the territories and a few, limited number of local transmission cases that happened with chikungunya. And then you've seen the reduction in numbers, both in travel-associated cases and local cases over time.

And that's what we might expect for Zika as well in what we've seen so far in 2017. And they have similar seasonalities as well. For West Nile virus, it's quite a different epidemiology. It's a virus that is maintained through an epizootic bird, mosquito-bird cycle. And so most of those cases are local, endemic cases occurring here in North America, and it's seasonal.

There are areas that might have ongoing, year-round transmission of West Nile because of tropical climates, but West Nile is quite a different epidemiology than we've seen with Zika and chikungunya and dengue.

DR. STOWELL: So, Mr. Hardiman, do we know the risk history for the blood donor in Texas who was identified in October?

MR. HARDIMAN: The one, the last donor in October was from

travel to Mexico, so pretty much locally, just across the border. So --

DR. STOWELL: Dr. Leitman.

DR. LEITMAN: So it's interesting. This past summer was one of the wettest summers ever in those states that had the highest populations of locally transmitted mosquito bite Zika, and that would be, of course, Texas, Puerto Rico, and Florida, but there wasn't an increase in Zika, serologically or clinically. So there must have been an increase in thriving *Aedes* mosquitoes because it was wet. And pools of water, as we know, remained around for a very long time.

So that would have been, it seems, the setup for a resurgence of disease, but it didn't happen. I think that's very telling. So to whoever wants to answer this, is the belief that herd immunity was so strong that there was Zika, but it wasn't spread locally? Or what -- so some thoughts on why we didn't see anything happen during those wet periods.

DR. STRAMER: I don't know that I'm going to answer your question, but just to use West Nile as an analogy, we really still don't understand the environmental factors that make a season good or bad. And I actually was surprised, in Carolyn's presentation, to see that CDC would make predictions, because if there is one thing we've learned from Lyle Petersen and our experience with West Nile is, you know, crystal ball is out of focus.

It's impossible because we really don't understand enough about the environmental pressures that cause the outbreaks to be massive. The one thing that we know about West Nile, it does seem to recur in the same states. I mean, we've had a lot of experience now with West Nile since 2003 with blood donation screening. And it seems the hottest, driest seasons drive the highest level of mosquito activity, such as we've seen when there was an explosive outbreak in Texas or as we saw this year in Southern California.

So even though you'd think a lot of water and pooling would exacerbate thriving mosquitoes and transmission of vector-borne disease, we seem to see it in a drier area. Well, this is West Nile, and the epidemiology is different. So if it's drier, birds may not be there, and mosquitoes are more reliant for a blood meal on humans. So it may be totally -- just different.

But I'm just saying, we don't understand. It's a long way of saying we don't understand the environmental pressures that move these arboviral agents forward.

I do have a question, as long as my light is on.

DR. BUSCH: Just, maybe Susan -- Mike Busch here.

DR. STRAMER: Oh, sorry.

DR. BUSCH: Just to add a little bit of comment here, so two points. One is, again, discussions with Lyle Petersen, for example, you know the massive hurricane this year in Puerto

Rico, you know, that flooded out all of the vector reservoirs.

So, actually, the prediction is that next year is going to -- we'll see a resurgence because when you get so much water, essentially the mosquitoes that were residing in homes and water, standing water, that all gets flushed into the ocean. So, in fact, there's been relatively limited mosquito activity. It's picking up in Puerto Rico now.

But in terms of herd immunity, I mean, some of those huge outbreaks in Yap and Tahiti, you know, 60%, 70% of the population got infected and was seropositive, so theoretically protected for some period from reinfection. In some regions in Brazil and in the French Caribbean islands, about 50% of the populations got infected in 2016.

But I'll show some data for Puerto Rico, and there's other data that less than 20% of the Puerto Rican population got infected in 2016, so there's still a fairly large susceptible population. And herd immunity shouldn't explain the absence of cases.

DR. STOWELL: I believe Dr. Baker has had a question.

DR. BAKER: Thank you. I believe my question is for Dr. Eder.

This is with respect to option 3, which is Question 5, posed to us. And this is the question about whether or not we should make our decision based on the donors' responses to questions about travel to Zika-endemic countries or sexual

contact or sexual contact with partners having travel risk. I'm curious about the questions posed. Is there some uniform standard questionnaire? And/or do we have examples or the exact questions that are posed?

DR. EDER: So blood centers, most blood centers in the U.S. do use a standard questionnaire, the donor history questionnaire. So there would be standard questions. The travel question is already there. It's "In the last 3 years, have you traveled outside the U.S.," I believe. And then you have to evaluate all of the places where donors have traveled, and then you have to figure out, you know, is it a Zika area, is it a malaria area?

So the questions would be standard and would be -- the travel question is already there. And the other question would be much like the donor educational material that was used in February before switching to ID NAT. So does that answer your question?

DR. BAKER: I think so, but just to be specific, so the questions posed about sexual contact with partners having travel risk, would that also be framed as a 3-year time frame?

DR. EDER: So the 3 years is a capture question. So no, it would be, you know, the information that was included in the donor educational material. And sexual contact is already covered on the DHQ, a very explicit definition of what is sexual contact, because some people don't know.

So it would be, you know, have you ever had -- so the educational information about, so donors -- the Zika symptoms. The donor educational material would come back to show donors what the symptoms are. The sexual contact definitions are already there. The question would be something like, have you ever -- have you had sexual contact with anyone who's traveled to a Zika risk or had sexual contact -- yeah.

MR. REES: Dr. Stowell?

DR. STOWELL: Dr. Stramer had a comment.

DR. STRAMER: Just to answer the question, when we first implemented the FDA guidance in February for Zika, we did have standardized questions. And we would -- assuming that we would bring that option forward, we could use the same questions as were used and validated previously.

MR. REES: Dr. Stowell? I have the guidance here just because it's -- I carry these things around with me, being regulatory. But one of the questions was, in addition to the above instructions, a donor should self-defer for 4 weeks after the last sexual contact with a man who has been diagnosed with Zika virus or who traveled to or resided in an area with active transmission of Zika virus in the 3 months prior to the sexual contact. Those were the type of questions that were provided in February.

DR. KINDZELSKI: Question regarding the same presentation. In the simplified roadmap, in answering the questions, it seems

to me that the options 2 and 3 are completely separate options. Is it possible that option 3 will be implemented as part of the option 2 for the non-endemic states? The questionnaires.

DR. EDER: So 1 and 2 are -- I'm sorry. Can you repeat your question?

DR. KINDZELSKI: I'm not sure.

(Laughter.)

DR. EDER: So it's some combination of -- so --

DR. KINDZELSKI: Is the combination of the screening test for the option 3, regional ID/MP NAT can be implemented for the non-endemic states where MP NAT will be performed?

DR. EDER: So you would want to -- so you're saying, can we combine questioning donors to trigger? Well, you know, we'd like you to vote on these options, and then when we get down to please comment, if there are other permutations. But the combined ID/mini-pool NAT was to get away from asking questions.

DR. KINDZELSKI: Thank you.

DR. ALLEN: Question -- I've got two questions. First, to either Dr. Gould or Dr. Busch, from the collections and storage samples, going back a number of years, do we have any information, for example, populations in Puerto Rico or Brazil, as to what was happening back between 2010 and 2013 with regard to Zika virus infection in the local populations?

DR. STOWELL: Dr. Gould?

DR. GOULD: I'm not that familiar with the literature. I'm looking. I know there's been some molecular clock analyses that have been done, to try to understand when Zika virus was actually introduced into the Americas, and I know there's some data suggesting that it might have been present in Haiti for example, prior to the recognized outbreak in Brazil. So -- but I'm not -- you may be familiar with it. Thank you.

DR. STOWELL: Actually, Dr. Busch is going to be speaking to us in the open hearing part for 15 minutes, so I think you can probably get some of this additional information from him at that point.

DR. BUSCH: Just specifically to that question, which I wouldn't address, I didn't plan to address, I agree, the molecular clock data, which is actually submitted for publication, it looks at the spread of Zika across, genetically across the Caribbean and Central America. It does indicate that the virus really wasn't around prior to 2015.

DR. ALLEN: Was not?

DR. BUSCH: Was not. And we are about to execute serosurveys we have saved through CTS's efforts. But we did a large serosurvey of chikungunya before and after that outbreak, and those samples are available from 2015. And then we have samples, 500 from four time points, April 2016 through April 2017, that will be serologically characterized.

So we have both a pre-epidemic, completely pre, and then

through the course for Zika incidence.

DR. ALLEN: Thank you. The second question actually moves to the actual laboratory testing of samples from blood and plasma. I assume that all the testing is being done now in the large regional labs, so as specimens are flown in, they are going to need to be parsed if we choose to do a combination of testing from some areas, not testing in others, or individual versus mini-pool.

I just want to confirm that there is a degree of sorting and pressure at the laboratory level, the regional laboratory level, to all of this, if that's what the recommendations are that are adopted.

DR. STRAMER: You're asking whether labs can function between mini-pool and ID?

DR. ALLEN: Well, I assume that they'll figure out how to function but --

DR. STRAMER: Well, because we do that for West Nile.

DR. ALLEN: Yeah, well -- exactly. I know there are situations like that, but that is what would happen. The sorting is really at the regional laboratory level.

DR. STRAMER: Right. And to answer your question, the publication that was published in *Nature* regarding molecular clock analysis stated that within times of variability, Zika was introduced into Brazil between August 2013 and July 2014. So it took that long a time before it was initially detected in

May 2015.

DR. ALLEN: But there is some evidence that it wasn't there before that time?

DR. STRAMER: Yes, August 2013, according to molecular clock.

DR. STOWELL: Dr. Lewis?

DR. LEWIS: I have two questions: The first is for Dr. Gould; the second is for Dr. Hardiman.

For Dr. Gould, looking at the case reports that were provided to us on transfusion-associated transmission, it looked to me as if these cases, these sort of positive cases, occurred with donors that were early in infection or in a window period, because they called up a donor center later to report symptoms.

So my first question -- and I'm sorry, this is going to be a multi-part question -- is, is that -- am I correct in that interpretation? Well, we'll start with that, and then I'll see -- because it will lead to the second question.

DR. GOULD: Okay. So I don't forget the questions, thank you. Yes. That's my understanding as well, from reading the literature.

DR. LEWIS: Okay. So I also got from the presentations that the typical clinical course includes a long tail during which viremia is likely to be substantially less. And so we tend to focus on positive data and tend to sometimes under-

appreciate the information contained in the lack of information.

So would I also be correct in the understanding that despite a very long tail of low-level viremia, we have no evidence that donations from patients during that low period of viremia have ever resulted in clinical illness through transfusion?

DR. GOULD: I'm not aware of any evidence.

DR. LEWIS: So it's correct that there is -- that we are not aware of evidence?

DR. GOULD: Correct. Correct.

DR. LEWIS: Okay. So that seems to me as a really striking piece of negative information. And so my next question is for Dr. Hardiman.

You emphasized in your presentation the decrease in sensitivity associated with mini-pool analysis.

MR. HARDIMAN: Yes.

DR. LEWIS: And I can picture, as a non-laboratory specialist, two ways that might occur. One is simply dilution of a low-viral titer dropping below the reliable sensitivity limit, but there's also another mechanism, which would be that antibodies from one donation could have a blocking effect on an assay. Would I be correct in interpreting your presentation as suggesting that you think the mechanism is the first and not the second?

MR. HARDIMAN: That is correct, yes. Each one of these positive donations was actually diluted in negative human plasma that had been tested and shown to be negative for Zika. So these were all tested individually but diluted 1 in 6 at the point of donation that was shown to be positive. So these weren't grouped together.

DR. LEWIS: So in a setting in which there is a large level of herd immunity, where one of the other pooled specimens might have antibodies, do we have any information on what that would do the sensitivity of the assay?

MR. HARDIMAN: Yeah. The antibodies shouldn't interfere with the molecular detection.

DR. LEWIS: Okay. Yeah, it was a naïve question.

MR. HARDIMAN: Yeah.

DR. LEWIS: I just wanted to ask you --

MR. HARDIMAN: No, I understand. I mean, it's a -- I think it's a good question because we haven't done this in a real live setting of mixing six donations together. And that's why we felt it's better to truly assess the individual positive donation, diluted 1 in 6 in negative Zika material to get a true determination of whether you would pick up that donation when it is diluted 1 in 6.

DR. LEWIS: Okay. Thank you.

DR. STRAMER: I don't know if you're -- if it would be helpful to review the four -- I just have a Zika PowerPoint

that I'm paging through -- if it would be useful to know the details about the four transfusion transmissions from three donors, two cases that have been published.

The first one was a male 55-year-old recipient who received a liver transplant and received a platelet, and that's what the infection source was. The second was a 38-year-male with thrombocytopenia, a trauma patient who died. Thrombocytopenia was one symptom that probably was unrelated to Zika but could have been. So that was the only symptom that potentially was related to Zika in these four recipients.

The next was a 54-year-old female with myelofibrosis. And the last was a 14-year-old female with AML. And those last two came from a split apheresis unit. I don't know if that's useful.

DR. STOWELL: Do we have other questions for our speakers?

DR. STRAMER: I have one for Dr. Hardiman, regarding the positive predictive values that were calculated. On slide 9, you show that during the IND collection period for U.S. collections, you had 100 reactives, and 29 were confirmed positive.

MR. HARDIMAN: Correct.

DR. STRAMER: So those are the numbers that I would use to calculate a positive predictive value. But then on a subsequent slide, slide -- I can't read -- 15, you used 14 out of 23 to calculate your PPV, versus 129.

MR. HARDIMAN: Yes.

DR. STRAMER: So I was curious why that was.

MR. HARDIMAN: Yeah. We used the different time scale here. Obviously, we cut off the data here in October 2016, which was the data that we supplied for the licensure of the assay.

DR. STRAMER: Oh, I see. This is one further a year.

MR. HARDIMAN: The other is the full clinical trial of --

DR. STRAMER: Okay.

MR. HARDIMAN: -- over the whole group, so --

DR. STRAMER: So then through October 2017, the positive predictive value would be 29% as opposed to the earlier period that you showed 61%?

MR. HARDIMAN: Correct.

DR. STRAMER: Okay. Thank you.

DR. STOWELL: Dr. Lewis.

DR. LEWIS: I just want to editorialize for a second. That question illustrates the exact issue related to the spectrum bias, because what's happening over time is the average titer in positive patients is changing. So there is no single number that is the positive predictive value or the sensitivity or the change in sensitivity between ID NAT and mini-pool.

And that, I think, is a challenge for us all to consider, that none of the numbers presented represents what will be true

next month or next year or 2 years from now.

DR. STRAMER: They're all fixed in time, so you define it by the time period you're looking at. So the longer period we have, as shown by all speakers, with a decreasing prevalence of Zika is going to reduce the positive predictive value. Sensitivity should be -- sensitivity is an independent measure, but PPV will reduce as the amount of data we accrue increases and the prevalence of the agent seems to be declining.

DR. LEWIS: So I think the statement that the sensitivity is a fixed value is incorrect because of the issue of spectrum bias. The sensitivity of the assays is a function of the distribution of the viral load among those who are positive at any time, and that changes over time.

And so I think the challenge here is that we're going to be asked to comment on strategies that we hope to be effective with a lack of ability to see into that fuzzy crystal ball and know what the distribution of active versus distant versus very old infection will be at that time.

DR. STOWELL: I think, if there are no more questions for the speakers, that we'll take a break now of 15 minutes or thereabouts. So let's come back at -- I'm sorry? Yeah. So we'll be back at 10:50.

(Off the record at 10:36 a.m.)

(On the record at 10:51 a.m.)

DR. STOWELL: Welcome to the Open Public Hearing, for

which I need to read into the record the following announcement.

Welcome to the Open Public Hearing session. Please note that both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee, FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any firms, their products, or if known, their direct competitors. For example, this financial disclosure information may include the firms who may have made payment of your travel, lodging, or other expenses in conjunction with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

At this point we have only one request, which is from Dr. Mike Busch from Blood Systems. And -- okay. We have a second?

Okay. So, Dr. Busch, if you would take about 15 minutes

or so?

DR. BUSCH: Yeah. Maybe a little longer.

(Laughter.)

DR. BUSCH: So as indicated here, I'll cover four topics, and all of these are studies that were funded by NHLBI, CDC, conducted at BSRI/CTS in close collaboration with the commercial vendors, so addressing the durations of viral RNA in blood compartments as well as body fluids; looking at the issues discussed in terms of the dynamics of the epidemic and the shifting pattern of infected donations through the course of the epidemic as well as the proportion of the Puerto Rico population that was infected during the large outbreak in 2016; the infectivity by intravenous transfusion-mediated exposure in animal models; and then specifically address consequent safety impact were we to convert to mini-pool from ID NAT.

Okay. Great. So in terms of disclosures, yeah, I do work for BSRI. We were the confirmatory lab for Roche, Grifols, and also Cerus -- misspelled, I apologize -- INDs. And I'm an employee of BSI. I'll show data on RNA detection in whole blood from Grifols that is not an investigational claim. And I'll discuss an off-label use of that. And then also I'm the PI on these other studies, and I probably should disclose, my wife works for Abbott Laboratories, which now does have a EUA-claimed Zika assay.

So the main study that I'll be presenting data from is a

NHLBI-funded and CDC-funded supplemental study under the REDS-III program, to investigate the natural history of Zika virus infection in RNA-positive blood donors to characterize the evolution of viral and immune parameters over time, the distribution of the virus in blood compartments and body fluids, characterize the viral and immune responses associated with clearance and clinical progression, and evaluate clinical outcomes. And about half of these donors, just for your information -- I won't go into this -- did develop symptomatic Zika infections following their viremic donation.

And then we've established a very large sharable repository of samples that have been distributed to over 20 collaborating, both commercial and academic, groups, to evaluate new and develop new assays, as well as through the government agencies, through WHO and NIAID, to a number of industry groups, and then also being used in the standards.

So this study was launched in June 2016 and is going to continue through next September. Given the absence of an outbreak in 2017, we will be able to continue to accrue through next year's outbreak, if that happens, in Puerto Rico and the continental U.S.

The study initially involved Puerto Rico in one blood but was expanded as the outbreak and the screening was implemented in the continental U.S. to include all of the blood systems, blood centers, the New York Blood Center and American Red

Cross.

And the original goal was 130 infected donors and purposely trying to recruit a substantial proportion that were dengue seronegative, which is relatively unusual in places like Puerto Rico, where 90% of the population has dengue antibodies, so that we could compare the kinetics of viremia, the rates of symptoms, etc., in individuals who had prior dengue exposure from those who did not.

The protocol involves the index donation, and we're able to capture plasma units as well as packed red blood cells components off the index donation, and then serially for the time periods of 1 week, 3 weeks, 6 weeks, 3 months, 6 months, 9 months, and 1 year. We're actually considering recalling the donors a second year out to just further characterize immunity for after further periods of time.

So one of the things that we were quite interested in and appreciated was that these viruses, the arboviruses associate with red cells, so both our group and then Maria Rios here at FDA and Susan Stramer, etc., we've all demonstrated that West Nile virus and then dengue virus has significant associations with red cells, so it can be detected for months following clearance of plasma viremia, and probably some discussion later from those infections as to whether there's any suggestion of infectivity.

But reports began to appear, actually, in early 2016, and

there have been a series of papers just showing here that demonstrated with fairly small numbers, generally travel-acquired infections followed over time, that the virus could be detected in red cells for periods of several months following clearance from plasma and urine.

So this is showing data from 53 infected donors detected and enrolled into the study. This data was presented by Mars Stone at AABB. And you can see that again, for the index donation time zero here, we have data from the plasma units and from the packed, leukoreduced packed red cell components.

And you can see that the virus is quickly suppressed, from being fairly high titers to essentially undetectable within typically one to several weeks in plasma, whereas the red cell positivity persists over time in the large majority of people and then goes negative at about 12 to 24 weeks post-infection. And this again is packed red cells.

We also have whole blood aliquots that show similar persistence of virus over that first, you know, 2 to 3 months. PBMCs typically go negative within several weeks, although you do see some erratic sort of intermittent detection. Urine again goes negative rather quickly.

Saliva is positive at week 1 but negative subsequently. And then semen, we've recently published, we do detect in asymptomatic donors persistence in semen in a proportion, about a third of the donors, although we've never demonstrated and

did attempt to demonstrate infectivity in semen.

Again, just pointing out this persistence in whole blood and red cells, and then also emphasizing here that, actually, about 10% of donors never develop red cell-associated virus. And that's both based on follow-up, serial follow-up samples from the donors enrolled in this study, but also, we have data from about 120 packed red cell units from index, a substantial proportion of which had IgM. And in a similar finding, about 10% of the IgM-positive donations did not have red cell-associated virus.

So reasons we don't fully understand, don't understand at all, in fact, 10% of people do not develop this red cell-associated virus.

So this persistence of the virus in whole blood is actually very potentially useful. And many assays, now CDC, Abbott, and now Hologic, with the Aptima assay that Jeff alluded to, is about to get a whole blood claim. So by using whole blood instead of plasma, you can actually diagnose infection more readily for longer periods of time, so useful for symptomatic cases or travelers.

