DEPARTMENT OF HEALTH AND HUMAN SERVICES
UNITED STATES FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE
94th Meeting

Wednesday, April 1, 2009

8:00 a.m.

Hilton Washington DC North/Gaithersburg
720 Perry Parkway

Gaithersburg, MD

C O N T E N T S

Page
Opening Remarks:
William Freas, Ph.D., Acting Executive Secretary

Statement of Conflicts of Interest:
William Freas, Ph.D., Acting Executive Secretary

Committee Updates

Updates from DHHS Advisory Committee on Blood Safety and Availability:
Richard Henry, Deputy Director for Blood Policy and Programs, DHHS

Summary of September 12, 2008 FDA Workshop on Approaches to Minimize the Risk of Transfusion-Transmitted Babesiosis in the United States:
Sanjai Kumar, Ph.D., DETTD, OBRR, FDA

Topic IA: Blood Donor Screening for Hepatitis B Virus (HBV) infection by Nucleic Acid Testing (NAT)

Introduction of Blood Donor Screening for HBV by NAT:
Robin Biswas, M.D., DETTD OBRR, FDA

Estimation of HBV NAT Yield for Blood:
Modeling and Yield Data:

Michael Busch, M.D., Ph.D., Blood Systems, Inc.
Susan Stramer, Ph.D., American Red Cross

FDA Perspective on Modeling and Yield Data:
Richard Forshee, Ph.D., OBE, FDA

Topic 1B: Testing Donors of Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/Ps) for HBV Infections by NAT

Introduction of Testing Donors of HCT/Ps for HBV by NAT:
Melissa Greenwald, M.D., CDR, USPHS, DHT, OGTGT, FDA

HCT/P Donor Data:

Susan Stramer, Ph.D., American Red Cross

C O N T E N T S (Continued)

Open Public Hearing

Jeff Linnen, Ph.D., Gen-Probe
John Saldanha, Ph.D., Roche Molecular Systems
Steven Kleinman, M.D., AABB
Glenn Mones, National Hemophilia Association
Susan Rossman, M.D., Gulf Coast Regional Blood Center, ABC
Corey Dubin, Committee of Ten Thousand

Questions for the Committee

Testing Donors of HCT/Ps for HBV by NAT

Questions for the Committee

Topic II: Potential Testing Strategies for T. cruzi Infection by Blood Donors

Introduction:
Robert Duncan, Ph.D., DETTD, OBRR, FDA

Epidemiology of Chagas Disease:
Susan Montgomery, DVM, MPH, CDC

ARC Experience with Blood Donor Screening for T. Cruzi:
Susan Stramer, Ph.D., American Red Cross

Blood Systems, Inc., Experience with Risk Questions and Testing for T. cruzi:
Michael Busch, M.D., Ph.D., Blood Systems, Inc.

FDA Perspective on Risk Analysis:
Richard Forshee, Ph.D., OBE, FDA

Open Public Hearing

Michael Busch, M.D., Ph.D., American Red Cross and Blood Systems, Inc.
Steven Kleinman, M.D., AABB and American Red Cross
Glenn Mones, National Hemophilia Foundation
Merlyn Sayers, M.D., Ph.D., Carter Blood Care
Susan Rossman, M.D., Gulf Coast Regional Blood Center, ABC

Open Committee Discussion

PARTICIPANTS:

Frederick P. Siegal, M.D., Chair
William Freas, Ph.D., Acting Executive Secretary

MEMBERS

Mark Ballow, M.D.
Henry M. Cryer III, M.D., Ph.D.
Adrian Di Bisceglie
Maureen A. Finnegan, M.D.
Simone Glynn, M.D., MSc, MPH
Blaine F. Hollinger, M.D.
Roshni Kulkarni, M.D.
Katherine A. McComas, Ph.D
Francisco J. Rentas, Ph.D.
Donald. D. Trunkey, M.D.
Ann B. Zimrin, M.D.

CONSUMER REPRESENTATIVE

Richard A. Colvin, M.D., Ph.D.

NON-VOTING INDUSTRY REPRESENTATIVE

Celso Bianco, M.D.

TEMPORARY VOTING MEMBERS

Harvey J. Alter, M.D. (Topics 1A and 1B)
William C. Blackwelder, Ph.D
William Bower, M.D.
Jay H. Hoofnagle, M.D. (Topics 1A and 1B)
James H. Maguire, M.D. (Topic II)
Kenrad E. Nelson, M.D.

P R O C E E D I N G S

Opening Remarks

DR. FREAS: Mr. Chairman, members of the Committee, members of the public, I would like to welcome all of you to this, our 94th meeting of the Blood Products Advisory Committee. I am Bill Freas. I will be the Acting Executive Secretary for today.

At this time, I would like to go around and introduce the members seated at the head table. I will ask them to raise their hand when their name is called so those in the back of the room can see who you are.

Starting on the right-hand side of the room--that is, the audience's right-hand side--the first chair is Dr. Kenrad Nelson, Professor, Department of Epidemiology, the Johns Hopkins University.

Next is our Consumer Representative, Dr. Richard Colvin from the Committee of Ten Thousand and Clinical Assistant in Medicine, Division of Infectious Diseases, Massachusetts General Hospital.

Next, Dr. Simone Glynn, Branch Chief, Transfusion Medicine and Therapeutics, National Institute of Health.

Next is our non-voting Industry Representative,

Dr. Celso Bianco, Executive Vice President, America's Blood Centers.

Next is Dr. Jay Hoofnagle, Director, Liver Disease Research Branch, Division of Digestive Diseases and Nutrition, National Institutes of Health.

Next is Dr. Donald Trunkey, Professor, Department of Surgery, Oregon Health and Science University.

Next is Dr. Ann Zimrin, Associate Professor, Department of Hematology/Oncology, University of Maryland School of Medicine.

Next is Dr. Blaine Hollinger, Director, Eugene B. Casey Hepatitis Research Center, Baylor College of Medicine.

Next is Dr. William Bower, Office of Blood, Organ and Other Tissue Safety, Division of Healthcare Quality Promotions, CDC.

Next is our Committee Chairman, Dr. Frederick Siegal, Medical Director of the Comprehensive HIV Center, Saint Vincent's Catholic Medical Centers, New York.

Around the corner of the table, in front of the podium, Dr. Mark Ballow, Chief, Division of Allergy and Immunology, Department of Pediatrics, State University of New York at Buffalo.

Next, Dr. William Blackwelder, Senior Biostatistician, Center for Vaccine Development, School of Medicine, University of Maryland.

Next, Dr. Katherine McComas, Associate Professor, Department of Communications, Cornell University.

Next, Dr. Henry Cryer, Chief, Trauma and Critical Care, Division of General Surgery, University of California, Los Angeles.

Next, Dr. Harvey, Alter, Chief, Infectious Diseases, National Institutes of Health Clinical Center.

Next, Dr. Roshni Kulkarni, Professor and Director, Pediatric and Adolescent Hematology/Oncology, Michigan State University.

Next, Dr. Adrian Di Bisceglie, Acting Chairman, Internal Medicine, St. Louis University School of Medicine.

Next, COL Francisco Rentas, Director, Armed Services Blood Program Office.

Next, Dr. Maureen Finnegan, Associate Professor, Department of Orthopedic Surgery, University of Texas, Southwestern Medical Center.

Committee members Dr. Willarda Edwards and Andrea Troxel could not be attending today's meeting.

Statement of Conflicts of Interest

DR. FREAS: I would now like to read into the public record a conflict-of-interest statement for this meeting.

The Food and Drug Administration is convening the April 1st and 2nd Meeting of the Blood Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the Industry Representative, all participants of the Committee are special government employees or regular federal employees from other agencies and are subject to the federal conflict-of-interest laws and regulations.

The following information on the status of this advisory committee's compliance with federal ethics and conflict-of-interest laws including, but not limited to, 18 U.S.Code Section 208 and 712 of the Federal Food, Drug and Cosmetic Act are being provided to participants at this meeting and to the public.

FDA has determined that all members of this advisory committee are in compliance with the federal ethics and conflict-of-interest laws. Under 18 U.S. Code, Section 208, Congress has authorized FDA to grant waivers

to Special Government Employees and Regular Federal 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 conflict of interest.

Under 712 of the Food, Drug and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to afford the committee their essential expertise.

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

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

The committee will discuss, for Topic I, Blood Donor Screening and Testing of Donors of Human Cells,

Tissues and Cellular Tissue-Based Products, Hepatitis B Infection by Nucleic Acid Testing. This is a particular matter of general applicability.

For Topic II, the committee will discuss Potential Strategies for Selective Testing of T. cruzi Infection in Blood Donors. This is a particular matter of general applicability.

For Topic III, the committee will discuss FDA's Current Considerations on Requirements to Permit Plasma Obtained from Whole Blood Donors to be Distributed for Further Manufacturing Use. This is a particular matter of general applicability.

For Topic IV, the committee will hear an Overview of the Research Programs of the Laboratory of Molecular Virology, Division of Emerging and Transfusion-Transmitted Diseases. There is no conflict of interest required for this topic.

In addition, the committee will hear updates and informational presentations on several topics. These updates and presentations are not for discussion by the committee and, therefore, committee members were not screened for their financial interests related to these

presentations and informational updates.

Based on the agenda and all financial interests reported by the members and consultants, no conflict-of-interest waivers were issued under 18 U.S. Code 208(b)(3) and 712 of the Food, Drug and Cosmetic Act.

Dr. Celso Bianco is serving as the Industry Representative acting on behalf of all related industry and is employed by American's Blood Centers in Washington, D.C. Industry representatives are not special government employees and do not vote.

With regard to FDA's guest speakers, the agency has determined that the information being provided is essential. The following information is being made public to allow the audience to objectively evaluate any presentations and/or comments.

For Topics I and II, Dr. Michael Busch and Dr. Susan Stramer have associations with firms that could be affected by the committee discussion. For Topic II, Dr. Susan Montgomery is employed by the Center for Disease Control and Prevention. As part of her official government duties, she has associations with firms that could be affected by the committee discussions.

In addition, there may be regulated industry and other outside organization speakers making presentations. These speakers 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.

The Conflict of Interest Statement will be made available for review at the registration table. We would like to remind members, consultants, participants, that if the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial or imputed financial interest, the participant needs to exclude themselves from such discussion and their exclusion will be noted on the record.

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

So ends the reading of the Conflict of Interest

Statement.

We have one little change, a little administrative note. By every committee member's name tag, there should be a little--it looks like a remote for a t.v. We are going to try, when we get to the voting questions, to vote simultaneously. The question will be flashed on the screen and it will say, push 1 for yes, push 2 for no or push 3 for abstain. You will be voting by pushing a button rather than raising your hand.

Hopefully, this will be easier, but that will be found out by the end of the day. Don't lose these. They should have your initials on the back on blue tape. So it is all personalized just for you.

Before I turn the microphone over to the Chair, I would like to request that everybody check their cell phones and either put them in the silent mode or the vibrate mode or turn them off. Thank you.

Dr. Siegal, I turn the meeting over to you.

DR. SIEGAL: Thank you, Mr. Freas, and welcome everybody to April Fool's Day. I think we should proceed since we have heard everything and welcome the new technology with great hope.

So we will start with the Committee Updates. Dr. Richard Henry, the Deputy Director for Blood Policy and Programs for DHHS, will speak on the DHHS Advisory Committee for Blood Safety and Availability.

Dr. Henry.

Updates from the DHHS Advisory Committee on Blood Safety and Availability

MR. HENRY: Good morning. Thanks for having me.

[Slide.]

I am Richard Henry. I am from the Office of Public Health and Science. I am the Department's Deputy Director for Blood Policy and Programs. Rather than a full discussion, I have been asked to provide a brief update on committee functions.

[Slide.]

Last month, the Acting Assistant Secretary for Health, Dr. Steven Galson transmitted a letter to our chair, Dr. R. Bracey. In it, he highlighted several instances where the Department has moved on some of the recommendations made in our May, 2008 meeting.

Three of them include the NHLBI's establishment of the Red Cell Storage Age Study, RECESS, which is a

prospective, randomized, blind superiority study. He also mentioned the grants submitted in response to NHLBI's solicitation on basic research of RBC storage lesions have recently undergone scientific review.

Also mentioned, NHLBI is supporting the SCANDAT European database research study on the effects of storage time and the risks of short- and long-term outcomes post RBC transfusion.

[Slide.]

Our December, 2008 ACBSA topic was predicated on several realities. First: a commitment to donor health as well as to the transfusion recipient is necessary to build a robust and health donor base; donor selection processes have the potential to direct health abnormalities or risk which could affect the donor and even public health; adverse events to the donor either as a result of the process of donating blood such as injury, syncope and loss of iron or discovery of abnormal screening results can impact donor's health.

So the committee was asked to make comments on the responsibility of blood and plasma centers to donor and public health.

[Slide.]

At the conclusion of the meeting, several messages were transmitted to the Secretary. The committee said that, annually, approximately 10 million people donate allogeneic blood for transfusion or source plasma for further manufacturing, many on multiple occasions. These encounters with blood and plasma collection centers can result in outcomes that are of health significance to the donors.

Current practices vary regarding collection of safety data, notification and medical follow up related to adverse health information

[Slide.]

After these comments, the committee suggested several issues that the Secretary considered. The first one is event reporting and donors. Published data suggest disproportionate rates of adverse events in donor subgroups. The committee supports efforts to develop a comprehensive national reporting system for blood and plasma donor adverse events.

[Slide.]

Informed consent. Although now generally

adequate, the committee recognizes room for improvement. Currently performed nationally with regional variation. The risks of donation, especially repeat donation, warrant further evaluation.

[Slide.]

For donor notification and follow up, further standardization is needed and questions remain what method of notification is best such as electronic messaging, phone messaging or, perhaps, mail. Should the donor be able to select these. What categories of test warrant notification such as sickle cell?

[Slide.]

Then, under wider health screening, we had several key areas. Whereas the committee saw the opportunity for wider health screening, several comments and concerns were expressed such as: mission dilution and conflicts of interest at the blood-center level; unexpected adverse outcomes; undue incentives for the donor and also the donation center; reconsideration of the donor hemoglobin acceptance value, risk acceptance of significant number of "anemic" males while excluding normal females.

[Slide.]

And, lastly, the committee recommends that the Secretary consider donor safety and health management as a topic for our Healthy People 2020 goals.

[Slide.]

A brief update on the donor or biovigilance--we are calling it biovigilance but it is, at this point, still hemovigilance. We have just a few time-table updates.

The donor-based biovigilance system currently located in OPHS which is the Office of Public Health and Science is scheduled to begin live, limited application in October of 2009. The recipient-based biovigilance system done at the CDC is scheduled to begin pilot this month and initial live application in the fall of '09.

The TTSN from HRSA has been pilot tested and awaits further action.

[Slide.]

Our next activities are ACBSA members that we have recently selected and have Secretarial approval to seat them will be seated at the next meeting which is at the end of this month, April 30 and May 1. We are going to hold that at the Universities at Shady Grove which is a new area for us. The meeting details are on our website at

HHS.Gov/Bloodsafety.

Questions?

DR. SIEGAL: Are there any questions? Thank you for your brevity.

The next speaker will be Sanjai Kumar, Ph.D., from FDA summarizing the FDA Workshop on Approaches to Minimizing the Risk of Transfusion-Transmitted Babesiosis in the U.S.

Dr. Kumar.

Summary of September 12 2008 FDA Workshop on Approaches to Minimize the Risk of Transfusion-Transmitted Babesiosis in the United States

DR. KUMAR: Good morning.

[Slide.]

I am Sanjai Kumar and I work at FDA. So I am going to give a summary of the FDA-sponsored workshop on Babesia. The workshop was held on September 12, 2008 at the NIH campus. Here is the workshop announcement here and here is an artist's rendition of the life cycle.

Just very briefly, these are here intraerythrocytic protazoan Babesia parasites here which look pretty much, under the microscope, non-distinguishable

from a ring-form falso paramalaria parasite. Here they are exo-otic [ph]. That is the vector here. Here is the white-footed peromyscus mouse, wild mouse, that is in the field; the deer, which serve as carrier for the ticks; and here is the dead-end host. And here is the risk of transfusion from the blood donor from infected donors which is the mostly shorthand here today for the workshop.

[Slide.]

So babesiosis is still a rather obscure disease so that is why a little background is in order. This is precisely the reason why we had called this workshop so this does not remain an obscure disease anymore. It is a malaria-like illness caused by, as I said, intraerythrocytic protozoans of the genus Babesia. They belong to the phylum Apicomplex here which has some very famous notorious parasites, for example, Plasmodium toxoplasma. They are very closely related. There are several species. Those are prevalent in the U.S. but the most common is Babesia macroti.

Clinical symptoms range from asymptomatic to mild disease to life-threatening infections. So, in young, healthy adults, mostly the disease remains asymptomatic or

causes mild flu-like symptoms. But this group here, young children immunocompromised, those were asplenic and the elderly are the highest risk of getting severe disease.

About 5 percent of infections result in death, also. We have the dubious distinction in the United States of having the most clinical cases and transfusion-transmitted cases in the world of Babesia infections here so this is like our own American malaria going on here.

Endemic transmission is reported in the Northeaster and Northwestern states. In between, it s upper Midwestern states here.

There are all types of tests that one could think of. Those that are used; blood-film microscopy, PCR test, antibody test. But none of these are FDA-approved and none are probably adequate enough to screen blood donors. We will go into detail about that. And it is not a nationally reported disease in all the states. In some states, it is, but not on all the states.

[Slide.]

So, just very quickly, what was the reason called for calling this workshop. It was very well established endemic transmission is occurring in the United States in

many states. And these numbers possibly are much higher, but these are well-recognized reported cases of at least 80 incidents of transfusion-transmitted babesiosis in the U.S. and probably numbers much higher.

Recently, there has been a great surge in number of annual incidents of transfusion-transmitted babesiosis and associated deaths. We will talk about that. Also, it becomes more urgent here now. Recently seven cases have been reported from New York City in the last few months of transfusion-transmitted infections.

As I said, there are no approved laboratory tests and there is a significant amount of information gap regarding the rate of transmission, number of clinical cases and number of asymptomatic carriers because these asymptomatic carriers who pose the highest risk of transfusion-transmitted infections--because they remain undetected.

Also, that is why there was a need to discuss the possible approaches, how we can minimize transfusion-transmitted incidence including donor testing and pathogen-reduction technologies.

[Slide.]

So here is broadly the scientific agenda. We discussed, since somebody made a comment during the workshop, that this was the first whole-day discussion on babesiosis ever probably. So we had to start from the very basic, also, with the biology of the parasite, pathogenesis, transmission, epidemiology of babesiosis, mostly in this country.

The risk of Babesia infections that could occur through donor transfusion and what donor components cause it; laboratory tests and what are the possible approaches we could discuss, and then we had a panel discussion in the end of each session.

Dr. Barbara Herwaldt gave a very nice a talk on the historical recognition of Babesia species. So, as I said, in the beginning of the talk, Babesia macroti is the most prevalent species but there are many other species; for example, WA-1, CA-1. So these names were given based on the state it was isolated first; WA1-2 in Washington State, California State 1, 2, 3 based on the more isolates get recognized. That is how the names are given.

Collectively, they have been recently called Babesia duncani.

Then another index in the 1990s from Missouri State called MOI. This is called Babesia divergens-like. So it is different from these species. The species which is most prevalent in Europe is Babesia divergens and I think, because of the difference in the vector components, we don't see this species in this country so far. But this one gets closer. There is a difference here between these species but Babesia divergence is a lot more virulent and fatal with death in 50 percent of the infected cases.

Then there are other species in Europe which are a little different, but all this is important because antigenically they are so different that one test, ELISA or IFA test may not recognize other species. That is why it is important.

[Slide.]

I gave a brief talk about the detection methods of Babesia parasites. As I said, all the standard methods are there. Microscopy. One could inoculate animal models and amplify parasites. There are no culture methods so that is the limitation for Babesia microti. In vitro culture cannot be done, unlike malaria. There is the DNA-detection test, PCR test, real-time PCR. All those are

there. Antibody testing is available, IFA, ELISA. But none of these are FDA-approved.

So, now, the question remains, which is these tests, if any, would be suitable to screen blood donors for Babesia infections and also, from the antibody test, that there is a big problem with specificity and sensitivity.

So the question is if, in some regions, the ELISA picks up to 17 percent of the population if you screen and possibly infection is not that high. So if you use these tests, possibly we will be picking up a lot more donors which are truly infected with Babesia and then how to re-enter them and how to defer them. So that is a problem.

And then there is the problem of antigenic variation so that one antibody test may not be applicable to pick up all species.

[Slide.]

So there was a talk by Peter Krause here as he looked at the number of babesiosis cases in New York State here. This is the number of cases, here. So this actually begins in early '80 and '86 here. You see the numbers in the table is close to 50 and then here, by the Year 2006, the numbers are reaching close to 200. So that is one

thing.

The second thing is it makes the case here this is used mostly in the early--close to 90 percent of the clinical cases were reported and those were about 40. In the young, healthy diseases, the disease remains asymptomatic.

[Slide.]

Again, Peter Krause was the first one to demonstrate here that the disease remain subclinical if not treated for up to two years or more even. So these are the cases which are of most concern, asymptomatic carriers here. So, with treatment, the infection can resolve earlier. But, in the absence of treatment--and we don't know what percent of those who were infected remain asymptomatic for this long period. This is the biggest challenge for blood safety, these patients.

[Slide.]

So this is the result of the American Red Cross's study. They have been performing serology to look at the baseline Babesia antibodies in blood donors in Connecticut which is one of the endemic states. This is 1999 through 2007. This is done by IFA.

So, over the years, you see some variation here but the antibody seropositivity remained close to 0.8 percent to, I believe, 1.7 percent is the highest. So the seroprevalence is rather stable in the endemic area here.

[Slide.]

This is another one here. So these are the different counties of Connecticut here. So the disease is not equally prevalent. There are hottest parts with in the state and within countries here, also. So, by ELISA, they pick up a lot of cases, 6.6 percent. It is hard to believe that 6 percent of the population is infected.

And there are no statistical differences in the states which they call endemic and non-endemic here. But, when they use the IFA--so this is the first cut here--when they the IFA, there is statistical difference in endemic states where they classify as 1.4 percent and non-endemic states is much lower, 0.3 percent here.

Then they looked at the relationship between antibody positivity and PCR because the question is, once somebody is antibody-positive, what do we do if they are truly infected as a surrogate of previous exposure. So they found in only 19 cases, they were able to get a

subsequent sampling and they found that overall 53 percent of those which carried antibody also were parasite-positive.

So there is a rather high rate of relationship between seropositivity and the presence of parasite based on DNA detection. Here is Sharon O'Callaghan from FDA. She presented the fatality reports to Babesia. And I think that is what got all of us worried.

The first reported case in recent times, from 1998 here, one mortality. Then silence for many years. Nothing happened. And then, since 2006, the fiscal years, rather, there were two cases in 2006, three in 2007 and three cases in 2008 here and a total of nine fatalities. After those, eight happened in the last three years only.