There's actually quite a bit of interest and a large intent to now test whole blood samples from the very large studies that the NIAID is executing. And there's similar studies from CDC, etc., to monitor pregnant women who've enrolled in longitudinal studies and being sampled monthly, to

understand the infection rates as detected in whole blood.

So these studies did freeze whole blood, and the plan is to test the whole blood samples along with urine and plasma to better ascertain incidence in these studies that had been confounded by poor antibody performance, potentially useful for solid organ and stem cell donors and semen donations.

So, but is this infectious? And that's, you know, that's sort of a very important question. To date, there's been no documented transmissions by transfusion or other routes from these red cells that have persistent RNA after plasma viremia has been cleared.

We've done studies onto susceptible increased, you know, genetically manipulated virocells to make them more susceptible, been unable to demonstrate transmission from red cells. We've inoculated red cells from humans that had RNA on the red cells after clearance of plasma into interferon knockout and antibody-treated mice without ability to demonstrate infection.

We've actually fed blood from these donors onto *Aedes* mosquitoes and been unable to demonstrate infection. And there's planned studies to transfuse units from -- both donor frozen red cells from these time points as well as macaque red cells after they clear the viremia in transfusion studies in macaques.

But I think, importantly, is the absence of any evidence

of transmission from humans to other humans via transmission in Latin America, and particularly in Puerto Rico and the Caribbean Islands where we did screen plasma RNA, and we know that there would have been large numbers of donations given by people after they would have cleared the plasma viremia. They would have had red cell-associated virus, and there's been no transfusion transmissions done, although there's been no prospective, you know, observation of recipients to ascertain a transmission rate.

So, tentatively, we don't think the red cells are infectious. What we think is happening is that the erythroblasts are infected during the acute infection. And I'll show you that it -- actually, we don't detect red cell bound viruses until approximately 3 days after infection.

So we think the erythroblasts produce red cells that then survive, with very low levels of Zika virus RNA, their normal lifespan, which is approximately 120 days. So at least our position currently is that plasma screening is sufficient. There's really not a need to convert to screening to testing whole blood.

Now, conceptually, you know, it's kind of discussed, there's this stages of infection. There's the ramp-up viremia stage. There's potentially -- especially with very low dose or mosquito inoculation, there may be an eclipse period, we term it, where after an exposure there's a period before you develop

a disseminating viremia, but that's very brief. And then there's increasing viral loads associated with plasma. And then the whole blood or the red cells become positive, and that persists for quite a long period.

But again, rather quickly, as I'll show you, about 7 days after infection, seroconversion occurs. IgM antibodies, neutralizing antibodies occur. And we've developed a schematic of stages based on the absence of antibody and then differing viral loads that define the progression from a period of low-level viremia, antibody-negative, to high-level viremia, antibody-negative, through to early post-seroconversion, as the viral loads are then suppressed. And then later stages, so-called tail end, after you have low-level virus that isn't even reproducible on ID NAT, these kinds of stage 5 cases.

So this, although this is actually the 53 donors who we enrolled, this is their profile at the date of donation, so at index donation, we're picking people up in all of these different stages of infection, ranging from the acute ramp-up phase through to this tail-end viremia that's barely detectable as you saw in the clinical data. This is the kind of infection seen in the U.S., where they're barely detectable by even ID NAT and have high levels of antibodies.

So if you follow these donors over time, and this is a subset of the donors who were seronegative at index, they seroconvert briskly to IgM and IgG. And then they lose IgM,

persisting in the range of 250 days, on average. IgG levels also drop, so you can see there -- and many of these are dengue seropositive.

So the cases in black here had dengue antibodies at baseline. And because they had pre-existing memory to dengue, they actually show a very profound boost in antibodies initially. And the IgG signal here, that's the high-intensity signal, is probably partially triggered IgG from dengue that is cross-reactive. And you can see that if you look at neutralization titers.

So this is an individual who was picked up in acute viremia and pre-IgM and seroconverted their IgM and their IgG. But if you look at the neutralization titers, they did develop a nice Zika-specific neutralization reactivity, but they also boosted all their pre-existing dengue titers.

So this is kind of the challenge with serologic testing, is if you've got populations such as almost all of Latin America where a high proportion of people have dengue, you're going to boost all that dengue memory in parallel with inducing Zika reactivity.

So one of the things -- actually, Jay Epstein, a year and a half ago, called and said do we have data from macaques on the doubling time of acute viremia? And at the time we had very limited data, but now there's large numbers of macaques have been infected. This is data that we particularly focused

on. It's from colleagues at the University of Wisconsin, where they inoculated macaques with modest-dose subcutaneous inoculation.

And these macaques went through viremia and then seroconverted. And we were particularly interested in characterizing what we call the doubling time of acute viremia. And this was done by Brad Biggerstaff at CDC. So he modeled all the acute daily viral loads following infection and was able to calculate a doubling time of 5.3 hours. So this is the fastest of all the viruses. So we do this routinely. For West Nile, it's about 10 hours, etc. So this is a very rapidly replicating virus during acute viremia.

Now, the reason we wanted to do this is by knowing the doubling time of acute viremia, we can look at the viral loads of donors who were picked up in the pre-IgM phase of infection, and then we can back-extrapolate, knowing the doubling time. So if you note, this is just -- this is -- these are individual index donation samples. And they have ranging viral loads from very low copy to very high copy. This is actually the log. So they do go up as high as 10^8.

But what you're able to do here is to estimate, based on the viral load and the doubling time, how long prior to that donation was that donor infected. And it's actually expressed as the estimated time since infection that was detectable by NAT.

And then applying that, we can -- Brad was able to then look at downstream data from these infected donors and estimate the time from that initial detection of infection, the acquisition of infection, to the clearance of the RNA. And on average, there's about an 11.7-day period of NAT detectability, and with a wide range, so you can see here the distribution.

So, though, although, you know, it averages about 11.7 days, there are people who might have NAT detectability out at 25 or 30 days. These are confidence bounds around these mean estimates, so quite a range. But by knowing the length of NAT detection, one can then do a variety of other things, as I'll illustrate in a minute.

So we've now done this on a bunch of other parameters, so this is looking at the time from -- all of these are indexed off of estimated date of infection. So serum IgM converts at 7.5 days. Red cells become positive a little over 2 days after infection. This is the primary NAT assay, 11.7 days. This is the Grifols assay, which was run in eight replicates. So if you ask, you know, how long does it take for at least half of those eight replicates to become reactive, it's identical between the two assays.

If you ask -- if you only require one of the eight reps to be reactive, you can actually extend the detection period by a month. So by making the test more sensitive by running eight replicates, you can even detect plasma viremia for a much

longer period.

But most important, the red cells and the whole blood are positive out to close to a hundred days. So you can detect -- and what we think is happening is the red cells -- the erythroblasts are infecting the red cells that are essentially born during the acute infection, live their normal life span.

So what Brad was able to do by knowing that duration of NAT detection, he was able to take the data from the Puerto Rico outbreak and update an analysis which was published in late 2016 to look at the entire 2016 epidemic year and estimate the number of people infected. From the NAT yield rates and the duration of viremia, he was able to derive an estimate that about 600,000 people in Puerto Rico were infected during that 2016 outbreak.

But that's in a population of 3.6 million. So based on this approach, only 16.4% of the Puerto Rican population was infected during that year. And other serosurveys are indicating in the same ballpark, around 20%.

Now, as noted, the pattern of detecting infected donations will shift dramatically as the epidemic evolves. And this was evident in the Puerto Rican outbreak. This is data that Phillip Williamson, is leading the development of the publication, was presenting to AABB. But you're seeing here the number of positive donations with the Roche assay through the course of the 2016 outbreak.

But the proportion that are ID NAT only, mini-pool negative, went from -- the number that were mini -- percent that were mini-pool negative went from a very small proportion of only 7% to up to close to 60% at the end of the epidemic are ID NAT only, would have been missed by mini-pool.

And similarly, the IgM reactivity of the NAT yield donations goes up from a small percentage to over 80%. So the patterns of infected donations detected shifts dramatically.

In addition, if you contrast the Puerto Rico yield cases in black with the domestic U.S. cases in red, again, data presented at AABB, this is based on Roche screened donations, you can see that whereas in Puerto Rico a large proportion of the infections are IgM-negative and mini-pool NAT detectable, some of the IgM negatives are front-end early infections that were ID NAT onlys.

In continental U.S., and in the tail end of the Puerto Rican epidemic, the large majority of infections are very low-level viremic, so ID only, and IgM-positive.

Now, in terms of the impact of mini-pool testing, one approach to look at that is to say, okay, what are the analytic sensitivities to these assays? And this is data derived from the Roche package insert and actually Grifols, the CE marked package insert.

So these are the claims. This is different samples, so these are not head-to-head comparisons of the same analytic

standard. But Roche had a 95% LOD of 8.1, whereas the Grifols 5.9, if you -- Grifols is always run in pools of 16, Roche pools of 6. So if you simply multiply the 95% LODs by the pool size, you can estimate what would be the analytic sensitivity at a 95% performance rate if you were to do pools instead of ID NAT.

And then you can take the yield data -- so this is similar to what I showed. As discussed, you can sort the NAT yield donations as to whether they were IgM-negative or IgM-positive. And as discussed, if they're IgM-negative, you see a wide range, including very high viral load samples, whereas once you seroconvert, you suppress the viremia very quickly and you pick up these low-level, tail-end seropositive infections.

And if you just show, just here, this is essentially what we just calculated as the approximate sensitivity of mini-pool NAT. And you can see you'd probably miss these low-level ones. And indeed, when Roche did simulated mini-pools, as Tony presented, the red dots here represent the donations that were negative on simulated mini-pool. The black dots were positive.

So about 8% of the front-end IgM-negatives would have been missed by mini-pool whereas 77% of these tail-end infections would have been missed by mini-pool.

There's another approach to ask the same question, which is using the doubling time, which I just presented, of 5.35 hours. So, essentially, if you know the doubling time and you

know the lengths of the window periods -- and as I indicated, there's about a 7.5-day pre-IgM window period that we think is the highly infectious phase before you have neutralizing antibodies. And by simply applying the number of doubling times that you go through -- so if you go from 1 to 2 to 4 to 8, that's three doubling times. So for Roche, at pools of six, there's 2.5 doubling times for a lot. Grifols, at pools of 16, there's four doubling times. So you multiply the number of doubling time times the doubling time, and you get the number of hours that you would reduce the window period if you were to run pools.

And so this gives you a very similar rate of around, you know, 7% to 10% reduction in the total pre-IgM window period, so just a different approach that's yielding a very supportive conclusion.

So the last point here is the infectivity. So we do have funding again from NHLBI and CDC and are doing a number of experiments, infecting macaques, specifically looking at the dynamics of acute transfusion transmission infection in macaques, characterizing the minimal infectious dose through escalating dose inoculation studies, both of the pre- and post-seroconversion window period stages.

And also, downstream, we're going to be evaluating pathogen reduction on very high titer human plasma that will then be inoculated into macaques. And these animals are also

being monitored for tissue persistence.

So in recently published work, we demonstrated infection in a number of macaques using actually the Brazilian plasma that was associated with the transfusion transmission case that was reported. And we can demonstrate very rapid acute viremia, including infectivity, that is -- if we use the NAT assays, we can -- blood screening NAT assays, we can detect that virus for longer. These animals do seroconvert and develop neutralizing antibodies.

So the experiments are still in progress, but I'll show you data on escalating dose infectivity of pre-antibody viremic blood and then soon to be initiated will be studies infecting animals -- exposing animals to higher titer units that are early post-seroconversion, and then the pathogen reduction experiments, which will again use very high-titer plasma, both human plasma, and then because we're infecting macaques, we also have high-titer macaque plasma, and red cells, etc., to use in these experiments.

So just to show you, first in immunodeficient mice -- and this is actually work that was funded by Grifols to look at mouse infectivity, because NIH wouldn't allow us to do this stuff. Simone said no.

So in any event, what we're looking at here is serially diluting -- again, this is the Brazil plasma that was associated transfusion transmission. So we're serially

diluting it to very low copy number, below the limit that we can even count, estimating it. And then we're inoculating it into either tissue culture virocells -- and you don't detect infectivity until you get up to about 800 copies in virocells.

So you need -- you know, there's about 200 copies per infectious unit in plaque-forming units. But, in contrast, if you take mice that are -- whose innate immune system is knocked out by infusing antibody to interferon, those mice are extremely susceptible. So we can demonstrate mice getting infected pretty consistently once we're down at 50 copies, well below 1 PFU.

So these mice are, you know, extraordinarily susceptible, but they have no immune system. In contrast, in macaques, we actually have to get up to fairly high doses. So you can see we exposed macaques to these serial low doses, and they did not get infected until we got up into the range of 3,000 to 9,000 copies.

So you actually, in macaques, you need a fairly high dose of virus from this acute ramp-up phase plasma to transmit. And this is just showing graphically here, with again, the mice being very susceptible, whereas macaques' cell lines are relatively resistant.

So these experiments are being repeated and extended with additional plasma from Puerto Rico donors. We're also planning very soon to look at antibody-positive plasma to directly, in

macaques, address the question that's so important. We also are going to be inoculating red cells and packed red cells from these humans as well as animals to assess that, and then again, the pathogen reduction.

So from my perspective, and this is my personal position, is that I do think mini-pool NAT is good. One is we're missing lots of viremic donations that are -- because we're doing only ID NAT on a single sample. If we did replicates, we'd extend and detect people longer in plasma. Plus, there's this persistent red cell virus.

But the window period, the pre-seroconversion window period that we believe is highly infectious or moderately infectious, the ID onlys period of that is really quite short, whereas the, you know, detectable phase by mini-pools would be much longer.

Whether blood is infectious at these very low doses, in the ramp-up phase and particularly once you're in the tail-end when you have neutralizing antibodies, I think is unlikely. We know from our experience with West Nile and with dengue that that's the case. So it's speculated but still to be proven that that's not infectious once you have neutralizing antibody.

And so this period goes fast. So from travel-acquired -- again, almost all the travel-acquired infections picked up in the U.S. are these tail-end seropositive units. There's small numbers of window-phase infections. But people who travel

generally don't give blood within a few days.

So I think if -- and even in -- so in the continental U.S., there's very few local outbreaks that could be responded to with triggering ID NAT, but even in Puerto Rico where the population is highly susceptible still, I think that mini-pool NAT is a way, as we've learned to do with West Nile, to monitor the population. If an outbreak does recur, we can quickly trigger ID NAT and maintain safety through that practice.

And these are all the people involved that I won't list, but again, lots of people, both at my group and then Don Brambilla, then the fabulous analysts at RTI, Simone and Steve, who are here. I particularly also want to acknowledge Brad Biggerstaff, who has been very, very helpful in recent statistical analyses, and then the colleagues at Roche, Hologic, Phillip Williamson at CTS, and particularly the group at Puerto Rico, who was extraordinarily cooperative in enrolling people and has unfortunately, you know, had to face the tragedy of the hurricane. Thank you.

DR. STOWELL: Thank you.

Does anybody from the Committee have any questions for Dr. Busch?

DR. STAPLETON: Yes. Hi, Mike. A couple of questions. First, I guess, have you looked at platelet infectivity in any way, or RNA levels?

DR. BUSCH: I did. I think I showed platelets on the --

DR. STAPLETON: Did I miss it?

DR. BUSCH: Yeah. Well, I forget if it's on that slide. But we did look at platelets early and specifically sorted the platelets, rich plasma, and there was -- it's not on the slide? Okay.

It was detectable for about a week, which is about the lifespan of platelets. So I wouldn't be surprised if platelets, megakaryocytes get infected and the platelets that are produced during acute infection become positive for RNA. Whether they're infectious or not, I don't know, but they don't live very long.

DR. STAPLETON: And have you looked at packed cells resuspended in whatever buffer you want to use to see how much of the neutralizing antibody remains in the packed cells?

DR. BUSCH: No. I mean, we do have packed cell -- we did get lots of packed cell units that, you know, they were leukoreduced packed red cells. And many of them did have antibody, but we haven't looked at the levels. We've just sorted them so far by IgM. Haven't looked at that yet.

DR. STAPLETON: Yeah. Thanks.

DR. STOWELL: Are there -- oh.

Dr. Stramer.

DR. STRAMER: Just two minor clarifications, Mike, and we're all susceptible to this. At the end when you talked about the tail-end infections in your conclusions, you

mentioned that they were viremic. So I don't think we know if they're viremic because we don't know if they're infectious. So I think you meant to say RNA-positive.

DR. BUSCH: Yeah, fair enough. Certainly the red cell RNA signal, we don't think is intact infectious virus. If there's residual pre-plasma RNA detected, is that virion-associated? And, you know, the problem, the challenge becomes the term "viremia." Does that imply infectious virus? And then if so, how do you quantify infectivity?

DR. STRAMER: Technically, it does.

DR. BUSCH: Yeah. PFU is a very insensitive measure of infectivity. As we can see, there's infectious virus when you transfuse it into mice that are well, well below the levels that define a plaque-forming unit, so --

DR. STRAMER: And then I just had one clarification on slide 21, since the PowerPoint's still up. When you talked about the doubling times for the difference between Roche and Grifols, because those are -- I mean, they're nonlinear; they're logarithmic. So wouldn't the Grifols -- this is really minor, wouldn't it be three doubling times --

DR. BUSCH: Well, from --

DR. STRAMER: -- to get to a pool of 16?

DR. BUSCH: If you go to from 1 to 2, 2 to 4 --

DR. STRAMER: One to -- 4 to 16?

DR. BUSCH: -- to 8, 8 to 16.

DR. STRAMER: Aren't there -- they're --

DR. BUSCH: They're doubling. Doubling.

DR. STRAMER: I know they're doubling, but I thought they were on a logarithmic scale, not a doubling scale.

DR. BUSCH: No, it's doubling.

DR. STRAMER: Okay. That's fine. Either way.

DR. BUSCH: Yeah.

DR. LEITMAN: So, Mike, it was a very persuasive and tour-de-force presentation, but your conclusions are not where I thought you were going to be heading. So you conclude -- recommend use of mini-pool NAT with triggering to ID NAT. Why trigger at all? The purpose of screening blood donors is not a public health service surveillance purpose; it's to prevent transmissions to recipients, particularly the ones, the most susceptible, which would be pregnant women or their partners.

So why pick up the general low-level whatever if what you want to do is interdict those that will cause what you don't want in recipients?

DR. BUSCH: Right. I mean, I think we learned with West Nile. We just did -- we started with mini-pool NAT. We had breakthrough transmissions. All of them were attributable to low-level viremic pre-seroconversion. And so that led to the concept of triggering, and tightening of that triggering criteria to one positive we convert.

The reason we convert is because if there's an

autochthonous outbreak, a local outbreak, we don't want to miss those low-viremic, front-end infections. We don't probably care much about those tail-ends because they're probably not infectious. We're already missing lots of tail-ends by just doing singlet plasma-based ID NAT.

But if we have a new outbreak in Puerto Rico or in Florida and we pick it up by mini-pool NAT, and it's determined, either in Puerto Rico, obviously, but in places like the U.S., if it's determined that there's a local transmission beginning to take place, not travel-acquired, we want to not miss those low-viremic, front-end infections. Those could be infecting people.

So that's the concept that we've developed for West Nile. It's a model that we understand and know how to operate. And it would allow, you know, response to a local autochthonous outbreak by going to ID NAT and interdicting those low-level viremic seronegative units.

DR. STAPLETON: Maybe this is obvious. I don't mean to -- but I assume that means that, to answer Dr. Leitman's question, is that because the mini-pools will pick up the early higher titer, antibody-negative infections, that that's your screen.

DR. BUSCH: Yeah. It'll pick up 90% of them, with mini-pool, the front-ends. But we're missing 10%, the low-level viremics that are high risk for transmission. You know, we're missing a lot of the back-ends with mini-pool testing.

No question.

DR. ALLEN: More of a comment than a response to Dr. Leitman's very important question. The point is that what we're doing if we follow this design is to use the blood bank or plasma and blood collectors for the surveillance system because we don't have any other population that's being studied. Is it really important for the recipients? Not so much, if we had another means of detecting it. We don't. So that's the tradeoff.

DR. BASAVARAJU: So I just had a question. So the way that you presented this, it sounds almost definitive that if you're ID NAT positive, mini-pool -- or I'm sorry, if you're mini-pool NAT negative and IgM-positive, you're definitely not infectious and don't present a risk to a recipient. But that's theoretical, right? I mean, you haven't studied it in a way --

DR. BUSCH: No. I didn't say it was definite.

DR. BASAVARAJU: Yeah.

DR. BUSCH: It's, you know, it's from our experience, which is pretty definite with West Nile. I mean, we have decades of screening, and we clearly are missing lots of low, tail-end infections with West Nile. The red cell positivity persists, just like with Zika. And we've never seen a transmission from seropositive, blood-by-blood transfusion.

There is, I think, one or two transplant-related transmissions that have occurred with seropositive back-end,

but not -- so the experiments still need to be done in macaques to unequivocally prove it, but the reality is that we still only have those four transfusion cases in the whole world and, you know, so there's not a lot of evidence that there's transmission or clinical consequent transmission of Zika to begin with. And of these --

DR. BASAVARAJU: There was those 12 in Micronesia or whatever, French Polynesia, where there was RNA-positive donors where the transfusion occurred in --

(Off microphone comments.)

DR. BUSCH: No evidence of transmission.

DR. BASAVARAJU: They did -- well, the recipients didn't have any evidence of disease, right? But I mean, it's been --

DR. BUSCH: Right. And they've recently -- relatively recent publication, they did get back to some of those recipients and test them for antibody. The problem is the population all got infected by mosquitoes, so --

DR. BASAVARAJU: I guess the concern is if you don't know that that's definitely not the case, do you want to be giving that blood to a pregnant woman?

DR. BUSCH: Yeah. I guess my response would be that in settings where we're screening with ID NAT, for every unit we're picking up, especially as the epidemic moves through that population, we're missing another four or five that had you done 10 replicate ID NATs, you would have picked up on plasma,

and we're probably missing 10 that if you'd tested red cells, you would have detected it.

So if you're worried about transfusing Zika virus, low-level Zika virus RNA-positive blood, you know, the answer is we should be screening whole blood. And I don't think there's any evidence of infectivity of that, so I don't think that's warranted. But, you know, we're -- moving from ID NAT to mini-pool NAT is an incremental move from what could be done, which would be, okay, let's run 10 replicates on every donor and pick up another month worth of viremia.

So there's a lot of tail end. We're just seeing a taste of it. If you look at the data that you saw, for example, from Jeff, two-thirds of the reactives that were real were not repeatable on their own test when run in replicates. So if you -- you barely picked them up, you were lucky to get them.

So you need to understand that there's a persistent tail of these viruses in blood that is being detected, and it's great what's been accomplished, and congratulations to the companies, fabulous, we've done a good thing, but we're not -- you know, mini-pool would pick up the vast majority of infectious units, and then we can trigger, like we do West Nile, to get the outbreak low-level viremics.

DR. STOWELL: I think we have a few other people who would like to speak at this session.

Dr. Kleinman.

DR. KLEINMAN: Yes. Thanks, Chris.

So I'm going to present a joint statement from AABB, America's Blood Centers, and American Red Cross. And I am going to propose, we're going to propose a -- I know you have a complicated roadmap with multiple questions and several options, but we have another option to put out there, another variation on the theme.

So, anyway, AABB, America's Blood Centers, and American Red Cross appreciate the opportunity to present this statement on the blood community's experience with Zika virus testing. AABB's Transfusion Transmitted Diseases Committee and its arbovirus subgroup prepared this statement with assistance from America's Blood Centers and ARC representatives to the TTD Committee.

While we recognize that the August 26, 2016 guidance document also allows the use of FDA-licensed pathogen inactivation for plasma and platelets, or licensed pathogen inactivation for red cells or whole blood, when available, our statement today will only focus on the testing part of the guidance.

The AABB TTD presented a statement about a year ago, at the November 18th BPAC meeting, recognizing the nature and extent of the worldwide Zika-related health emergency focused in the Americas during 2015 through the first quarter of 2017.

At that time, we were supportive of efforts to reduce

transfusion transmission and to provide the safest blood possible, but we also raised some concerns. These involved the process used to develop and implement the guidance, and the balance of resource commitment versus potential benefits, and the precedent being set about further expectations for blood donation testing.

Nevertheless, the industry obviously complied with the guidance, and ID NAT was fully implemented by December 2016. As part of our prior statement at that time, we asked the FDA to have a formal public review of the policies recommended in the August 2016 guidance, with the specific objective of modifying the guidance, if appropriate, to achieve a balance of benefits and resource use. And today, we thank the Agency for convening this meeting for this purpose.

So starting in May 2016, in response to the growing Zika epidemic, the increasing reports of linkage to a congenital Zika syndrome of unknown scope, the neurological complications in adults, the four Zika-infected transfusion recipients in Brazil, and the threat of local transmission in the U.S., blood centers in the continental U.S. began implementing investigational NAT.

And then with the August 26th guidance, which required a phased approach to nationwide implementation, as we've heard today, of course, that was accomplished by November 18th. These efforts were supported by the two NAT manufacturers, as

we've heard today, Roche and Grifols, and we commend their efforts that provided high quality reagents, new testing platforms, software training, and support.

Without their effort, implementation could not have occurred, especially given the requirement to test each donation individually, while other viral agents are tested by NAT in small mini-pools.

Now, to review our experience, the addition of Zika virus ID NAT consumed all available resources and surplus capacity at most blood centers, at the expense of the implementation of other projects, and at a cost, using only cost recovery pricing, that was estimated in a recent article of about $137 million per year.

As previously noted, given the current situation, we doubt that the blood community can be expected or able to repeat a similar regulatory mandate in the near future. Simply stated, we now have limited personnel and laboratory capacity to urgently increase testing volume should the need arise.

So a little bit of review of the data that we heard today: If we combine the data collected under the two investigational NAT protocols in the continental U.S., doing that through November 4th of this year, indicates that about 13.6 million donations have been tested, with 469 initial reactives, of which 54 in the continental U.S. were confirmed positive using the FDA allowed IND definitions. So that gives us a confirmed

positive rate of about 1 in 250,000 donations.

We agree that the specificity of these tests is excellent. Again, just to repeat it, 99.997% for each of the tests. However, due to the low frequency in a non-epidemic area like the continental U.S., when we calculate the positive predictive value over both tests, it's only 11.5%.

As is characteristic of many mosquito-borne arboviral infections, the epidemic had been explosive, but it was followed by a decline over months, with a limited number of infections detected in the U.S. mainland and Puerto Rico over the past several months.

As we've heard today, testing in Puerto Rico yielded a total of 338 reactives, but only two -- I don't know if that's still correct, but two since the middle of February 2017. But in contrast to the data collected in the continental U.S., the positive predictive value of testing in Puerto Rico was extremely high, at 97.5%, due to a far higher background rate of transmission.

Closer examination of the continental U.S. data shows that only 10 of the confirmed positive donations, so that's about 18.5%, were antibody-negative, these being the window period units, and these were confirmed by the less sensitive alternative NAT. All others were antibody-positive, of which seven had sufficient viral loads to be reactive by the alternate NAT, and 37, or 69%, had very low viral loads. They

were not repeatable in the presence of antibody. So the vast majority of these donors who confirmed positive were attributable to travel-related remote infection.

And now we're going on to the infectivity. Just to repeat what Mike has said, all available data to date indicate that units from donors with remote infections are not infectious versus those units with higher viral titers prior to IgM seroconversion.

And just again to review, it's the antibody-negative units that have been linked to transmission of other known arboviral agents such as West Nile and dengue viruses.

Of note, the last confirmed positive donations in the continental U.S. were all related to travel, and they occurred during the weeks of August 30th, September 20th, October 4th, and October 16th. No blood donors were identified during this period due to local transmission events in the 50 U.S. states.

So the blood organizations' proposal for ongoing NAT in the continental U.S. is to follow a comparable model as used for West Nile virus, which is mini-pool NAT in small pools, so that's for all 50 states, in contrast to the FDA option, option 2, I think. So it's mini-pool NAT in small pools, with conversion to ID NAT following reports of -- only following reports of local vector-borne transmission, similar to Mike's last conclusion.

Thus far, such transmissions have been reported promptly

in South Florida and Texas, and these would serve to trigger ID NAT, which would continue until all evidence of local transmission has passed.

Now, what do we think the outcome of this would be? Well, from review of the Puerto Rico experience, there were 206 Zika IgM-negative donations in the window period, of which only 14 or 6.8% failed to be detected by mini-pool NAT. So if we extrapolate from that, the 206 window period donations in Puerto Rico are approximately 21 times more than the 10 window period units observed in the U.S. over the entire -- in the continental U.S. over the entire Zika epidemic.

And since each dataset represents about 1 year of testing, we can assume the same potential false negative rate for mini-pool NAT in a comparable outbreak in the U.S., if we were to have one. And so when we do the math, 10 donations per year times 6.8%, where we get about 0.7 donations per year, or 1 every 1.4 years; that is, if we put mini-pool NAT in place, we might miss one infectious donation every 1.4 years.

And then if we converted to ID NAT, of course, the sensitivity testing would be increased during the time in which it is needed and without wasting the resources of doing it all year round.

We believe this appears to be a viable compromise, especially as the Zika epidemic has declined. Resources, of course, would be available to trigger ID NAT as needed.

Now, I want to go on to another topic that hasn't been touched on today but I think is very important. Because of the low positive predictive value of the screening assay in the continental U.S., accurate tracking of test results in blood donors requires some kind of supplemental testing.

This issue is of vital importance because it affects donor counseling. It's quite different if you're a false positive versus a true positive. It affects consigning notification, the triggering of look-back procedures, and also impacts public health surveillance due to sharing of blood donor screening results with state public health departments.

Now, under the IND, we had these supplemental testing protocols, but with FDA licensure of a screening assay, the availability of confirmatory testing is an issue as it's no longer required for users of this assay, and we don't know if it's going to be available.

We have asked the manufacturer of the approved test, and essential laboratory use for such testing, during their IND, to make that supplemental testing available going forward, and we will report the progress of these discussions to FDA when they are complete.

Now, another important post-licensure issue is how to effectively monitor the number and rate of confirmed positive donations, since such information will no longer be collected by the test kit manufacturer. We do know that that

information's reported to ArboNET, so that might be a mechanism, but of course, we'd have to assure good reporting.

However, of note, a switch to mini-pool NAT dramatically lessens the impact of the lack of supplemental testing, since there are many fewer false positives detected. That's because when we get a positive mini-pool, we have to test it -- we retest the individual donations. And if they're all negative, we often conclude that's a false positive.

And we have all these issues facing us now, but they'll be amplified if and when the second manufacturer's screening test becomes licensed.

So to return to our main point, in conclusion, we strongly encourage the FDA to consider options other than ID NAT, as they're doing at this meeting, especially a mini-pool testing option that is consistent with ongoing testing for other viruses capable of causing significant disease in a transfusion recipient. And just to remind everybody, we do mini-pool testing for HIV, HPV, HCV, and West Nile virus.

Finally, we'd like the Agency to articulate its approach to its decision to modify the testing recommendations of this guidance if the epidemic has waned and does not appear to be recrudescing in the near future.

So I thank everybody for the opportunity to offer these comments.

DR. STOWELL: Thank you, Dr. Kleinman. Would anybody else

like to speak to this issue, from the audience?

(No response.)

DR. STOWELL: Okay. Hearing none, maybe we could go back to Anne Eder's slide number 28, I believe it is. In my set here it's numbered as 28.

(Off microphone comments.)

DR. STOWELL: Okay. Yeah that's -- basically I'm looking for the roadmap.

DR. LEWIS: Would it be possible for me to ask a question of Dr. Busch?

DR. STOWELL: Yes.

DR. LEWIS: So, Dr. Busch, it seemed to me that you were presenting data suggesting that there are two different periods of time in the life of an infection in which there are viral loads that are low enough where they might be systematically missed by mini-pool but picked up by individual NAT. One is the early part of the early doubling after the -- starting a few days after infection and then of course the long tail.

And you repeatedly said, if I understood correctly, that it is your opinion that in the long tail when the viral load is low, that it's unlikely to be infectious, or less likely to be infectious. But I thought I heard you say that in the early part with the same viral load, you are worried that the patient was more -- or the person was more infectious.

So are you suggesting that it is not just the viral load

that determines infectivity, but for the same viral load, you're more infectious early on than you are in the tail? Does that -- does the question make sense?

DR. BUSCH: That makes good sense. Yes. And that's correct, and it's true for, you know, all the viruses we deal with, retroviruses, etc. There's two factors here. One is when you initially get infected, you essentially -- there's a bottleneck of transmission where, you know, if -- people get bit all the time, and yet they may not get infected. But once that virus takes off, it's very fit. And as you see, it's replicating at extraordinarily rapid levels, and systemically in the blood plasma, levels rise very rapidly.

So that virus is extremely fit. It has not gone through mutations and other factors that make the virus less infectious inherently. In addition, you develop very high titers of neutralizing antibodies. And particularly in settings like, you know, Puerto Rico, where the population has prior dengue, I didn't get into it but actually the antibody anamnestic responses are extraordinarily brisk because you have all this dengue memory that takes off.

And, in fact, the length of the window period is actually shorter in people who've had -- the viremic period is shorter in people who've had prior dengue because their immune system is all primed to take off within days. And that neutralizing antibody suppresses replication and suppresses the infectivity

of the virus. It's called neutralizing antibody because if you mix it with virus, it suppresses, blocks infectivity.

So it's two factors that result in those tail-end infections being much less at risk, given comparable viral loads. One is possible viral fitness issues or defective virus or just RNA persisting, and the other is very high titers of neutralizing -- endogenous neutralizing antibodies.

DR. STAPLETON: That raised a question for me, for you, Mike. Are there any data that the adaptation to humans alters the infectivity in mosquitoes?

DR. BUSCH: I don't know about mosquitoes.

DR. STAPLETON: Or humans either, for that matter.

DR. BUSCH: I mean, we're doing deep sequencing of red cells, viruses, full genomes, etc., and not detecting -- and other have done this too, and not detecting mutations that are being selected for, causing, you know, potential infective virus.

DR. STOWELL: Okay. So this is our, sort of our roadmap. Somebody said, raised their hand while I was speak -- oh, I'm sorry.

Dr. Epstein.

DR. EPSTEIN: Yes. I just wanted to follow up on the discussion that was just taking place, because I think it all comes down to Mike's slide number 21, if that could be projected again, which is the estimate of increased risk

related to the mini-pool testing. And it's the same issue. It's assuming that antibody-negative units that are viremic are infectious, how many would you miss?

And, you know, that's the same estimate in effect that Dr. Kleinman was showing; his 6.8 is the same as this range of 7.4 to 11.9. It's the same issue. You have a rapid ramp-up. You have delayed detection with mini-pool; you're going to miss some of the earliest ones. We don't know for sure that they're infectious, but they may be. Certainly the ones at higher titer are more likely to be infectious, but these are viremic units in the absence of antibody.

Okay. So the question that we're really facing here is if we move to a mini-pool strategy and an outbreak occurs endemically -- we're less worried about the travelers. People don't tend to donate within 1 to 2 days of returning from travel. So you have that delay. You're more likely to be either at the point where you have a high viremia and mini-pool won't miss it, or if it's even longer delay, you're antibody-positive, lower titer, and we think infectivity is less, but either way the mini-pool will detect it, okay, until the very, very end of the tail.

All right. So what we're worried about are these early cases in the seronegative infected individual and the fact that there's a small proportion that would be missed. When does that matter? That matters if you have an acute autochthonous

transmission outbreak within the U.S. or its territories, because there'll be a delay in noticing it.

You'll notice it when you start to see some of the high viremics that are picked up by mini-pool, and then you'll have a delay until you start ID NAT triggering. So it's the tradeoff, in effect, between that added risk, from the mini-pool strategy with triggering, and the logistic advantages of conserving resources, maintaining infrastructures, and you know, reducing burdens. That's what we're talking about here.

Now, those issues are all real, but I'm just trying to focus on what they are. It's missing the earliest cases while you wait to trigger. That's what we're talking about.

DR. STOWELL: Dr. Stramer.

DR. STRAMER: I agree with Dr. Epstein, and it's the exact same risk that we deal with in all 50 U.S. states every single year with West Nile when we convert from mini-pool to ID NAT. So it's something that we understand, and we accept as a small residual risk for West Nile, but it's something we do when we do have West Nile transmissions that are frequently fatal. They're rare. So we would expect the same logic would apply to Zika.

DR. STAPLETON: Perhaps, but there are some differences. I mean, there's certainly geographic differences in West Nile and Zika for our local infections.

DR. STRAMER: Right, which makes West Nile risks even

higher.

DR. STAPLETON: Exactly. And then there's a lack of the pregnant woman, the neurologic -- well, not neurologic, but the pregnant women.

DR. STRAMER: Right, but I mean, West Nile is caused -- I mean, it's invariably fatal if it goes into an immunocompromised host, so --

DR. STOWELL: Did you want to comment, Dr. Busch?

DR. BUSCH: Yeah. To Jay's point, I agree completely. Turning this around, though, 90% of the acute pre-seroconversion viremic donations will be detected. And we are very experienced now. We've moved to an individual mini-pool reactive, one turns us on to ID NAT.

In this case, in Puerto Rico, that would be the same. Within a day of picking up a mini-pool positive, we would have ID NAT in place. We'd convert. I think, in the U.S., because of the majority will be travel acquireds, there'll need to be some further investigation into confirming that this is autochthonous, so it may be a few days. But again, the mini-pool testing is picking up 90% of those highest risk units. And so we do have a very active, you know, capacity to detect the autochthonous outbreaks and convert.

DR. STOWELL: Dr. Kleinman, did you have a comment?

DR. KLEINMAN: Yeah. I just want to -- if we're doing a risk assessment, I just wanted to add one additional item. Not

only do you have to -- what's the outcome we're trying to prevent? If we're trying to prevent the most severe outcome, which is, you know, an infection transmitted to a woman who's pregnant or may get pregnant, then we need to also look at how much of our blood actually goes to that population of transfusion recipients. And we all know that number is very, very small.

I don't have an accurate estimate, but I'm sure that it's -- I've seen estimates that would suggest it's less than 5% of RBCs clearly to pregnant women. I mean, they get blood postpartum, obviously, if they hemorrhage, but for women actively -- there will be some subgroups of people who need to be transfused, sickle cell patients who are pregnant, but I think on a -- and some blood would go into young women who aren't pregnant but are in an age group where they could get pregnant in a month or two.

But still, I think that if you want to look at likelihood of an adverse effect, event happening, you'd have to have a infectious unit go to a susceptible person for the outcome.

Now, if our outcome is preventing Guillain-Barré, well, that could happen in anybody. So I think the Committee also has to assess if there -- if they can tolerate a level of risk, then what outcome are they trying to prevent, and what's the risk for each given outcome?

DR. ALLEN: Just a question, perhaps for FDA

representatives. Option 3 includes implementing, I assume, enhanced donor screening questions. We haven't heard any data on that today. Has anybody studied what the sensitivity and specificity of these questions, the screening questions?

DR. EDER: I can provide just a little information. First, the combined approach doesn't use questions. So option 3 is just -- there was some data out of French Polynesia that the questions missed most RNA-reactive donations, so they're not terribly effective, or they weren't in French Polynesia.

DR. STOWELL: Okay. Dr. Stramer.

DR. STRAMER: I mean, we generally use questions when there's nothing else to use, when we have to default to questions, like malaria. And we know the malaria questions are notoriously nonspecific, horribly nonspecific, and we have cases of TTM. So, I mean, neither sensitive nor specific. I mean, there are lots of agents we can give examples of that for.

DR. ALLEN: Can I just make one other comment? Obviously things have changed a lot over the last couple of decades. There's a lot more donor screening using computer-based questioning and so on. But we also know that donors get fatigued by the numbers of questions, and we'd really like a very simple, clean process, if possible. I just raise the question because it's in the discussion.

DR. STOWELL: The geographic capture questions that we use

are, as Dr. Stramer said, are notoriously a morass, and also, they're probably amongst the most frequent post-donation information that we receive that has been inaccurate and we have to correct, because they forgot that they went to Thailand in the last year and so on and so forth.

Okay. So if we could go back now to the roadmap from the -- yes. There we go. Okay. So what I would like to do is to go through Question 1 and 2 and then quickly -- I think we can probably go through them quickly. In terms of Question 3 and Question 5, I think the two differences here are Question 3 is basically a testing strategy, which doesn't rely upon other kinds of donor screening questions and so forth. Question 5 would really be a strategy which uses a combination of a screening by donor history as well as some testing system. And then finally, Item 6.

So let's start then with Question 1, and I'll start with the question. Is there anybody who thinks that we should eliminate all of the current safeguards or any of the ones that have been proposed with respect to testing, donor history, and so on? And if you think that we can dispense with them, please let us know why.

(No response.)

DR. STOWELL: Is it the sense of the Committee that we would not recommend this strategy, to eliminate all safeguards?

(No response.)

DR. STOWELL: Okay. So let's put this one to, put this one to a vote, if you could activate our voting machines here.

So the question is, at this time, do the available scientific data on the course of the Zika virus epidemic justify the elimination of all blood safeguards for Zika virus pending another significant outbreak in the United States or its territories?

(Committee vote.)

DR. STRAMER: Chris, when do you want Industry's response?

DR. STOWELL: Oh, comment. Right now.

DR. STRAMER: Okay. No.

LCDR EMERY: Does the Consumer Representative have anything that they want to say?

DR. BAKER: Not at this time.

LCDR EMERY: Dr. Kathleen Sullivan, are you on the phone at this time?

(No response.)

LCDR EMERY: She has not answered, so we will not have her in the voting pool at this time.

(Pause.)

LCDR EMERY: The Committee has voted in majority. I will read the individual votes for the record.

Dr. Stowell, no.

Dr. Baker, no.

Dr. Escobar, no.

Dr. Leitman, no.

Dr. Lewis, no.

Dr. Rees, no.

Dr. Stapleton, no.

Dr. Allen, no.