[Slide.]

I will go over this very quickly. This is a talk, I think, while looking at the novel technologies, what we could do to bring on here. So this is a talk which had--this is a work which had caught my attention recently. This is a protein-based array to look for antibodies, antibodies that could distinguish--that could recognize antigens which are clinically distinguishing antibodies.

For example, this is the case of borrelia, Lyme

disease, here. So, out of close to 13 in an open reading frame, there are some antigens which are seen by different clinical states of patients here. So the idea here is, and this is the concept I am promoting now, is that if one could develop a microarray for--protein array, rather--for Babesia, a genome, which is not available so far, and then screen for antibodies, different clinical groups of patients.

So one might be able to recognize antigens, those that have antibodies against those only are against a certain clinical state, that might allow us to distinguish between an antibody-based assay between different clinical states here. And then, again, this has the great potential --one could put malaria, Babesia, Leishmania, possibly HIV on one array.

So, probably we will need this kind of technology if we want to solve these problems.

[Slide.]

This is a talk given by Victor Berardi from Immugen. That is a company which has been providing service to clinical labs and state labs for Babesia testing. Again, they are looking at what is the true relationship

between the presence of parasites as demonstrated by microscopy and the presence of antibodies here.

So the 32 patients they had were black-film positive. IFA works great. It is very sensitive, 100 percent they could pick up. The other tests, which they were looking for IgM and IgG also, they come pretty close here except ELISA is not that sensitive here.

So, perhaps IFA will do the job of picking up most of the cases but, still, the question remains how long those antibodies persist after infection is gone.

[Slide.]

Again, the same question asked in a different way. This time, they came by parasite positivity based on PCR here. And, by immunoblot, they could pick up here 100 percent of the--75 percent positivity here. So this is a very even number here so it is easy to look at percentages here. 75 percent here, but IFA, again, comes out the winner here.

So these antibody tests are rather sensitive. But the question still remains, the persistence of antibodies here.

[Slide.]

Ritchard Cable from American Red Cross gave a very nice talk. He looked at the different algorithms, how to identify and defer Babesia-infected donors. So he looked at--his question was, if you could defer donors based on the time of year, because there is a belief in the Babesia field that the transmission season persists mostly based on the deer, the prevalence of deer, and tick activity during July and September, during the summer months.

So it is true there are more antibodies here, close to 1.4, 1.5, percent, again in Connecticut donors. But, then, again, I don't think one can rely totally on that. Look, here is activity in March when it is still winter. In January, it is still pretty high. So probably prevalence of antibodies are there year around and one doesn't know whether the infection is going on in the wintertime so that there is a recurrent sense that is known to happen also or the symptomatic infections persist.

So, probably time-based difference will not be very valuable.

[Slide.]

Again, this is looking at the hottest parts

within the county. So there are some counties which are asterisked here that have a higher prevalence per 10,000 donors. But, then, again, there are still other counties with a considerable lower transmission rate and they still have a significant amount of seroprevalance here.

[Slide.]

So the question here that he posed to us, if we could define donor identification based on region, state, blood center, smaller geographic units--so, probably none of these may work very effectively. He concluded that more seroprevalence studies are needed to define endemic areas even in a crude manner. What should be the cutoff of the seroprevalence that needs to be established?

But the biggest question, how would one keep the endemic areas current because this transmission, the hardest parts are going to vary year to year and probably month to month even.

[Slide.]

The two talks were given on pathogen-inactivation technologies. So one of these is ostelin-based. These are the compounds which intercalate with the purine, pyrimidine, bases in the DNA. And then one shines--exposes to a long-

wave U.V. light that kills the Babesia parasites as a pathogen.

The other one is riboflavin. It has been used similarly and causes a great reduction.

[Slide.]

There was one talk by Darlene Folan from Rhode Island Blood Center here. So they are proposing to test for Babesia parasites by using a very selective population here. Their need was spurred by one donor who caused a transfusion-induced infection in three neonates, then another one in a sickle-cell patient, a Babesia infection.

So they are proposing to test approximately 300 blood donations. That is her talk there. They are proposing to test by PCR which was done by Immugen and then those who are found positive for PCR, they will be confounded by antibody testing. PCR-positive blood would be discarded and then the donor would be notified. Those which have PCR-negative blood will be used for donations in this very specific population which would be neonates, sickle-cell patients and possibly, in the future, patients who are undergoing treatment for malignancies.

[Slide.]

SO here is the summary of the panel discussion. I think I should really stop now. My time is up, I guess.

[Slide.]

These are the people I should--

[Slide.]

So what came out of this? There was a task force that was set up here under the auspices of AABB and we have members from FDA, CDC and American Red Cross, AABB. So there are some solid things that are happening. We meet every month, rather by teleconference. So there is a plan to set up a biovigilance database for transfusion-transmitted Babesia infection. That is something very badly required,

The update of the Babesia fact sheet to be distributed among donors in endemic areas. So there are some plans like in a lab meeting there, discussions on recent Babesia seropositive data, epidemiology data, that is happening. And then there needs to be new funding for Babesia research which is needed.

We had a scientific committee, program committee, who advised us on the program agenda and the speakers and all. I need to thank them and the people within FDA who

were very instrumental with the workshop.

And I stop here.

DR. SIEGAL: Thank you, Dr. Kumar. Are that questions for Dr. Kumar?

All right. Then let's proceed--we are a little ahead of time--to Topic IA, Donor Screening for Hepatitis B Virus by Nucleic Acid Testing. The first speaker will be Robin Biswas. Dr. Biswas is with FDA.

Topic IA

Blood Donor Screening for Hepatitis B Virus (HBV) Infection by Nucleic Acid Testing (NAT)

*** * ***

Introduction of Blood Donor Screening for Hepatitis B Virus (HBV) Infection by Nucleic Acid Testing (NAT)

DR. BISWAS: Good morning.

[Slide.]

For the remainder of the morning until lunch, we will be discussing blood-donation screening for Hepatitis B virus infection by nucleic-acid testing.

[Slide.]

FDA seeks advice and input from the committee on issues related to blood-donor screening for Hepatitis B

virus DNA by nucleic-acid testing to prevent transfusion transmission of HBV.

[Slide.]

Consistent with current regulations and guidance documents, all blood and components for transfusion in the U.S. are tested for Hepatitis B surface antigen and antibody to Hepatitis B core antigen.

[Slide.]

Here are the estimated residual risks of transmission of HVB, HCV and HIV by blood transfusion. All I wanted to point out here was that you can, if you compare HBV risk with HCV and HIV risk, there is almost a log difference there. And, at the time these estimations were made, blood was tested for HBsAg and anticore and, in contrast, HCV and HIV were also, in addition to the serologic test, were tested by NAT.

[Slide.]

Here are list of the HBV NAT licensed for screening blood. In April, 2005, we licensed the COBAS AmpliScreen HBV Test manufactured by Roche. And, in August, 2008, we licensed--actually, we licensed the HBV NAT part of the Procleix Ultrio Assay which is manufactured by Gen-

Probe.

In December, 2008, the waning days of 2008, we licensed the COBAS TaqScreen MPX Test. It is a multiplex assay for HIV, HCV and HBV and I should have put that it is manufactured by Roche and will be replacing the COBAS AmpliScreen.

[Slide.]

Although these are licensed screening tests, there is no FDA recommendation or requirement to perform HBV NAT routinely as screening tests but some blood establishments do so currently voluntarily.

[Slide.]

Here I have listed the limits of detection, the sensitivity of licensed HBV NAT assay by pool size using the--I have shown the individual sample testing and the maximum sample testing permitted. What I wanted to really draw out here was the range, the large range, between the sensitivities.

If you just look here, you can see that there is quite a range there from about 170 to about 4 IU/ml. per ml.

[Slide.]

At the Blood Products Advisory Committee in the

summer of 2004, the COBAS AmpliScreen HBV was discussed. That was before we licensed it. The committee, at that time, recommended licensure. The committee did not recommend the test as an alternative to HBsAg. The committee did not vote on whether the data supported use of the assay in minipools of 24 samples as an added test to HBsAg and anticore.

The same summer, the Secretary's Advisory Committee on Blood Safety and Availability discussed the matter. This committee considers scientific data, cost-effectiveness, feasibility and the overall public-health benefit.

Now, at that meeting, it was said that the estimated benefit using the 24-sample pool in addition to the then currently HBsAg and anti-HBC testing--it was stated that an additional, about 50, infectious donations a year potentially contaminating an estimated 84 blood components would be interdicted and only a small proportion of recipients will develop acute or chronic HBV disease with morbid sequelae.

It was estimated that 0.16 quality life years would be saved per infection prevented. At that time, it

was clear that small pool and ID NAT was not feasible and the role of increasing vaccination of donors and recipients, protecting both against Hepatitis B, was also raised.

So, therefore, there was no recommendation for donor testing based on assessment of limited added value to the public health.

[Slide.]

We think it is now time to reconsider donor screening for HBV NAT. We have approved two more HBV NAT assays using highly automated Multiplex systems making testing of smaller pools and individual donations feasible.

There is a lot of new data on utility or yield meaning donations that are HBV NAT positive and serologic-test negative. And there is an increasing recognition of the importance of Hepatitis B so-called breakthrough infections in donors who have been vaccinated against Hepatitis B and who should have been protected.

[Slide.]

This slide just shows the sequence of viral markers for HBV and the acute HBV infection where the person recovers. As you can see a little bit here, HBV NAT first appears and then, a few weeks later, a week or two-

to-five weeks later, HBsAg appears and then, a few days after HBsAg, anticore appears and anti-HBc remains in the person's circulation more or less for the remainder of the person's life.

Even if they recover, in this case, the HBsAg goes down, HBV DNA wanes and anti-HBs, the protective neutralizing antibody, comes up and the two antibodies in that slide, Anti-HBc and anti-HBs, do remain for pretty much the remainder of a person's life.

[Slide.]

Chronic infection HBV, in the acute phase of the chronic HBV infection, you get the same sequence of the viral markers. In this case, the person, the individual, doesn't recover and HBsAg is still detected, remains. And HBV DNA basically remains there although, sometimes in chronic cases, you don't detect it.

HBV DNA; depending on test sensitivities, HBV DNA is detected two to five weeks after infection and up to 40 days before HBsAg and, occasionally, even longer. It rises slowly at relatively low levels during HBsAg-negative acute period. Also, it is detected during chronic infection and, occasionally, detected in recovered infections where the

person is HBsAg-negative and has anti-HBc and anti-HBs.

[Slide.]

The utility of NAT in reducing risk of transmission of Hepatitis B by transfusion in the U.S. is restricted solely to the early HBsAg-negative phase of HB infection. This is because blood for transfusion in the U.S. is tested for HBsAg and anticore. Anticore is detectable, as I showed, very shortly after HBsAg and remains detectable lifelong irrespective of chronicity or recovery.

[Slide.]

A particular NAT's added value to blood safety depends on the number of HBV DNA-positive, HBsAg-negative, units it can detect in that early phase of infection. This number, which is referred generally as yield, depends on the relative sensitivities of NAT and the Hbsag assays.

[Slide.]

Now, yield can be obtained in two ways. You can do it by getting the actual number of DNA-positive and serologic-marker-negative donations detected in blood establishments during clinical trials and also post-licensure screening.

You can also do it by estimating it by calculations, so-called modeling, using the incidence rates for Hepatitis B in donors and window-period reductions by NAT compared to HBsAg assays. There will be a lot of talk about this, both from the next speakers.

[Slide.]

The issue about Hepatitis B vaccination. There has been widespread introduction of HB vaccination in the U.S. in the past two, two-and-a-half decades. Overall, there are higher rates in donors then in the general population and very high rates in young donors. It can go up to 70 or more percent.

Vaccinations with the HB vaccine, which is a recombinant antigenic HBsAg protein, elicits neutralizing protective antibodies to Hepatitis B surface antigen. So it is against anti-HBs, not anti-HBc.

[Slide.]

Now, breakthrough infections. We will be discussing this a lot in the next few hours. A vaccinated donor exposed to HBV can, nevertheless, be infected with HBV and get a so-called breakthrough infection. The index donation is HBV NAT-positive, anti-HBs-positive, and HBsAg-

negative, anti-HBc-negative.

On follow up, some of these donors develop HBsAg and/or anticore. So the vaccination has not prevented infection in these cases. These breakthroughs are characterized by generally low viral load, anti-HBs positivity, HBs negativity, and they are asymptomatic. They have no clinical symptoms.

So there are some questions if the virus intact--is it infectious for sex contacts. Probably no. Chronicity? Probably no. And, for us, the most important question is are those donations from these donors infectious to recipients.

[Slide.]

Now, another issue is that, last summer, it seemed as though the data that was coming in, that more than half of HBV NAT yields are breakthrough Hepatitis B infections. This finding raises two issues; one, yield data estimations in modeling using earlier donor HBV incidence rates and window-period reduction data from non-vaccinated donors with well-established disease course may not be applicable--well, they aren't applicable--to these breakthrough infections.

This is because incidence rates and window periods are compiled by seroconversion rates to HBsAg and anticore which are changed in breakthroughs. The dynamics seem different. Well, they are different. We will be seeing more of that. And the breakthrough yields are missed by HBsAg and anticore when the donor goes into a bloodbank.

Much of the available literature indicates that HBV NAT-positive, anti-HBs-positive--that is the protective neutralizing antibody--HBsAg-negative, irrespective of whether you detect anticore or not, the units generally do not transmit Hepatitis B.

[Slide.]

So, very quickly, can blood that is HBV NAT-positive, anti-HBS-positive, HBsAg-negative with our without anticore transmit Hepatitis B.

Well, there is a study by Satake sort of delving into that. In his publication, he showed that 22 blood donors with an HBV NAT-positive, anti-HBs-positive, HBsAg-negative, with or without core, low DNA, anti-HBs levels were unknown, no transmission were recorded.

Then there is a report by Dreier, et al. One

donor was the same thing, HBV NAT-positive, anti-HBs-positive, HBsAg-negative. In this case, the anticore wasn't there. With intermittent HBV NAT, low DNA, over a seven-year period with relatively high levels of anti-HBs, eleven recipients were tested and there were no transmissions recorded.

Then there is the experiment performed by Prince, et al., at New York Blood Center. Three chimps were infused with inocula from three patients, HBV NAT-positive, anti-HBs-positive. Anti-HBc was positive. It is IgM anticore. HBsAg was negative, DNA relatively low. Anti-HBs levels weren't given and there were transmissions recorded.

[Slide.]

There are two more papers. This is the very big multicenter study performed by Mosely, a very famous one in the 1970s. If you delve into that paper, well, about over 200 recipients receiving HBsAg-negative blood--DNA, there is no information. I guess they didn't have it in those days, but one presumes that some of them would have been DNA-positive--and anti-HBs with a sample to negative ratio of more then 10, there were no transmissions recorded.

Then there is the report from Gerlich in Germany, a vaccinated platelet donor. This donor became anticore-positive three years post-vaccination. They went back to some stored samples that they had and the HBV DNA was detected. And they reckoned that, at one time, this person was donating blood which had a level of about 100 copies DNA per donation. He had 1,000 mIU of anti-HBs.

Well, anyway, lookback was done two years prior to the anti-HBc seroconversion when he was donating platelets and included 65 recipients and no transmissions were recorded.

[Slide.]

But there is the Hong Kong study and this study stands out against the previous cases. This is a donor of hematopoietic stem cells. They were HBV DNA-positive, anti-HBs-positive, anti-HBc-positive, HBsAg-negative. The DNA was low but was there and anti-HBs levels are unknown.

Now, the recipient was negative for HBsAg and core and anti-HBs prior to transplantation. Follow up testing at six to seven months after transplantation, the recipient tested positive for HBsAg and also the E-antigen.

Although this donor would not be accepted in the

U.S. because of anti-HBc reactivity, the point is there is evidence of transmission despite low-level viremia with anti-HBs.

[Slide.]

Then there is another case from Gerlich about the Danish donor. This case also stands out against the previous cases. This donor was HBV DNA-positive, anti-HBs-positive, HBsAg-negative in one assay but was positive in the other. The anticore, I don't know. It wasn't in the paper. But I presume it might have been positive.

The DNA was low, 200 copies per ml. The anti-HBs was low. Now, one recipient was positive for anti-HBc and anti-HBs on follow up. There was no sample prior to transmission. However, the conclusion was that the recipient was infected by the transfusion. Denmark has a very low prevalence rate for HBV markers. According to Gerlich, it is about 1 percent.

There were three other recipients and they were not infected. So, again, this donor would not be accepted in the U.S. but the point is there seems to be evidence of possible transmission.

[Slide.]

So, therefore, currently, it is our opinion that there are no assumptions of non-infectivity to recipients of units from donors with breakthrough infections. This is because of transmission in the presence of anti-HBs, or at least there is evidence of that.

There is no assumption of lack of morbidity or mortality to recipients, especially when many are immune-compromised and, for neonates and children who are more likely to develop chronic Hepatitis B than adults when exposed to HBV, even without other preexisting conditions.

This is because, in some breakthrough infections, there is development of HBsAg and anticore and this indicates a true infection in the donor.

[Slide.]

So what we really need are studies to investigate unit infections and studies are needed to assess the infectivity of blood donations from Hepatitis B-vaccinated donors with breakthrough infections. Mike Busch will be addressing that question and there are proposals under discussion for studies using interesting animal models which will be described by Mike.

[Slide.]

Now, on this somewhat complex slide, we have modeled the estimations of yield for the different assay formats alongside the sensitivity of the assay. In the column here, this is the yield, or the yield rate, of non-vaccinated regular infections, if you will, relative to PRISM HBsAg and that data comes from Sue Stramer. She will be showing this data to you again.

Then, in the last two columns, we have adjusted to include non-vaccinated and vaccinated yield cases using ratios of non-vaccinated to vaccinated yields. Now, in the one-to-one, what we did there was to assume that, for one breakthrough--there was one breakthrough infection for one regular non-vaccinated yield.

This is because, as I said, in the summer, it seemed as though about 50 percent of the yield was vaccinated and 50 percent was from non-vaccinated regular infections. So those are the numbers in the one-to-one.

Now, in the one-to-two, that comes from data which will be mentioned by Sue Stramer. It comes from Red Cross data. What they have found is that, amongst having tested more than 3 million, 3 million-plus, donors, or donations, there have been nine yields.

Three of those are from non-vaccinated regular donors--Sue will call them infectious donations--and six vaccinated donors with anti-HBs in their circulation. So, as you can see, the--so, then, in the parenthesis, we have projected positive components interdicted per year for the different assay formats.

We did that by assuming that there are, using the rate, using the yield rate, and assume that there are 15 million donations a year, and also that, for each donation, you get 1.7 transfusable components. So those are the--potentially, in brackets, you have the potentially infectious units that would be interdicted a year.

Now, admittedly, we know the complexities and the difficulties in doing something like this, and there will be a lot of criticism of the way the data was obtained. We have used modeling data. We have used actual observable data. So there are some weaknesses here.

But, really, the point is that we wanted to show you that, for example, an Ultrio 8 assay is more sensitive, will pick up more than an Ultrio 16. Then, going up the slide, MPX 6, Ultrio 1 and MPX 1, that there is an increasing pickup, increasing detection, of possibly

infectious components.

[Slide.]

So what are the conclusions of all this? Current modeling estimates of HBV DNA yield do not include HBsAg-negative, HBV DNA-positive, breakthrough infections occurring in donors who have previously been vaccinated against Hepatitis B.

The proportion of HBsAg-negative, HBV DNA-positive, breakthrough infections of total HBV DNA yield might be increasing as more vaccinated individuals become donors. You know, the group, the young donors who are--a large proportion of them are vaccinated, they get older as time goes by, so to speak.

There is no assumption of non-infectivity for Hepatitis B of a donation from an individual with a breakthrough infection. There is no assumption of lack of morbidity or mortality to a recipient of donated blood when exposed to Hepatitis B virus.

[Slide.]

Before I go through the questions, I just want to acknowledge Richard Forshee who will be speaking, and Elliot Cowan who helped me with the slides and made some

great comments, and from Jay and from Paul and from Hira.

Shall I go through the questions, Dr. Siegal? Yes? Okay.

[Slide.]

1; Does the committee agree with FDA that units from donors with apparent vaccine breakthrough HBV infections, HBV NAT-positive and anti-HBs-positive should be presumed infectious pending further studies?

2; Please comment on the value and design of candidate studies using animal models to assess the infectious potential of units from Hepatitis B-vaccinated donors with breakthrough Hepatitis B infections?

3; Considering the estimated yield of HBV-infected window-period donations, and the answer to Question 1, please comment on the benefit of routine screening of blood donors for HBV NAT if testing were performed using available licensed tests on minipools, assuming a sensitivity of at least 100 IU/ml for individual samples.

That's it.

DR. SIEGAL: Thank you very much, Dr. Biswas.

We are now going to hear from Sue Stramer and

Mike Busch. They will have 40 minutes between them to give three talks.

Estimation of HBV NAT Yield for Blood:

Modeling and Yield Data

DR. BUSCH: Thank you very much and thanks to Robin for an outstanding orientation.

My challenge is to really lay the groundwork for what Sue Stramer will be presenting which will be a lot of empiric data.

[Slide.]

What I want to do, then, is to address issues around HBV incidence and viral dynamics and infectivity. As Robin summarized, in the current environment, we really rely on modeling to estimate residual risk and to project the yield of new tests.

There is data you will see on actual yield of fairly large-scale trials but these trials are modest in size relative the residual risks that we are dealing with. So the approach that, now, for 15 years has been employed to understand residual risk and predict the yield of new assays, uses what we term the "incidence window-period model."

This requires derivation and understanding of the rate of new infections in the donor pool, the incidence rate, and understanding of the window periods, both the infectious window period, the time from a donor developing a viremia that could transmit when transfused to the detection of markers used for screening. That infectious window period, when multiplied by the incidence rate, allows you to calculate the residual risk.

And, also, the differential window periods between a proposed new assay and a current assay--and that window-period difference, when multiplied by the incidence rate, allows you project the yield of a proposed new assay.

[Slide.]

Now, focusing first on incidence rates, Hepatitis B incidence is relatively difficult to measure in the donor pool. For HIV and Hepatitis C, we can observe donors, repeat donors, going from negative to serologically positive based on antibody tests with good confirmation.

For Hepatitis B, although we test donors for the antibody to the core antigen, that test is not specific and we don't have confirmatory tests. So we have not employed, in the past, in the U.S., with any reliability, anticore

seroconversions as an accurate approach to measure HBV incidence.

So a method was developed by the REDS group now about ten-plus years ago that employed the rate of surface-antigen conversion in repeat donors to impute an incidence rate. Now, this is a problematic strategy for several reasons. One is that surface-antigen tests, even when employing the so-called confirmatory neutralization assay, are prone to false-positive results. This is attributable either to passive HBsAg in vaccinated individuals who can give blood in the weeks following vaccination and actually have detectable, appropriately detected surface antigen but they are not infected. They are vaccine recipients.

Also the neutralization tests, themselves, have been demonstrated to have false neutralization results. You will hear a fair bit of data about that from Sue Stramer.

Second, once we have eliminated the false-positive neutralization results, which we are able to do, as Sue will describe, we then have to recognize that HBsAg is not a persistent marker in most infected people. In most people who develop HBsAg infection as adults, it is a

transient marker.

So we need to account for the fact that HBsAg that we are detecting in our repeat donors, in the majority of cases, is a transient marker. We need to understand the duration of HBsAg in acute transient cases relative to chronic cases and the relative frequency of acute resolved versus chronicity.

And then we also need to recognize that not all infected people develop surface antigen. Even in the absence of vaccination, studies done many decades ago in trials in prison populations demonstrated that, in the range of 10 to 25 percent of individuals who were infected with HBV develop unequivocal infection and were sampled at regular intervals failed to develop detectable surface antigen.

In the context of vaccinated populations, as you kind of heard alluded to from Robin and as I will sort of summarize in a conceptual slide, and you will see data from real cases from Sue, the rate of non-detectable surface antigen in acute infection is probably much higher. So a large proportion of vaccine breakthrough infections probably failed to develop detectable surface antigen.

So, if we are trying to estimate HBV incidence based on the rate of surface antigen seroconversion, we need to account for the fact that not all acute cases will demonstrate HBsAg infection.

So, when we factor all of these parameters together, we can derive an adjustment factor that can be applied to the observed rate of surface-antigen conversion in repeat donors and multiply that adjustment factor times the observed rate and impute an HBV incidence rate.

Historically, the REDS group on several publications and then the Red Cross subsequently have evolved this conversion factor. But it is in the ballpark of 2.4. So you multiply the rate of observed surface-antigen conversions in repeat donors times the 2.4 adjustment factor to estimate total HBV incidence.

Now, that is in the repeat-donor population. If you want to estimate total HBV incidence in all donors, you need to recognize that about 20 percent of donations are given by first-time donors. We know, from a variety of studies, that first-time donors have two- to three-fold the incidence of repeat donors. So there is a further adjustment.

[Slide.]

Now, over the last four or five years, there have been newer approaches that have been developed to measure HBV incidence. One approach is to use the rate of detecting donations that are DNA-positive but negative for surface antigens and anticore. This is applicable in countries that do employ routine HBV DNA screening.

In studies from Japan and from Germany, this approach has been used to estimate HBV incidence and the results were actually quite consistent with the model approaches that I described in the previous slide, not directly applicable here in the U.S because we don't have systematic HBV NAT at this point.

A second approach recently described by a group from France did employ anti-HBc seroconversion rates, but it employed, then, a large number of additional assays to confirm which of these anticore conversions represented real HBV infections versus non-specific anticore, still a problem and this study has been somewhat criticized.

Finally, a new method that the Red Cross developed that you will hear about employs the duration of HBsAg positivity prior to the development of anticore. So

it uses this same concept of measuring the rate of transient acute infection as is used with the DNA approach but, in this case, it is using the detectable surface antigen to anticore window period as a tool to measure the rate of new infections.

This can derive the rate of new infections in both repeat and first-time donors.

[Slide.]

So, the other piece of information that is critical to all these calculations beyond the measurement of incidence is the understanding of the window period. That is both the sort of marker-positive window period as well as the infectious window period.

And, really, I think the seminal study here was a collaborative study with FDA and REDS led by Robin and published now about seven years ago. In this study, a large number of HBV seroconversion panels were characterized with respect to the rate of increasing viremia in the pre-HGsAg and early HBsAg-positive period.

This study also involved evaluation of a number of prototype individual and minipool HBV NAT assays and a series of HBsAg assays.

One of the key parameters that we use to describe the dynamics of viremia and project the value of new tests is what we term the doubling time which is the time it takes for the concentration of virus in blood to increase two-fold. And, for HBV, based on analysis--you are actually only seeing a fraction of the panels in this slide. It is not projecting--but we derived an estimate of 2.56 days which is the time it takes for HBV DNA to increase two-fold in the plasma of these infected plasma donors.

This work was recently extended by a large study of Japanese HBV acutely infected donors detected by NAT and then serially monitored with respect to increasing HBV viral loads. In this study, by Yoshikawa, you can see that most of the infections--this is the doubling time and the number of acute HBV infected individuals who evidenced that doubling time.

You can see quite similar data from this study with most of the individuals having doubling times between two and three days but occasional outliers, individuals with slower ramp-up viremia.

[Slide.]

So, in the study with Robin, again, we used this

doubling time slope. And then we, again, both empirically and through modeling estimates of the sensitivities of different surface-antigen assays and different prototype HBV NAT assays applied both in minipool and ID NAT, we used these data to derive this figure which, importantly, shows that, as the surface-antigen tests improved--and these are the more contemporary surface-antigen tests, for example, from Abbott and Ortho, Assays A and B here--that, in fact, we could detect viremia at levels as low as 1,000 or so copies and that that, in fact, overlapped with the capacity of these minipool NAT platforms that were being employed at the time or the prototype assays from the two major blood-screening manufacturers.

So this really led, in great part, to, I think, the decision about five years ago that, with the pooled NAT systems, we really weren't going to achieve significant further window-period closure relative to what were anticipated to be soon-licensed HBsAg assays, that really to achieve significant closure and reduce that HBV window period would require conversion and implementation of individual donation NAT.

[Slide.]

This work was further confirmed in a composite analysis that Mary Kuhns at Abbott led that looked at a variety of surface-antigen assays from a number of publications relative to the HBV DNA concentrations.

This is the Auzyme test which the U.S. employed for probably about 20 years. You can see its sensitivity to detecting HBV viremia is about 6800 copies. In contrast, the PRISM assay, which is now employed predominantly here in the U.S. for HBsAg detection, detects viremia at about 1500 copies and a number of the newer contemporary surface-antigen tests available around the world can detect viremia down in the range of 1500 copies, so just further evidence that surface-antigen tests essentially have improved and exploited, also, the fact that, with wild-type HBV infections, there is excess production of surface antigen.

So you are not only detecting virion-associated surface antigen but the excess of HBsAg that is produced. And this allows the HBsAg assays to detect viremia at relatively low viral load set points.

[Slide.]

This is a very new paper from the Japanese group that I think is quite important for this discussion. It

actually defines a phenomenon that is called acute occult HBV infection. The concept of occult HBV infection is usually applied to individuals who are chronically infected and have anticore without surface antigen decades after acute infection in whom one detects low levels of HBV DNA.

There has been a lot of interest in the study of this phenomenon, particularly in the blood-donor context outside the U.S. where anticore screening is not employed and where HBV NAT assays have detected large numbers of individuals with HBV DNA who are negative for surface antigen but in whom anticore is present. So they are picking up lots of occult infections whereas, in the U.S., this is really not relevant to the discussion because we screen for anticore. So our focus is on acute infections.

What this study did was to enroll and follow a large number of HBV NAT-yield donors to also go back to stored repository samples from these donors and characterize the viral-load dynamics not only of the ramp-up phase with the doubling time we discussed earlier, but also the peak of HBsAg and the declining levels of HBV DNA in these individuals.

What they observed was a pattern of rising and

declining viremia that is pretty much what we would have expected based on the classic earlier studies. But they documented three cases that were similar, actually, to what was found in the early prison-inoculation work who failed to develop detectable surface antigen through the entire course of acute HBV infections.

In all three of these cases, they actually had mutations not in the surface-antigen detection region of the virus but in the pre-core or core regions that resulted in reduced excess surface antigen production.

These cases are shown here in red. They are relevant because I think what we will see later from Sue, and I will illustrate in the next two slides, is what I think happens in vaccine breakthrough infections is a very suppressed viremia similar to what is observed in these cases here where the viral loads come up at a fairly typical rate but then tend to plateau at a modest level of viremia of 100 to 1000 copies, and then the virus is cleared.

So these acute occult infections are a phenomenon that have been known for decades and were best characterized in this recent study.

[Slide.]

Just to, again, summarize sort of schematically, in non-vaccinated donors, we think that the viremia comes up relatively slowly at about two-and-a-half-day doubling time. In most individuals, the levels of viremia and the levels of surface antigen result in a positive surface-antigen assay. Most adults infected, who would be the typical blood donor, will resolve that infection.

There are, though, a small proportion of acute infections that do not develop detectable surface antigen.

[Slide.]

Now, in contrast to that, what we think--and you will see a lot of data on this--may be going on vaccine breakthrough infections are sort of added here as the red line, is that the viremia comes up fairly consistent with the typical doubling time but then it tends to be suppressed, or blunted. And you see a low-level sort of plateau of viremia that then declines.

One of the very important issues of discussion today will be pool size and whether, in order to detect these vaccine breakthrough infections, we can rely on minipool NAT versus we need to either reduce pool size or

to go to ID NAT. I think the evidence you will see from Sue would suggest that most of these vaccine breakthrough infections are being detected by minipool NAT and, therefore, it may well be that retaining pooled NAT in order to interdict these units is going to be a reasonable option.

[Slide.]

Now, just in the last section, what I want to describe is the challenge of understanding the infectivity of these viruses with respect to transfusion risk. This slide just sort of summarizes the three major viruses that we are all interested in; HIV, Hep C and Hep B.

I show it to contrast, again, the doubling time for both HIV and HCV are in the fraction of a day, so a very rapid ramp-up phase doubling time, such that introduction of pooled NAT can reduce the window periods for these viruses to very brief, four- or five-day, time frames and the incremental gain of going from minipool to ID NAT is really very modest because the window period closure is brief given the rapid doubling time.

[Slide.]

So, in contrast with Hepatitis B, we have a very

slow ramp-up time, a longer potential infectious window period and a higher predicted yield of moving toward either minipool NAT or even individual donation NAT to try to interdict that.

But the key question is what is the infectious dose by the blood transfusion? How much virus is needed and what is the length of the infectious window period?

Now, the first approach that was employed by the REDs group and then by Steven Kleinman and myself specific to HBV used a strategy of back extrapolating. Knowing the doubling time of the virus and assuming that as few as one viral particle in a transfused unit of blood might be infectious, we could calculate the length of the theoretical infectious window periods.

So, in doing this, we used the data from both the REDS study and the Japanese studies that offered us information on the viral doubling time. We knew the sensitivity of either surface antigen or NAT assays in terms of at what viral load would these assays score positive, and then we basically applied a simplifying assumption that as few as one virion in the typical plasma volume in a red cell unit, which was 20 mls, would be

infectious.

Now, obviously, that assumes a worst-case with respect to red cells, that one virus in a transfusion would transmit. But there are higher-volume components, FFP and apheresis platelets, which would have more plasma and, theoretically, could have a longer window period.

[Slide.]

But, from that analysis, what we were able to do was to estimate the time prior to surface antigen detection either by the Auzyme or the PRISM assays, that one would be infectious either down to 1 copy or 10 copies per 20 mls so that the estimated infectious window period in the context of the current PRISM assays, and you will hear about this later, was 38.3 days.

There is also a period prior to development of a detectable or even 1 copy per ml we term the eclipse period when the virus is still really resonant in the target tissue prior to a disseminated viremia. But you will see these numbers in some of Sue's presentations.

That is a very simplifying model approach, that there are no other variables influencing transmissibility, that simply one virus in a unit will infect. But, as we

know, there are a number of other variables, both viral and host, that could influence the infectivity. The virus, itself, could have mutations that would impact its fitness. There could be differences in infectivity of different genotypes of HBV or the other viruses.

There could be defective interfering particles that are being produced during acute infection, co-existing antibodies, either within the transfused product, such as in vaccine breakthrough donors, or because patients often get multiple transfusions, so they are simultaneously getting a unit that has a little bit of HBV and units from vaccinated donors that have anti-HBs and how does this influence the infectivity.

[Slide.]

And then, as we will see, as donors move through the acute ramp-up into the sort of early plateau and peak and then viremia phases, the infectivity shifts and we will see actual evidence of that. It is very clear in SIV, HIV and Hepatitis C, and we will see similar data for Hepatitis B.

Other factors are host-related, the susceptibility--the immune competence of the host could

impact--and then whether the host has any pre-existing immunity, either acquired previous infection or vaccine-induced or other innate immune responses that would reduce their susceptibility to HBV infection.

[Slide.]

So, in terms of HBV specifically, there is data, much of it summarized by Robin and I will just touch on a few of those studies and also a few different studies to directly try to understand the infectivity.

Now, there are animal model studies and the classic data comes from chimpanzee infectivity studies, both older studies that have been re-examined with newer assays as well as more recent studies, particularly those conducted by Yoshikawa in Japan, inoculating chimps with ramp-up virus and characterizing the infectious unit to DNA copy number relationships.

And then, very importantly, I think, and the opportunity that I think is most amenable to investigation of vaccine breakthroughs, are new data using chimeric mice in which they have replaced the liver hepatocytes of the mouse with human hepatocytes. I will show you data that, to me, is convincing, that these chimeric mice models are

really excellent model systems for assessing the infectivity of these vaccine breakthrough infections.

And then there are human studies. There are isolated cases, and Robin summarized, a series of papers that have reported individual cases or small series to understand whether units could be infectious in different stages.

Robin reviewed the data from the TTVS Jim Mosely studies which showed no transmissions from units that had antibodies to Hepatitis B and then systematic look-back studies, and I will show this data from Satake's work recently.

[Slide.]

But the most probably important data I think is coming from chimp or these chimeric mouse model systems, and particularly two studies that I will show you the results, the key results, of.

The first paper--again, both of these come from Yoshikawa's group in Hiroshima--infected a chimpanzee with human plasma and then sampled this animal at very frequent intervals and did very careful studies freezing plasma from these specimens drawn from this animal during ramp-up phase

of viremia. This is in the middle of the ramp-up. The specimens of interest here were harvested from these animals at 57 days and then a downstream sample was also studied at 244 days when the animal was still viremic with HBV DNA, had very low levels of antisurface, had converted their anticore.

So what was done was to take the plasma from this Day 57 sample and very carefully thaw it and serially dilute it, requantify the serial dilutions and then inoculate, beginning with a very low copy number and working their way up to try to establish the minimal infectious dose.

And when this work was done, what they found that 10 virions--this material was transfused into a small series of target chimps, that 10 copies in the entire transfused material were sufficient to transmit with a range of 3 to 30 copies.

So this is telling us that the virus derived from the early ramp-up phase, particularly when treated very carefully in terms of rapidly freezing and then immediately thawing and infusing, is extraordinarily infectious really supporting our earlier model assumptions that as few as 1

to 10 virions could transmit.

Now, that same material that had been pedigreed in terms of the infectious dose in chimps was then subsequently used in this paper related to the chimeric mouse system.

[Slide.]

What this slide simply shows is the mice that were used at the target for challenging with this chimpanzee-derived plasma, and what this is showing is that these mice, again, through genetic engineering--these are knockout mice in which not only have they knocked out the immune system, SCID mice that lack a number of immunologic functions, but they have engineered them such that the livers in these mice are very fragile and essentially these mice are barely able to live.

As soon as you infuse human liver into these--human hepatocytes into these animals, they replace the mouse liver with human liver cells. So these animals have in the range of--70, 80 percent of the hepatocytes are derived from humans and they develop essentially normal levels of human serum albumen within these mice.

[Slide.]

And then, when this same experiment as I just described for chimps was done inoculating this material into mice, what they found was that actually 3 copies into these mice was infectious from the acute ramp-up phase with a range of 2 to 4 copies. So the infectious dose within mice, the 50 percent infectious dose was estimated at 3 copies.

But they also, then, took the plasma that was collected from the convalescent phase after antibodies had developed so anticore had converted and antisurface was just beginning to appear.

[Slide.]

When they did these exact same titration studies, they determined that 300 copies was required. So there was a 100-fold reduced infectivity that evolved within the virus or as a consequence either of viral evolution in terms of fitness or in terms of the presence of immune complexes that suppress the infectivity in this later phase of acute HBV infection.

[Slide.]

This just compiles the data from the studies I just described but adds in a study that the FDA led, Dr.

Zhao here, which actually took the material from chimp inocula that had been pedigreed here in the U.S. and went back and quantified with contemporary viral-load assays the concentration of HBV DNA that corresponded to a 50 percent chimp infectious dose.

What they demonstrated was that, in the three inocula, 3, 78 and 169 genome equivalents were the minimal infectious dose, the 50 percent minimal infectious dose, with three different genotypes suggesting that there may be some differential infectivity of different HBV genotypes.

[Slide.]

Then the final study, just to highlight, and Robin did allude to this, is that the Japanese lookback studies where Satake, et al., conducted a systematic look back when donors in Japan were detected as converting to HBV DNA-positive or surface-antigen-positive or converting to high-titer anticore positive, they went back to stored specimens in the freezers, because they have a national systematic repository, and identified a fair number of DNA-positive specimens that had very low levels of DNA not detected by their large pooled NAT.

What they determined in these studies was the

recipients who were later traced and tested, if they received a unit of window-phase blood, typically red-cell components, that were anticore-negative and DNA-positive, that 50 percent of these recipients were determined to be infected.

So it is not as high an infectivity as you might predict from the animal studies perhaps reflecting the effect of component storage. The typical transfused unit is refrigerated and processed and the infectivity may be reduced but, nonetheless, a high level of infectivity of window phase.

In contrast, when they took the DNA-positive samples that had anticore, either representing acute resolving or occult infections, only one of these 33 units transmitted for an overall 3 percent transmission rate. The one transmitting unit that was anticore-positive was a jumbo plasma, 400 ml, and lacked anti-surface. So there was no anti-surface present in this donation so I think probably the most comprehensive human data to support the conclusions from the animal model studies.

[Slide.]

So, just to conclude, I think the minimal

infectious dose--it's challenging to derive an unequivocal answer as to what that is with respect to transfusion-transmitted HBV.

With respect to the window period, there is, I think, quite good data coming from the animal models, both the chimp and the chimeric mouse model, although there is clearly going to be appropriate questions as to how generalizable those data are to the human situation. But I do think that the data supports the conclusion that as few as 10 copies in the entire transfused volume probably could be infectious short of additional reduced infectivity attributable to storage of the components.

In contrast, in later phases, the infection and, in particular, in vaccinated people, I think the evidence would support that there is reduced infectivity to particle relationships probably in the ball park of 100-fold lower infectivity based on the animal-model work.

In addition, there is not very well-proven data from HBV transmissions from chronic set point. Virtually all the lookback studies from occult B infections have demonstrated no transmission.

I think clearly, as the committee has been asked

to do, the critical question is the infectivity of these vaccine breakthrough infections and this is clearly the question that needs to be addressed through future studies in chimps or chimeric mice.

Thank you.

DR. SIEGAL: Thanks, Dr. Busch.

Now we will hear from Dr. Stramer.

DR. STRAMER: Thank you.

[Slide.]

I have two presentations.

The first will summarize the publication that has been accepted in Transfusion that really focuses on incidence and residual risk of Hepatitis B infection among donors in the United States. And that is using HBsAg as the model. From that above data, I am then going to estimate, as Robin has already highlighted, the residual risk and yield of HBV NAT using different platforms and different pool sizes.

[Slide.]

In the interest of time, I have cut many of the modeling slides out and Mike and Robin have already reviewed them.

[Slide.]

But what I will cover is the current HBV incidence and residual risk have been derived from two different models; one is the seroconversion model--

[Slide.]

--And the other is the HBsAg yield model that have already been described.

[Slide.]

Both yielded an incidence in donors from 2006 to 2008 with a conversion to PRISM of 3.45 to 3.43 per 100,000 person years of observation. That yielded a residual risk by either model using a window period of 30 or 38 days, a risk of 1 in 280,000 to 1 in 357,000. Both methods and both window periods yielded statistically identical results; that is, there was no significant difference in those rates.

This is a decrease from what we have observed nine years ago using the Red Cross donor population of approximately 1 in 100,000 as the risk.

[Slide.]

I will talk about the impact of vaccination on the reduction of HBV incidence and residual risk especially

in our younger donors.

[Slide.]

Overall, 44 percent of our donor population is vaccinated as determined by anti-HBs and otherwise HBV uninfected individuals. But it is greater than 65 percent, as Robin has already alluded to, in donors of less than 30 years.

[Slide.]

Then I am going to transition and talk about at estimates of residual risk and yield using HBV NAT which uses the above incidence calculation that I have just described and to find NAT window periods from publications in the package inserts along with the doubling times of the virus. So this will cover ramp-up viremia and it excludes infected donors with different ramp-up kinetics as has already been discussed such as vaccinated donors.

These sort into three groups; by platform and pool size the most sensitive being individual donation NAT using the MPX system--that is the Roche system--and then equivalence was found between ID NAT using Ultrio and a minipool size of 6 using the MPX assay.

Lastly, the least sensitive but comparably

sensitive were minipools of 8 and 16. Actually, according to the models, as Mike showed, they approximate the sensitivity of HBsAg assays and that is why, about five years ago, we chose not to adopt these methods because, with the adoption of ultrasensitive HBsAg methods, the results were fairly comparable.

So, again, to remind you of our historic incidence rates, they have used repeat donors only to calculate residual risks. And, using the repeat donors in the REDS study of 1991 to 1993, there was a risk calculate of 1 in 63,000. Then, using Red Cross data, we calculated, in 2000 and 2001, a risk of 1 in 205,000.

So, when we calculate these incidences, this is using the HBsAg yield method--these slides refer to as Method 2--we calculate, as I have already referred to, an incidence of 3.43. The advantage of this method over the routine seroconversion method is that it can include calculations of first-time lapse as well as repeat donors and you can use the ratios--that is, the proportions of relapse to repeat or first time to repeat and apply those ratios to the seroconversion model so that you can get total donation residual risk calculated from those.

But let's suffice it to say for now that we calculated an incidence of 3.43. Using the seroconversion model and the proportions that I just alluded to, we calculate an incidence of 3.41.

[Slide.]

Now, applying those, I am sorry that the colors don't show up on these slides--they are kind of truncated themselves, or blunted--these are the rates that we have calculated using a 38- or 30-day window period with the two incidences. So this is the range that I just talked to you about, 1 in 280,000 to 1 in 357,000.

So those are our current residual risks using PRISM HBsAg.

[Slide.]

So what has happened over time? So let's say we go back about nine years, nine or ten years, looking at the two models and asking what was the residual risk nine years ago and how has that changed.

So, using the seroconversion method, we have gone from about 1 in 100,000 to the 1 in 282,000--this is just using the 38-day window period for simplicity--and using the seroconversion model--excuse me; that was the

seroconversion model--using the HBsAg yield model, similarly, we went from 1 in 100,000 approximately to 1 in 280,000. So you can see the that residual risk has declined over time.

[Slide.]

So, now, what is the impact of vaccine. So we took approximately 500 donors from two of our regions and we tested them for anti-HBs. These were HBsAg and anticore non-reactive donations so that NCHBS in these donors would indicate vaccination.

[Slide.]

So now, if you look at the results of this, I have told you already 44 percent of our donors appear to be vaccinated. The highest numbers occur in the youngest donor groups.

[Slide.]