Dr. Basavaraju, no.

Dr. Kindzelski, no.

There are 10 noes, there are 0 yeses, and 0 abstentions.

DR. STOWELL: If we could go to Question 2 then, please. Okay. So Question 2 is do the available scientific data on the course of the Zika epidemic identify a risk to the blood supply that justifies continuing universal ID NAT testing? So are there members of the Committee who would advise us to continue with ID NAT testing for Zika, and if so, please explain what your rationale would be.

DR. STAPLETON: I had a question about whether or not the option of mini-pool testing will be an option.

DR. STOWELL: Yes, because that will be in one of the, like choice -- I think Question 3.

DR. STAPLETON: But that's a regional question, the way it's worded.

DR. STOWELL: Well, I think we're going to maybe have to discuss a little bit about how that might all fit together. So this is, this literally is exactly as it says, ID NAT testing on every single donor everywhere. Okay.

Susan?

DR. STRAMER: Wouldn't the response be the last option that FDA provided, Option 7, where we design our own? To answer your question, since another -- if we don't believe any of the options are, exactly as written, are what you want to vote on, vote in favor for.

DR. EPSTEIN: I think when we come to the question of mini-pool, we could have a part A and a part B. One is selectively in states and the other is in all states.

DR. STOWELL: All right. So the question up for vote is Question 2, do we continue doing universal ID NAT testing?

(Committee vote.)

DR. STRAMER: Chris.

LCDR EMERY: Dr. Sullivan, are you on the phone at this time?

(No response.)

LCDR EMERY: I have not heard from Dr. Sullivan. She won't be in this voting group either.

DR. STRAMER: Do you want to hear from Industry before you show the votes?

DR. STOWELL: Don't anybody look.

DR. STRAMER: Okay. No.

LCDR EMERY: The Committee has voted in majority. I will read the individual votes into the record.

Dr. Stowell, no.

Dr. Baker, no.

Dr. Escobar, no.

Dr. Leitman, no.

Dr. Lewis, no.

Mr. Rees, no.

Dr. Stapleton, no.

Dr. Allen, no.

Dr. Basavaraju, no.

Dr. Kindzelski, no.

There are 10 votes of no, there are 0 abstentions, and 0 yeses.

DR. STOWELL: Okay. If we could go on to Question 3, please. So Question 3 is asking us whether we think the data will support the regional use of infectious disease NAT in some regions of the United States with the use of mini-pool NAT in others, and then with a trigger for moving from mini-pool NAT to ID NAT, analogous to the situation we currently have with West Nile.

I sort of wonder if this is the one that we may want to introduce variation in and where that region could be defined as the whole United States. And so one possibility would be doing mini-pool NAT in the whole United States, with conversion to ID NAT based upon detection of viremic donors within some sort of a formula like we use for West Nile currently.

DR. STAPLETON: I'm curious if, perhaps from industry, get

some feedback. If you look at where the cases have occurred in the U.S., they're almost all travel anyway. And if you look at outside the southern Zika belt, if you will, whether this might not be a reasonable thing to consider. And why, from an industry standpoint, would this -- would it operationally be something that would be difficult to do, or would it, from a -- expense-wise, you would save some donors, for sure.

DR. STOWELL: So my perspective would be that the issue really is travel, not endogenous local epidemics of Zika infestation. And I think part of the states that show up there are the states that have the most people and have the most travelers going in and out of them. And those are also the individuals that are least likely to produce infection in transfusion recipients. And we have very localized and very low levels of endogenous infection.

DR. STRAMER: It's certainly less burdensome to do partial ID NAT with some mini-pool NAT, versus all ID NAT. So the question really is one of need or value. I mean, if we're not seeing any local Zika transmissions in these, whatever they are, 13 states, then why would we do ID NAT and not do ID NAT when the need is there? For example, when we had the outbreak in South Florida, we would have triggered Florida for -- South Florida for ID NAT, or the same thing for Texas.

And the travel-related cases can occur anywhere. I mean, clearly, they occurred more frequently, as Dr. Stowell said, in

California because that's where most people are. I mean, that's the state with the highest population, or New York, and those are where people travel.

DR. STAPLETON: Yeah. I apologize. I was thinking more of Question 4, so I may have jumped ahead a little bit. Sorry about that.

DR. STOWELL: So, Dr. Epstein, you were going to comment.

DR. EPSTEIN: Yes. Questions 2 through 6 were designed to follow declining levels of stringency, as it were. So I think it's in the FDA's interest to have Question 3 addressed as written, but then to also offer a modified question, do the available scientific data on the risk of transfusion-transmission Zika virus support the use of mini-pool NAT in all states? That way, people who feel we should retain ID NAT on this risk-tiered model can vote in favor, or of course, against, while still having the option to consider only use of mini-pool NAT throughout the United States.

So I would rather -- rather than edit the question, I would rather we have it first answered, and then pose an additional question.

DR. LEITMAN: Chris, so there are many states -- a majority of states in the United States have never seen a locally transmitted infection. The likelihood that they would be sentinel areas for recrudescence of local infection has to be very, very close to zero. I'm not going to say I believe in

this, but logically, I could see making a case for no testing in those states and mini-pool testing in the states in which local recurring -- local transmission has occurred.

The reason I don't -- why logically I can follow that but operationally that may not be great, it's very hard for blood centers to completely turn off and then turn on, as opposed to have low-level mini-pools going on. That's operational. That's sort of a business operational model as opposed to a sort of transmission model or a public health model or transfusion safety model.

I just wanted to get that into the record. Though if that was one of the options, I'm not sure I would vote for it, but maybe other Committee members could comment on that.

DR. STOWELL: Yeah. That is a possible option. I mean, my thought about that is most of the cases we see in this country are travelers. They probably are not infectious. On the other hand, you know, we're trying to intervene and prevent infection in susceptible patients. And it may pan out over time that we decide that this is not a useful strategy. I think at this point, I think it'd be premature to stop screening altogether. That's my opinion.

DR. BASAVARAJU: I just want to also ask, just to maybe spark some discussion amongst the Committee, so you know, in the early days of the Zika epidemic, there was, I think, some uncertainty as to how much of the epidemic would be fueled by

secondary sexual transmission. There was also some uncertainty as to the burden of Guillain-Barré amongst people who were infected, so how many people would get it, how severe would it be, and whether there was any other neurologic manifestations of Zika that were yet unrecognized, as well as there's obviously a concern for Zika in pregnant females.

So I think, at least to this point in time, it doesn't look like secondary sexual transmission is going to be a significant threat. The prospect of Guillain-Barré in a transfusion recipient who gets Zika sounds remote. And the risk seems now to be in pregnant females.

So if mini-pool NAT doesn't definitively identify -- you know, if somebody is, for example, mini-pool NAT-negative, IgM-positive, we don't know if that person is still infectious or not. Do you -- I just don't understand why this is -- you know, why are we considering this if you -- if the susceptible population is pregnant females, and you don't know that this technology could sufficiently, you know, remove that risk, I don't know if many -- you know, so this paper actually, in full disclosure, I think this map comes out of a paper that, you know, we actually wrote at CDC, so you know, it's sort of flattering to see it up on the -- but the caveat to that really was that, when we wrote that, was that the sensitivity of mini-pool NAT was acceptable enough to where it would, you know, identify risk.

But based on the data that I've seen, I just -- I don't know if I'm convinced of that. So if your population that you're worried about is pregnant females, I don't know if mini-pool NAT really is going to -- if you screen somebody who might have Zika, they're mini-pool NAT, is that really going to prevent microcephaly? And I don't know if we know the answer to that.

DR. STAPLETON: I think we know, from Mike Busch's data, that you're going to miss 10% of the most likely to be infectious units, right.

DR. STRAMER: Well, depending on how you do the calculation, 6.8% to 10%, depending on what dataset you use. And it's all a question of risk. If we look at the worldwide experience with Zika, we've had four transfusion transmission. We've had no transmissions to those -- none in the dataset that I show, and actually of women in childbearing age, I mean, in the four transfusion transmissions. And there's been no report of transfusion transmission to a pregnant woman who developed illness in the background of over 800,000 cases reported in the Americas.

So it's -- and, you know, again, these are the risks we live with, with other agents by using pools, HIV or West Nile. And, you know, we're not having the same discussion. Why is it acceptable to transfuse a mini-pool-negative, ID NAT-positive HIV unit? Why aren't we having those discussions?

DR. BASAVARAJU: You know, there's also other diseases that we know occur through transfusion. There's like anaplasmas, you know, hepatitis E, Saint Louis encephalitis, and we don't screen for them even though a non-pregnant person who gets it could actually get really sick. But here, you know, I just -- the logic of mini-pool NAT, when you're worried about pregnant females, you know, it doesn't -- I'm not necessarily seeing it here.

DR. STOWELL: But the real risk to pregnant females is not being transfused and getting Zika that way. It's going to be because there's local transmission or because of a sexual partner who has traveled or because they travel to an endemic area. I mean, you could argue, if that's the only goal, spending the money to do mini-pool testing and/or ID NAT testing, we should buy mosquito nets and air conditioners for women who are pregnant in the locales which have a climate to support the virus and the --

DR. BASAVARAJU: Or just maintain a Zika-negative pool of blood for those patients all year round.

DR. STOWELL: Well, that's an option we can consider, or that's one of the questions we have to consider.

So let's -- could we please go to -- yeah, okay. Here we are. So this is the option that the FDA would like us to vote on. Is there -- so basic, continuing of ID NAT in some areas of the United States, and do mini-pool testing in others, and

the details to be worked out.

DR. LEWIS: So, question about what we're voting on. Is the vote -- if one were to vote in support of this option, would one be voting for the specific choices regarding the states?

DR. STOWELL: No. I've -- yeah. So I think this, the way this question is posed here, it's too difficult to answer because there's too much detail in it. So I think we will have to break this down somehow to make it manageable. And I think -- so looking at it, I think there are a couple ways to break this down. And one of this -- one of these, a part would be do we go to some combination of mini-pool and ID NAT testing? That would be the first part.

And the second part is what would be -- what would the regional guidelines be for doing this? And the third part would be what would be used as a trigger for moving from mini-pool to ID?

Yes?

DR. NAKHASI: Hira Nakhasi, FDA.

I think what FDA would like to, as Dr. Epstein mentioned, based -- if we go back to that slide, please, the option, what was -- 3? Can I go back to the slide? Because I think that's important thing you have to remember. It's not just transmission. Did -- there are mosquitoes there, so that is the -- if somebody comes, has an infection, mosquito bites, so

the reason we put those things is because of the problems of *aegypti* there, and also the traveler what's live in New York and also.

So I think what we would like people to vote here, Committee to vote, if they like -- should they recommend ID NAT in those states or not? If that's the -- and then we can go in the questions -- in the 7, which is Question Number 7, where you can modify whether you want mini-pool NAT everywhere and then also the trigger. I think that would be the better way of -- in my opinion, at least.

DR. BASAVARAJU: So you're saying that -- well, the vote here is do you advocate for ID NAT in those affected or potentially affected states, right?

DR. NAKHASI: Exactly. Yes.

DR. BASAVARAJU: Not the question of mini-pool NAT, right?

DR. NAKHASI: Mini-pool in the rest of the country.

DR. BASAVARAJU: What if you want it in these areas but you don't want mini-pool elsewhere? Because that would not be -- if you vote yes for this, could it be construed as that?

DR. NAKHASI: No, no. They are linked together. So you have to vote ID NAT in those regions, whether or not, and mini-pool NAT in the rest of the country. And then we could, you know, if the -- whatever, you know, your vote is, we could then say, okay, if you agree that it has to be mini-pool NAT everywhere, and then trigger based on the infection, and then

go to the trigger.

DR. LEITMAN: Could I just comment? This would be changing a 10-year blood bank transfusion medicine standard of mini-pool testing for a virus for which there's no serologic test, and that's West Nile virus. This is changing that standard for a virus whose prevalence, right now, is much lower, seasonally, than West Nile virus and whose consequences, I think, are less likely to be seen because the population at risk is so much smaller than the immunosuppressed population. This would be a very big change for our standards to vote for ID NAT for this specific virus and it -- from what we know and have heard this morning.

DR. ALLEN: And I think that's a very good point. My point was going to be, I could argue with the geographic shading here. New York and I think, what, New Jersey and Pennsylvania, if I'm looking at it correctly, were included primarily because they get a lot of travelers from Puerto Rico and just in general. The same would hold true for the Northern California area around San Francisco, but if you go north of there, it's a very different population.

So I -- and Northern Arizona and New Mexico, Texas Panhandle, I mean, one could argue that the gray shaded areas are not necessarily the most precise, but we're doing that on statewide basis, but that's not the way the blood is collected. So I would just say I would like to see a little more

flexibility in the question in terms of the shaded areas, if we're voting on this.

DR. STOWELL: I mean, I think that that is a problem for us. If we say yes to this, which ones are we saying yes to? And this is why I was suggesting maybe we should vote first on the general strategy of mini-pool testing that would reflex to ID NAT under certain conditions, and then the second piece would be, where would we do this, and the third piece would be what would be the triggers to move from mini-pool to ID.

DR. EPSTEIN: Yeah. If we come back to the question itself, the question doesn't specify the states. The question says at-risk states and territories. So what I would suggest is that if the Committee members wish to advocate a combined strategy of ID NAT and MP NAT, they can vote the question as stated, and then we can have a discussion of how should we define an at-risk state.

FDA has put forward a concept that an at-risk state is a state where we have *Aedes aegypti* mosquitoes, or we have a history of a high incidence of Zika in travelers. Now, we can have a discussion of how we might otherwise classify a high-risk state, but this is to ask about a mixed strategy of ID versus mini-pool. The question itself does not define the states.

DR. STOWELL: Okay. So then literally we'll be -- we're voting on the concept of whether or not the data support a

strategy which is based upon geography in the United States and the use of mini-pool testing?

DR. EPSTEIN: Correct. And it begs the question of how would we define at-risk. And then we would appreciate a discussion.

DR. STOWELL: Okay. Is that clear to people, what they are asking us about? No. Okay. And so I think, as I understand it, we're being asked, do we think the data support a strategy which uses geography to determine whether or not we do mini-pool testing or ID NAT testing.

DR. STRAMER: So then a yes vote means they'll be automatic ID NAT just based on history? Or the presence of mosquitoes that may or may be infected?

DR. STOWELL: Correct, within some --

DR. STRAMER: It may not be the states on the picture, but it'll be some ID NAT with no -- with the rationale being *Aedes aegypti* is present or there's a large number of travelers but not necessarily ongoing transmission?

DR. STOWELL: Correct. I think I understand that.

DR. EPSTEIN: If I could clarify. What I'm suggesting here is that vote the question as written. Those who think a mixed strategy based on geography makes sense could say yes; those who object say no. But then the Committee can comment; if yes, what criteria should be used to determine at-risk state. And you may disagree with how FDA framed it.

DR. LEWIS: And then just to clarify your clarification --

(Laughter.)

DR. LEWIS: The Committee could recommend the definition of at-risk being based on surveillance or geography or insect load?

DR. EPSTEIN: Yes.

DR. LEWIS: So all of those are still on the table?

DR. EPSTEIN: Yes.

DR. LEWIS: Okay.

DR. EPSTEIN: Although I would comment that with West Nile, which is of course a different situation because you have a zoonotic cycle, you know, birds and mammals, those measures have not been predictive despite extensive epidemiologic surveillance, mosquito pools, chicken flocks, infected horses. And yet those measures have not predicted human outbreaks in either direction.

So I'd be very, very cautious, you know, putting stock in that alternative. The most reliable predictor has actually been monitoring donors. But be that as it may, you know, other options would potentially be available. Yes.

DR. LEWIS: But just for the clarification, my interpretation of what we're being asked is simply whether a mixed strategy is admissible, with the question of how at-risk would be defined being completely separable.

DR. EPSTEIN: Yes. That's precisely what I'm offering the

Committee.

DR. STRAMER: Okay.

DR. STOWELL: This would not be an obligate geographic determination of risk. That would be an option, but it's not, we're not limited to that definition of risk. Correct? Okay.

Is everybody clear? Yes.

DR. BASAVARAJU: So -- sorry. Last question: So the option of regional use of ID NAT with no mini-pool NAT elsewhere is not something that FDA wants and put on; is that right?

DR. EPSTEIN: Again, I don't object to having that question before the Committee also. If there's a sense you'd like to vote that option, I know Dr. Leitman had raised the possibility of that concept. And, you know, we're open to that suggestion. We can either do that as a part 3c, or we could do it as under Option 7, additional options.

Again, if the Committee wishes to consider that, I think that's fine.

DR. STOWELL: So that could be another option, but that's not the question that's here.

MR. REES: But Chris, Dr. Stowell, I think then what Basavaraju's saying is that if we don't want to then commit to yes or no to this particular question if we know that that would be an option at 7 that would be -- that's where I would be conflicted. If you -- your answer to this question might be

driven by if that will be a possible option that we can vote on in 7.

DR. STOWELL: Okay. Would FDA like to frame a question for us in that fashion?

DR. EPSTEIN: Yes. I've already suggested that we have a part 3b, which is do the available scientific data on the risk of transfusion-transmitted Zika virus support the use of mini-pool NAT in all states. And we can have a part (c). I don't know which it's going to be, whether it's ID versus no testing, or it's mini-pool versus no testing.

We'd have to discuss, you know, what you think is a credible alternative. But perhaps the simple version of it would be do the available scientific data on the risk of transfusion-transmitted Zika virus support discontinuation of all testing in some low-risk states?

DR. STOWELL: So this would be question (c)?

DR. EPSTEIN: It'd be part 3c, yes.

DR. STOWELL: Or 3c. Okay. So --

DR. EPSTEIN: And again, it gets more complicated because if you discontinue testing, do you then retain donor questions for risk?

DR. STOWELL: Can we go back to the beginning of Question 3? There we go. Okay. And then go to 3b. Well, logically, don't we need to answer this one first before we go to 3a?

DR. EPSTEIN: Well, again, 3a is more stringent, and we're

trying to look at --

DR. STOWELL: Okay.

DR. EPSTEIN: -- decreasing stringency, short of no --

DR. STOWELL: So let's go back to the original question.

DR. KINDZELSKI: Sorry. Question?

DR. STOWELL: Yes.

DR. KINDZELSKI: Is the question, latest one, 3c, right, all states, does it also mean that the triggers will be discussed, to go to ID NAT?

DR. EPSTEIN: Well, I think it becomes necessary to discuss triggers.

DR. STOWELL: That was actually --

DR. EPSTEIN: How would we know?

DR. STOWELL: Yeah. Because that's under, actually, Question 4 addresses the triggers for moving between mini-pool and ID NAT.

DR. EPSTEIN: Yeah.

DR. STOWELL: So that would be a separate question.

DR. EPSTEIN: Yeah. We take the word "local" out, just in some states. If you would, in 3c, just take the word "local" out.

DR. STOWELL: Yeah. Okay. So let's vote on 3c to start.

Dr. Busch, do you have a comment?

DR. BUSCH: The 3, as written, references both states and territories, whereas 3b that was just framed out just refers to

states. Puerto Rico is a, you know, had a massive epidemic. There is virtually no activity now. The French Caribbean islands, they tested during the outbreak, then they stopped.

I'm in favor of mini-pool NAT in Puerto Rico as well as the rest of the U.S. But I just want to emphasize that if you look at that question, it includes the territories. So I do think the Committee should be alert to that distinction between 3 and 3b.

DR. STAPLETON: I would think we should include territories in 3b.

DR. STOWELL: In 3c, in this question here?

DR. STAPLETON: No, 3b.

DR. STOWELL: 3b? Okay.

Dr. Epstein?

DR. EPSTEIN: I'm happy to add states or territories.

DR. STOWELL: Okay.

DR. EPSTEIN: I think the underlying concept is the same.

DR. STOWELL: Okay. So for both 3b and 3c, states and territories?

DR. EPSTEIN: Yes.

DR. STOWELL: Okay. So let's come back to 3c then. And some states and territories, if we could add that. Okay. So this, then, is the question. Is there further discussion of this question, or do people feel prepared to vote?

Oh, I'm sorry. Dr. Baker.

DR. BAKER: Hi. Question: So the U.S. does actually have six U.S.-affiliated Pacific jurisdictions. And we have differing relations with the territories versus those that are not territories. So does this then preclude or limit our involvement to those that are strictly territories, particularly given that FSM, the Federated States of Micronesia, is not a territory, my understanding, but we have some engagement with them on public health matters.

DR. EPSTEIN: Our authorities would only be where we have jurisdiction. I think we can take the comment into account and consider what we would do. But, you know, this is about setting policies that we can then enforce.

DR. ALLEN: Could we go back to Question 3b again for just a second? Okay. If a Committee member votes yes on this one, do they abstain on Question 3c? Or in other words, if you say it's in all states and territories, the use of MP NAT in all states and territories, then when you look at 3c, it says some states and territories. So I'm just looking. Do we have a bit of a --

DR. EDER: So our assumption would be that if you vote mini-pool in all states, if you vote yes there, you'd be voting no for (c), to not test at all in some states, if you already said that it would be mini-pool in some states.

DR. STOWELL: So if you say yes to (b), then you would say no or abstain to (c).

DR. LEITMAN: I didn't interpret it that way. I thought (c) was sort of a subgroup of either (a) or (b). You could vote yes on (a) or yes on (b) but retain the option of (c) for some states and territories.

DR. ALLEN: Can we go back to 3b and just see if a little wording change could --

DR. STOWELL: I went into this question --

DR. ALLEN: We hear is, does it support to continue to use mini-pool NAT testing in all states. So it's mutually exclusive with the next one.

DR. STOWELL: But I would argue that if we modified this slightly to say is there support for the use of MP NAT testing as part of an overall strategy, that would enable us to say yes there and still yes on 3c, if that's the way we believe.

DR. ALLEN: But I don't think that's the sense of the two questions. I think one is saying that we are going to continue to test on at least a mini-pool basis everywhere. Question (c) says no, we're not going to do that. We have the option of ceasing mini-pool testing in some places.

DR. LEITMAN: (c) doesn't tell you what you're going to do in the states you don't discontinue. It just says you have the option of discontinuing. You may want to use ID NAT in some states, multi-pool NAT in some states and regions and territories, and nothing in others. So (c)'s not enough to give full guidance to the FDA, or full recommendation. I think

(c) needs multiple parts.

DR. STOWELL: Yeah.

DR. STRAMER: We really didn't have a discussion on a hybrid strategy of no testing versus some testing, be it an ID or mini-pool. So one has to consider some -- well, first of all, if there's no testing and a traveler does return to that area and does have a titer that's mini-pool NAT detectable, we will never know that, and we will never detect that unit. So that's an additional risk that we would be assuming.

And then from a practical standpoint, we have labeling. So some units will be labeled as Zika NAT negative and others will not. And that may be problematic for a transfusion service, you know, I want only Zika labeled or I want unlabeled. I mean, it just gets into a lot of logistical complications which don't relate necessarily to safety, just relates to the dual inventory, shipping, inter -- just confusion.

DR. LEWIS: Can we look at 3, the first -- 3a for a second? So if we leave open the question of how at-risk state or territory is defined, this option includes the possibility that today or next year, no states or territories could be defined as at-risk. And therefore, if one were to vote yes on this, this would include, as a subset of that option, an option where everything is MP NAT and then there is some trigger to be defined later to move to ID NAT.

And so I think the problem with this is the questions, they're really not mutually exclusive. And at some point, we're just going to have to have the pattern of the votes give a general impression to the FDA of our preferences, and that if they were hoping for unambiguous input, those hopes should be dashed.

(Laughter.)

DR. STOWELL: Yeah. You know, I almost think that we could actually jump over this Question 3 and 4 and go to 5 and 6, because Question 5 is basically asking us, would we recommend a strategy based upon donor history questions and testing triggered by that. That's that general approach, which I think most of us are thinking is not a very good way to go about it.

And we can also talk about the Zika-negative inventory business as well. So I think those will be easy to rule in or rule out. And this brings back, brings us back to Question 3, which -- and if we do that, then that means we're back saying, which I think is the sense of the Committee, that we'll use some strategy which combines mini-pool testing and ID NAT testing.

And the triggers for that we can discuss, whether it'll be based on the history of where the cases have occurred, and so it's going to be that map, or whether there's going to be based upon local monitoring or as we detect donors who are positive

or whatever that particular trigger happens to be.

DR. STAPLETON: The other issue is if, for 3b at least, is if there's no more Zika in 2018, this would need to be readdressed, I assume, unless there were built in an at-risk component to that.

DR. STOWELL: Yeah. I don't think if they end up recommending doing Zika testing and then the Zika virus totally disappears off the planet, that we'll continue --

DR. STAPLETON: Well, it won't disappear, but it has -- from other places, so --

DR. STOWELL: Yeah, yeah. So would the FDA be perturbed if we went, jumped ahead to Questions 5 and 6? So we can kind of winnow the list down?

DR. EPSTEIN: I think that's fine.

DR. STRAMER: Okay. So could we go to -- oh, here we go.

DR. ALLEN: Could I ask one other -- just make one other comment? And it might give increased flexibility if we were to say areas -- instead of states and territories, areas of the United States, including its territories, something a little more generic that would now allow appropriate definition by geography or other factors to be defined, as information becomes available on down the line.

DR. STOWELL: That would make sense. The other thing, also, I'd sort of point out is they aren't actually asking us to write the regulation here. They're asking, really, what

should the approach be? And then they're going to work out the details, and then we'll hear about what the details are. So I think, let's focus on what's the main approach.

Okay. So Question 5 is would we use basically donor history questions to trigger selective ID NAT performance? And this would be based upon travel to Zika endemic areas, sexual contact with a traveler or somebody who has Zika, as you see written there. So this would rely upon the donor history as the trigger for selective testing. Any comments about the desirability of that approach?

DR. LEITMAN: That sounds like a terrible idea.

(Laughter.)

DR. LEITMAN: I'm not sure why it's even there. This would be the most complex, difficult, and impossible to comply with for any transfusion service. You'd have to -- the screener in a screening booth has to note something that's conveyed to the phlebotomist, who then labels the donor card or the unit with testing of a certain type -- no, has to label the tube, the pilot tube, so has to understand that a pilot tube is drawn for something and not drawn for something else based on -- there's communications from one totally different physical area of the collection center to the phlebotomy area.

And then there's dual inventories. This a disaster. It's waiting for accidents and errors to happen.

DR. STOWELL: I would concur from experience with our own

donor program. Any other comments about this option?

(No response.)

DR. STOWELL: Okay. So let's put this to a vote, Question 5. Would selective ID NAT performed based upon the donor's responses to questions about travel to Zika endemic or epidemic countries, sexual contact with partners diagnosed with Zika, and/or sexual contact with partners having travel risk for Zika provide an adequate and appropriate safeguard against transfusion transmission of Zika virus?

DR. STRAMER: Do you want my opinion?

DR. STOWELL: Yes. What is your opinion?

DR. STRAMER: Okay. No.

(Laughter.)

LCDR EMERY: Dr. Kathleen Sullivan, are you on the phone at this time?

DR. SULLIVAN: I am, and I also vote no.

LCDR EMERY: That is noted.

(Committee vote.)

LCDR EMERY: The Committee has voted in majority. I will read the individual votes into the record.

Dr. Stowell, no.

Dr. Sullivan, no.

Dr. Baker, no.

Dr. Escobar, no.

Dr. Leitman, no.

Dr. Lewis, no.

Mr. Rees, no.

Dr. Stapleton, no.

Dr. Allen, no.

Dr. Basavaraju, no.

Dr. Kindzelski, no.

There are 11 noes, there are 0 abstentions, and 0 yeses. Thank you.

DR. STOWELL: Okay. If we could go on to Question 6, then, please. All right. So this is the selective inventory option, that we would maintain an inventory of ID NAT-negative blood components for pregnant women, fetuses, and neonates, and maybe others to be defined. Do people have comments about this as an option?

DR. ALLEN: Can somebody from the blood industry answer, is this currently being done for any other reason? I know it was done at one point for a while with parvovirus at least, and I don't know where that stands currently.

DR. LEITMAN: CMV.

DR. STRAMER: CMV, yeah.

DR. LEITMAN: But you get around CMV by losing -- leukoreduction filters.

DR. STRAMER: Leukoreduction. I know, but for neonates and some populations, people still want CMV-negative plus leukoreduced. And it's not that it's a nightmare. We

over-screen to ensure we have enough. But in hospitals, you know, they prefer, you know, not to carry dual inventories.

DR. EDER: So speaking from a transfusion service, it is very error-prone. The closest similarity is CMV. Some hospitals, a very few, still rely on selecting CMV seronegative. Most hospitals are also reducing the risk of CMV because it's between 70% and 90% leukoreduction, which takes care of CMV.

So it's a minority practice that some try to select CMV seronegative. But the history, the experience, you're going to make mistakes. You can't identify all patients who need the special component.

DR. LEITMAN: This option also means that every region, state, territory, in which there's no Zika incidence, either through travel or through local acquisition, would still be required to hold a double inventory. So it makes -- it establishes a practice in areas that don't need it.

DR. STOWELL: Other comments?

DR. ESCOBAR: Yeah. I mean, I think that as long as there still exists an unknown risk to a female that can transmit this to the baby, I think it's a problem. I mean, it could be minimal, but still, if it happens, it's a disaster if you have a congenital malformation.

You know, I know it's kind of unknown, maybe it's still low, but it's still possible that that could happen. So

that's, you know, the problem that I have.

DR. STOWELL: So the problem is, if we did -- if we went to this strategy, is that mistakes would be made, and the woman might get a unit which was not screened; is that what you're saying? Yeah.

DR. ESCOBAR: Correct. Yeah. If it doesn't get done --

DR. STOWELL: Right. So if we were not screening except for the units which were designated for pregnant women --

DR. ESCOBAR: Right.

DR. STOWELL: -- intrauterine transfusion and so on, so forth, because --

DR. ESCOBAR: I know logistically it could be very difficult, but I mean, as a clinician, to me, it's not acceptable.

DR. STOWELL: Other comments?

(No response.)

DR. STOWELL: Okay. So the proposition, I think we're ready to vote on this? And the Industry says?

DR. STRAMER: No.

DR. STOWELL: So the question is, would the option to provide ID NAT-negative blood components to selected patients based on clinical indications, for example, pregnant women, intrauterine transfusion, neonates, and Zika virus-untested blood components for all other transfusion recipients provide an adequate and appropriate safeguard against transfusion

transmission of Zika virus? Am I getting a note?

(Off microphone discussion.)

DR. STOWELL: Oh. We haven't voted on the last one. Sorry.

(Off microphone discussion.)

DR. STOWELL: Let's go ahead and vote, please.

LCDR EMERY: Dr. Sullivan, are you there?

DR. SULLIVAN: I vote no.

LCDR EMERY: All right. So noted.

(Committee vote.)

LCDR EMERY: The Committee has voted in majority. I will read the individual votes into the record.

Dr. Stowell, no.

Dr. Sullivan, no.

Dr. Baker, no.

Dr. Escobar, yes.

Dr. Leitman, no.

Dr. Lewis, no.

Mr. Rees, no.

Dr. Stapleton, no.

Dr. Allen, no.

Dr. Basavaraju, yes.

Dr. Kindzelski, no.

There are 11 votes. There are 9 noes, 2 yeses, and 0 abstentions. Thank you.

DR. STOWELL: So let's go back to Question 3. So I sort of see Question 3 in two parts, and the first is do we think that a mixed strategy of mini-pool testing and ID NAT testing is workable and appropriate? And the second would be what would be the triggers to decide where to do and when to do mini-pool testing as opposed to ID NAT testing?

And those triggers could be because of history, basically by geography, or the triggers could be evidence of local infection. Does that seem a reasonable way to subdivide the question?

DR. EPSTEIN: Yes. It's distinguishable from the option of having no testing in a geographic area, right. We sort of have three tiers, ID NAT, mini-pool NAT, no test. In the no test option then, you know, does that mean no safeguard? Or does that mean we then reintroduce risk factor-based testing for deferral?

We've risk factor screening as a basis for testing, but that doesn't mean that you've rejected risk factor screening for deferral. So it is a complex landscape. I think the simplest thing for the Committee would be first to vote the industry proposal, which is mini-pool everywhere with a triggering strategy, because that's sort of a clean question, and it's also been requested by the industry that we consider it. So perhaps you can get over that.

DR. STOWELL: So then let's reframe the question to say

something to the effect, do the available scientific data and so on --

DR. EPSTEIN: Well, we have 3b.

DR. STOWELL: Three -- oh. Do the available scientific data on the risk of transfusion-transmitted Zika support the use of mini-pool NAT in all states? And then would the secondary question be, would the scientific data support the use of ID NAT triggered by, and then whatever it is we decide that it should be triggered by?

DR. STRAMER: Why couldn't you just add to this question with ID NAT triggers to be determined?

DR. EPSTEIN: We could. I mean, the presumption is that there'd be triggering based on some index of increased risk.

DR. STRAMER: Right.

DR. EPSTEIN: And we're presuming anytime we talk about MP NAT, it involves a triggering strategy.

DR. STRAMER: Okay.

DR. EPSTEIN: That's an underlying assumption.

DR. STOWELL: Dr. Lewis.

DR. LEWIS: So I'm afraid that we've gotten ourselves logically in a -- hogtied. That makes (a) and (b) the same question. If we go back to (a), if we defer the definition of at-risk so currently no states or territories could be considered at-risk, and then there's some sort of trigger to make them at-risk, it's the exact same strategy.

So with all due respect, I think that we have -- we should have taken them in order. And then I think, I think we can answer the question that's posed by starting with 3a. So 3a includes, in its options, having some very high trigger we would all agree to, which would basically be -- and mini-pool in all states and territories until something egregious happens. It includes low-level triggers that would make it a very aggressive strategy for moving into ID NAT.

And if the question (b) is interpreted as saying, oh, but of course, we mean there could be a trigger, then it's 3a again. So I think we ought to either have lunch, or I think we should vote on 3a.

DR. STRAMER: It could be --

DR. STOWELL: As I read 3a, however, I -- okay. So yeah. So this has to do with the definition of at-risk. So --

DR. LEWIS: And the previous clarification from the Agency was that we were allowed to separate the definition of at-risk from this question, which I thought was enabling but apparently not.

DR. EPSTEIN: I think the subtle point, if I might, this has to do with whether, in the next iteration of guidance, we pre-specify certain states as at-risk versus we wait for triggering. That's the difference. What we mean by 3a is that certain -- based on a concept of risk, we pre-specify and say, under the next iteration of guidance, certain states will start

with ID NAT.

The alternative is that it's all based on triggering. That's --

DR. LEWIS: Okay. So now you've made them different.

DR. STRAMER: That's not --

DR. EPSTEIN: Well, that's right.

DR. STRAMER: That's not the way we defined it previously. You said at-risk could be geography; it could be a number of different options.

DR. EPSTEIN: Correct. But it's about whether we pre-specify the states, or as we say, you shall test in Florida, period, because we think that there is some degree of persisting risk. Now --

DR. STRAMER: So this is not mini-pool NAT in all states with some type of trigger?

DR. EPSTEIN: Correct.

DR. STRAMER: Okay.

DR. EPSTEIN: I'm trying to distinguish (a) from (b) --

DR. STRAMER: Okay.

DR. EPSTEIN: -- at least as the FDA understands these concepts. In (a), the idea is that we take everything we know now, and we specify certain states and say, okay, in those states, ID NAT continues. The alternative of 3b is we say, all right, we think we should have testing everywhere, but it's mini-pool, and moving to ID NAT will be based only on a

triggering strategy because you see something. That's the difference between 3a and 3b.

DR. STOWELL: Okay.

DR. STRAMER: Quick, vote before we change our minds.

DR. EPSTEIN: Yeah.

DR. BASAVARAJU: So if you believe just in geographic ID NAT and no mini-pool elsewhere, which one do you vote for?

DR. EPSTEIN: You'd vote for (c).

DR. BASAVARAJU: Okay.

DR. EPSTEIN: Again, we're not asking you to choose among them now, just to vote each one. And then we'll see what the sense of the Committee is on each one.

DR. ALLEN: So if there is overlap among the questions, the fact that we vote one way on one and what's perceived to be a different way on a second part is an acceptable --

DR. EPSTEIN: You're allowed to do that. Yeah.

DR. STOWELL: So let's take the first one, Question 3a -- is there further discussion, first of all?

DR. LEITMAN: Just one last thing. I would assume that at this time next year, we would be revisiting this, even as an update. And if data are more of the same, even more of the same, nothing new has occurred, we might change -- we might be asked a couple of questions by the FDA. So this is not the end-all, the be-all and end-all. This is until we next review it.

DR. STOWELL: All right. I think we're ready to vote on 3a. Do the available scientific data on the risk of transfusion-transmitted Zika virus support the regional use of ID NAT in at-risk states and territories combined with the use of MP NAT in the other states?

DR. STRAMER: Do you want my opinion?

DR. STOWELL: Yes.

DR. STRAMER: As phrased, no.

LCDR EMERY: Dr. Sullivan, how do you vote?

DR. SULLIVAN: I vote no.

(Committee vote.)

LCDR EMERY: The Committee has voted in majority. I will read the individual votes into the record.

Dr. Stowell, no.

Dr. Sullivan, no.

Dr. Baker, yes.

Dr. Escobar, yes.

Dr. Leitman, no.

Dr. Lewis, no.

Mr. Rees, no.

Dr. Stapleton, no.

Dr. Allen, yes.

Dr. Basavaraju, no.

Dr. Kindzelski, no.

There are 11 votes total. There are 8 noes and 3 yeses

and 0 abstentions.

DR. STOWELL: Okay. Question 3b, is -- do people have comments on this alternative, further comments?

(No response.)

DR. STOWELL: Okay. So the question -- oh, Dr. Allen.

DR. ALLEN: When it says that, does that mean all versus none, or all versus some? I find the series of questions still to be somewhat confusing, and I understand the difficulty of editing and coming up in the process as we're moving forward, but I find it's still confusing.

DR. STRAMER: To my understanding, this is what the AABB proposes, where we have mini-pool NAT in all states, and we have an ID NAT trigger that remains to be defined.

DR. EPSTEIN: Correct.

DR. KINDZELSKI: Can we put in this question, trigger to be defined for ID NAT?

DR. EPSTEIN: Sure, with an ID NAT trigger to be defined.

DR. KINDZELSKI: So it's -- because just as it stands, it's just --

DR. STOWELL: Yeah. So after the word "territories," "with a trigger for ID NAT to be defined."

DR. EPSTEIN: Yeah. You see, that was actually in the original Question 3a, if you look at it. We had a series of two questions about defining the trigger. But this is fine.

DR. STOWELL: Okay. Further comments? Industry comment?

DR. STRAMER: Yes.

(Laughter.)

DR. STOWELL: Okay. So please vote, everyone.

LCDR EMERY: Dr. Sullivan, are you still on the line?

DR. SULLIVAN: I am. I vote yes.

LCDR EMERY: So noted. Thank you.

(Committee vote.)

LCDR EMERY: The Committee has voted in majority. I will read the individual votes into the record.

Dr. Stowell, yes.

Dr. Sullivan, yes.

Dr. Baker, yes.

Dr. Escobar, yes.

Dr. Leitman, yes.

Dr. Lewis, yes.

Mr. Rees, yes.

Dr. Stapleton, yes.

Dr. Allen, abstain.

Dr. Basavaraju, no.

Dr. Kindzelski, yes.

There are 9 yeses --

DR. ALLEN: I will be happy to change my vote to a yes.

LCDR EMERY: -- 1 abstention and 1 no.

DR. ALLEN: I would be happy to change my vote to a yes, which is what I believe to be the best option. But I had

already voted which -- inconsistently with the previous question, so I -- but I'm happy to change it.

DR. STOWELL: That's perfectly all right.

DR. STAPLETON: Do you mind my asking why you voted no? I'm just curious to hear your thinking.

DR. ALLEN: I was going to vote yes for the next option, with ID NAT in certain areas and no screening in others.

DR. STOWELL: So Question 3c, any comments?

DR. LEITMAN: I'm a little confused. If you already voted yes on something, can you vote yes again? Or is it no?

DR. STOWELL: Yes. You can be inconsistent.

DR. EPSTEIN: You don't have to be consistent.

DR. LEITMAN: I don't have to be consistent? Thank you.

DR. STOWELL: Consistency is the hobgoblin of little minds.

DR. ESCOBAR: Well, I think you look at each question kind of independently, not looking at what you responded before, and I think -- at least that's the way I've been answering.

DR. STOWELL: Industry comment?

DR. STRAMER: Yes, the way it's written. I should say, with the caveats that we would have, you know, two standards, and perhaps some confusion with labeled, unlabeled, and travelers may not be detected.

LCDR EMERY: Dr. Sullivan, how will you vote on 3c?

DR. SULLIVAN: I vote no.

(Laughter.)

LCDR EMERY: Thank you.

(Committee vote.)

LCDR EMERY: The Committee has voted. I will read the individual votes into the record.

Dr. Stowell, no.

Dr. Sullivan, no.

Dr. Baker, no.

Dr. Escobar, yes.

Dr. Leitman, yes.

Dr. Lewis, no.

Mr. Rees, yes.

Dr. Stapleton, yes.

Dr. Allen, abstain.

Dr. Basavaraju, yes.

Dr. Kindzelski, abstain.

There are 5 yeses, there are 4 noes, and 2 abstentions, out of a total of 11. Thank you.

DR. STOWELL: Does anyone have any additional comments?

DR. LEITMAN: Just one thing. The reasons, the indications to trigger from MP to ID, would simply a rise in the population of *Aedes* mosquitoes be enough? And the reason I ask is I don't think it would be enough. A rise in the vector does not mean that the infectious agent is around. So I would just like to hear a comment on whether mosquito population

itself is enough to change a trigger.

DR. STRAMER: You mean an uninfected or not known to be infected?

DR. STOWELL: We don't use it as a trigger for West Nile, for example.