My, these colors are awful. But, anyway, if you look at the numbers I told you nine to ten years ago of a residual risk for HBV for 1 in 100,000, then we are now at 101,000 and 280,000 with a 38-day window period. And you look at where has change occurred. The majority of the change has occurred for the youngest donors.

So, nine years ago, risk in 16 to 19 year olds was 1 in 36,000 to 1 in 44,000 and now is it 1 in 531,000. So that shows you the obvious impact of vaccination.

[Slide.]

So now how do we apply these data to NAT. I have already told you we have a defined incidence. To calculate yield, we need window periods. So there was a comparative study of NAT methods published by Assal looking at Ultrio single unit and MPX in pools of six. We also used what is published in the NAT PIs. We used an HBV doubling time, as Mike talked about, of 2.5 days.

So what do we know from these studies/ We know that the MPX in a pool of six was equivalent to the TIGRIS performed individually with window periods of 22.6 and 20.6 for the two methods respectively.

What do we know from the PIs if we want to look at other pool sizes? We know that we have to deduct ten days from the 22.6 days if we go from minipool NATs to more sensitive ID and we have to add seven days going from Ultrio ID to a minipool of eight.

Now, if we want to go to a minipool of 16 from a minipool of eight, this is one doubling time, so we just

add 2.56 days. Again, the same limitations. It assumes that the kinetics in individuals with acute ramp-up viremia and it does not consider the impact of vaccine on the dynamics of early infection.

[Slide.]

So, again, residual risk, you should understand that if we want a low ratio, fewer infectious units remaining, that is greater safety. And the yield is what we detect by these new methods. So a high yield is good. That gives us greater safety, too, or greater removal.

[Slide.]

So, first, focusing on yield. So here we want high yield. So the test pools of one by MPX gave us a yield in 1 in 466,000. Then, going to the next two methods which were statistically identical of pool sizes of six or Ultrio and one, of 1 in 713,000 to 1 in 830,000.

And then the yield is the least, as Robin has already indicated, by using a pool of 16 or a pool of eight. But these rates relative to the confidence intervals are relatively comparable. And you can further see this if we look at the residual risks.

[Slide.]

So here the residual risk is the lowest when you use the pool size of one with the MPX, the Roche assay. Next is minipools of six or a pool size of one with Ultrio. Lastly, and quite overlapping relative to residual risk, are a pool size of 8 and 16.

[Slide.]

So, to summarize what I have just shown you in the first half of my talk, there is a decrease in HBV incidence in residual risk from two models. I showed you early, nine years ago, 1 in 100,000 for a residual risk nine years ago. Now, with HBsAg, we see 1 in 280,000 to 1 in 357,000.

Vaccination has had a dramatic impact on the reduction of HBV incidence and residual risk, especially in young donors. In the absence of considering the impact of vaccine and the dynamics of early infection, the impact of NAT is the greatest with the MPX system performed individually.

And these, again, are the numbers that I just referenced, the residual risk, where residual risk increases as the pool size increases and yield decreases as the pool size increases.

But one thing that I would like to call your attention and, again, why we had the position five years ago that we did. You can see the HBsAg residual risk by the models and pool sizes of eight and 16 are relatively comparable. So this is the modeling data.

[Slide.]

However, model data does not equal observed yield.

So how do I go to my next presentation?

[Slide.]

This is now the presentation of observed yield. This is the Red Cross study we did so I would like to thank my collaborators.

[Slide.]

The objective of the study was to evaluate the yield of HBV DNA-positive donations that are otherwise undetected--that is, HBsAg and anticore nonreactive using a combination of individual donation and minipool NAT of 16.

I have already told you that the yield is expected to be the highest in ID NAT so we focused the study to do a lot of individual donation NAT testing.

We used the Ultrio on the TIGRIS platform and this was intended as a supplement to the existing GenProbe

license for a screening claim which was granted in August 12 of last year for minipools up to 16 donations. We also wanted to determine the rate and characteristics of HBV DNA-positive yield donors.

[Slide.]

So we involved three of our five national testing labs at the Red Cross who fully converted to the Ultrio system on the TIGRIS, which is the automated platform. The remaining two labs remained on HIV HCV on the manual platform.

[Slide.]

So, from IG NAT, we would have expected to see the highest yield and we calculated up to five window-period donations that we would have expected to see and one additional from minipool NAT. Part of the study design was to take the ID NAT-positive donations and dilute them into pools of 4, 8 and 16 so we could project the yield in the other pool sizes.

[Slide.]

So what were our results? By minipool NAT, we tested 1.3 million donations. We had an unresolved pool rate of .21 percent, a 0.5 percent or 1640 minipools

resolved to reactive donation. So they were reactive in minipool and then reactive again individually. We tested 576,000 donations by ID NAT with 945 reactive donations for a grand total of 3.7 million donations tested with 2400-plus reactive donations.

After you have a donation that resolves by NAT, you then do discriminatory testing so that you know if it is HIV, HBV or HCV infected. And, of those results that were reactive, 83 percent of those discriminated into one virus or another.

Of those that were non-discriminated, we saw very high rates of false positivity when you do ID NAT only because it is only one round of resolution. So, if you have a reactive donation, that donation and its products are destroyed. Whereas, for minipool, we saw a false-positive rate of 1 in 48,000 and that is because you have two rounds of testing, the minipool, and then you have a second chance to resolve false positives where you do resolution testing.

And these donors are eligible for re-entry and we have been submitting those to FDA.

[Slide.]

So now what about the discriminated results. I told you that 82 percent of the NAT yields discriminated. Of interest, 98 percent of those were concordant--that is, the NAT results and the serology results agreed. So the value of NAT here--so you can see the value with NAT for serology, we are already picking up 98 percent of what is NAT would pick up. So we are talking about the 2 percent that is the incremental yield.

So, of those, they broke into HIV, HCV and HBV discriminated positives but what is important is those that confirmed. So we had two confirmed for HIV for yield of about 1 in 2 million which is our expected yield. We have 15 confirmed for HCV which is about 1 in 250,000, which is the expected yield. And we had nine confirmed for HBV which is a yield of 1 in 410,540.

[Slide.]

So, out of minipools, eight of the nine were minipool positive. I already told you that, in a minipool of 16 by the models, we would expect to see a yield of 1 in 2 million. But, instead, the observed yield was 1 in 389,796 and, from ID NAT, we only saw one positive of all the ID NAT donations tested which is 1 in 577,000.

Of the eight minipool positives, six were anti-HBs-positive donors who were likely vaccine breakthrough infections. We know that these were vaccinated individuals. Assuming a 44 percent population of our donors who have been vaccinated, this gives you a yield on 1 in 271,000 for vaccine breakthrough because they all occurred in minipools, this is adjusted to 1 in 229,000.

Two of these five individuals developed HBsAg. Four of five converted anticore. Of those who were non-vaccinated, we had a yield of 1 in 689,707. Assuming that 56 percent of the donors were vaccinated, and those that were yields of minipools--that is, the minipool yield was 1 in almost 900,000, which, again, is quite a bit different than the 1 in 2 million that I had mentioned.

One of two of those developed HBsAg and both of them core converted. The one donor that was reactive only ID, of the nine there was only one that required ID NAT for detection. If you look at the other pool sizes, these are the signal-to-cutoff ratios--the numbers in red indicate when they were reactive--this one unit could not be detected consistently in a pool size of 4, 8 or 16.

So, again, the bottom line for the results were

nine yield with eight detected in pools of 16, one detected by a pool of 1.

[Slide.]

Now, to run through quickly, although this slide is hard to see, the nine yield donors, all except one, were repeat donors. All except one were detected in pools. The oldest donor we had was an unvaccinated donor who was our ID NAT only donor.

I think I will skip these because they are too hard to read and I will summarize these in other slide.

[Slide.]

Seven of the nine donors, we had long-term follow up for. And these are the donor codes, just so we can tell them apart. These, in pukey yellow, were the ones that were non-vaccinated. These were the vaccinated donors. And the numbers here indicate the mIU/ml, the amount of anti-HBs present. These were the time of day followed, the viral loads indicated, and all of them had relatively low viral loads except one who was a non-vaccinated donor who produced greater than 10^8 copies per ml and had unbelievably high concentrations of HBsAg.

The duration of DNA is listed here, the three

donors who HBsAg, the time period post-index in which they produced HBsAg and the time and the duration of positivity. This is when anticore converted and they all were, and I will talk about this first one separately, but they all were IgM-positive to anticore.

This is important indicating that they were all acute infected donors.

[Slide.]

Now, I mentioned to you that we did anti-HBs testing of 520 donors. This is the concentration of anti-HBs where the cutoff of 10 is way down here. So what we saw for our vaccine breakthrough donors, as far as the concentration of anti-HBs, was very, very low concentration.

Now, relative to their partners, and I didn't tell you when I skipped two slides, at least five of these, six probably, had gotten their HBV from their sexual contacts and we followed four pairs--we have done long-term follow up of four pairs.

[Slide.]

So, if you look at the DNA concentration, just in 500 random HBsAg carriers that we detect, these partners of these vaccine breakthrough donors had very high

concentrations of HBV DNA. So, relative to low concentrations of anti-HBs in the donors, you can understand how transmission would have occurred.

[Slide.]

Okay. We also did molecular studies. And I would like to thank my collaborators Wolfem[ph] Gerlich, Paul Coleman and Jean-Pierre Allain. In the molecular studies is where we proved identity between donor and partner, sexual contact, in four pairs that we studied in detail.

Looking at the full genome sequencing of six of these, the ones in yellow represent vaccinated donors and the other here represent non-vaccinated donors, Swede A2, a B genotype, FD. We have also hit a C genotype which wasn't by full-length sequencing so it isn't represented.

[Slide.]

So, now let me show you some profiles of these individuals with breakthrough infection. I will start from the simplest to the most complex.

[Slide.]

So the colors, at least these have maintained. Pink here with the X are viral loads and this is the TMA

result, the Ultrio result. So, here in this first donor, who never converted anticore or HBsAg, here you can see the DNA concentrations coming down. Everything else was negative except for his memory to anti-HBs. So, over time, he produced quite high concentrations of anti-HBs.

He had no presence of, again, any other Hepatitis B marker except for the decline in HBV DNA. And his highest viral loads were, like, 100 to 200 copies per ml.

[Slide.]

So this individual is a little bit more complicated only because, in this individual, we do have an anticore IgM response and an anticore response. But, otherwise, decline in DNA with antisurface coming up well in advance of anticore which you would expect in a vaccine breakthrough. This is a secondary, or an anamnestic anti-HBs response to memory from vaccine.

[Slide.]

Here is another individual. The difference here is this individual did produce low-level HBsAg.

[Slide.]

This is an occupational exposure, not a sexual exposure. His kinetics are a little bit more robust, let's

say. So here he had HBsAg, HBV DNA. Here the DNA is decreasing. Here is the anti-HBs, again preceding the anticore and the core M. But at least this individual produced higher concentrations of antibody faster. Perhaps his inoculum was higher from his occupational exposure.

[Slide.]

Here we have someone who was more typical where here you have a very high concentration of HBsAg, high concentration of HBV DNA. This is an acutely infected individual with vaccine, then produces anticore and, lastly, produces antisurface.

[Slide.]

So, if you take our data, our nine yields over nearly 4 million donations tested, we had an overall yield of 1 in 410,000. Looking at other studies to compare this to, all the Roche studies had a combined yield of 1 in 400,000 but those were done with less sensitive HBsAg assays.

So then, when they were retested by PRISM and you remove the PRISM positives, their yields, so that you can compare these directly, but they were all screened by ultrasensitive HBsAg tests, was 1 in 610,000,

Then a study done by nine ABC centers using pools of 8 yielded a yield of 1 in 283,000. I am almost done.

[Slide.]

So, in summary, the Ultrio assay was comparable to the Duplex assay. I didn't show you those data. We had nine HBV yield samples, the rate I have mentioned before, 1 in 410,000, by minipool, 1 in 380,000. Six of nine of our individuals were immunized with the rates, as I have mentioned before, and three were not immunized.

[Slide.]

So what can we conclude from all of this? From the modeling studies, we had seen quite different rates and from ID NAT, we saw 1 in 466,000 as the yield to 1 in 713,000. So then, when we went to minipools, a minipool of 6 by Roche at 1 in 830,000 was comparable to the ID NAT yield in Ultrio.

Then, moving to pool sizes of 8 or 16, we saw higher yield rates that would have been modeled. However, we found, and all of the studies found, higher rates of 1 in 300,000 to 1 in 600,000 relative to the numbers that I quoted before of 1 in 1.3 million to 1 in 2 million.

So, in our study, what was important is that our

minipool NAT observed yield in both vaccinated and non-vaccinated donors suggest that there is no difference between the minipool size of 8 or 16. The modeling studies and our observed yield studies show that these were comparable.

We only had one donor who was not detected in a minipool of 16 and he required ID NAT for detection.

[Slide.]

I just want to close with one slide of a study that hasn't been mentioned relative to our anti-HBs-positive units infectious.

[Slide.]

This study was just published in the Journal of Hepatology. Here the donor's index sample was negative for surface, positive for anticore with a low level anti-HBs, just like in my donors, and low-level DNA, so very comparable to the donors that I showed you.

There were two infected recipients. One had a pre-transfusion sample and one did not. Following these donors at 4 and 8 days, for Recipient 1, he converted HBsAg anticore IgM. He had 185 copies of DNA and he was genotype D with the same sequence as the donor.

The second recipient was also followed although there was no pre-transfusion sample. He produced a high level of HBV DNA and was genotype D and, like the other two individuals, they all had identity relative to sequence.

Thank you.

DR. SIEGAL: We will now hear from Dr. Richard Forshee, Ph.D., from FDA, FDA's Perspective on Modeling and Yield Data.

FDA Perspective in Modeling and Yield Data

DR. FORSHEE: Good morning, everyone. I am Rich Forshee with the FDA. I am part of the Risk Assessment Team in the Office of Biostatistics and Epidemiology.

[Slide.]

There are three major issues that I am going to discuss today. First, I am going to provide some additional background on vaccination rates in the U.S. for hepatitis and how those have changed over time. Second, I am going to provide our perspective on the confidence intervals for yield that have been presented earlier. And, finally, I am going to close with some general comments about some of the remaining uncertainty and unanswered questions that we think need to be addressed.

[Slide.]

By means of background, we know that the incidence of acute Hepatitis B has declined in the United States over time. According to the CDC disease surveillance data, the incidence for all ages in 2002 was 2.8 per 100,000. Importantly, this is a decline of 67 percent from 1990 data.

When you look at the younger age groups, the 0 to 19 age group, there we have seen an 89 percent decline since 1990.

[Slide.]

As we will see, one of the reasons for this is the widespread use of Hepatitis B vaccines. Currently, the recommendation is that all infants, beginning at birth, receive a series of Hepatitis B vaccines. Also, all children who are less than 19 years old who have not been previously vaccinated are recommended to receive it, and there are several categories of adults who are at high risk that are recommended to receive it.

As has been mentioned in earlier presentations, the HBV vaccine contains a recombinant version of the Hepatitis B surface antigen and the HBV vaccine is highly

effective. The WHO has estimated that it produces protective antibody levels in more than 95 percent of infants, children and young adults, although the effectiveness is lower in older adults.

[Slide.]

In order to better understand how this is affecting the issues we are discussing today, we analyzed data from the National Health Interview Survey from 2000 through 2006. This contained more than 200,000 respondents. We extracted data on demographic characteristics, Hepatitis B vaccine status and blood-donation history.

For this analysis, we were defining received a Hepatitis B vaccination as having received at least one shot. This is going to be very similar to what we would get if we restricted it to receiving all three shots because 86 percent of the people in the sample who received at least one did, in fact, receive the entire series. We used appropriate methods for analyzing the data.

[Slide.]

This shows our estimates by one-year age categories of the proportion of respondents who have received the Hepatitis B vaccine. So the point to note is

that, the younger age groups were up over 60 percent that have received it and this declines as you go to older age groups.

[Slide.]

We know that there are many factors that are going to affect the probability of receiving a Hepatitis B vaccine so we estimated a logistic regression controlling for a number of demographic factors so that we could isolate the independent impact of each one of these factors.

What we are showing in this slide is what our estimated Hepatitis B vaccination rate is by age between 2000 and 2006. So, on the slide, you see two bands representing the confidence intervals of our estimates and we see the line in the middle of each band representing what the point estimate is for those age groups.

A couple of things I want you to take away from this slide. First, I want you to note the shift upward in vaccination rates from 2000 to 2006. So this shows that we have a trend upward particularly in the younger age groups and, second, note that it is also beginning to shift out so that, even as you are getting into the young-adult age groups, you are starting to see higher vaccination rates.

[Slide.]

There is also an interaction when you look at blood donors. When you look specifically at the vaccination rates among blood donors, this is even higher than you saw in the general population. Notice that our sample size is smaller here because we are looking only at the approximately 5 percent who donated blood. But we are getting estimates in the 70 percent range for the youngest age groups.

In the logistic regression model, this difference between non-donors and blood donors is statistically significant.

[Slide.]

All of this data from the National Health Interview Survey is consistent with the data that Dr. Stramer presented earlier showing that we are getting higher blood--HBV vaccination rates and that those rates are even higher among blood donors. So, currently, the vaccination rates are above 50 percent in the younger cohorts and, in blood donors, we are up around 70 percent in the younger-age cohorts.

We know that there are very high vaccination

rates in the 0 to 19 age cohort so we expect these rates to continue to increase for the foreseeable future. Now, the important point of this is that this can have an impact on our HBV testing among blood donors.

[Slide.]

We know from the Zhao paper that was discussed earlier that HBV vaccine recipients can test positive for the surface-antigen test for up to 21 days and, as discussed earlier, there have been breakthrough infections in HBV vaccinated individuals.

As was discussed, typically, these are symptomatic and usually have low viral loads and it is unknown whether or not units from vaccinated individuals with breakthrough infections are going to carry a risk for transfusion-transmitted HBV.

[Slide.]

Now, I would like to turn to discussing some of the information on the yield that we are getting from the different NAT tests that are being discussed. What I am showing in this slide is some of the same data that has been presented by Dr. Biswas and Dr. Stramer, but this is showing it in the graphical format.

What we are looking at here is at the yield of blood components--so we have multiplied donations by 1.7--by the sensitivity of the test for non-vaccinated donors only. Again, as was discussed previously, vaccinated donors, because of the different characteristics, different kinetics of the infection. We cannot estimate the non-vaccinated donors from the data that was presented in the Stramer paper.

So the point of this slide; this is showing the mean estimates of yield from the different tests. So we have 13 cases using the component method, using the Ultrio 16. We have 19 cases using the Ultrio MP8, 31 at the MPX with a 6 minipool. We have 36 with Ultrio NAT and we have 54 with the MPX ID NAT.

Now, these were calculated by multiplying 15 million donations by 1.7 components time the window period times the incidence divided by 100,000. The point that I want to make here is that the confidence intervals that we are looking at are based on our uncertainty about the incidence.

So, in the calculations of these confidence intervals, the donations, the components and the window

period was all constant at whatever incidence level we were looking at.

[Slide.]

Now, the reason that this is important is that, while we have uncertainty about the incidence, if the incidence is high for one test, it will be high for all of the tests. So here, for example, if we have an incidence that is at the high end of 5 per 100,000, that is going to shift the yield up for every one of the tests.

[Slide.]

Similarly, if the incidence is on the low end of the estimate, it is going to shift the yield down for all of the tests. So, even when we have overlap, the overlap on these estimates is the result of our uncertainty about incidence rate, but incidence rate will be constant across all of the tests.

So what we did, to try and give you an understanding of what the difference in yield would be according to the different tests that are used was we estimated the difference in yield using the mid-point of the incidence rate, the lower 95th percent band and the upper 95th percent band for the incidence rate.

[Slide.]

That is presented on this graph. So, on each one of these, it is showing the incremental yield based on 1.7 components per donation, so it should go to more sensitive NAT tests. So, for example, going from the minipool of 16 to a minipool of 8 would yield 6.1 additional yield with a range going from 3.9 to 9.5.

Going from Ultrio with a minipool of 8 to MPX with a minipool of 6 would yield 11.6 cases. And going from the MPX 6 to Ultrio ID, 5.1 cases and from ID Ultrio to ID MPX would yield 18 cases. Again, the confidence intervals here are calculated based on the lower and the upper 95th confidence interval of the incidence rate.

[Slide.]

Just a couple more general comments on the presentations from Dr. Busch and Dr. Stramer. Overall the data and analysis seem sound. There are a couple of caveats that we wanted to once again remind the committee of. The assumptions of residual risk in the yield modeling are primarily based on the incidence rates from HBsAg PRISM and these models do not include the breakthrough infections in vaccinated individuals.

This is the point that Dr. Biswas was making with his slide trying to show the potential number of yield when we adjust for the vaccinated population. We know that we are getting some breakthrough infections from the vaccinated population. We are seeing a ratio of about 1 to 1 or 1 to 2 in the empirical data that we have so far. And the yield that we are showing here is only from the non-vaccinated, so we have to realize there is this additional yield from vaccinated individuals.

[Slide.]

There is a good bit of good news that we should be aware of as we consider this issue. First, there are several lines of evidence that suggest the risk of clinical symptomatic cases of HBV is declining. We have had a strong increase in vaccination rates. We have shown this in our modeling of the survey data and it was shown earlier in the data from blood donors that Dr. Stramer presented.

We have seen a decrease in reported cases of acute Hepatitis B infections and we have seen a decrease in the estimated residual risk in blood donors. Again, this was from Dr. Stramer's presentation.

All of this is likely due to some successful

public-health interventions that include the HBV vaccination programs as well as programs to reduce risky behavior.

[Slide.]

So, while we have a lot of good news to report, there are also still some concerns that we have, having discussed this issue at the FDA.

First, at least some vaccinated individuals are experiencing breakthrough infections. The estimated residual risk that we have seen from the HBsAg PRISM incidence window modeling approach does not include vaccinated donors and those are becoming a higher and higher proportion of the blood-donor population.

The breakthrough infections that do occur are unlikely to be detected without NAT. This was shown in Dr. Dr. Busch's slides where he showed that the level of viremia will typically not reach the level at which HBsAg PRISM would detect the infection. Finally, as Dr. Biswas discussed earlier, the risk of transfusion-transmitted infections due to units of donors of breakthrough infections cannot be dismissed at this time.

There are also some questions where more

information would be very useful. Currently, we don't have good information on the rate of breakthrough infections among HBV vaccinated individuals. The reason that we don't know this is that there are limitations with the HBsAg window-period modeling.

Since HBsAg will not pick up the infection from vaccinated individuals, we cannot calculate the incidence and use that in the incidence window-period modeling. Also, we do not know the kinetics within vaccinated individuals and so the window period may be different in that group.

So we have a big unknown about exactly what is going on among the vaccinated population in terms of the rate of breakthrough infections that may be out there. It would be possible to get some insight into this with further NAT window-period modeling since the NAT test can pick up the breakthrough infections. Dr. Busch, I believe, alluded to this when he was talking about how some countries are using a NAT incidence window-period modeling, but that is not appropriate in the U.S. at this time because we do not have a wide enough base of NAT that has been used to develop this information.

[Slide.]

So, some of the final thoughts that we have are that HBV NAT would add an additional margin of safety and yield some units that would not be identified by current testing. The more sensitive the test that is used, the more units of yield that we will see.

However, many of the units that are identified would be breakthrough infections in HBV vaccinated individuals, but I do want to emphasize that the number that I have presented in this presentation are just those that would come from non-vaccinated individuals. So any addition breakthrough infections would be on top of the numbers that I have presented in my part of the presentation.

I would like to thank all the people that have worked with me on this presentation at FDA including Robin, Dr. Jay Epstein and Hira Nakhasi as well as my colleagues in the risk assessment group, Dr. Mark Walderhaug, Steve Anderson and Hong Yang.

if there are any questions or comments, I or my colleagues would be happy to address those. Thank you very much.

DR. SIEGAL: Okay. Thank you very much, Dr.

Forshee. Perhaps we would wait for questions until after the second part. Are there pressing questions now for any of the presenters?

DR. RENTAS: I was just wondering, one of the questions that we are being asked to answer here, No. 3, assumes a sensitivity of at least 100 IU/ml for individual samples. How do you come up with that number?

DR. FORSHEE: May I defer to Dr. Biswas to answer that.

DR. BISWAS: This had to do with the fact that, when we licensed the AmpliScreen four or five years ago, four years ago, the sensitivity, as I showed on one of the very earliest slides, it was the sensitivity using the 24 pool format was 105, 106 IU/ml. The time is now different and we the possibility of using smaller minipools and ID NAT. There has been an increase in automation.

It didn't make sense to go for, say, a 200 or a 300 IU sensitivity. Remember, as I showed on two of the slides, the MPX at pools of 16 had a sensitivity of 166, 167 IU/ml. So it would have been really going backwards and that didn't make any sense to us.

DR. KULKARNI: I have two questions. The first

one is does the vaccination status of the recipient influence infectivity. The reason I say is that some of the data presented showed no infectivity and I was wondering if this is the same status if the recipient was a neonate, just had a vaccination, hasn't had time to have a response, migrants who haven't had vaccinations and patients who get repeated transfusion such as rare bleeding disorders, sickle-cell disease, who continuously get transfusion.

That is Question No. 1.

Question No. 2 is about the donor breakthrough. Is it related to the number of doses of vaccination they got, like, are these breakthroughs seen in those donors who received only one shot versus two shots or three?

DR. BISWAS: There are probably people in the room who can answer better than I can into the number of shots, but the breakthroughs, I would include people who had one shot, two shots, or a full three shots.

In regard to your first question about protection of the other recipient, I really don't know the answer to that. It is a very great question and I would think that there would be some protection there. But I don't know the

complete answer to that.

DR. FORSHEE: I would just add that I think that that is one of the areas where we have some concern about the uncertainty that we are seeing right now and that, at the moment, we feel that we cannot dismiss the possibility that there could be transmission. What that probability of transmission is, I don't feel that we have a good handle on that although we do have some evidence that was presented by Dr. Stramer and by Dr. Busch earlier.

DR. HOOFNAGLE: I had a question about your yield by sensitivity of the test. You say it is a yield of HBV per year. Is this the total number of cases in the United States or is this like 40 cases per 100,000? What is the denominator? I didn't quite understand.

DR. FORSHEE: This is the total cases in the United States. This was calculated--

DR. HOOFNAGLE: So it is total number.

DR. FORSHEE: Yes.

DR. HOOFNAGLE: Not divided by anything.

DR. FORSHEE: No; we have multiplied an estimated 15 million donations times about 1.7 components per donation.

DR. TRUNKEY: I have a couple of--well, a comment about your chimeric model. It bothers me a little bit because it doesn't have human RES or human lymphocyte data. Although it does corroborate the chimpanzee, it just doesn't seem to me to be a good model, but I may be wrong on that.

DR. FORSHEE: Dr. Busch would have to respond to that.

DR. TRUNKEY: Okay. The other question I had, though, is how many of the breakthrough hepatitis cases go on to develop chronic hepatitis?

DR. BISWAS: I don't think that is really known. I think that Mike said that most of them do not. I mean, up until now they do not go to chronics. Mike?

DR. BUSCH: To my read of the literature, there is only one referenced case of a breakthrough infection that developed chronic hepatitis with no actual details in the reference. So all the evidence would be that virtually all of these breakthrough infections, prior to these studies, have been detected simply by anticore conversion without chronic surface antigen.

So the expectation is that essentially none of

these--or very rarely will they develop chronic surface-antigen carrier status. Whether they could become chronic in the liver as classic HBV infections do and eventually become occult infections and, when these people become immunosuppressed, they could reactivate, I think, is completely unknown at this point.

But they are clearly suppressed acute. They never have demonstrated an acute symptomatic infection and, again, there is only one sort of peripheral reference to a case that became a chronic carrier.

And then, with respect to the chimeric-mouse system, I think the point is well taken one theoretically could create a mouse that was chimeric both with respect to human hepatocytes and human immunity and could vaccinate that mouse, et cetera. So you could theoretically develop this model further.

But, in terms of minimal infectious dose, there are studies that have been done by the Japanese where they have added passive antisurface and shown that they can reduce the infectivity recently. So I think, in terms of studies of minimal infectious dose and particularly the infectivity, the potential infectivity, of these vaccine

breakthrough plasmas which are available, I think the mouse model could be informative.

Clearly, everyone would prefer to do the studies in the chimp where you could infuse large volumes of these plasma components but, so far, the availability of chimps for these studies has not been possible. So that would still be something we hope could be accomplished.

DR. SIEGAL: Dr. Alter.

DR. ALTER: To talk to that point, you have to look at the mouse model as purely an infectivity model. It is not a disease model but it will tell you whether there is an infectious dose or not. I think, for that, it is good. And the beauty of the mouse model is that you can use a huge number. I mean, it is expensive, but you can use many, many more than you do chimps so you can get averages.

So I think it is a good model for infectivity. I think Mike's data show that. The Japanese data, you can find a dose. And chimps are a dying entity so you cannot--chimp studies are going to be very limited.

DR. SIEGAL: Dr. Nelson.

DR. NELSON: When we screen donors for

infectivity with surface antigen, there can be mutations or reasons that the surface antigen is negative and rarely you find these mutations. But I wondered, when they are found, is there evidence that they are clustered? In other words, could the same virus, rather than randomly distributed, be an outbreak, if you will? Is there data on that?

DR. FORSHEE: I don't have an answer for that. Do you, Robin?

DR. BISWAS: I didn't really hear the question sort of acoustically.

DR. FORSHEE: I believe the question was are the mutated outbreaks sometimes clustered rather than purely random across the U.S.

DR. NELSON: Yes.

DR. BISWAS: I don't know the answer to that question.

DR. SIEGAL: Dr. Busch.

DR. BUSCH: I don't know about the clustering, but I think one of the important findings that has come out of these NAT studies is were the surface-antigen tests failing to detect HBsAg in carrier donors or acute donors attributable to surface-antigen mutations and the failure

of the assay simply to detect high-level viremia.

We would be finding donors who are surface-antigen negative but detected by NAT in whom viral loads were very high. And we are not finding those. So I think the evidence is that the surface-antigen tests are actually--and, obviously, the companies have constantly improved those tests to detect these variants--that we are not seeing surface-antigen mutant failure to detect with an frequency, not only in the U.S. but in the international studies that have applied NAT.

DR. SIEGAL: Dr. Stramer, I know you were up there to say something. I am sorry to have overlooked you.

DR. STRAMER: Yes. I had several comments to questions. Regarding our breakthrough cases, 100 percent of them all cleared virus. They cleared surface antigen and they cleared DNA and produced a strong HBs or a strong anticore response. So, at least in our limited experience with six, none of those were chronic carriers.

All six also received all three doses of the HBV virus so it wasn't like they received one and then it was incomplete immunity. They all received all three.

I would like to also say if the sequence donors

that we had, the breakthrough cases, all except one were wild-type virus. Only one had the GlyArg mutation and amino acid 145.

And then, also, I would like to comment regarding smaller pool sizes or ID NAT. The conditions, really, haven't changed in the laboratories and that is the same prohibitions to us decreasing pool size or going to ID NAT exists regarding capacity in the laboratories. So that was part of my point to show when the data show for observed and modeled that the difference in yield between a minipool of 16 and a minipool of 8 are negligible, if any. So I would really like the committee to consider that information.

DR. SIEGAL: Dr. Alter.

DR. ALTER: Sue, while you are there, one of the assumptions in the vaccination programs was, and the reason why booster doses weren't thought to be needed, was that, if someone was re-exposed they would have a rapid amnestic response which would protect them. Have you shown this amnestic response in these people?

DR. STRAMER: Yes. I showed you the profiles. They, perhaps, weren't very clear on the slides. But all

of them produced a very strong secondary immune response.

DR. ALTER: How soon is that, within a week?

DR. STRAMER: It was longer than a week, perhaps several weeks to a month. But they all produced a strong immune response.

DR. SIEGAL: Thank you both. Anyone else?

DR. HOLLINGER: Sue, while you are still there, I have a couple of questions--since you are still up there. What was the ALT level of these donors?

DR. STRAMER: I think you have asked me that question before.

DR. HOLLINGER: I know, but not before this meeting.

DR. STRAMER: Yes; that is quite right. There was no ALT testing done on these individuals.

DR. HOLLINGER: Okay, because it is a real important issue and I am sorry it wasn't done. It should have been done, I think.

The other question, which I have asked you before, is about the partners of these donors. As you know, there is a question that is usually asked about whether they have had any contact with patients with hepatitis before. The

issue is why was that question not answered. Did they assume that, because they were vaccinated--maybe we have to change the question--but it was assumed that because they were vaccinated they were not at risk because they had a partner who was Hepatitis B-positive or what?

Can you sort of give me an idea, when you have gone back--and also the question that was asked before about how many vaccines they have received. And I have some other questions, too.

DR. STRAMER: The partners--the donors had no idea that their partners were HBV-infected. The only reason that they found out they were HBV-infected is because they, themselves, were HBV-infected and so, to identify risk, we asked them, well, in addition to vaccine and documentation of three doses of vaccine, what were your other risk factors, or risk indicators.

When I found out they had partners, we requested the partners to come in and that the partners were tested. So it was only post that the donors were identified, themselves, and the partners came in, that we identified all the partners as high-titer HBsAg chronic carriers.

Do you have more questions, Blaine?

DR. HOOFNAGLE: Maybe we will come to this later, but what happened to the recipients. One of the issues we haven't heard at all is whether post-transfusion Hepatitis B is still occurring in this country. Do you know?

DR. STRAMER: Well, in these particular donors, we haven't done the lookback. Many of the risk factors in the donors occurred prior to, or subsequent to, their prior donations. So when they had the new sexual partner, we could identify when exposure probably occurred. And their prior donations occurred on a point previous to the exposure, so we didn't conduct lookback on these. And lookback is actually not a requirement.

DR. HOOFNAGLE: So these blood samples were not used.

DR. STRAMER: Yes; if they are positive, of course, they are interdicted and discarded or used for research. But when we talk about lookback, we typically talk about prior donations.

DR. HOOFNAGLE: Yes; I know.

DR. HOLLINGER: One of the issues, I think--I am always bothered a little bit about the question about breakthrough vaccines or whether this is vaccine failure or

something of that nature. Perhaps, that is a semantic thing, but there is an issue here.

I don't think that you know what their anti-HBs status was prior to the index blood. So we don't know, really, whether they had antibody prior to that and it is conceivable that they had had not a very good response or, perhaps, a suboptimal response, to this vaccine.

If you look at the genetics of this, there were only, I think, one or two individuals that had an A2, genotype A2, which is the ADW2. And the ADW2 is what is a vaccine is made from. That is the primary vaccine that was made in this country and mostly throughout the world.

Many of these other people who acquired infections were AYWs. They were either genotypes F and I think there was a G and an H. There was a C and a B, I think, also.

Now, some of those could be ADs, but they also could be AYRs and so on. And my understanding is that many of them were not ADW2s. So there could have been a very poor response to the vaccine in general in these individuals and may not have had any antibody response.

What you are seeing at the index case, when they

already at least have nucleic acid detected in their blood, may actually be an abortive response, an antibody response, to this infection which is acquired at that time. So I do think that is probably an important issue here about these "breakthrough" cases and what they might mean and whether they really are infectious or not at this point, even though nucleic acid might be detected.

DR. BISWAS: Could I just say something about HBV transmission. I just want to state that we do get occasional reports of HBV transmission by blood. And they can be fatal.

DR. FINNEGAN: I just wanted to follow up on the question of what happens to the recipients. In Dr. Biswas' paper, he talked about the Danish study where one recipient got sick and three did not. Did they expound on was this person immune-compromised and what kind of disease did he have?

DR. BISWAS: It wasn't mentioned in the paper. That was not mentioned in the paper.

DR. SIEGAL: Dr. Bianco.

DR. BIANCO: The discussion has focused on the breakthrough infections. But I would like to know, and Dr.

Biswas probably knows, when the discussion in 2004 and 2005 came up about the HBV NAT, was the pickup recognized at that time and the pickup recognized today, using the pools of 16 or 6, very different, statistically different? Do we see a change in the real effectiveness or efficacy of the test or are we focusing on the breakthrough infections that we really don't know if they are infectious or not.

DR. BISWAS: At the time, the argument that was made five years ago was that there was no way could one do smaller pools or ID NAT. Automation was not--there was very little automation. And the argument that was made at the time was that the pickup wasn't enough. In the clinical trials, it was two yields per, I think, 700,000, something like that, and the yield was one yield for about 350,000 donations.

So the argument was made that the increment was not enough to really affect--do something good for the public health. The change really is that there is automation and now it is very much easier to do smaller pools and ID NAT which, as I showed in the slide and I think other people have also shown, that the pickup can be increased easily.

DR. ALTER: Another thing that happened beside test sensitivity was another cohort, four-year cohort, of young people entered the donor pool, vaccinated young people. So there is a lot more people in that category.

But, in terms of Blaine's point, think we have to assume, and we know, that antibody titers wane and some people don't respond, 5 percent, and they are not rechecked usually. And we know that antibody titers wane over time, but the assumption has always been that you will get this rapid boost and you will not get clinical infection.

But what we are now finding is that some people are getting infected but it is an aborted infection, in general, so that gets us--so it is not totally surprising that this is happening. But I will bet, if we had pre-existing antibody levels, we would find that that group was very low or absent.

But now we are driven into the next question; are these aborted infections transmissible. That is what we are faced with.

DR. SIEGAL: Dr. Hollinger.

DR. HOLLINGER: I just want to comment on the Yoshizawa paper the Mike talked about as well as in the

chimpanzee thing because I think there are some issues that just need to be brought out. The Yoshizawa paper was done with only about three or four chimps. And the other chimps that were used, the other two chimps that were used, they were reinoculated several times, either with the same genotype or with a different genotype in order to preserve and conserve the chimpanzees which they had and a delay time between their inoculations was only 17 weeks which is probably, in my opinion, not enough time to wait and to see, particularly with low-level infections, whether or not these animals were actually infected also with that same genotype or a different one.

So that is a lot of differences when you look and then try to come down to a conclusion of the 10 copies per ml. The better study--I mean, they did it with acute-phase plasma and that was an important thing, I think. None of them have ever done it with a sero-negative plasma--that is, just plasma which is HBV DNA-positive but no other markers. These had markers.

The Purcell [ph] study which is Zou's study was done with 55 chimpanzees where they looked for the copies per ml for infectivity. And that ranged from 3 up to--I

think their genotypes were A, C and D, if I remember right. And it ranged--as Robin mentioned, it ranged from 3 up to 169 genomic equivalents per ml.

So it is hard to know. But I do think there is--and I think Yoshizawa saw this also, there were some genotype differences in the rapidity with which these animals acquired their infection in terms of genotypes. So I think we don't know, really, what are the chimp infectious dose 50s. That means that 50 percent of the animals don't get infected and 5 percent do when you are looking at--whether you use 10 copies per ml or 170 copies per ml.

So we always have to keep this in mind when we are looking at these studies about these low-level occult infections whether or not they might be transmissible or infectious. And then the other issue is the anti-HBs and we will deal with that coming down as we discuss it a little later.

DR. NELSON: Blaine, is it copies per ml? I think you talked about copies per transfusion; right?

DR. HOLLINGER: Yes; I'm sorry. You are absolutely right. They talked about copies--Yoshizawa

talked about 10 copies, not per ml.

DR. NELSON: In other words, the total challenge.

DR. HOLLINGER: You are absolutely right.

DR. NELSON: Right; not per ml.

DR. HOLLINGER: That is not per ml. And the same thing was true with the Zou paper. It was copies that resulted in 50 percent of the chimps becoming infected. Yes. Thank you.

DR. Di BISCEGLIE: I was going to save this comment for later, but I think I need to say it now. I could see where an outsider, listening to this conversation, might go away with the impression that there is a raging epidemic of post-transfusion Hepatitis B going on this out and, I mean, we really have heard no evidence that this is a clinical issue.

The rate of Hepatitis B in the country is coming down. Anecdotally, clinically, simply we don't see it. The CDC has not detected post-transfusion Hepatitis B as being a problem. Dr. Biswas alluded to some reports from the FDA. We haven't heard whether those have been investigated and really been shown to be due to transfusions.

He mentioned death but, of course, we are talking about trivial hepatitis seroconversion events, not clinical disease. So I really feel like I need to say that to frame the further discussions and questioning.

DR. HOOFNAGLE: I would second that. These calls about fatal post-transfusion Hepatitis B, what they usually are are fatal reactivation of Hepatitis B in patients with bone-marrow transplant or chemotherapy who are given blood transfusions. So they immediate assume it is the blood transfusion. We see this a lot, which is reactivation of Hepatitis B which is very real and which really demonstrates that the patient who has cleared surface antigen and has only anticore and, even if they have anti-HBs, they have the virus in their body because the virus, it can be reactivated.

For instance, if you take someone--if you take their liver and transplant it into someone else, the rate of Hepatitis B in the recipient is, like, 75 percent. So most people who so-called recover from Hepatitis B harbor Hepatitis B virus in their liver. This is the basis for the use of anticore testing as a way to get rid of post-transfusion hepatitis.

I am afraid you quoted all the negative studies. There are many positive studies in the literature showing the infectivity of anticore-positive blood. The most convincing one, actually, was done in the Netherlands where they did a random--believe it or not, they did a randomized controlled trial with a consent form in which they gave patients transfusions either with blood that was positive for anticore or that was negative.

And, of course, the study was stopped precipitously when they had a 10 percent rate of Hepatitis B in the recipients of blood that was anticore surface-antigen negative. Now, those were the days before HBV DNA testing so you would love to be able to go back and test whether they actually had HBV DNA.

But, in the few instances that I have been able to get a hold of, most of the so-called infectious people are HBV DNA-negative. But I think there is no question that people with anticore who have recovered can be infectious--not all. It is probably 5 or 10 percent. It is probably intermittent replication of virus that comes up and it probably requires a whole unit of blood.

This is why the chimpanzee studies were also

negative like Fred Prince's study. They are not infusing the chimp with a full unit of blood. They are giving him a milliliter. That is what I did and I got negative results as well.

DR. BISWAS: There is no double that the bulk of the literature showed that blood with DNA and anti-HBs, and many of those would have anticore, did not transmit. However, there are some indications that, under certain circumstances, can transmit from the two papers that I mentioned.

The other issue is that, when reports do come in to the FDA, we do look at it and occasionally there are fatalities, and it looks very much like, although one can't sometimes prove it 100 percent, but, when you do lookback and look at the results of, say, a conversion of a donor, and put that together with when the person got--when the recipient got the hepatitis, it does look as though transmission actually occurred.

They are very rare but my point is it is very rare but that it still does occasionally--very rarely--occur.

DR. HOOFNAGLE: The other issue in the literature

that is always a problem is false-positivity when testing for HBV DNA. This is a test that is very difficult. You can easily get contamination and get a positive.

So many of the cases in the literature, the instances in the literature, they have stored serum that has been frozen away and they thaw it out and they test a bunch, and it is prone to problems. And I have to say that, in most of these studies, there are not controls. There is no look at people without these markers or anything.

So the only result is a positive result. And that is what has plagued this field so long. The studies that were actually presented today are very good because that type of thing has been very nicely shown not to be the problem.

DR. FORSHEE: If I may just quickly respond to that. I just want to emphasize that, in the results that I presented for the non-vaccinated population that is using the HBsAg PRISM incidence window-period modeling, and so we don't have the issue of NAT false-positives in the data on projected yield that I presented.

DR. SIEGAL: Dr. Bianco.

DR. BIANCO: Just a quick comment. Dr. Biswas,

it would be--none of the recent fatality reports that come out of FDA have mentioned a death associated with an infectious agent. So it would be very important to have a category like that so that we could have a better idea of what--it would be very, very useful.

DR. BISWAS: Right. Thanks.

DR. SIEGAL: Apropos of the lack of a raging epidemic, it also should be mentioned that there are now effective antiviral drugs for Hepatitis B which may contribute to the control of the occasional breakthrough case that we see.

Are there any other comments?

DR. COLVIN: Just one quick comment. Although, I agree that there is not a raging epidemic of transfusion-associated Hepatitis B infection, it is also very reasonable to think that we could make a rare disease even rarer in a cost-effective manner by implementing a new test. So if we can make it even rarer, that is still a valuable change in clinical practice that we could possibly make at some point.

DR. SIEGAL: Any other comments? If there are not, I would suggest that we take our break now in the

interest of coherence for the next topic, Topic IB. So let's take 15 minutes.

[Break.]

DR. SIEGAL: While people are assembling, if you could please quiet down, Dr. Blaine Hollinger has asked for a couple of minutes to make a brief presentation apropos of the previous discussion.

DR. HOLLINGER: We had some comments about outcome and I thought I would show something that Roger Dodd and I published in January in Transfusion on HBV lookback and traceback.

[Slide.]

But I used the data, and what I am doing here, is just using the data that we used or the assumptions that we used in there to look at outcome over time annually and over 25 years. Now, apply them to the yield ratio here of 1 in 410,000. We actually had a yield ratio that we used there of 1 in 205,000 so I just doubled it, or halved it, basically, which made it easier to make the computations.

But I thought it might be interesting to look at because I think it is important to know that not everybody who gets Hepatitis B dies of Hepatitis B. In fact, the

vast majority don't. The vast majority do very well.

But this looks at here the estimated number of post-transfusion events annually and over 25 years. It took into account, and I used here in doing this, this estimate, that there would 75 percent transmission of these units. I don't think it is that high. I think it is much less than that, perhaps closer to 20 percent or so.

But I used that 75 percent, so take that into account when you look at these numbers. Also, I think most of us understand that 50 percent of recipients are not alive after five years, and about 40 percent after 10 years, and maybe 25 percent after 25 years. So those all have to be taken into account in this evaluation as well.