DR. EPSTEIN: The experience with West Nile is the closest that we have. And there was a lot of optimism that we could use zoonotic surveillance, and extensive programs were set up, you know, through the arbovirus program of the CDC, involving sentinel chicken flocks, monitoring horses and mosquito pool testing routinely. And none of it was predictive of the human outbreaks. So it didn't work.

Now, would it be different for Zika? I just don't know. I think, right now, we don't have evidence that we could depend on environmental monitoring, either way, to on-trigger or to off-trigger.

DR. STOWELL: So can we come back to Question 4?

DR. STRAMER: Oh, no.

DR. STOWELL: Would you like commentary on these? Would the FDA like commentary on Question 4?

(Off microphone discussion.)

DR. STOWELL: I gather that's a yes?

DR. EPSTEIN: Yeah.

DR. STOWELL: So the two options which have been put forward, or we're not -- actually are being asked to comment

here, not to vote, on what could be used as a trigger to move from mini-pool to ID NAT. And the first would have to do with the number of viremic donors found within a 7-day period in a particular region, state, county, whatever.

And the second, if I understand it correctly, would be a combination of that and the occurrence of cases of patients with symptomatic disease due to Zika within that same geographic area.

So right now, with West Nile, we're doing it just on the basis of our mini-pool NAT results, or is the trigger more complex for that, for West Nile?

DR. STRAMER: The trigger, as defined by AABB's Association Bulletin 1405, is based on one presumed viremic donation. But de-triggering criteria gets a bit more complicated.

DR. LEITMAN: Oh, sorry. I was just going to comment back to Susan's comment about mosquito surveillance. If we had uniform mosquito surveillance in the United States, by all counties, you know, local and statewide, and it was dependable and reliable, we could and we should then rely on vector-borne surveillance. The issue is it doesn't exist, or it exists irregularly.

DR. STOWELL: Dr. Allen?

DR. ALLEN: We haven't really heard data on this. Certainly modeling of different options and how they would play

out should be available as data of the type that was presented earlier today becomes more widely available.

Second, I think we definitely ought to include surveillance of symptomatic clinical cases. To ignore that information would not be wise, and I certainly agree with the use of what other data are available from other kinds of surveillance, including certainly of mosquitoes.

This is an area, in my view, that needs to be flexible and reevaluated periodically, depending on what technology is available and what ought to be done. I think what I would say broadly is that for this as well as other infectious diseases, we need to be looking at the current options all the time, the available data all the time, and revising our decisions as the data change.

DR. STOWELL: Dr. Stramer.

DR. STRAMER: The first sub-bullet here is verbatim for what we do for West Nile, which, you know, I would argue that if you have a PVD in Montana, it doesn't mean you have local transmission in Montana. So to trigger for PVD in Montana because the person went to Cuba 2 weeks ago would not make sense. And I would still argue that we need to work with our local and state public health department partners to really determine when local vector-borne transmission is occurring.

DR. BASAVARAJU: But I guess, just to counter that, so if you've got a PVD in Montana, that could still be a sign of a

lot of returning travelers who may be infected, right. So like, I guess this trigger would not necessarily be just for local cases. It would be also for a large number of returned travelers because you would no longer have a travel deferral, or you don't have a travel deferral.

DR. STAPLETON: Yeah, well, and the fact that you can have sexual transmission from the returned travelers, I mean, it's a little different. But I mean, I can -- yeah. So I would agree that I would be more in favor of, you know, statewide or U.S.-wide.

DR. STRAMER: U.S.-wide what?

DR. STAPLETON: So that this would apply to the whole U.S. You wouldn't say --

DR. STRAMER: But we said that it would be ID NAT trigger, but I guess defining the trigger.

DR. STAPLETON: Right.

DR. STRAMER: So based --

DR. STAPLETON: So if you have a positive test in Montana, you --

DR. STRAMER: Trigger some geographic area in Montana because the donor came back from Cuba.

DR. STAPLETON: Right, right.

DR. STRAMER: And potentially could infect his wife?

DR. STAPLETON: Right. I mean, there --

DR. STRAMER: I would say it all depends, too, on how you

define a PVD, but anyway.

DR. STAPLETON: I mean, the majority of these are going to be false positives.

DR. STRAMER: Exactly, right.

DR. STAPLETON: Right. So that will de-trigger very rapidly once that's determined.

DR. STRAMER: Well, we have to determine a de-triggering strategy.

DR. STAPLETON: Yeah. Right.

DR. STRAMER: I mean, the devil's in the details. Right.

DR. STAPLETON: Right. Right.

DR. STOWELL: Dr. Lewis.

DR. LEWIS: So looking at the second sub-bullet, the phrase "a defined geographic" -- well, collection area makes it less ambiguous. I was going to say it's very vague because it could be, for example, that we trigger based on an outbreak or an epidemic in an area that many U.S. people travel to, so that the trigger in Montana could be because there's a whole bunch of people coming back from Puerta Vallarta, and that's where the geographic area is.

So I wonder if what we ought to do here, since we're just commenting, is try to rewrite the second one a little bit. And we could change the "and" that's just before numeral 2 to an "or" and then get rid of everything after "clinical cases," with this idea that the trigger would be some combination of

presumptive viremic donors and surveillance of symptomatic clinical cases, with the details yet to be determined.

But I think the comments of the Committee reflect that this -- that a simple rule is unlikely to be sufficient, and we really need to think about a lot of different possibilities.

I'm also concerned that there's a little bit of fighting the last war going on here, this general statement that generals always fight the last war, especially if they won. And the exact details of the last epidemic are unlikely to be reproduced in the next epidemic. And we're trying to come up with rules that are robust to history not repeating itself perfectly.

DR. STOWELL: I think what the FDA is really looking for from us is, again, a more general sense of do we endorse the idea of having some sort of a trigger system which is based upon appearance of either positive donors and/or cases in the region, which I think is what people are basically supporting.

You know, if at some point the FDA would like to come up with sort of more specific suggestions that we could vote up or down, I think that that would be a possibility. But I think the sense of the Committee is that -- and this is what we were sort of aiming at, at the beginning, that this general approach is going to be, would be useful. But the details would have to be worked out.

DR. LEITMAN: So for West Nile virus, a positive donor is

positive for only -- with only one route of acquisition of the virus. But for this virus, there's several routes of acquisition. So it seems important, if one gets a positive mini-pool, then does discriminate testing, finds the infected donor, that you have to -- whatever strategies one uses at the blood center, contact that donor and determine how they got infected, because if that donor and their spouse just got back from Cuba or Mexico, that's probably not a reason to trigger. But if they're in Florida and they haven't left, and their spouse hasn't -- or their partner hasn't left, then that might be, that single might be.

So it's at -- in the other -- for West Nile virus triggering, we don't look in -- we don't necessarily contact the donor before we act. It's a testing --

DR. STOWELL: Right.

DR. LEITMAN: -- algorithm as opposed to a --

DR. STOWELL: And I think Susan suggested that --

DR. STRAMER: Yeah. For Zika, within our SOPs, and this is probably true nationally, we contact the donor immediately for Zika to find out the risk factors. I mean, it's part of our IND data collection, so that some -- a practice that could continue, moving forward. Within 24 hours, we have -- you know they make all attempts to contact the donor.

DR. STOWELL: I think she also made the point earlier that you'd have to work with the public health department of the

region to determine whether this is a local case or imported.

I believe that Dr. --

DR. GOULD: Gould. Gould.

DR. STOWELL: Gould, thank you.

DR. GOULD: Thanks. Just to add to that, I was just going to say, one of the difficulties with this triggering strategy for Zika is the time that it would take for a state or a local jurisdiction to determine whether there is potential local transmission. Often it, you know, might occur in a asymptomatic pregnant woman, and it's very difficult to determine the timing of infection.

There's confirmatory testing that often needs to be done, and then tracking down the patient for an interview, and sexual partners. So it could take weeks and even months to really determine whether there may be local transmission occurring. So it's just one of the limitations of this.

DR. STRAMER: Just to add, for both South Texas and South Florida, the only cases where we've seen autochthonous transmission in the U.S., they both preceded, by a long shot, any observation of a positive blood donor. So in those cases, they were much more sensitive, even with the states doing confirmatory testing.

But we could work it out with the state where we don't wait for the confirmatory testing. You know, we have to act much more quickly. And it means better communication perhaps

than we've had in the past with state and local public health departments.

DR. STOWELL: Any other comments?

Oh, Dr. Busch.

DR. BUSCH: Yeah, just two points. One is with mini-pool screening, the specificity of an ID reactive coming out of a mini-pool is actually very good. So if we get reactive mini-pools and then you find an individual reactive, that's almost, by definition, a confirmed positive in our experience with West Nile.

The other is with West Nile, the disease penetrance is actually quite low, only, you know, a small percentage of people get sick. And only one in several hundred is a reportable neuroinvasive. So mini-pool NAT has proven to be much more sensitive to local outbreaks than clinical case reporting because there's lots of viremic donors before you actually begin to catch clinical cases.

It's the opposite with dengue. There are several hundred clinical cases before you'd find a viremic donation because it's a very penetrant information.

And the same with Zika, you know, close to half of people with Zika get sick, and then people are alerted to it. So my point is, I think the mini-pool reactivity resolving to an individual donation, determining if it's autochthonous, definitely great trigger.

But I think we also have to pay close attention to clinical cases because those could well precede, as Susan just indicated, could well precede the detection of a mini-pool positive case in a local autochthonous outbreak, so the combination of both mini-pool surveillance to trigger if it's autochthonous -- and we can resolve that through the donor center questioning -- and clinical case monitoring, because if there's a new outbreak starting in Puerto Rico, etc., we should confirm.

DR. STOWELL: Dr. Kleinman?

DR. KLEINMAN: Yeah. Actually, Mike made the same points I was going to make. But I just want to emphasize that at least in the joint organization statement, the concept -- we didn't go into the detail of triggering, but the concept was that you would trigger based on autochthonous transmission so that you would have some evidence that it was a locally acquired infection.

And we don't think that every travel-related infection should require triggering. Now, if you have multiple travel-related infections perhaps, maybe. I mean, so I don't think that the criteria are clear yet, but the emphasis was not to trigger with just one mini-pool positive in the event that that was a travel-related infection and maybe the only one you're going to see in the next months.

We haven't talked about de-triggering criteria. How long

do you keep going with ID NAT until you satisfy yourself that you can stop doing ID NAT and revert to mini-pool NAT? Again, that, I think, would have to really correlate with what's going on in the region.

So I think what I'm saying is this is a complex subject. It took us I would say 2 years to get the right answer for West Nile virus, as we learned more. And I think that for the Committee to think it can write the criteria here is a little bit ambitious.

And I think you -- I would recommend that you come up with a sort of an approach, which is I think up there, which is you rely both on blood bank findings in mini-pool and in some way rely on clinical findings and that you let a group of people figure out how to translate that into operational policy. You can't make operational policy with 15 people around a table in 15 minutes. It's just not going to happen.

DR. STOWELL: Just watch.

(Laughter.)

DR. KLEINMAN: Well, I've been watching for the last 3 hours, so I hope to be surprised.

DR. STOWELL: Well, I don't think we're going to surprise you.

I think the -- we've given the FDA the sense of where we think we need to be going with these criteria. And so once again, I thank everybody in the Committee and all of our

presenters. And we will break for lunch and be back in -- how about if we come back at 2 o'clock?

(Whereupon, at 1:22 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(2:04 p.m.)

DR. STOWELL: Good afternoon, everyone. We're ready to reconvene, if people will please take their seats.

This afternoon we have a topic, which is an informational session on the Transfusion-Transmissible Infections Monitoring System. And we also will have a Committee Update.

So here to give us an update on the monitoring system is Alan Williams.

DR. WILLIAMS: Hi, everyone. I'm Alan Williams with the Office of Biostatistics and Epidemiology in CBER. And I'm here representing what's known as the Transfusion-Transmissible Infections Monitoring System, or TTIMS. Now, you may catch me referring to it as T-T-I-M-S, but I think TTIMS is kind of catching on as the stable name for it.

This Committee has discussed this potential program a number of times and, in fact, recommended that a blood safety monitoring system that's stable and accurate be put into place in the U.S., and we're pleased to be able to show you data today representing some of the progress of this program over the last 2 years.

So in long sentence, what TTIMS is, is a representative and sustainable system that collects data from blood donors on HIV, HCV, hepatitis B, both incidence and prevalence, as well as donor risk factors, advanced laboratory measures, and

associated demographic variables that may influence blood safety. And there's one publication that you could look at for further details that's referenced here in *Transfusion*.

Usually, when we discuss TTIMS, we always give a nod to the REDS-II transfusion-transmitted retrovirus and hepatitis virus rates and risk factor studies that collected data at a number of centers from 2011 to 2013.

The progress made in this study really established a strong foundation for TTIMS. It demonstrated the feasibility of collecting and standardizing demographic data, transmitters and transmitted infection marker and risk factor data among blood donors on a large scale that could be considered representative of the U.S.

The study also did a tremendous amount of work on defining consensus test result definitions for TTI markers that could be considered standardized across the different sites for the study.

And then finally, the platform was recognized as establishing a highly capable basis for longer term future study of transfusion-related challenges, particularly infectious diseases that could occur. And then this carried through to the TTIMS design.

In terms of structure and governance, TTIMS is generously funded by the Food and Drug Administration, by the NIH's National Heart, Lung and Blood Institute, and the Office of the

Assistant Secretary for Health and HHS. Right now it's a 5-year funding contract with awards made in September of 2015, primarily to two coordinating centers, which you'll hear from in the course of the session.

First is a Donor Database Coordinating Center, which collects the epidemiologic data from blood donors and donations, and then second, the LRCC or Laboratory and Risk Factor Coordinating Center.

In terms of governance, there's a steering committee, which has representatives from each of the vested agencies in HHS; there's an executive committee, which serves as the guiding body for the TTIMS program; and individual analysis workgroups for each of the individual areas of study that meet regularly.

There are manuals of operating procedures, like any large study, covering each of the coordinating centers and the governance process itself.

So, to date, all institutional review board approvals have been received. There is a confidentiality certificate in place to protect study data. There's finally OMB approval for the donor risk questionnaire, which was received in July of this last year. And there is a firewall in place that prevents FDA from receiving donor or site identified data. That's very important, to allow FDA to both fund and receive data from a study involving a regulated entity like the blood community.

So, first, the Donation Database Coordinating Center, or DDCC, is managed by the American Red Cross. And this receives data and manages samples from five collaborating sites listed here, both American Red Cross centers, Blood Systems, New York Blood Center, OneBlood in Florida, and Creative Testing Solutions.

You'll hear more from this in a moment, but the work scope for DDCC is to maintain a central database which comprises approximately 60% of the total U.S. blood supply, which is monitored for the hepatitis markers and HIV.

The DDCC manages the consensus test result definitions. It validates all the data exchange processes within the study and produces quarterly data analysis, including prevalence in both donors and donations, estimates of incidence, which come from a number of methods, including NAT yield, which is nucleic-acid only positive result for a donor reflecting early infection, repeat donor seroconversion, and recency analysis that's being done in the LRCC.

And, ultimately, these will be considered to form residual risk estimates for the safety of the blood supply.

The next coordinating center is the Laboratory and Risk Factor Coordinating Center. It got chopped off a little bit at the top. But this is managed by the Blood Systems Research Institute, again with data and samples contributed by the same subcontracting blood centers, including all of Red Cross and

all the blood systems.

The LRCC coordinates the risk factor interviews from all HIV seropositive donors as well as hepatitis C and hepatitis B infected donors with recognized incident infection. And they're responsible for integrating the risk factor data with the marker data and then ultimately perhaps comparing those with the prior REDS-II marker and risk factor data, although the blood community has been changing over time, so that's not quite as straightforward as I think originally thought because of changes in the collection dynamics.

LRCC maintains a biospecimen repository and is conducting state-of-the art laboratory studies, which you'll hear in today's session. Some of these laboratory studies include genetic analysis of viral isolates from HIV and probably HCV in the future, evaluation of donor HIV antibodies using assays capable of characterizing recent HIV infection.

And this work has been conducted using stored samples from HIV seropositive donors as well as current samples. And it's hoped and, in fact, probably likely now that the use of recency analysis will be successful in estimating incidence with an increased power to assess changes in incidence over time, such as evaluating a pre- versus post-policy implementation.

The use of the recency assays was actually discussed at some length by this Committee in December of 2014. And it's good to see that this work has moved forward and produced some

very interesting data.

The risk factor interview really got started just a short time ago because of the OMB approval. The risk factor involves standard demographics as well as specifics on sexual, drug, parenteral, and contact exposures that might have resulted in infection.

There are questions related to monogamy among donors, which I think is new to a questionnaire for a study like this, some questions about HIV pre- and post-exposure prophylaxis and antiretroviral therapy in donors, which there has been some experience that donors have been appearing on these therapies.

It gets at the motivations and rationale for appearing for blood donation. And it'll be administered in both English and Spanish. So as mentioned, the OMB approval was received in July, and it's a 5-year approval.

I want to close just with a comment on the challenge of measuring some of these blood safety related outcomes, which are very rare and somewhat difficult to measure in some cases.

Measuring prevalence among blood donors is fairly straightforward, because testing is done anyhow, and it's a matter of collecting the data and assessing it. Unfortunately, prevalence doesn't have a clear relationship to blood safety because prevalent infections are removed from the blood supply.

Where the safety issue comes in is with respect to new incidence that might be in a window period. A blood unit could

be capable of transmitting infection prior to coming up positive in a test. So measures of incidence are very important here and directly relevant to determining residual risk.

Incidence can be measured by HIV antibody seroconversion, particularly in repeat donors with multiple observations, and it's simply a number of observed new infections over the number of person-years observed.

Then there's NAT yield, which is a really rare event, when an individual has a new infection, has only nucleic acid test positive but has not yet produced antibody. They are relatively rare and, as I'll show in a future slide, not terribly stable over time. It's a little hard to potentially use them statistically.

And then recency analysis, as I mentioned, holds some promise as having higher power to assess incidence for comparison purposes over time.

Residual risk estimates are reflective of transfusion safety and directly involve use of the incidence rate and infectious window period.

And then risk factor profiles will also need to be modeled into this whole data collection system to determine what donors are over-represented in some of these recent infections and try to think about interventions that might be appropriate in the future.

I'm just going to close with two slides that Dr. Stramer presented at the December 2014 BPAC to illustrate some of the prior data and some of the difficulties in drawing conclusions.

Shown here is a slide just showing prevalence over time in the American Red Cross system. And you see fairly stable prevalence in quarters, from 0.382 per 10,000 to a low of 0.229 per 10,000, really quite stable over time. So were you to see a two to threefold increase in prevalence, that would probably be readily detectable.

On the other hand, the NAT yield cases also reported by Dr. Stramer show a range from 1 to 11 over the course of -- measured between 1999 and 2016. So, clearly, there's a lot variation in these data, and it's really difficult to determine changes over time that are anywhere within this range.

So those are some of the challenges in measuring outcome. And as I mentioned, there will be two data talks today.

The first is by Dr. Whitney Steele. Whitney is with the American Red Cross and closely involved with the donation database coordinating center. She's going to be talking about data from that coordinating center.

And then second, Dr. Brian Custer from Blood Systems Research Institute will be talking about the proportion of HIV seropositive donors with recently acquired infection in the U.S.

After those two talks, I'll come back and just give a very

brief wrap-up, and we'll be happy to take questions.

Thank you.

DR. STOWELL: Thank you.

Dr. Steele?

DR. STOWELL: I'd also like to point out to the Committee that this is primarily for information. We're not being asked to vote on anything or make any specific recommendations.

DR. STEELE: Good afternoon. My name is Dr. Whitney Steele, and I'm the co-PI of the TTIMS Donation Database Coordinating Center.

Today I'll be presenting on the objectives of the TTIMS DDCC and data on the prevalence and incidence of three transfusion-transmissible infections in the blood donor population.

There are many independent blood centers and blood systems in the United States. Because of this, there is no one blood collector that is capable of providing a complete picture of transfusion-transmitted infection, or TTI, rates and projected risks nationally.

As overall donor infection rates are low, large datasets are needed to monitor possible trends. Until recently there was no mechanism for monitoring risks on a routine basis as there was no centralized ongoing collection of data in U.S. blood donors and donations, including testing information. These data are essential for monitoring blood safety, the

results of policy changes and evolving collection practices.

The objectives of the DDCC, as Dr. Williams said, fall into two main categories: collect and maintain high quality data and analyze the data to provide reliable national estimates. More specifically, the DDCC monitors HBV, HCV, and HIV in U.S. blood donors by developing and maintaining a database that includes information on nearly 60% of the blood supply.

To do this, it was essential to develop consensus-positive definitions that could be used across all participating blood centers. In addition, the DDCC was charged with developing daily data exports, quality control processes, and facilitating the work of the LRCC.

The DDCC also performs relevant data analyses and reports results to stakeholders such as the FDA and NHLBI. This includes calculations of prevalence by categories of interest and calculating incidence by various methods, as well as residual risk.

This slide -- which is very complicated, and I don't expect you to read all of it -- presents how data are communicated between the blood centers and the DDCC, and between the DDCC and the LRCC.

Daily testing data is delivered to the DDCC by the test providers, which are both CTS and the Red Cross, and monthly demographic files are sent by each participating blood system.

The DDCC sends daily pick lists of potentially eligible units to each center for retention of plasma units. The DDCC sends monthly case-control reports to the LRCC so that there is a double-check of which sample should undergo additional recency and molecular testing.

Prevalence and incidence rates were calculated for the first 2 years of TTIMS data. Prevalence is presented here for donations. For TTIMS to be considered incident, a donor must have a negative tested donation followed by a positive donation within the 2-year interval presented here.

Incidence density is calculated using the traditional formula shown, of the number of incident donors divided by the total person-time at risk. The residual risk was calculated using the window period method, which is the incidence rate multiplied by the window period.

One of the important first aspects of TTIMS was to build consensus-positive definitions for each agent. For each marker, donors are considered consensus-positive if they are either confirmed NAT yield or have concordant serology and nucleic acid reactivity.

Confirmed NAT yields are serology negative and discriminatory NAT reactive on an independent sample. Concordant NAT/serology positives are repeat reactive on serology and discriminatory NAT reactive.

In addition, HIV consensus positives also include HIV

controllers. True HIV controllers suppress their HIV infection in such a way that there is very little RNA is present. To confirm them, their antibody reactivity is retested using 10x NAT panel testing to ensure that RNA is present in at least one replicate.

This is the first data slide, and there will be lots of data slides. The data presented here are from the first 24 months of TTIMS. The database contains testing and demographic information currently on nearly 14 million donations from the four major U.S. participating blood systems, the American Red Cross, Blood Systems, New York Blood Center, and OneBlood. All four together represent more than 60% of the blood supply.

The first slide is the overall consensus positive rates for each agent and are presented per 100,000 donations. The number of consensus positives includes both NAT yield positives and serology plus NAT reactive samples. There were 365 HIV positives, which includes the few identified HIV controllers, for a rate of 2.6 per 100,000 donations. There were 912 HBV positives, for a rate of 6.5 per 100,000 donations, and around 2,700 HCV consensus positives, for a prevalence rate of approximately 20 per 100,000 donations.

This is the overall consensus positive rates for each marker, over time. While there have been 24 months of data collection for TTIMS, these 24 months do not align directly with quarters. Therefore, the first month on all of the

temporal graphs do not align directly with quarters. So the September 15 stands alone, and the final time point on each line represents only 2 months, July and August of 2017.

The top green line here represents the prevalence of HCV consensus positives for each time point in the study from September 2015 through August 2017. They range from a low of approximately 17 per 100,000 donations to a high of 27 per 10,000 donations. The notable increase in HCV seen in the last 2 months of TTIMS data will be explored further in subsequent slides.

The middle blue line represents HBV, which ranges from 5 per 100,000 to 8 per 100,000 over time, and the bottom red line is HIV. There is much less temporal variation in HIV, with the prevalence hovering around 2.5 per 100,000 donations.

This presents the consensus positive rates by sex. Overall, 53% of the donations in the database of the 14 million are from males; 53% are from males, and 47% are from females. The prevalence of all markers is higher in males than in females.

The prevalence of HIV in males is 4 per 100,000, compared to 1 per 100,000 in females. The prevalence rate of HBV of nearly 9 per 100,000 in males is more than twice of that in females. The prevalence rate of HCV in males of 24 is greater than that of 15 in the female donations.

This slide provides a more detailed breakdown of the HIV

consensus positive rates by sex over the 24 months. The top solid line is for males, and the lower dashed line is for females. While we can see that it looks like there is a great deal of variability from quarter to quarter, the rate in females is always between 0 and 2 per 100,000 and the rate in males between 3 and 5, clustering closely to 4 per 100,000 donations.

This slide shows the temporal variation in HBV prevalence by sex. Again, the solid line is males, and the dashed line, females.

In this slide, for HCV, we do see the significant increase in the last 2-month time period of July and August of 2017 for males only. This provides further explanation for the overall HCV increase seen in the overall rate, isolating it to males instead of to both males and females.

Now we're moving on to consensus positive rates by age. The majority of donations come from donors in the middle age groups, and this is on the left side of the screen. Come from the middle age groups, 55- to 69-year-olds, give nearly 30% of all donations, followed by 40- to 54-year-olds, and then 25- to 39-year-olds.

However, the highest prevalence rates of all three agents are in younger age groups, with donors aged 25-39 having the highest prevalence of HBV and HCV, and 18- to 24-year-olds having a slightly higher prevalence of HCV than the other

groups.

These are the consensus positive rates by race/ethnicity. On the left side of the slide you can see the proportion of donations by the self-reported race/ethnicity of the donor. The majority of donations in the database are from white donors, 80%, with 9% from Hispanic/Latino donors, 4.5% from black donors, and 2.5% from Asian donors.

The highest prevalence of HIV and HCV per 100,000 donations is in black donors and for HBV in Asian donations with nearly 100 per 100,000 donations.

This presents the consensus positive rates by donor status, first-time versus repeat donations. The majority of donations, as is typical, are from repeat donors, 84% versus 16% from first-time donors.

The prevalence of HIV in first-time donations is six times the prevalence of that in repeat donations. The prevalence of HBV, of 36, is approximately 40 times that of repeat donors -- repeat donations. The prevalence of HCV in first-time donations of 102 is 25 times higher than that in repeat donations.

Once again, we're going to break down these by the temporal variation. In this slide we see the breakdown of HIV prevalence over time for first-time donations and repeat donations. There were 197 HIV positives from first-time donors, and the rate per 100,000 with the 95% confidence

intervals can be seen in the solid line on top. There were 168 repeat HIV positives, with the prevalence rate shown by the bottom dashed line.

Here is the same breakdown of prevalence over time for HBV by first-time donors on top and repeat donations on the bottom.

Finally, we have the breakdown of first-time and repeat donation prevalence for HCV. It's important to note that there is very little variation in prevalence in repeat donations, which is that bottom green line, but that there is an increase in prevalence for first-time donations that we'd seen before in July and August of 2017. This also helps to explain the increase seen in overall HCV prevalence rates.

Because of the coverage of the four blood systems participating in TTIMS, we are using the Department of Health and Human Services regions to look at geographic differences. On this map, we're going to show the two highest prevalence rates for each agent, starting with HIV.

So let's see if they fly in. No. So the two highest regions for HIV are the Southeast and the South Central, with 6 per 100,000 and 4.2 per 100,000; for HBV, Southeast and West, with around 10 per 100,000 for both; and finally, HCV, with nearly 50 per 100,000 in the Southeast and 21 per 100,000 in the South Central region.

Because of the interest in understanding the higher overall prevalence rate of HCV, I'm only going to show one of

these really elaborate line graphs, but just for HCV. Here we're presenting the regional and temporal breakdown of HCV prevalence.

On the left side of the slide, for reference, you can see the percent contribution of donations from each region. The most donations came from Region 4, which is the green bar, which is the Southeastern region. This region also has the highest prevalence of HCV for all time periods of TTIMS, and the variation is seen in the green corresponding line across the top.

So now we're moving on from prevalence to incidence and residual risk. TTIMS plans to monitor incidence in multiple ways: to use incidence density, using seroconverting repeat donors; using NAT yield as a proxy for incidence; and using recency testing as part of the LRCC activities. Finally, the plan to use residual risk, using window period times the incidence.

So these are the NAT yield rates by quarter for the TTIMS period. And we saw them earlier for the Red Cross for an earlier time period.

While NAT yield rates can be a proxy for incidence as they represent recent infection, the rarity of these events results in variation over time and large confidence intervals. Each bar in this graph represents the NAT yield rate per 100,000 donations, and the number in the little box above is the actual

number of yield donations detected at that time point.

For example, the tallest bar, in Quarter 2 of 2016, is the HCV NAT yield rate of 1 per 100,000 donations. And if you look above it, that represents 18 HCV NAT yield positives in that particular quarter. The black bars are the 95% confidence intervals for each one of those prevalence estimates.

As NAT yield rates can be -- as NAT yields can contain both first-time and repeat donors, it's interesting to note that there is basically a 50/50 split between first-time and repeat donors for HBV and HCV yields, while for HIV the split is 25% first-time donors and 75% repeat donors.

So this is the traditional way that we usually calculate incidence rates in blood donors. These are the incidence rates for HIV, HBV, and HCV. These incidence density rates are calculated using repeat donors that have two or more tested donations in the period of study.

Only a fraction of repeat positive donors in TTIMS met these conditions. Thirty-four of HIV repeat positives were considered incident donors, 22% of HBV repeat positives were incident, and only 10% of the HCV repeat positives were considered incident.

HIV incidence was 2.1 per 100,000 person-years, for HBV was 1 per 100,000 person-years, and for HCV was 1.9 per 100,000 person-years.

For residual risk, the window periods used are shown on

the slide, reflecting the periods associated with the testing in use at all of the centers. The residual risk for HIV was 1 in 1.9 million, for HBV was 1 in 2.3 million, and for HCV, 1 in 2.6 million.

In summary, as far as fulfilling the objective of monitoring for DDCC, the DDCC proportion of TTIMS has established the capacity to monitor infection prevalence using data from the four blood systems. We've developed consensus positive definitions that are used across all four; we've established the processes needed for secure data transfer, quality control, and identification of positive units; and we've developed analysis programs to generate routine quarterly and annual monitoring reports; finally, we've analyzed and reported on the 24 months of tracking, including the 14 million donations seen here.

The other objective of TTIMS was the analysis of prevalence in incidence. We see here that prevalence rates are very low still among donations from U.S. blood donors, ranging from 2.6 per 100,000 in HIV to 20 per 100,000 for HCV.

They are highest in donations from first-time donations, which are 4 to 35 times higher than repeat donation rates, in males higher than females, HCV and HIV positive donations from the Southeast and South Central regions, HBV positive Asian donors -- in Asian donors, and HBV in the Southeast and Western regions, and in younger donors, especially for HIV and HBV.

The only significant trend to date is the increase in HCV prevalence in donations collected in the Southeast, South Central U.S., particularly from first-time and male donors. And we hope that risk factor analyses will investigate the risk for these donors.

Incident rates are low compared to historic rates, with corresponding residual risks between 1 in 1.9 million and 1 in 2.6 million.

One of the other objectives of TTIMS was to monitor policy changes. While data from the TTIMS DDCC can be used to look at changes in infection rates in response to changes in policy, it's always important to keep in mind that a relatively large change in infection rates would be needed for statistical significance, that changes in rates are also influenced by changes in collection practices, such as the impact of the current focus on right-type donations, shifts in donor demographics, and the epidemiology of the disease in the underlying population.

For example, once sufficient data are available, TTIMS will be used to evaluate TTI prevalence and incidence before and after the four participating blood systems implemented the change from lifetime MSM deferral to the 1-year MSM deferral.

In summary, I'd like to thank -- I'm not supposed to thank too many people because there's an acknowledgement slide that Dr. Williams will present at the end, but I did want to thank

Dr. Stramer, who's the PI of the DDCC, and Ed Notari, James Haynes, and Diane Nelson, who helped me put the data together and the slide presentation. Thank you.

DR. STOWELL: Thank you. Dr. Custer?

DR. CUSTER: All right. Thank you. Also I want to thank BPAC and FDA for the opportunity to present the information that we're starting to emerge from the Laboratory and Risk Factor Coordinating Center part of TTIMS.

So really the purpose of this talk is to update you on one specific project that we've worked on, which is the proportion of HIV seropositive donors with recently acquired HIV infection, and then also updates on some of the other activities that we're working on. But, certainly, the bulk of the presentation will be about HIV recency analyses.

I will begin by just quickly reviewing -- although they already have been provided -- what are the objections of TTIMS. So first is to have a biospecimen repository that permits us to do many of the different analyses that we are doing. And then these three next ones are the three topics that I will cover in various degrees in this talk.

The first is the performance of the recency analysis from the plasma samples for donors who are HIV concordant positive, and then to look at factors that might be associated with recently acquired infection, such as sex, age group, self-reported race/ethnicity, donation status, and other

characteristics, and in collaboration with the DDCC, to investigate ways we might use this information for calculating incidence, in particular in first-time donors.

The second objective that I'm going to speak about is some of the early viral sequence analysis that we're doing. So we are sequencing HIV, incident hepatitis C, and incident hepatitis B infections. I'm only going to report data though for HIV today.

And, finally, to conduct the risk factor analyses for the infections, for donors who have infections, and compare those to a group of donors who are uninfected or false positive, so like sort of standard case control study design. And again, this just started, and I'll give you an update on where we are with that.

And then we will do some additional analyses when data start to come in related to that part of the project. And the larger objective is to try to integrate all of these different sources of information together to try to maybe come to some new insights than we currently have available with respect to infections in donors in the U.S.

So moving really specifically to speak about the HIV recency work that we've done, the context for this is that changes in donor eligibility policies, such as the change to a 1-year deferral for MSM, may lead to differences in the characteristics of presenting donors. And then in those donors

who have infections, aspects of the time of infection acquisition may also change relative to donation.

So the data that I'm going to sort of present here are a baseline of what we saw really pre-change of the policy. A couple of things that I did want to cover with respect to that, we do have first-time donors represented in this analysis and repeat donors. They clearly don't have the same period of observation.

And so it's an important concept to get at, that of course the date of donation defines when they tested seropositive, and then going back in time, we have a fixed date of when the person was previously negative for repeat donors, but we have no idea what the time of infection acquisition was for a first-time donor.

So what that means is structurally already, we expect to see some differences in the proportions of recently acquired infection in first-time donors compared to repeat donors.

So the concept here is really for, again, donors that are NAT positive and also seropositive, is to use what we used to call a detuned assay to look at the antibody maturation characteristics, and based on that assay, to define somebody as either having recently acquired infection or longstanding infection if their antibody response is over a certain level.

In a little more detail around that than looking at this, there's lots of aspects of this that really matter. If you're

going to use something like the LAg Avidity assay to classify people as either having a recently acquired or a longstanding infection, all of these details really come into play.

So the assay that we're using as a part of TTIMS is the Sedia LAg Avidity assay. The mean duration of recent infection in that for clade B infection is approximately 130 days, with a confidence interval there. And we have issues where some people may be false recent.

And so to put this into a little more detail, again -- I guess it's not showing up, so I apologize for that. I will quit trying to slide the cursor around. That when you actually use this assay, the cutoff matters, because below a certain cutoff, you define that person as having a recently acquired infection; above that, you won't.

And so we also then end up being concerned about these people who might be below the cutoff and so could be defined as recently acquired infection but actually don't have a recently acquired infection, and these are the false recents that we're talking about.

So in the donor population, we don't have a good understanding of the false recency rate, but it is something that we will continue to look at and think through ways to address.

This particular assay uses a normalized optical density or ODn, with internal calibrators in each run. And the way that

this works is shown -- interesting. All right. So I guess I will first tell you what we're trying to do here.

So we're classifying as either recently acquired or longstanding infection. It's a convenient sample, so all of the samples I'm going to talk about today are really a convenient sample. We aren't getting every single sample that's available.

We do have samples that were available before TTIMS started, based on either blood centers or labs collecting and storing samples. And so we've analyzed those. And then we have samples available after the beginning of the TTIMS period. And so we have about 645 before TTIMS started and 214 after TTIMS started that we're able to look at with respect to this.

And so we will also do some analyses related to the overall proportion with recently acquired infection and various demographic and donation characteristics. And then these were compared using standard chi-squared statistics, with a p value of less than 0.05 being considered statistically significant.

So turning to the LAg Avidity assay itself, the cutoff, by the package insert for this, to define somebody as recently acquired is 1.5 optical density, normalized optical density. Anybody who on this assay -- any sample on this assay that tests a 2 or lower is repeated in duplicate. And what I'm showing you here are the results from the TTIMS program of that initial result, the initial optical density and then the

optical density of the duplicates.

The purpose, of course, is to show that there is really very good correlation for the most part in terms of the ability to reproduce the results for any given sample.

The actual results now are shown here, broken out by year. So, again, we had different numbers of samples available for different years, but going all the way back to 2010 up to 2017, the total number tested are sort of represented in this central column. And then the number that are classified as recent in each of those periods are shown.

And the essential point is that across the years, someplace around 30% or 1/3 of samples are being classified as a recently acquired infection. And there's a little bit of variability, but there's no evidence of statistically significant differences over time, and that includes both all of the samples that are available before TTIMS started and then in the periods that we actually have available in TTIMS; no evidence right now of any sort of change in the proportion of people who are being classified as a recently acquired HIV infection.

Looking at some of the different donation and demographic characteristics, there is a statistically significant difference between the proportion of people who are classified as a recently acquired infection if they're a repeat donor versus a first-time donor, for the reasons that I largely

talked about at the beginning of the talk.

We're also seeing a statistically significant difference with more males likely to have a recently acquired infection compared to females. But we are seeing recent infection in females also. And then a strong relationship with age, with lower ages much more likely to have a recently acquired HIV infection compared to older age groups. Again, I don't think that any of that's too surprising, but still important for us to start to understand where we're seeing recently acquired infection in the donor population.

Looking at race and ethnicity, we really don't see any evidence of differences in the proportion of people who have HIV infection being classified as recent or not by whether they're white, Caucasian, black of African-American or other races. We do have a substantial amount of missing information for race and ethnicity, particularly going back in time.

But I think, importantly, that proportion of about 28% being classified as a recently acquired infection is right on target with all of the other race groups, so I don't think there's evidence of bias there necessarily, and the results are very similar also for Hispanic or not Hispanic ethnicity, and then again, with the unknown samples in that. So we don't really see evidence of differences by race or ethnicity in terms of recently acquired HIV infection.

If you stratify a little bit further, so now breaking it

into both the first-time and -- first-time versus repeat and also age groups, you do start to see some differences. There still is this very highly significant relationship with younger ages, both in first-time and repeat donors, being more likely to have a recently acquired infection.

But the number of first-time donors, the proportion of first-time donors that have recently acquired infection in each age category is a little bit lower than in the repeat donors, where in particular, pointing out that 16- to 19-year-old repeat donors, almost 58% of those people are having a recently acquired HIV infection.

One layer further, then break this into both males and females, and first-time and repeat, and then the different age groups. But the pattern still bears out, that the youngest age groups, as they're moving into probably risk behaviors, are more likely, are at risk, higher risk for having a recently acquired infection.

Then thereafter, though, I think that it becomes a little just -- there's a fair amount of just variability with different proportions being seen. There clearly are some trends with decreasing proportions of recent over time, as donors are older, but I would not say there's any obviously specific relationship other than that relationship with the youngest age group.

The next part of the project is just to give you an update

on what we're doing with respect to molecular sequencing. So again, this is HIV, hep B, and hepatitis C. And we're targeting different reasons using the same strategy that was used as part of the REDS-II study. So these are a specific area of HIV; it's 1,275 base pairs of the pole region, really focusing on protease and reverse transcriptase genes. For HCV, it's a 363 base pair in the core region, and for HPV, it's a longer base pair region, including envelope and polymerase genes.

So the work is done to do the extractions and then followed by next-generation sequencing using MiSeq. And we are going to, of course, as part of the TTIMS program, monitor HIV genotypes and drug resistance. In addition, we'll be doing the same thing for the incident hepatitis C's and B infections, although I'm not going to show you any of that data today.

The data that we do have for HIV so far, a total of 134 have been sequenced, and we've done the analyses on them. And the finding is that 131 of those are clade B infection, and we see only three different -- one clade C and two recombinant forms in the 134 that have been circulated or have been sequenced so far.

This is very consistent with sort of a longer term set of monitoring that's gone on with respect to these trends in the donor population. So the next slide is just adding our initial TTIMS data to what is a previously presented table. I'm

looking at what proportion of various infections are clade B versus circulating recombinant forms or other non-B subtypes over time.

And you can see that right now, the 3 out of 134, or 2.2%, is really very consistent with what's been seen over many different donor studies over a longer period. We'll continue to monitor this, of course. This is just the first set of this, and so these patterns can change over time.

Looking specifically then at the drug resistance, the drug resistance that we've seen has been primarily in reverse transcriptase. All of the 134 samples that have been sequenced, 19 have shown some level of resistance, with the vast majority of those, 14 having resistance to K103, which is a nonpolymorphic mutation selected for, for people that are on nevirapine or efavirenz. It's one of the most common mutations that you see in the population. We are seeing some evidence of other drug resistance in the donor base, but nothing that is sort of out of expectation.

In terms of sort of how many donors might be having evidence of multiple mutations, the majority do not have multiple mutations. Only two had three -- only four had two mutations, and another four had three mutations, so some high variability there, but the majority, again, are just single mutations and primarily again being this K103N.

The next update is just -- truly just the last two slides,

are where are we with the process? So the complex process of trying to get the risk factors going was really related to the Office of Management and Budget. We started this well over a year ago, and it took more than a year to get approval. But as Dr. Williams already said, we do have approval.

Following that approval, we had to go back to each of the respective IRBs to get authorization for what was the cleared OMB risk factor interview that we're allowed to give. Sites are now coming up and doing the risk factor interviews. And efforts are underway to go back, to try to capture anybody who would qualify under the TTIMS program, so going back to September 2015 to try to collect those risk factor interviews. We certainly know that we're likely to have some challenges with contacting people. But we are going to do that. All of the sites are doing that.