In addition, we looked at 1.45 components for each unit of blood in looking at this. So, annually, 14 million donations over 25 years, 350 million donations, just a multiplication there. Acute symptomatic Hepatitis B hospitalized. What was taken into account here is about 28 percent of these individuals would develop symptoms and about 70 percent of those would be hospitalized.

I am not sure that is true of patients who get a lower load. But, anyway, if you use that computation, you

see that only about seven-and-a-half people would be hospitalized using that 1 in 410,000 yield. Seven-and-a-half people would be hospitalized in a year and then, assuming patients die over time, that would represent about 188. This would be just 25 times that, 188 over 25 years would be hospitalized.

In terms of a look at chronic hepatitis, only one-and-a-half of these individuals would develop chronic hepatitis. And that is based on about 4 percent patients developing chronic hepatitis. In immune-compromised people, it is going to be higher but most of those people are not going to be alive in 25 years.

In many patients, most of us believe it is actually much lower than that in terms of the development of chronicity after an acute Hepatitis B infection. And then, over 25 years, taking into account the number who are going to die in that period of time, only 15.7 chronic cases in that period of time,

Death from fulminant hepatitis assumed about 1 percent of hospitalized patients, 0.075 annually and 1.9 over 25 years, and cirrhosis and HCC about 1.25 over 25 years with cirrhosis and hepatocellular carcinoma.

So the important thing here is that the numbers over 25 years are really relatively small considering that there will be 350 million donations that will tested in that time period.

[Slide.]

I just have one other that I just was going to show, and I will be glad to answer questions on that, but the other one was a study that Robin talked about. This is the Satake study. This, to me, is a very critical study where we are looking at anti-HBs and its role in transmission.

As most of you know, the Japanese Red Cross, since 1997, have been saving all of their donor bloods. So they are able to go back and look at these donor samples and retest them for HBV DNA. And, in this evaluation which went from 1997 to 2004, when they did that, they had 22 individuals. Now, this is the outcome following transfusion of HBsAg-negative but HBV DNA-positive blood in the presence and absence of anti-HBs.

There were 22 individuals that got blood that was HBV DNA-positive and had anti-HBs and none of them--none of them--developed Hepatitis B. On the other hand, there were

37 individuals that HBV DNA-positive blood but no anti-HBs and 27 percent of those developed chronic Hepatitis B.

Now, the question you could ask, and I have always asked, is why not 100 percent? Why didn't they all get infected. There are a lot of reasons possibly for that. One is, that you are in Japan. There are a fair number of patients there who already are immune to Hepatitis B. They did not test the recipients to see who was immune or not.

Secondly, we don't know about concurrent administration of transfusion which may contain anti-HBs in it and, therefore, may have neutralized the virus. We don't know the concentrations of virus and a variety of other things. But this study, I think, is a very important study when we discuss about transmission of blood that has anti-HBs in it.

Thank you.

DR. NELSON: Blaine, did they measure the level of anti-HBs? Is that above a 10 IU cutoff and is it vaccine-induced or natural or what.

DR. HOLLINGER: They didn't have that information--I asked Dr. Satake about that. They didn't do concentrations of anti-HBs nor did they know how many were

vaccinated. So, I'm sorry; I don't have that information.

DR. SIEGAL: Okay. Thank you very much, Dr. Hollinger. Let's hold any other discussion until we have gone through Section 1B and let's start with Melissa Greenwald, M.D., Commander, U.S. Public Health Service for the FDA, Introduction of Testing Donors for HCT/Ps for Hepatitis B by NAT.

Testing Donors of Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/Ps) for Hepatitis B Virus Infection by Nucleic Acid Testing

DR. GREENWALD: Good morning.

While they are getting my slides ready to be projected, I am in the Office of Cellular Tissue and Gene Therapies at FDA. As you will hear, I am going to slightly shift your attention away from blood donors but not entirely, actually, and talk about Hepatitis B virus NAT testing in donors of human cells, tissues and cellular and tissue-based therapies which is very hard to say, and so we say HCT/Ps instead.

[Slide.]

Here we go.

[Slide.]

Today, I am going to give you a little bit of background of HCT/Ps in general and then talk about what we do and don't know which is mostly don't know about yield data in HCT/P donors.

[Slide.]

So I am just going to start off with the basics about what is an HCT/P. We have a regulatory definition which states that they are articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion or transfer into the human recipient. Those are regulated by the Office of Cellular Tissue and Gene Therapies at CBER and, as you see, they encompass a wide variety of products.

[Slide.]

HCT/Ps can come from both deceased as well as living donors. Some examples of HCT/Ps from deceased donors include musculoskeletal tissues, dura mater, cardiovascular tissues and ocular tissues. And, from living donors, we have hematopoietic stem and progenitor cells that are derived from peripheral blood or cord blood, other cellular therapies as well as reproductive cells and tissues.

[Slide.]

I think it also important to keep in mind some things that are not HCT/Ps. This includes vascularized human organs for transplantation. The Health Resources and Services Administration provides oversight for organ transplantation and I am not going to ask you to consider organ donation testing today.

It obviously doesn't include whole blood and blood components or blood-derivative products, secreted or extracted products such as milk, collagen and cell factors--

[Slide.]

--minimally manipulated bone marrow for homologous use that is not combined with a drug or device, ancillary products used in the manufacture of HCT/Ps, cells, tissues or organs derived from animals other than humans, or in vitro diagnostic products.

[Slide.]

HCT/P donors are both screened and tested. Donor screening includes a medical history interview, a physical assessment of a non-living donor or physical examination of a living donor as well as a medical-record review. I am

going to talk about donor testing in more detail.

[Slide.]

So, in order that we would require screening and testing for a particular agent, it must be considered a relevant communicable disease agent or disease, and that is that RCDAD at the top. So here I just wanted to show you what are the relevant communicable-disease agents or diseases. And, over here, I will show you the ones that we require testing for. Obviously, you can see the Hepatitis B is a relevant communicable-disease agent or disease for HCT/Ps.

[Slide.]

The regulations require that HCT/P donors must be tested using an appropriate FDA-licensed, approved or cleared donor-screening test in accordance with the manufacturer's instructions for use and they have to be tested to adequately and appropriately reduce the risk of transmission of the relevant communicable diseases.

That language is there because the regulations don't list out what particular tests must be done for HCT/Ps donors. So, instead, we have guidance that will tell people the test that we currently consider to meet the

regulatory requirements to adequately and appropriate reduce the risk of transmission of relevant communicable disease agents or diseases.

[Slide.]

And so these next few slides, I just want to flip through and show you the various tests that we require.

[Slide.]

You can see that, for Hepatitis B virus, we ask for an FDA-licensed screening test for Hepatitis B surface antigen and for total antibody to Hepatitis B core antigen.

[Slide.]

Just to make the point that, in some instances, establishments must conduct more than one test to adequately and appropriately test for a single communicable disease agent or disease and there is currently no recommendation regarding HBV NAT testing.

[Slide.]

So, I am going to move into the discussion about our donors.

[Slide.]

Robin has really well covered why we are talking about HBV NAT testing today.

[Slide.]

So what I am going to focus on are the unique aspects of HCT/Ps donor testing. Those specifically are the format for the donor testing, individual donor testing versus minipool testing as well as really a lack of specific yield data that is known for our donor populations.

[Slide.]

So starting with the testing format, currently, all the licensed HBV NAT tests are labeled in such a way that donors of hematopoietic stem and progenitor cells as well as donor lymphocytes for infusion may be tested using either individual donation or minipool NAT testing. Otherwise, all of the other living donors and cadaveric donors of HCT/Ps must be tested using individual donation testing. Therefore, the potential yield of the HBV NAT test would be maximized for most HCT/P donors.

[Slide.]

But, as I already alluded to, the yield data specific to living HCT/P donors isn't available. There are two main reasons for that. One is that there is a lack of requirement for licensure to collect that information and the information is more difficult to obtain.

[Slide.]

So kind of looking through the requirements for licensure, through the requirements for licensure, in living donor populations, if you have a donor-screening test that has an indication for use in blood donors, the manufacturers may obtain an indication for use in what we call "other living donors" using individual donation testing without providing any additional data to FDA.

Those other living donors can include donors that are regulated by FDA such as HCT/P donors for hematopoietic stem cells, reproductive HCT/Ps. But it can also include donor populations that are not regulated by FDA like heart-beating organ donors, donors of human milk products.

[Slide.]

The reason that we don't require submission of clinical data in that instance is that those tests that are using the same type of blood specimens which is extensively evaluated for blood donors, that blood specimen being a peripheral blood that is obtained from a heart-beating individual and the yield has already been demonstrated in the blood donors.

We expect that the analytical performance of the

assay should be the same as established for blood donors.

[Slide.]

On the other hand, for pooled testing, we do require that clinical data be submitted in order to receive that claim. The minipool testing is inherently less sensitive than individual donation testing because of dilution of infectious agent with pooling the specimens.

To date, the only clinical data we have received for a pooled-testing claim has been for donors of hematopoietic stem cells and progenitor cells and, by extension, donor lymphocytes for infusion because it is the same donor population.

[Slide.]

So I have tried to walk you through that, as a result of the way the NAT tests are reviewed for licensure, the yield data is really only required to be collected in the blood-donor population. But also the number of living HCT/Ps donors that are tested on a yield basis, it is much smaller than blood donors and it would take a lot longer to collect yield cases.

There are multiple HCT/P living donor populations, as you have seen. So it would be very complicated to

collect clinical data for each of those individual populations.

[Slide.]

So what data is available? For HBC and DLI donors, will be presenting information to describe the prevalence of HBV as compared to that in the blood donors. I think that information is useful to be presented because it helps to consider the generalizability of the blood-donor data to that particular donor population.

[Slide.]

They have already presented data describing the difference in window-period closure between ID NAT and minipool NAT as determined by collected in blood donors. Because we believe that the test performance in living HCT/P donors should be comparable to the performance in blood donors, it is anticipated that the window-period closure and yield would be similar between the living donors and the blood donors.

[Slide.]

So if it sounds complicated to collect yield data for living donors, it is especially complicated to collect that for cadaveric donors. Cadaveric blood specimens are

considered a different specimen type than peripheral blood collected from living individuals. After death, there is decomposition of the blood, hemolysis and that could potentially result in formation of inhibitors.

Because of that, we are concerned that we make sure the test kits adequately perform in these types of specimens and so we allow that for tests that are licensed with an indication for use in blood-donor screening, that the manufacturers can submit some additional validation studies in order to obtain the cadaveric-donor specimen testing. And those would be comprised of spiking studies.

[Slide.]

Now, during the clinical trials for NAT on blood donors, any positive NAT test that may be determined to be a yield case--those are the HBV NAT-positive but negative Hepatitis B surface antigen and anti-HB core--must be confirmed by follow-up testing of a donor by alternate NAT methodologies and by demonstrating seroconversion of the donor.

For obvious reasons, you can't do this type of confirmation in a donor who is not living. We do have to currently rely on yield data in blood donors. Additional

research to determine new ways to confirm test results on a sample from a deceased donor may be useful for future consideration.

[Slide.]

So what we do know is that the Hepatitis B virus incidence in cadaveric donors has been estimated to be lower than that of the general population but higher than that in first-time blood donors. Dr. Stramer will be presenting some information regarding the estimated hepatitis virus incidence among cadaveric donors.

[Slide.]

The reasons for this estimated higher incidence among cadaveric donors as compared with first-time blood donors is not fully known and is likely to have several explanations. The donor screening must be performed by asking questions of someone other than the individual donor, the questioning of a relative or significant other while they are bereaved may affect the accuracy of their answers, and blood donors who are provided educational materials prior to donation may self-defer while cadaveric donors cannot do so.

[Slide.]

So, we acknowledge that are limitations in the specific data for donor populations and HCT/P donors.

[Slide.]

When making donor-testing recommendations, our goal is to provide the maximum benefit for recipient safety.

We look forward to your discussion today. So I will just walk through questions for committee real fast, or do you prefer I take questions first?

DR. SIEGAL: Why don't we ask questions now and then go on to Dr. Stramer.

DR. GREENWALD: Sure.

DR. SIEGAL: Anybody? Maureen?

DR. FINNEGAN: Actually, I have a couple. When you were talking about the data that is not available, are you saying that you don't have it or that the tissue foundations don't keep it?

DR. GREENWALD: I am saying that the data is not collected. It doesn't exist. And, were the data to be collected and aggregated like it is in blood donors--for example, just knowing how many positive test results you get--we are not sure what it would mean.

But, also, Hepatitis B virus NAT has not been

implemented in the donor populations.

DR. FINNEGAN: So, if I do an allograft ACL, there is no information on the allograft?

DR. GREENWALD: Okay. I listed a list of tests that we do require. So the donors are screened and tested. What I am saying is that the donors should be negative for all those tests but the donor has not had Hepatitis B virus NAT.

DR. FINNEGAN: The second question is, have you done any lookbacks on recipients to see if you could get some data, how many recipients from any of these tissues have had a conversion?

DR. GREENWALD: So, would this be in someone who had tissues that were transplanted--

DR. FINNEGAN: That is correct. If you go to your tissue foundations, and you have them look at the last two years of tissues that have been sent out, how many of those tissue recipients have converted?

DR. GREENWALD: First of all, we don't require lookback studies regulatorywise. But, of course, if anyone were to develop an infection after they get tissue transplanted, those would be investigated.

DR. FINNEGAN: Do you have a report on how many of those have occurred?

DR. GREENWALD: We don't. The problem is--I mean, we do get MedWatch reports sometimes. For example, when there was--well, I really can't talk about that.

DR. FINNEGAN: I am not trying to make your life difficult. What I am trying to say is I think there are means to get some of this information that is out there but maybe it just hasn't been looked at.

DR. GREENWALD: Potentially. And we are working on that within FDA. But it is certainly not collected in the industry as well as we have a lot of problems trying to figure out what the denominator is.

DR. FINNEGAN: And then my last question is, or maybe a comment, do you think that the incidence of HPV transfer from cadavers is because the cadaveric donors tend to be younger and a larger number of them have been vaccinated?

DR. GREENWALD: I think we have absolutely no information about that whatsoever. I would say that I think that the incidence of transmission of any infectious diseases from human tissues is going to be very low.

DR. SIEGAL: Dr. Cryer.

DR. CRYER: I would just comment that some companies are collecting this data because we, as surgeons that use the product, periodically will get a letter that says, one of our products that you implanted in somebody, we found out later a test was positive that we didn't know of at the time. And there is a surveillance process you are supposed to go through with the patient and report back to the company.

So companies are doing it. It sounds to me like you are just not collecting the data.

DR. GREENWALD: Well, individual companies are certainly--if they receive reports from somebody or they find out that they have distributed products and someone else gets a different test result or they go back and look and say that they didn't notice that there was a positive test result, something like that, they are required to do notification of the recipients of the test information and they do try to collect information.

What I am saying is that it is not required. And we require investigation in the regulations, but it is very vague as to what that investigation must entail. And,

depending on the circumstances, they don't necessarily always go and test every individual recipient of a tissue and see if there was transmission or that sort of thing.

DR. HOOFNAGLE: I am sorry to be obtuse, but I am still not quite sure what we are talking about. This is bone, cornea, semen? What are the organs? What about liver, lung, heart.

DR. GREENWALD: No, sir. The organs have oversight with HRSA and so we are talking about bone, semen, tendons, corneas, the hematopoietic stem cells, some types of bone marrow. Most of them are not an HCT/P.

DR. HOOFNAGLE: We don't know for sure that all of these organs are infectious, even if they come from someone? Hepatitis B; is that true? Like a bone? Do we know that?

DR. GREENWALD: I would have to go back and look at the specific viruses, but there has been transmission of various viruses by various tissues. But you are absolutely right that what we are lacking in data about which tissues transmit what at what dose, how processing may affect transmissibility, we have no information about that.

DR. HOLLINGER: Is there a requirement for the

kind of blood, type of blood, that is required for testing such as serum versus plasma and, if so, plasma, what anticoagulant is recommended? Or, does it matter?

DR. GREENWALD: It does matter. It depends on what the individual test has been validated for. It is going to be in the product insert. I can tell you that, for cadaveric donors--living donors is going to be exactly the same as blood donors. But, for the cadaveric donors, in things that have had a plasma indication, EDTA has been the only type of anticoagulant that has been studied and improved in the product insert.

DR. HOLLINGER: Okay. Thank you.

DR. SIEGAL: Any other questions or comments? All right, in that case, again, we hear from Dr. Stramer. This time, HCT/P Donor Data, from the American Red Cross.

HCT/P Donor Data

DR. STRAMER: Thank you.

This will be painless and short, hopefully. I am presenting the data that is available to us. I hope that it somewhat meets the needs of the review for HCT/P donors, but it is data that we have and, hopefully, has some relevance. What we have looked at

[Slide.]

What we have looked at are HIV, HCV, HBV prevalence and incidence in HPC donors. Basically, we did that as far as qualification of these types of donors for minipool NAT as opposed to ID NAT in which they were originally licensed. I will talk about the risks in cadaveric donors for HIV, HCV, HBV and HTLV.

[Slide.]

The first study covering HPCs, as I mentioned, was validation of minipool NAT as opposed to ID NAT for the HPC donors. The reason that we did that is initially, when the tests were licensed, HPC donors had to be performed by ID NAT. The way and the blood centers had interpreted HPC donors, not dissimilar to the way Melissa described them, was that we believe that these, the HPC donor samples--that is, peripheral blood stem cells, maternal cord blood or bone marrow met the definitions in 21 CFR 1271.3; that is, it is a product containing a part of a human blood separated by physical or mechanical means.

However, that opinion was not shared with FDA so we had to do the qualification studies. The additional reason that we believe that they should be considered the

same as the other samples is in the NAT clinical trials and all the prospective use of licensed assays, we have included samples from allogeneic, first-time, repeat donors, autologous donor, pheresis. So we believe that HPCs which also came from living donors were no different, and we didn't qualify any of the other donor types, so why should we qualify HPC donors.

[Slide.]

So the purpose of the study was to determine the infectious disease-marker prevalence and incidence rates for HPC donors to qualify their donations for minipool NAT by demonstrating equivalence to blood donation types already included in the intended-use statements for licensed NAT assays and prove that the risks associated with minipool NAT as compared to ID NAT for HPC donors are no greater than the differences between minipool and ID NAT for donations of whole blood.

[Slide.]

Points to consider about doing ID NAT, and this applies to all things that we do ID NAT for, is there are higher false-positive rates with ID as opposed to minipool NAT. Minipool NAT involves two rounds of testing in

contrast to ID NAT, so we have an opportunity to clear to false-positivity.

Especially for HPC donors, if you have a false-positive, the result is the loss of a valuable, sometimes irreplaceable, donor or their donation.

There are other considerations for ID NAT; increased cost, logistical complexity for HCP donations. We would have to sort tubes relative to the thousands of tubes that come into a testing laboratory and thus increase chances for errors.

So what we did is we took the prevalence of HIV, HCV and HBV determined by the tests that we routinely use. We also did the minipool NAT yield to approximate incidence and we collected data from two sources, 23 sites that collected HPC donations that we have done testing for that included approximately 140,000 donations and we compared that to a control population which included 6-and-a-half million allogeneic and 1 million autologous donations from a comparable time period.

[Slide.]

So to chase to the bottom line here, what you see here are the rates for HIV, HCV, anticore and HBsAg looking

at all whole-blood donations, autologous blood donations separately, and combined--that is peripheral stem cells, bone marrow and cord, all together.

The numbers in the middle for autologous, for the first three agents other than HBsAg, were the highest and significantly different than the other groupings. So, autologous, in this analysis, came out higher than whole blood or HPCs for the first three markers. And the only time that HPCs was higher than a whole-blood component was for HBsAg. In this case, the HBsAg screening test that was used was one that was associated with many false-positive results. So that 25.44 rate per 10,000 donations has to be looked at with a grain of salt.

[Slide.]

So now, if you look at the same data for NAT, you can see the whole-blood NAT rates--that is, per 10,000 for HIV, HCV and we didn't have any data for HBV so it is unfortunately now relevant to this discussion, but you can see the HIV and HCV rates.

Autologous were higher than for HCV than combined whole blood. But combined whole blood was lower than either autologous or the combined HPCs. The 0.93 there

really revolves around the fact that, for the HPCs that we got for NAT, no confirmatory testing was done relative to autologous and combined whole blood.

So, in a way, we were comparing apples to oranges. But those were the data that we had.

[Slide.]

So, in conclusion, the overall comparison of prevalence rates showed that in 3 of 4 cases, the autologous donors were actually significantly higher than the combined HPCs or whole-blood donors. One case, HPCs were higher, but that was because it used a test with very poor specificity.

We didn't see any differences in HBV yield, at least for HIV and HCV with the higher numbers that I showed you, although not significantly different in HPC NAT reactives, mostly unconfirmed. So, therefore, we believe that the populations of HPC in controlled donors--that is, autologous donors--are not different in the context of performing NAT.

Based on these data, FDA did allow us to use minipool NAT for testing HPC donations.

[Slide.]

So, just to see if the data were consistent, we took the Ultrio ID NAT yield data that I presented or the ID NAT data that I presented earlier. Based on the fact, I should say that even minipool was licensed, because West Nile virus for HPCs was not licensed in minipool and we could only use individual donation testing, we didn't convert to minipool. We keep everything, now, and we do everything for HPCs ID NAT.

So, to do a valid comparison, I took the ID NAT of the combined and our autologous donations relative to HPCs. But, basically, what you see here are the same trends and almost the same numbers that have I showed you earlier for several years ago, so we are seeing higher numbers for autologous in comparison to combined HPCs.

And for yield, and in this case, we do include HBV, we only had two yields that came out of ID NAT for combined whole blood, none in autologous and none in HPCs although numbers were small.

[Slide.]

So I am not sure what value this has other than to say donations from living donors should be treated the same way as the other donations that we do as far as

routine testing including autologous and any other blood component.

[Slide.]

Let me now switch gears and talk about residual risk among tissue donors. Melissa already referenced the Zou paper that was published some years ago. What this did was try to calculate incidence in tissue donors so that we could compare that to first-time allogeneic whole-blood donors.

So let me go through the methods quickly. We took the confirmed positive rates for HIV, HBsAg, HCV and HTLV among tissue donors. These came from five centers involving 11,391 results. All centers used the American Association of Tissue Bank reviews and testing standards as required.

We took a prevalence ratio by gender between tissue donors and first-time blood donors as one of the factors to calculate incidence. The first-time blood donors came from 2000 to 2001, the same period as we had the tissue donors from 1.6 million first-time allogeneic blood donors.

So we took the prevalence ratios of tissue to

first-time donors to estimate the incidence rates and we multiplied the prevalence ratio times the first-time blood-donor rate to get an incidence estimate among tissue donors. So we took prevalence so that we could see how much higher prevalence was in the tissue donors relative to first-time donors and then multiplied that by incidence in first-time donors to get the incidence among tissue donors.

The first-time donors incidence was calculated by using repeat-donor incidence times a factor that we knew for HIV, HCV and HBV. And then we applied the incidence times the infectious window period just to derive risk which is the same as for blood-donor screening.