And then the specific updates really for you right now is there's not a lot of numbers to show. But as of the 27th of the month, we had completed six HIV risk factor interviews, one HPV NAT yield, one hep C NAT yield, and seven controls. There are 61 pending and in the process.

There's, of course, a standard sort of study protocol process that goes into contacting the donors, 61 cases and 23 controls. We are seeing refusals, but right now those refusals are about on target with what we'd expect and not excessive so far.

So where we are with LRCC activities at this point is that we really have everything that we're planning to do as part of the LRCC up, established, and running at this time. Specifically, with respect to the HIV LAg Avidity assay, this assay permits the classification of donors who have seroconverted into a recently acquired or longstanding infection, both in repeat and first-time donors.

This allows calculation of incidence in first-time donors. This is an approach that we're investigating right now as part of the TTIMS investigating team. There are some challenges in some of the formulas, and so we have to make sure that before we start really doing the calculations, we've got the right way of conceptualizing this. But it will permit us to calculate incidence in first-time donors.

The other thing that it can do is it increases the accounts of newly acquired infections, potentially allowing us to control some of that variability you saw in the NAT yield over time, to see if we have some more consistent trends with this larger population represented.

The final thing to point is that younger age and repeat donor status are highly associated with having a recently acquired HIV infection in both males and females.

Thank you.

DR. STOWELL: Thank you, Dr. Custer.

Dr. Williams?

DR. WILLIAMS: So for those of you who have been through literally decades of discussions about the need for a blood safety monitoring system in the U.S., we think that TTIMS is showing successful data collection per some of the original surveillance goals as recommended by both this Committee and the HHS Advisory Committee for Blood Safety and Blood Tissue Safety.

The study has achieved stable outcome measures, and these will support residual risk calculations for blood safety. And there are risk factor data under collection through donor interviews, and these will be a valuable adjunct to the other epidemiologic data.

It seems there's a reasonable expectation that future TTIMS data will definitively address any effects of blood donor eligibility policy changes. And referring specifically to the donor eligibility change that took place in December of 2015, as you'll recall there were a number of discussions prior to the policy change of what the impact might be. Would it increase prevalence of HIV in incoming blood donors? Would the overall donor pool expand?

It appears that there has been no significant change in blood donor HIV prevalence since December 2015. There is natural variation, but it appears that there was no driving force for an increase in HIV prevalence.

Likewise, although the dynamics related to the overall

size of the donor pool are complex, there appears also to not be an observed impact on overall donor pool size directly related to the policy change.

There was, as you may have caught, an elevated HCV prevalence value, a single point, observed among first-time male donors in the Southeast, South Central U.S. during the July-August time frame. It is a single point, and it's under evaluation. The data are real; it's just, you know, what they may contribute to an overall change in trend over time. And what the risk factors might be remains to be determined. But I think it's a signal potentially, if not an aberration in data, which is probably unlikely given the size of the numbers.

The LAg Avidity mean duration of residual, of recent infection of 130 days shows meaningful demographic correlations and holds strong promise as an estimate of HIV incidence with increased statistical power among donors. And we think there has been an epidemiologic framework established to address future blood safety challenges that may come along.

So taking away one of the logos and speaking with an FDA hat just for a couple of slides, this Committee will recall a discussion in April of 2017 about a recently published *Federal Register* notice, which requested comments related to blood donation eligibility and particularly both design of studies as well as comments concerning changes away from a time-based deferral toward individual risk deferrals.

This was detailed in a presentation to the BPAC in April. And I think CBER is committed to, you know, a process to try to assess carefully and produce and improve the predictive value of the donor eligibility screening process. And FDA will not only consider emerging data from the TTIMS but, as well, the comments received to the docket that I just mentioned and any additional new scientific data that is received as it continues to reevaluate and update blood donor deferral policies.

And these observations may also serve as a basis for consideration of future scientific studies that may be needed, whether within the TTIMS structure or elsewhere.

So we now have a rather sizable group of participants in TTIMS. These are acknowledged here. I'll just mention the institutions rather than the names. The American Red Cross is well represented, as well Quality Analytics, Blood Systems Research Institute and BSI, OneBlood in Florida, New York Blood Center, Creative Testing Systems.

The FDA and National Heart, Lung and Blood Institute are both active players, as well as the Office of the Assistant Secretary for Health and HHS. And this is really quite an active group with the scientific discussion.

And I'll just close with our first group picture, which is in the lobby of Building 71 at our last steering committee meeting. And we were able to hold a meeting in this beautiful building that CBER now lives in. So thank you very much.

DR. STOWELL: Thank you. Do any of the members of the Committee have any questions of our speakers?

(No response.)

DR. STOWELL: Okay. Thank you, Dr. Williams.

In which case, then we'll go on to our last item, which is an update from David Leiby. And once again, this is just for our information. FDA is not seeking advice or guidance on this last --

DR. LEIBY: Thank you. I can only surmise if you're still here, you must have a particular interest in ticks.

I've been asked to provide a summary today on the public workshop which was held in April of this year at the Natcher Conference Center on the NIH Campus. And this was on the Emerging Tick-Borne Diseases and Blood Safety. This was co-sponsored by AABB, America's Blood Centers, Department of Defense, FDA, HHS, and NIH.

The objectives of the workshop were as follows: It was to discuss tick-borne pathogens that continue to emerge as threats to blood safety, the effectiveness of current and potential mitigation strategies, and a general approach to decision making on blood safety interventions.

By design, the workshop was to be forward thinking and horizon scanning, so we were interested in those agents who will pose or perhaps will pose a problem in the future. It was also designed to be informational, not policy driven. And

lastly, it enlisted the leaders in the field, several of which are actually in the room here with us today.

It was also designed, as I already alluded to, to focus on emerging tick-borne agents and diseases, and for that reason, there was limited discussion on Lyme disease, babesiosis. There's been tens of thousands of cases of Lyme disease, and to our knowledge there has not yet been a case of transfusion-transmitted Lyme.

There has been a recent workshop on babesiosis, and there is currently testing under IND. And hopefully, perhaps blood screening will not be too far away. So we did not discuss those two agents at the workshop.

The topics for discussion at the workshop included the biology, epidemiology, and clinical burden of *Anaplasma phagocytophilum*, which is an agent that has been transfused at least 11 times, transmitted by transfusion, as well as several other emerging tick-borne agents.

We discussed the performance characteristics of currently available diagnostic assays for these agents. And we also talked about the known and potential risks of transfusion transmission posed by tick-borne agents. And we talked about the current potential mitigation strategies. And lastly, we also looked at considerations in the decision-making process for safety interventions.

What I'll do with the remainder of this talk is to provide

highlights of the 10 speakers who were at the workshop and then close with a generalized summary of the workshop, and also some discussions that were had by two panel groups which we had at the workshop.

Our plenary presentation was given by Peter Krause from Yale University. And he started by pointing out that there's approximately 30,000 cases of Lyme disease each year in the U.S. Lyme is transmitted by *Ixodes scapularis*, also known as the deer or blacklegged tick.

But what he wanted to point out was that there's at least five other agents transmitted by this very tick. These include *Babesia microti*, *Anaplasma phagocytophilum,* Powassan virus*, Borrelia miyamotoi*, and also *Ehrlichia muris*-like infections.

Peter went on and stated that many tick-borne infections occur, but actually few are transfusion transmitted. In fact, he stated that the pathogenesis of tick-borne agents determines risk of transfusion transmission. Geographic range and incidence of tick-borne infections are, in fact, increasing. They are not going away. And with that, we see a concomitant rise in transfusion-transmitted tick-borne infections.

He pointed out that the discovery of tick-borne infections takes time, and the control of tick-borne and transfusion-transmitted infections is difficult. In fact, he suggested this requires a team effort, with scientists, physicians, those in the field, among others.

He closed with an idea about identifying the agents at risk for transfusion transmission when we're talking about tick-borne agents. And he mentioned that one characteristic would be those that are present in peripheral blood, like *B. microti* and *Borrelia burgdorferi*. As we've already said, *Borrelia burgdorferi* does not seem to be transfusion transmitted.

They also need to be high titer in blood and long duration. A recently described *Borrelia miyamotoi* fits that description. And, of course, they have to be able to survive blood bank storage conditions.

The next talk was provided by Cara Cherry at the CDC, and she talked about the epidemiology in the background of *Anaplasma phagocytophilum.* Anaplasma is a small, gram-negative, intracellular bacterium which infects granulocytes, forming morulae, which you can see in the upper right-hand corner.

The etiologic agent of -- it is the etiologic agent of human granulocytic anaplasmosis. The first case was reported in 1994 and became nationally notifiable in 2000. The vectors are nymph and adult ticks of *I. scapularis* and *Ixodes pacificus. Ixodes pacificus* is the West Coast version of the eastern deer tick.

Reservoir hosts in this case are not well understood, but there is a worldwide distribution in northern latitudes. It's

primarily found in the Northeast and the Upper Midwest of the U.S., and its geographic range is expanding due to reforestation and increased deer population. This was a recurring theme, which I'll come back to.

We had a nice talk by Stephen Dumler of the Uniformed Services in Bethesda on the Clinical Aspects of HGA. He pointed out that HGA is not a rare infection but can be fatal 0.6% of the time. The average annual incidence in the U.S. between 2008 and 2012 was 6.3 cases per million persons. And the incidence increases with age. So those of us in the highest age brackets, 50 to 70, are at greatest risk. The female to male ratio, 0.68.

The overall seroprevalence in endemic areas is 3.7%, with some high areas of, for example, in Northwest Wisconsin, 14.9%, and some lower rates in portions of Connecticut.

Clinical symptoms include fever, headache, myalgia and arthralgia, nausea, but rash is rare. So that contrasts with Lyme disease in which about 30% of the patients you will see a rash.

Diagnosis by multiple ways: Blood smear, looking for microscopic evidence of morulae. PCR is actually fairly sensitive in the acute cases, 90% to 95%; unfortunately, the persistence of the spirochetes is rather brief. Lastly, serology, you can detect antibodies IgM and IgG, and then the classic fourfold change in IgG titers is quite important.

Treatment: sensitive to doxycycline and other antibiotics.

We shifted a little bit when Sam Telford from Tufts University provided a talk on other emerging tick-borne agents than *Anaplasma*. And as Sam stated, there is actually a cornucopia of emerging agents grouped in guilds. A guild is a common term that he likes to use as a group of unrelated species sharing a common resource, in this case, *I. scapularis* or the deer tick.

This tick, as I already mentioned, contains many agents, including the deer tick virus, also known as Powassan, *Ehrlichia muris, B. burgdorferi, B. miyamotoi, B. microti*, and there's actually several other agents that I'm not mentioning. Sam's point was also that if one of these agents is present, we should always look for the others because they're often co-infected.

Most tick-borne agents are present in the original site where risk was first noted. And this is quite a difference from mosquito infections, which we talked about today, which seem to come and go, whereas probably the best case of the ticks is Lyme disease was first discovered in Old Lyme, Connecticut. It's still in Old Lyme, Connecticut. It's just that the geographic distribution of the agent has spread across the U.S.

Tick seasonality correlates with the greatest transmission risk during May-August, commonly called the tick season, and

transmission will intensify due to suburbanization, or called farm to forest, and the failure to manage deer, which again are the tick reproductive host. And so they're very important for transporting the ticks and expanding the range.

We had a very good talk by Alfred DeMaria, who is here today with us, one of your panel members. And he talked about One State's Perspective on the Burgeoning Tick-Borne Diseases.

As Al pointed out, public health authority actually lies with -- is important because including state surveillance resides actually with the states. The Council of State and Territorial Epidemiologists was established in the 1950s. They engage the states in national surveillance to decide what is nationally notifiable. And they, in fact, determine how conditions are defined.

Al talked about the reporting structure. Cases are identified by healthcare providers, institutions, and labs. They're then reported to county and local health departments. They in turn report to state health departments, who then reports to the CDC.

Al shared with us that Massachusetts is tracking ongoing increases in cases of Lyme, babesiosis, and HGA, the big three, with peak case reports in May through September. And he also mentioned that co-infections are quite common.

Of concern in Massachusetts, they're currently tracking the emergence of *Borrelia miyamotoi* as well as Powassan.

I gave a talk on the transmission risks posed by emergent agents. I first talked about the factors which influence emergence of tick-borne agents. This is not inclusive, but these are very important ones, at least, I felt at the time: climate and weather, changing ecosystems, human demographics and behavior, and economic development and land use.

Now, when one wants to think about the requirements for transfusion transmission -- and these were touched upon, Peter Krause earlier, but first of all, just to reiterate, you have to have a blood donor with an active infection. The agent also must be present in peripheral blood, and for many tick-borne agents, they reside intracellularly.

For instance, in erythrocytes we find *B. microti*. In monocytes we find *Ehrlichia chaffeensis*, which is the etiologic agent of human monocytic ehrlichiosis. And lastly, in granulocytes we find *Anaplasma* as well as *Ehrlichia ewingii.*

The agent survives the collection process; that's key. And many tick-borne agents survive not only leukoreduction, irradiation, but also storage at 4 degrees. And there's probably no better representation of this than there's been multiple cases of transfusion-transmitted anaplasmosis in leukoreduced blood units.

Finally, to close out the circle, the agent has to establish infection in blood recipients. And those recipients at risk include those who are immunocompromised, those who are

multiply transfused, those with geographic risk because they live in a highly endemic area, seasonal risk -- as we've seen, certain times of the year it's more likely we'll see tick-borne infection -- and finally, the absence of effective interventions.

My talk was followed by a nice overview by Sue Stramer, who is also here on the panel, on the incidence of transfusion-transmitted HGA as well as other tick-borne agents. And Sue gave a nice overview of different kinds of agents that are tick-borne agents and then discussed the transfusion-transmitted cases.

And as she stated, in the absence of viable mitigation strategies, a wide variety of tick-borne agents pose increasing blood safety threats. Among viral agents, there is Colorado tick fever, which has had one case of transfusion transmission; Crimean-Congo hemorrhagic fever is also transmitted by ticks, but there's been no cases, to our knowledge; two cases of tick-borne encephalitis virus. One that I think bears watching is Heartland and Bourbon virus, which has recently been described in the Central U.S.

There are a number of rickettsial diseases: First of all, *Ehrlichia chaffeensis;* that's human monocytic ehrlichiosis. There's been no blood transfusion cases but three cases associated with renal transplants, one case associated with Ehrlichia species, one case attributable to Rocky Mountain

spotted fever. And as I already said, there's been 11 or more cases of *Anaplasma* associated with transfusion transmission. And these transmissions seem to be increasing and becoming more frequent, almost one per year at this rate.

Certainly other bacteria of concern: I talked about Lyme disease having had no transfusion cases. The recently described relapsing fever agent, *Borrelia miyamotoi,* has not had any demonstrated transfusion cases, but it has been demonstrated to be capable of being transfused by blood in animal models.

And lastly, in the protozoans, there's been over 200 cases of transfusion-transmitted *B. microti* and one case of *B. duncani* -- I'm sorry three cases of *B. duncani*.

Dr. Katz, who's in the audience, talked about different mitigation options for infectious risk of blood transfusion. And he gave an overview of these. He talked a little bit about donor qualification, which actually works quite effectively in many cases. He gave examples of HIV and malaria. But he pointed it actually depends on the framing, on framing relevant questions and who you ask.

He also mentioned leukoreduction, which as we heard today is effective for CMV, but it is not effective at all against tick-borne agents. It may reduce them but does not eliminate them.

Process controls can also be important, but as Lou

mentioned, errors can and do occur when unsuitable products are released.

Certainly, testing, efficacy has been demonstrated for a variety of agents, including *B. microti,* but the caveat there, of course, is cost and efficiency and the problems of introducing yet another test.

The option, the other option would be pathogen reduction, where the efficacy has been demonstrated for various agents, including some tick-borne agents, but again there are caveats: potential cell loss, cost of the product, and so forth.

A slightly different talk was provided by Raymond Goodrich from Colorado State University, who provided a conceptual framework for test development. And from his point, this was really about expectations, realities, and challenges associated with new tests in pathogen reduction systems.

And he lumped diagnostics and PRT together. And it was interesting in that he said expectations is that testing and PRT, they're quite easy to implement, works for all agents, does not impact product quality/safety, the costs are minimal and justifiable. But in reality, as Ray said, multiple hurdles actually exist. These hurdles, as he laid out, were technical in nature, but they're also related to social, economic, and regulatory complexities.

There's also many challenges for implementation of new tests and PRT. These include investment versus return, from

the perspective of the manufacturer, market size, are these regional/seasonal impacts, etc.

There's also regulatory hurdles, since the agencies require products to be safe and effective, and they also lead -- this leads to expensive and time-consuming clinical trials.

And Ray closed with several recommendations. The first was to create forums for discussion and collaboration between industry, private sector, and government agencies. He also felt it was important to develop tools for risk assessment and lastly to foster innovation through research funding.

The last of our talks was a little bit different, and this was by Judie Leach Bennett from Canadian Blood Services. And she talked about the ABO approach, or the risk-based decision making for blood safety.

This is actually a six-stage approach for making decisions about and evaluating risk and how you should implement it, or if you should implement it at all. This includes preparation, problem formulation, participation strategy, assessments, evaluation, and decision.

First, one needs to review the literature and advisory committee recommendations and assemble your team.

Then during problem formulation, you need to define and characterize the problem; you know, what are the questions you want to ask, what are the decision drivers, and what risk

management options to evaluate.

As far as the participation strategy, you have to define the need for risk communication and the stakeholder. You need to identify who the stakeholders actually are and develop a participation plan. And these may be patients, physicians, transfusion services, as well as others.

You need to accumulate the data, eventually make assessments of the results, and finally, make a decision based on which one of these routes you would like to go as far as risk-based management.

Then, in summary, and this is the outcomes of the overall day as well as from the two panel discussions, there was consensus that tick-borne agents continue to emerge. The geographic range continues to expand, particularly in the Eastern U.S., due to deer.

When the thought was posed about what are the agents of concern, the consensus was to look for those in peripheral blood, those at high titer and for long duration, and lastly, to pay particular attention to those with low disease to seroprevalence ratio, which may suggest asymptomatic infection in donors. I mean, many of the cases of transfusion-transmitted babesiosis are derived from donors who are, in fact, asymptomatic.

Now, as far as transfusion transmission, the consensus was yes, it does occur. It's highly seasonal, but there is year-

round risk. Older, immunocompromised patients at the greatest risk. And the current concern, actually, along all of the tick-borne agents we talked about, was human granulocytic anaplasmosis.

Now, when mitigation options were discussed: donor qualification, not effective for tick-borne agents; leukoreduction, not effective; process controls were not applicable; testing, certainly feasible with caveats, as I mentioned earlier; same is true for pathogen reduction, which is potentially effective.

It was clear, though, and among the panel discussions I stated that challenges do exist, and in many cases, conflicting influences and outcomes are problematic. The panel discussion, they did make a point that doing nothing was not an option, although at this point, perhaps, there's not many options, and their suggestions were for surveillance, which is ongoing, looking for clinical cases as well as transfusion cases and also ongoing education efforts.

Thank you.

DR. STOWELL: Thank you, Dr. Leiby.

Any questions for Leiby?

(No response.)

DR. STOWELL: Dr. Epstein, any follow-up comments? Oh, yes, I forgot about that.

Is there anybody in the audience who would care to comment

on any of the presentations we've had this afternoon? If so --

A brief comment. Yes. I need to read the Open Public Hearing announcement, so bear with me, please.

Welcome to the Open Public Hearing session. Please note that both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any firms, their products, or if known, their direct competitors. For example, this financial disclosure information may include the firms who may have made payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Dr. Kleinman.

DR. KLEINMAN: I'm Senior Medical Advisor to AABB. Just wanted to express one personal opinion, I guess, and that is in

reference to TTIMS when we're talking about potentially monitoring changes as a result of donor eligibility requirements. And then we touched on the fact that one of the hot issues is individual risk assessment of donors. And this is my pet peeve. We already do that. I mean, our current process is we do a risk assessment of each donor individually.

Now, people may not like the criteria we use. And what we're really talking about is revising those criteria. And, of course, it has to do with gender and sexual activity, but I'm just sort of making a plea that people don't fall into the trap of using that terminology because it suggests that we don't do individual risk assessment currently.

So thank you for bearing with me and having me prolong the meeting just slightly.

DR. STOWELL: Dr. Epstein, do you have any final words for the Committee?

DR. EPSTEIN: I just want to thank the Committee members for staying the course and for providing FDA with very helpful advice, and to you also, Dr. Stowell, for chairing. Thank you.

DR. STOWELL: Thanks to all of you on the Committee, again, for sticking it out and for this several days' discussions.

LCDR EMERY: I want to thank the public and the Committee and the product office for a good meeting. And if the Committee has any questions about travel, please see Joanne and

Rosanna out at the table. And thanks again for coming, and if you have any questions, come see me. Thank you.

(Whereupon, at 3:23 p.m., the meeting was concluded.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

116TH MEETING OF THE BLOOD PRODUCTS ADVISORY COMMITTEE

December 1, 2017

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Biologics Evaluation and Research.

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Shaylah Lynn Burrill

Official Reporter