[Slide.]

So points to consider here and that were highlighted in the paper are the risk for transplanted tissues is low since most products are treated to reduce or eliminate risk. And this is true for everything except for vascularized tissues in which transmissions have been documented, not through treated tissues.

However, a single infected donor has the potential to transmit to an average of 50 recipients. So this is quite different than the blood component.

[Slide.]

So, what were our findings? The estimated probability of undetected viremia at the time of tissue donation is higher among tissue donors than among first-time donors although lower than in the general population. And the use of ID NAT should reduce these risks.

I am going to just show you two data slide.

[Slide.]

These are the data from the paper showing you the markers on your left followed by the tissue-donor prevalence, first-time donor prevalence, which was used to determine the ratio, multiplied by the first-time donor incidence to give an incidence rate in tissue donors, then multiplied by the window period to give you risk.

So, in the far column, the one that begins with risk and is 1 in 55,000, 1 in 34,000, one in 42,000 and 1 in 128,000. Those are the estimated risks during 2000 and 2001 for tissue donors.

[Slide.]

So we took data today--we took the 2006, 2007 data for first-time allogeneic donors and reapplied all the same calculations to see if risk has changed and then

applied the window periods for NAT to calculate the risk or the risk reduction that we would see by applying single-unit NAT to tissue donations.

So the risk, the column in the middle, the 1 in 45,000, 1 in 36,000, 39,000 and 196,000 is virtually identical to what I showed you for 2001--2000 and 2001. So those risks from serology testing for tissue donors has remained consistent.

However, if we apply NAT using the window periods that have been published and discussed for HBV of 20.6 for individual-unit Ultrio testing, for example, you get a reduced risk for anti-HIV of 1 in 179,000, for HBsAg of 1 in 67,000. Basically, these have just dropped by half. Lastly, and the greatest reduction for anti-HCV from 1 in 39,000 to 1 in 556,000.

[Slide.]

So, to conclude, for the living donors, HIV, HCV and HBV rates are equivalent to blood-donation types already included in the intended-use statements for licensed NAT assays. The risks associated with minipool NAT for HPC donors are no different than other donors of whole-blood products.

And then, regarding tissue donors, undetected viremia at the time of tissue donation is reduced and reduced considerably, especially for HCV, with the use of ID NAT.

That's all I have.

DR. SIEGAL: Thank you, Dr. Stramer. Any questions for Dr. Stramer before we proceed to the Open Public Hearing?

DR. TRUNKEY: In the two countries, Japan and Germany, that use NAT, is that only for blood or is that also for tissue?

DR. STRAMER: I don't know but I am assuming, and I am pretty sure for Germany it is for tissue as well as for routine whole-blood donation.

DR. TRUNKEY: Has anybody looked at their process of how they came to the conclusion that the use of NAT was beneficial?

DR. STRAMER: I believe that, at least in Germany, it was a voluntary initiative. But I could be wrong. That is what I recall.

DR. TRUNKEY: What is the rigor or their process? Is it a good process?

DR. STRAMER: Their NAT process or their processing of tissues?

DR. TRUNKEY: No; the process that they came to the conclusion that NAT was beneficial.

DR. STRAMER: Well, I think they just--because they have done it for routine whole-blood donations, they just applied the same thing to tissues and organs. But I believe they do it all in pool tests and they don't separate the different donation types out for single-unit testing.

But here we show that, for tissue donors, it should be done individually.

DR. TRUNKEY: Can you give me an estimate of what the increased cost to go to NAT would be, for a single donor.

DR. STRAMER: For tissue donations?

DR. TRUNKEY: Yes.

DR. STRAMER: I believe, from numbers that I recall from several years ago, that there are 20,000 cadaveric donors per year in the United States. So you would have to multiply that 20,000 by the increased costs of going from minipool to ID NAT but recognizing, too, that,

for that cost, you are really not protecting one recipient. As I said, you are protecting up to 50 recipients.

DR. HOLLINGER: Just also a comment that I think maybe has to do with one of your questions is that Germany does not do anticore testing.

DR. STRAMER: Yes; they do. I'm sorry.

DR. HOLLINGER: I'm sorry; please.

DR. STRAMER: They do anticore testing.

DR. HOLLINGER: I thought they--

DR. STRAMER: No; they have implemented anticore testing several years ago.

DR. HOLLINGER: Okay. And Japan is still looking at low-titered anticore where the test is not very sensitive.

DR. STRAMER: Right; they accept low-titered.

DR. HOLLINGER: So they are accepting initially bloods that are less than 1 to 32. They do dilutions. So anticore that is less than 1 to 32, they will accept it initially and then do NAT testing of that. I wasn't aware--I thought Germany was still doing this.

DR. STRAMER: About two or three years ago, they recommended anticore.

DR. HOLLINGER: Okay. Thanks, Sue.

DR. SIEGAL: Henry?

DR. CRYER: Do we know if the incidence of infection decreased in Germany after they instituted this?

DR. SIEGAL: Dr. Stramer, I think that was directed at you.

DR. STRAMER: Yes, I know. I wasn't leaving. They have had significant--you know, it gets back to the question about clinical versus yield. Of course, they have found signature anticore yield and they have also done DNA testing. We know that these are all low-level HBV DNA-positives when DNA has been found.

But I don't think it is really translated to any improvement in clinical outcome in patients. So I think, even though they have had yields, it has been difficult to translate the clinical significance of that.

DR. SIEGAL: Dr. Bianco.

DR. BIANCO: Dr. Stramer, Germany uses larger pools for NAT. Do you want to talk about that?

DR. STRAMER: They use a pool size of 96, but they also ultra-centrifuge down 5 mls of their pool. So their rationale for using a large pool size is that the

input volume into the NAT test is highly concentrated. So, basically, it should equate with what we do when we only put in a half-ml input into the NAT assay if we are doing a pool of 16.

DR. HOLLINGER: And, Sue, along those same questions, what is the dilution--if they take 5 mls, then what volume are they testing at that 5 mls?

DR. STRAMER: I don't know what their resuspension volume is and then, of the resuspended pellets, how much input they actually put in the NAT assay. But I know, in comparative studies, it has come up fairly comparable to our use of pools of 16.

DR. SIEGAL: Dr. Epstein has a comment.

DR. EPSTEIN: A question for Sue. Sue, you stated that the result of your study comparing the HPCs to the combined first-time repeat donors showed no difference. I assume you are speaking no statistically significant difference because all the point estimates seem to show a difference. So how do you reconcile that?

DR. STRAMER: Clearly, one could say, based on lack of power, we may not have seen significant differences. But the numbers, at least for the prevalence in the first

study that we did, the first three markers were higher in autologous than they were in HPCs.

For HBsAg, I believe the only reason that they were higher in HBsAg is because they used the Ortho System 3 test which we know was plagued with false-positivity.

DR. EPSTEIN: But autologous isn't the right comparator. In other words, what we are interested in is the risk of an allogeneic transplant or an allogeneic donation. Again, all the point estimates for HPC allogeneic are higher risk than for allogeneic first-time and repeat blood. So I think it is very much confounding to compare it to autologous donors.

DR. STRAMER: And the reason we did that was, and the whole point of the study was, to say, do we have to qualify HPCs separately then we do, for example, autologous. When we do clinical trials of assays, we don't test autologous separately using separate procedures.

So the question was why should we then have to do that for HPCs when we don't do that for other components.

DR. EPSTEIN: Well, because the clinical implications of autologous transfusion are quite different is the answer.

DR. STRAMER: Well, many HPCs are also auto, so it is, I agree, confounded.

DR. EPSTEIN: Okay.

DR. SIEGAL: Dr. Cryer.

DR. CRYER: I have a couple of questions related to some of the first presentations before the break. First of all, I guess this was reviewed in 2004 before and it was recommended to not to do NAT screening. At that time, number one of the three reasons for not doing it was that you would pick up an approximate 50 additional donations that you would interdict a year out of compared to 20,000 that you are already getting. So, instead of 20,000, it would be 20,050.

And then it also went on to say that there was a relatively low incidence of anybody developing an active infection or symptomatic disease.

From what I have heard, I don't think anything has changed on No. 1. Is that correct? Would that be the right conclusion?

DR. BISWAS: What we are saying is that there is no assumption of non-infectivity, number one, of a unit from breakthrough infections which seem to currently--the

proportion is higher. The proportion seems to be getting higher of all yields. And the other point is that there is no assumption of no mortality or no morbidity from these breakthrough infections.

Remember, recipients, as I said, many of them are immune-compromised. They are not all healthy adults. There are many children, neonates, and children and neonates are highly likely to go on to chronicity, especially neonates. So that is what we are saying now.

DR. FORSHEE: Just two quick points, one with regard to the number that would be predicted to be interdicted. You are correct that the numbers are generally lower than 50 for the non-vaccinated, I think is an important point to keep in mind. The predictions that I was showing for the potential additional number of units interdicted is based on data that is only applicable for the non-vaccinated population.

So there is an additional set of the breakthrough infections with all of the uncertainty that we have been discussing about that report. But, in terms of the number interdicted from non-vaccinated, you are right, that we are still talking 50 or fewer for most of the tests that we are

looking at.

DR. CRYER: Could I follow up with one other thing. So, right now, we to roughly anticipate that there is 1 out of some 200,000 to 250,000 transfusions that is going to relate in a new infection of Hepatitis B.

DR. FORSHEE: I believe the resistance risk is estimated to be 1 in 280,000.

DR. CRYER: So, if you use the most aggressive strategy that has been tossed out today, best guesstimate, what would that change to if we did it?

DR. FORSHEE: If you went to the ID NAT using the MPX, I believe that estimate is it would be reduced to 1 in 2 million. Dr. Stramer, is that correct, that the mean estimate is 1 in 2 million?

DR. STRAMER: The 1 in 2 million is the yield for a minipool of 16. It was 1 in 488,000 was the yield for an MPX of 1.

DR. FORSHEE: And so the residual risk would drop to, I believe, 1 in 843,000 going to the 1 MPX.

DR. STRAMER: Yes; that's right.

DR. SIEGAL: Dr. Epstein.

DR. EPSTEIN: Coming back to Dr. Cryer's question

what is different, there is another major difference. In 2004, we approved one stand-alone test. Since that time, we have approved two what we call multiplex tests. In other words, it is an NAT test that concurrently detects HIV, HCV and HBV nucleic acids.

So the practicality of doing an HBV test has changed because the majority of systems are now using multiplex NAT. So the question is whether we want to set a standard for the minimum sensitivity for using these tests as screens for Hepatitis B instead of leaving it arbitrary and voluntary because we do think that it has become the prevalent use.

However, the subtlety here is that the sensitivity of these different multiplex tests is not the same for Hepatitis B. But we are still in the same ballpark of yields. In other words, we are talking dozens to 50-plus out of a baseline of detecting, as you correctly said, about 20,000 HBsAg and anticore and/or anticore positives.

So the marginal benefit of HBV testing has not changed under the new era but the feasibility of doing it with some defined benefit has changed because of multiplex

testing and because the highly automated, high-throughput systems have permitted the possibility of smaller minipools.

DR. NELSON: But historically, when HIV NAT testing was introduced, the actual yield was much lower than--the estimated yield was much lower than 50 yield cases per year and, in fact, what has been found, I think was even a lot lower than what was predicted when the NAT testing for HIV was introduced.

So that 50 per year is not bad in terms of an additional yield of new--I had a question of is the pool size for minipool testing predicted for the multiplex assays that are now available? Is that the same pool size as for the current use of the HIV and HCV multiplex assay or is the pool size different in the new Taq and COBAS?

DR. BISWAS: It is the same.

DR. NELSON: It is the same?

DR. BISWAS: Yes.

DR. NELSON: So it wouldn't require any changes except introducing a new primer, a new--

DR. STRAMER: Well, the tester license.

DR. EPSTEIN: Well, there is one caveat here. The labeled range of minipool size does not change.

However, it depends on the standard that one might set for the sensitivity of the HBV NAT. I know Sue made this point in her talk that the most common use of the Ultrio Multiplex test is pools of 16. The HBV NAT sensitivity at that level is about 170 IU/ml.

If we set a standard of 100, then you would have to use pools of 8. And that has been argued to be a logistic and potentially economic burden to the industry. So, although we have approved the products at the same pool for HIV, HBV, HCV, how we set the standard for sensitivity for HBV could potentially drive a different practice using different size minipools.

That really just affects the Ultrio because, clearly, the MPX, even at pools of 6, the data show that that is as sensitive, or in the same range, as the Ultrio in the individual sample mode. So MPX 6 would stay but, based on what sensitivity you require for HBV, it would, or would not, drive you to smaller minipools for Ultrio.

I think that is the point that Sue tried to make showing the empiric data didn't show a statistically significant difference. But what Dr. Forshee showed is that there is, in fact, a predicted difference in yield

rate. It might just take larger numbers.

DR. HOLLINGER: But, Jay, while you are still up there, using that same logic, then the MPX at 1, the individual test, is far better than the one at 6.

DR. EPSTEIN: That's correct. But, again, the point that emerges also is feasibility. I mean, I am not sure we are prepared to say that the system can handle universal single-sample testing any better now than it could in 2004. So that is one thing to consider.

I think we are not quite at a point of giving up on minipools. We are just trying to figure out where does the maximum benefit lie for what may be feasible. This is an open question to discuss. The advisory committee is being asked a public-health question. The Advisory Committee for Blood Safety and Availability was asked to look at the big picture which was cost, logistics, qualities, et cetera.

We are just asking you to try to focus on the science. But, be that as it may, the ultimate question is how far can we push the system because, clearly, single-unit testing by MPX trumps everything else. But, by how much, because remember you are dealing with this very, very

slow ramp-up and the difference in window-period narrowing is measured in days.

DR. HOLLINGER: So, under those same questions, then, you think that there is an area that you are comfortable with of what is safe and what is safe enough.

DR. EPSTEIN: That is why we have brought you to the table.

DR. SIEGAL: Dr. Stramer.

DR. STRAMER: Thank you. I would just like to comment because of the uncertainty relative to Dr. Epstein's comment about minipool size. That is part of the reason that we did the study that we did of about 4 million donations. The point of that was to see what pool size, based on real data, not model data, would be effective.

From that study, we didn't see any difference, and 4 million donations is quite a large study, larger than an clinical trial, to see if there was a difference between minipools of 1, 4, 8 or 16. And, even though we expected to see the highest yield by ID NAT, we didn't.

In reality, as I said, 8 of the 9 yields were detected in minipools of 16. There was no additional benefit in real life in minipools of 8.

I would just also like to comment, what has changed over time. What has changed over time is the fact that five years ago when we talked about minipool NAT, we hadn't yet implemented ultrasensitive HBsAg assays. From the modeling data that I have shown and that has been published, and that Mike showed relative to the Biswas studies, we know that ultrasensitive HBsAg assays approach the sensitivity of the minipool NAT.

So we believed, with the implementation of ultrasensitive HBsAg, we would no longer need to do minipool NAT. And that was part of the other motivation of the study to see, is that, in fact, true. Even with PRISM, in a very large study, what is the yield of minipool NAT and what pool size is needed to detect those yield donations.

DR. SIEGAL: Is there anyone else who wishes to comment? Dr. Blackwelder.

DR. BLACKWELDER: I just wanted to make one comment that, at the same time, results of 8 positive with the 16 pool and 1 positive in the ID, there must be a large amount of uncertainty about the comparison, as has already been noted, I think. In other words, confidence intervals

for a difference or a ratio of those yields would be very wide.

DR. SIEGAL: Yes?

DR. NAKHASI: Hira Nakhasi, FDA. I think I wanted to make a correction here to what Sue said. The yield at that time, at the pools of 24, was compared in the clinical trials with the PRISM study. So I think that is not true that it was not compared with the PRISM ultrasensitive.

Another thing, I just wanted to, I guess, emphasize the point, the difference of what was then what is now is I think what Robin has emphasized enough as well as Richard has emphasized very much that we now see these breakthrough cases, which was not at that time. We did not have that information.

And it still remains to be seen whether those breakthrough infections are really true causing an infection. That same aspect will be discussed and that is why we are asking that question. But the difference is now we see more of these breakthrough infection cases.

DR. BISWAS: I would like to add that please remember that the breakthrough cases are not picked up by

HBsAg. That has changed as well.

DR. Di BISCEGLIE: I was going to comment to Dr. Cryer the same thing that had changed was this awareness in growing number of virus breakthrough cases but, as he pointed out, there really is no evidence that these cases actually transmit Hepatitis B either causing infection or disease.

The absence of evidence is being taken to be that it can, in theory, occur. But we really haven't seen this. So the increase, or the decrease, from 1 in 200-and-something to 1 in 800-and-something residual risk is, in big part, these virus breakthrough cases. But what you are picking up is positive tests. You are not necessarily decreasing the number of infections because we don't know the extent to which these cases are, indeed, infectious.

DR. BISWAS: I agree that there is a lot of uncertainty, but I did, also, show a couple of publications where it appears that it is possible that a unit with DNA in it and anti-HBs--

DR. Di BISCEGLIE: Robin, I must say, the cases that you showed that transmitted--all had anticore positivity, I don't think you showed us a single case that

transmitted that did not have anticore positivity. I was looking particularly.

DR. SIEGAL: If there are no more comments--

DR. FORSHEE: May I make just one clarifying comment and I am sure Dr. Stramer will correct me if I don't have this exactly right, but the reduction from about 1 in 280,000 to about 1 in 800,000 by going down to the MPX 1, that would only be in non-vaccinated individuals because this data is based on the HBsAg.

So any additional breakthrough infections that were caught would be in addition to the reduction in residual risk among the non-vaccinated donors.

DR. SIEGAL: Dr. Alter.

DR. ALTER: Adrian, what you say is true, but this gets down to, or we always run between what is the absolute best, what is practical, what can you do at this time and what is the precautionary principle.

So the precautionary principle would say, look, if we can do a test that will decrease that risk four-fold, or three-fold, whatever those numbers come out to, and it is practical to do so in the current environment, and it is not too costly, why not do it because, if you wait to prove

that some of these units are infectious, you have lost a lot of time. And, if it turns out, in the end, they are infectious, you have potentially caused some infections that you could have prevented.

So that is what the precautionary principle says; let's not wait for absolute proof. If it is reasonable to do, if there is some chance that it could occur, then we should do it until proven otherwise. And I think that is what is underlying all these deliberations.

So we have gotten to the point now where we can do it. It won't cost very much. The test is actually going to almost force us to do it because only triplex testing will be available. So everybody is going to almost to do it. Why not do it?

DR. BISWAS: I would just like to add, in addition to that, please remember that some of these breakthroughs did seroconvert to anticore and did produce HBsAg. So it shows that there is replication going on in the liver. Something is going on. So I think that needs to be kept in mind as well.

DR. SIEGAL: Dr. Finnegan wanted to say something.

DR. FINNEGAN: No question.

DR. ZIMRIN: I just wanted to know, when you say that we are going to have to do it, we are going to do it at that sensitivity?

DR. ALTER: I don't know about the sensitivity, but I think the assays that don't have triplex are going to go out of existence so that will be the only test available. Where you set the limit, I don't know.

DR. HOOFNAGLE: The issue, though, is whether the FDA requires it. As you know, there are a lot of testing that went on for many years before the FDA required--anticore was one testing.

I would like to go back to the Red Cross study which was very good. I couldn't follow the beginning about how many pools came up positive that you then had to confirm? You got down to 9 confirmed cases; right? How many tested positive first? I thought you said that 82 percent could be confirmed, but I wasn't sure of that.

DR. STRAMER: Yes; 82 percent resolved. And then we had a number of donations that discriminated but then did not confirm because I didn't really have a chance to go through the entire algorithm for the study. But, even though something discriminated, it still could be a false-

positive.

So we did a lot of additional testing on the index and followed the donors to make sure that a discriminated positive donation was, in fact, a yield donation.

Did that answer your question?

DR. HOOFNAGLE: Not quite. I wanted to know how many specimens came up first among the 5 million blood units. If you say 82, that sounds like there was only 12.

DR. STRAMER: We had 2,000 that discriminated.

DR. HOOFNAGLE: 2,000.

DR. STRAMER: That discriminated but 98 percent of those were concordant serology positives.

DR. HOOFNAGLE: I see.

DR. STRAMER: So the benefit of NAT there is zero. The only benefit of NAT is the early window period.

DR. HOOFNAGLE: Okay.

DR. SIEGAL: We really should probably move on. So, if your comments are pressing, proceed.

DR. RENTAS: The reason why I asked my first question about an hour ago about the 100 IUs/ml is because I think testing for Hepatitis B for NAT is going to be a

done-deal. As you mention here, we are not going to have a choice. The manufacturers are moving towards, you either test for all three of them, or you don't test for anything at all. And I don't think we have a choice.

So I think what we need to come up with as a committee here is what we have been talking about, what the sensitivity will be. And that is what we are talking about ID versus a pool of 8, 16, 96, whatever it is.

I would like, Dr. Stramer, if you could please comment on this 100 IU/ml that the FDA is asking us to answer that question. If you could please comment on that, I would appreciate it.

DR. STRAMER: I believe the 100 is relatively arbitrary. So, if you look at relative pool sizes, if we are talking about minipool, the difference between 8 and 16, as I mentioned, was one doubling time. So, from the models and the observed yield, we didn't see significant differences. If we think minipool is important, well, a minipool of 8 to 6, that is two doubling times.

So the difference between a minipool of 8 and 16 is relatively trivial relative to 2 doubling time improvement that you get to with an MPX pool of 6. You

know, the bottom line for me is, as I said before, what we saw on the study, what we saw in the real world.

If we would have picked up nine yield donations, we would have done our dilutional studies and shown minipools of 8, detected them, and we couldn't detect them with pools of 16, then, obviously, we would want to do minipools of 8. But we didn't generate that data. So, for us to double our workload for HIV, HCV, HBV, increase the number of pools that we have to have to resolve, we are going to wind up, then, doing it for West Nile, decrease the pool size for West Nile to 8, it doubles the workload in the laboratory.

We don't have any data, at least in our own hands, that demonstrates that it has any value.

DR. SIEGAL: Okay. Are there any other comments? Indicating that there are not, I am obligated to read the following prior to the Open Public Hearing.

Open Public Hearing

DR. SIEGAL: Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public

Hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

For example, the financial information may include the company's or group's 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 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.

We have six people who are going to speak and Mr. Freas will introduce them.

DR. FREAS: The first two Open Public Hearing speakers will be presenting data. They will be coming up

here to the podium. The rest of them will be presenting comments from the microphone in the center of the room back in the audience.

Would Dr. Jeff Linnen, Director of Product Development, Gen-Probe, come up to the podium, please.

DR. LINNEN: As you heard, I am employee of Gen-Probe, Incorporated. We manufacture NAT assays. The Ultrio assay is one of those assays. This is done in a partnership with Chiron. I want to start out by thanking the FDA and thanking the BPAC for the opportunity to give this brief presentation.

So the purpose of my talk is really to give a little bit more information about the assay and to also give some information about the fully automated platform so there is a better understanding of exactly what we are talking about and then also to talk about some of the yield cases that came from the non-ARC trial that were mentioned briefly in Dr. Stramer's presentation.

So, just the background about the Ultrio assay. I think the point has been well made here that it is a triplex assay. So it simultaneously detects three analytes, HIV, HCV and HBV. It is based on transcription-mediated

amplification. We have discriminatory assays that have been used after initial reactive occurs to confirm the presence of the three viruses.

The assay has broad detection of HIV-1, Groups M, N and O--we actually used two regions of the genome to amplify--and it has broad detective for HCV and all genotypes for HBV. We have claims for serum and plasma and we have claims for testing blood specimens from cadaveric organ donors.

We are currently licensed for individual donor samples in pools up to 16. So this postmarketing study that you have heard was a requirement to get the claim for screening for HBV. And we have that to up to pools of 16.

There are two instrument platforms. I will describe the fully automated platform in this talk. Before I do that, I just want to show the limits of detection. I am showing both the 50 percent detective level, so these are the probabilities in IUs/ml where there would be a 50 percent probability of detection and a 95 percent probability. I have added the 50 percent detection because I think the incidence window-period modeling is based on that 50 percent detection.

So, as you can see for HBV--the sensitivity for HIV and HCV is very sensitive. You convert that into copies. For both HIV and HCV, we are talking about 12 to 15 copies sensitivity at the 95 percent level. For HBV, we are talking about--the 10.4 IUs is around 50, a little bit over 50 copies per ml. So it is clearly below the level of the most sensitive surface antigen detection. It is probably two- to three-fold more sensitive even in pools versus the most sensitive surface-antigen test.

This is the fully automated system. This is a high through-put system. We call it the TIGRIS system. It is in use for individual donor testing, in pool testing, worldwide. That is since 2005 because the Ultrio assay was CE-marked at the end of 2004. I have to point out, in the U.S. it is often used for individual donor testing for West Nile virus and, outside the U.S., it is becoming more widely used for individual donor testing, mainly for HBV.

Right now, we have two instruments installed for blood screening, a similar number of clinical diagnostics. The key thing here that this instrument generates 1000 results in 14 hours so, obviously, whatever the pool size is, you just multiply that times 1,000. The reason I have

14 hours at that point, additional reagents have to be added and the waste has to be removed from the instrument.

The time to first result is three hours and 38 minutes. Another result is about 100 results are generated every hour after that first result. Another important thing is the major advantage of having a fully automated system like this is all of the assay steps are controlled--okay; so there is verification that all of the incubation times and temperatures and all the steps have been performed according to what is necessary for the assay.

Now, this is an outline of the non-ARC study. So our postmarketing study was divided really into two separate studies with two protocols. I will just point out some of the differences here. The non-ARC study was mostly centers from the America's Blood Centers. Eight of the nine sites were from the ABC.

In this study, as opposed to the ARC study, both platforms were used, the manual platform and the TIGRIS platform. Probably about two-thirds of the donations were tested on TIGRIS.

Over 99 percent of the over 1.1 million donations were screened in eight donation pools so that pool format

was not used in the ARC study. And then, like the ARC study, the licensed surface antigen and the anticore tests were used according to the site's standard procedures and the confirmatory testing was very similar to that which was done in the ARC study.

This is a very brief summary of the yield cases that came out of the non-ARC study. So I have listed four here. These were all identified in pools of eight. One was identified on the manual platform, three on the TIGRIS platform.

The other thing to point out, at index, all of these were anti-HBs-negative. I have one that is highlighted there. That one, at the first follow up, showed a substantial increase in anti-HBs. The level went up to over 400 mU/ml. So, in that case, I think that is pretty good evidence that that individual had been previously vaccinated, although we don't have a clear history on that.

The other thing to point out, the supplemental testing was done with the previous, the stand-alone Roche assay. Interestingly, the first case from Oklahoma Blood Institute was non-reactive in that test but we were able to

quantify that sample as 200 copies.

The first two cases that are listed there, the one from Oklahoma Blood Institute and LIFE South, those are pretty much what we were predicting--that is, standard yield cases. They showed seroconversion; in the first case, 12 days after index and, in the second case, 20 days after index. And surface antigen appeared in both of those cases.

The next two, we were not able to demonstrate seroconversion but we were able to demonstrate the presence of DNA in at least one follow-up donation for each of those. So, in Case No. 3 from LIFE South, I believe it was 37 days post-index we continued to see DNA and then the case from Dayton, 23 days post-index.

Okay. So, again, I think Case No. 3 most likely represents another vaccinated donor.

Okay. To summarize. What I have done is I have added up the total number of donations that were tested in the combined studies. It was over 4.8 million donations. Now, what I am summarizing here is a little bit different than the way Dr. Stramer summarized it. This is what was identified through the screening, and I will talk about what was done in additional testing in different pool sizes.

So, there was a total of 13 yield cases identified in this study, 7 in 16 donation pools, for a rate of 1 per about 450,000. That was out of 3.1 million donations. There were four in eight donation pools, and those were all from the ABC centers, at a rate of about 1 per 283,000 and that was out of 1.1 million donations. Two were identified in individual donor testing for a rate of about 288,000.

Now, in additional testing, what we found out is that all of these, except one, can be detected in pools of 16. So maybe it is a surprising result based on the analytical sensitivity, but that it why it is analytical sensitivity, not clinical sensitivity. The overall rate, taking into account all of the different formats of testing, was 1 per 372,000.

Our conclusions. The postmarketing study confirmed the feasibility of fully automated blood screening for the three analytes, HIV, HCV and HBV, in U.S. blood centers. Now, I say confirmed because we have been doing this since 2005. So we know that the system works in the testing that has been outside the U.S.

The second conclusion is that we had 13 HBV DNA

positive donations that weren't detected with the current serological testing and I think everyone considers this to be higher than what would be predicted by modeling. I think that has been discussed pretty thoroughly here.

Of the 13 cases, the other remarkable thing was that six appeared to be from vaccinated donors and that is based on questioning the donors and/or anti-HBs results. And this, I think everyone agrees, was the key unexpected result of this study and we see it as really an unforeseen risk to the blood supply and, because some of the data--I don't think you were able to see the details from Dr. Stramer's presentation, but the seroconversion windows can be quite a bit longer in the vaccine breakthrough cases.

The other, I think, surprising finding from the study is that pools of eight in 16 donations were effective in identifying HBV yield cases. I think, back in 2004, it was considered that pool testing would not be affected but I think, at least from our perspective, we think we have found a significant amount of yield even in relatively large pools.

I just want to end with an important slide to acknowledge the principal investigators from this study and

also to acknowledge the members of the Clinical Affairs Departments from both Gen-Probe and Chiron.

So, thanks again for the opportunity to give this presentation.

DR. FREAS: Thank you, Dr. Linnen. Our next Open Public Hearing speaker is Dr. John Saldanha from Roche Molecular Systems.

DR. SALDANHA: Thank you. I am an employee of Roche Molecular Systems and we make the AmpliScreen test and the MPX Multiple NAT assay. I would like to thank BPAC for giving me the opportunity to present some data. What I am going to show you are the results of the clinical trials we have done specifically for Hepatitis B virus.

So, these data were published by Sandy Linants in Transfusion last year. And these were the results of the Roche AmpliScreen HBV test which was done under and IND and also post-licensing. The test was licensed in April, 2005, so, initially, we ran the test under and IND from August 2002 to April 2005 and then, additionally, routine testing from April to December last year.

In total, over 3,300,000 samples were tested and there were seven samples that were NAT-reactive. These

samples were all surface-antigen-negative and anticore-negative. But I must say, at this point, this was pre-PRISM testing so none of these samples were tested on the PRISM with the U.S. cutoff.

Of the samples, four of them remained surface-antigen-negative after they were retested on the PRISM when the PRISM assay was available. So, out of the seven samples, four remained antisurface-antigen-negative.

The second clinical trial we did was for the MPX test. This is the Roche automated platform for multiplex screening. It is a multiplex test for HBV, HCV, HIV-1 group MNO and HIV-2. The clinical result was done in 2005 and, during the studies, over 62,000 samples were tested in pools of six and over 9,000 samples were tested individually. I should point out that the test, according to the package insert, we recommend the testing in pools of six or individually and the usual format here is in pools of six.

One sample was picked up in a pool of six and was shown to be HBV NAT-reactive. It was negative on the COBAS AmpliScreen when tested in pools of 24. And it was both PRISM, anticore and Hepatitis B surface-antigen-negative.

So, looking at the total yield data that we have for both the AmpliScreen and the MPX, these are in U.S. donors, there were a total of eight donations of which five were missed by the PRISM. In the second column, you can see the quantitation that was done. I have actually put it in IUs as well because this is what the FDA are looking at for the cutoff so I think it is easier to translate.

And I draw your attention to Sample No. 2 which had a relatively high Hepatitis B yield which is about 720 IU/ml and had a very low PRISM cutoff. The other three samples were below the level of quantitation which is about 40 IU/ml.

Then, looking at the follow-up, we had three donors who we could follow up and I think, in most of these cases where the Hepatitis B titer is very low, it is essential to follow up in case of false-positives. There was one donor, Donor No. 7, who had a very high anti-HBsAg titer of 2,340 mIU/ml and this was clearly a breakthrough case.

One donor, Donor No. 2, was nonreactive for antisurface and this was a window-case donation so that the donor had a very high copy number, was followed up for 177

days and the first donation that seroconverted to surface antigen was after 14 days. The anticore converted after 28 days and the antisurface came up after 14 days as well. The donor remained DNA-positive for 21 days after the index donation.

The second donor who was what we think is a breakthrough was followed for 167 days. They were non-reactive for surface antigen throughout the follow up and nonreactive for antisurface as well. But the anticore did come up positive and they were positive for DNA for up to 22 days.

The third, that was very odd because they were followed up 59 days and they were nonreactive for all the serological markers. We think was a low-level chronic carrier without any serological markers. So we had the full range of donors here. We had a window case, a breakthrough and a chronic carrier for Hepatitis B.

So, looking at the overall rates, if we just look at the COBAS AmpliScreen data, and these were tested in pools of 24, the rate is 1 in 844,000. These are excluding all the PRISM positives. With the MPX, is it 1 in 72,000. This, I think, is not a rate that we should look at because

we only tested 72,000 donations. The n number is not very high, so I realize that is probably not accurate at all. And, if we combine all the data to get the yield for Hepatitis B in the U.S., it works out at about 1 in 690,000.

The other bit of data that I would like to show you are data that we have done from some of our studies overseas. This is really to show you the power of the test in picking up window-period donations. As I said, we picked up one in this study.

We did studies in Thailand and we tested about 240,000 donations. Of these, 27 donations were negative for surface antigen and core using the PRISM to give a yield of 1 in 8,500 which is very high. But this assay was able to pick up window-period donations. And, again, going back to the discussion we had on the cutoff of 100 IU/ml, I think this seems a reasonable cutoff because the PRISM assay, I think the cutoff for that is between 200 and 300 IU/ml so it make sense to have the cutoff lower than that. Otherwise, there is no point in doing NAT if it is set at that level.

Finally, I would like to thank the people from Puget Sound Blood Center who generated most of the data.

This is Mark Destry, Sandy Linants and Carol Taylor.

Thank you.

DR. FREAS: Thank you, Dr. Saldanha. Our next Open Public Hearing speaker is Dr. Steve Kleinman representing the AABB.

DR. KLEINMAN: Thank you. I am here today as a consultant to AABB so I have a financial arrangement with them and I will be reading a statement of that organization, but, just for full disclosure, I have done consulting work for both Chiron and Roche both of whom make NAT assays. I don't think that influences this statement, however.

This is a joint statement signed onto by both AABB and American Red Cross. I will read the statement.

Over the past several decades, there has been progressive reduction in the risk of transmission of HBV by transfusion based on the use of HBsAg tests with increased sensitivity and widespread use of the HBV vaccine. However, on the basis of modeling studies, HBV remains the most common clinically important viral infection transmitted by transfusion with residual-risk estimates several-fold greater than those for HIV and HCV.

The recent FDA licensure of two manufacturers'

automated triplex NAT assays, used either in minipools of 6 or 16 donations or for testing individual donations, may offer an opportunity to further reduce this risk.

Both licensed assay systems appear to perform adequately in terms of analytical sensitivity and specificity and, when applied to contemporary U.S. donors, they generate incremental yields of 1 in 300,000 to 1 in 600,000 HBV DNA-positive donations not detected by current serological tests. This rate is similar to the yield rate of HCV minipool NAT and substantially higher than that for HIV minipool NAT. The HBV yield donations tend to contain low copy numbers of HBV genome that are not detected by currently available ultrasensitive surface-antigen assays.

It has been shown, as we have talked about all morning, that these HBV yield donations include two sample types. First, there are sero-negative window-period donations in unvaccinated donors that are likely to be infectious. Such window-period donations have been found at a rate that is similar to that predicted by modeling.

Secondly, and unexpectedly, at least half of the NAT yield donations identified in all of the U.S. clinical studies represent subclinical infections in vaccinated

individuals characterized by HBV DNA in the presence of low titers of anti-HBs. Acute HBV infection in these individuals occurred years after vaccination predominantly through contact with their sexual partner who was a chronic carrier.

The possible finding of vaccinated HBV NAT yield donations was not included in the models and infectivity of these additional yield samples is unknown. Understanding the infectivity through the transfusion mechanism of these vaccine breakthrough NAT yield cases is critical. It appears that the HBV minipool NAT yield rate is higher than expected as a result of the widespread use of HBV vaccine and the result in detection of these vaccinated individuals.

Of the yield donations presented in the Red Cross study, and that was 3.8 million screened donations, two-thirds of these, or six of nine, were vaccine breakthrough cases all of which were detected by minipool NAT using a pool size of 16. The total yield of the study was nine HBV DNA-positive donors of which eight, or close to 90 percent, were detected by minipool NAT with a single ID NAT-only donation not detectable in any pool size--that is, 4, 8 or 16.

The data suggest that the efficient detection of the vaccine breakthrough cases by minipool NAT is likely related to a low level or a prolonged viremic phase. Modeling studies indicate that maximum yield of HBV window-period donations can be achieved only through the use of ID NAT. In contrast, the clinical studies conducted have shown that the majority of HBV NAT DNA-positive yield donations were detected by minipool NAT. Thus, the adoption of minipool NAT will offer an incremental improvement in HBV transfusion safety by the detection of serologically non-reactive donations from donors with acute infection whether they were previously vaccinated or naive.

At the present time, neither surface antigen nor anticore testing can be eliminated since these tests continue to detect donations that HBV NAT fails to detect. Parenthetically, I will say we didn't see that data today, but it is well known and it has been presented in the past. It is possible that eventually HBV NAT may displace one of these serological tests but this will require additional large studies.

In summary, HBV minipool NAT is now available in multiplexed automated NAT screening formats and these tests

are able to detect a number of HBV DNA-positive individuals. Such expanded screening will have unknown clinical benefit. In addition, its use cannot be offset by the discontinuation of any current testing. Widespread adoption of HBV minipool NAT is predicted to occur in the future, in part as a consequence of the operational advantages of the fully automated triplexed NAT systems. The Roche automated system is already only available as a triplexed assay and we expect that, over time, the same will be true of the Chiron system. Based on these considerations, it is reasonable for FDA-licensed blood establishments to implement HBV minipool NAT on a voluntary basis until the FDA mandates such testing. This mandate should be consistent with FDA-approved labeling of the two manufacturers' test that allows NAT in minipools of up to 6 or 16 donations. There is no benefit to smaller minipool sizes from either modeling studies or clinical trials.

We oppose a mandate for ID NAT at this time due to the relatively small increased yield observed in the Red Cross study--only one out of the nine cases--increased donor deferral and donation loss due to false positivity and logistics of a 6- to 16-fold increase in test volume

and cost. We, as an industry, recognize the potential benefit of minipool for HBV and, therefore, believe that this test should be adopted.

As a final comment, the absence of effectiveness reimbursement mechanisms by which hospitals can recover the increased cost of blood-safety initiatives implemented voluntarily or after an FDA recommendation remains a serious flaw in the regulatory process. HBV NAT is an example of such an initiative that will come as an unfunded mandate if FDA recommends its use.

Thank you.

DR. FREAS: Thank you, Dr. Kleinman. Our next Open Public Hearing speaker, Glenn Mones, representing the National Hemophilia Foundation.

MR. MONES: My name is Glenn Mones. I am pleased to address the committee as a representative of the National Hemophilia Foundation. NHF is the oldest and largest organization representing individuals affected by bleeding and clotting disorders many of whom are also affected by complications caused by tainted blood products prior to the implementation of the safety standards we have today

NHF has historically supported and continues to support an approach to blood, blood and plasma-derived products and tissue safety that errs on the side of maximum safety. We believe that, whenever the ability exists to improve the margin of safety, even incrementally, the imperative to protect all recipients of these products outweighs cost concerns and other issues.

Based on this attitude, NHF has long supported broad use of NAT testing. NHF's Medical and Scientific Advisory Council, composed of many of the countries leading medical professionals treating bleeding and clotting disorders addressed this in MASAC Recommendation 187, MASAC recommendations concerning the treatment of hemophilia and other bleeding disorders, approved by MASAC on November 15, 2008 and adopted by the NHF Board of Directors on November 16, 2008.

In Subsection B(3) of Section 2, Recommendations to Manufacturers of Coagulation Products, the document states that, "Nucleic acid testing offers significant incremental sensitivity over the HIV antigen test and serological tests for HIV, HCV and HBV. This can best be accomplished by testing individual donors or very small

donor minipools."

In Section 3, Recommendations to the Food and Drug Administration, the document goes on to say that, "The Food and Drug Administration is responsible for regulating the manufacturers of coagulation products to ensure that licensed products are safe and effective. Many of our recommendations for manufacturers should be regulated proactively by the FDA."

Although these recommendations are aimed primarily at the specific products used most commonly by individuals with bleeding disorders, we believe they can and should be applied broadly to blood, plasma and tissues.

NHF supported broad use of NAT testing before the existence of the newer and very practical multiplex tests. We supported broad use before we learned what we now know about breakthrough infections and the potential for additional transmissions through blood, plasma and other donations. We believe the time is right to implement this added measure of safety by mandating this test for all donations and, thereby, further protecting all individuals who rely upon them.

We thank the committee and the agency for taking

up this important issue and for allowing us to speak today.

MR. FREAS: Thank you very much, Glenn, for your presentation.

MR. MONES: Thank you.

MR. FREAS: Our next speaker is Dr. Susan Rossman from the Gulf Coast Regional Blood Center.

DR. ROSSMAN: Thank you. I have no personal financial interests but I have done clinical trials for both Roche and Ortho at my center. I am representing today the 74 members of America's Blood Centers, ABC. We provide about half of the volunteer blood supply in the United States. Our U.S. members are not-for-profit community-based organizations that are licensed and regulated by the Food and Drug Administration. Hema Quebec, our Canadian member, is regulated by Health Canada.

We thank FDA and BPAC for the opportunity to comment on the possible recommendation for use of HBV NAT for blood-donor screening. I want to remind you that we already use two serologic assays for the screening of blood donors for HBV, one, extremely sensitive for the detection of HBsAg that is well correlated within infectivity, and one, much less specific for antibodies to the core antigen

of HBV. This assay does not correlate well with infectivity but removes most individuals that have had a past HBV infection.

Interestingly, the potential recommendation for the performance of NAT for HBV represents a new paradigm for blood-donor screening for infectious diseases. We are being asked to screen blood donors because new tests became available not because we are confronting an epidemic with substantial risk of transmission to blood recipients as has happened with HIV or West Nile virus.

The move from evidence-based decision-making to an unattainable zero-risk blood supply is a source of great concern for our members. Previous BPAC and the Advisory Committee on Blood Safety and Availability meetings addressed assay sensitivity of minipool NAT for HBV DNA and concluded that its contribution to blood safety was limited and did not justify implementation. Only individual donor NAT appeared to increase the yield of detection of infected donors.

Actually, Robin Biswas from CBER FDA is the first author of a quite elegant paper we have heard about today from Transfusion indicating that sensitivity of minipool

NAT was similar to that of current serological assays.

More recently, clinical trials using one of the multiplex assays were carried out by the ARC and we have heard about that also today. As described in the AABB statement, ARC identified nine donors with low viremia and low levels of anti-HBs among 3.8 million donations. Several were considered breakthrough infections in vaccinated individuals.

As mentioned in the briefing document prepared by FDA, there is no evidence that units collected from these donors are infectious. The only way to document infectivity would be experimental attempts to infect non-human primates. Considering the current restrictions, it is unlikely that these experiments will be ever carried out to clarify this question.

Essentially, manufacturers bundle the three tests in response to users' hopes for operational simplicity and reduced cost not because of an epidemic or a recognized need for higher sensitivity of specificity of existing assays. We have been told by the assay manufacturers that an FDA recommendation increases the value of the kit and will lead to price increases. In addition, a

recommendation for HBV NAT will force laboratories in our member centers using the FDA licensed HIV HCV NAT assays to move to the combined assays for HIV, HCV, HBV. We are not convinced by the data that has been presented that this change will significantly improve safety for the recipients.

Finally, we do not understand the recommendation for a minimum sensitivity of 100 IU/ml individual samples as suggested by Question 3. It is an arbitrary number that is not based on data. We agree with the AABB statement indicating that reduction of pool sizes short of individual NAT is impractical and will not significantly increase the sensitivity of the combined assays.

ABC members suggest that implementation of NAT for HBV be a decision made between blood centers and their local medical community. They can assess the importance of HBV in their communities and know best how to allocate the resources they have available.

Thank you very much for the opportunity to present.

DR. FREAS: Thank you, Dr. Rossman. Our final Open Public Hearing speaker is Corey Dubin representing the Committee of 10,000.

MR. DUBIN: Good day, Mr. Chairman, members of the committee. I am the President of the Committee of Ten Thousand. We have been in this process--this is our 20th year and we are glad to still be here. It is important to state that the Committee of Ten Thousand takes no grants or dollars of any kind from the manufacturers of biologics, drugs or medical devices--i.e., no FDA-regulated agencies. And I, personally, have no interest, no stocks, none of that.

That said, as you asked us to do that, Bill, I think it is not about zero risk. It is about the precautionary principle. I stand before you co-infected with HIV and hepatitis. Luckily, I am surviving and I am thankful to be that.

What concerns us today is that you all get disconnected from us again. There was a time when you were disconnected from us and we heard similar things. Now, I am not comparing this discussion to HIV. That is not my goal for a moment. But I am stating the importance of the connection between this committee and us, the end users. When I say "us," I don't mean hemophilia because, when I think about the issue before us today, I think more about

our other constituency at the committee, immune-compromised people, HIV-infected people, who depend frequently on blood components. Neonates come to mind when you talk about blood components and the risk there.

For us, it is the precautionary principle that is important. We are not suggesting this is an epidemic but we are suggesting that this is another step that takes us to another degree of safety. We are not unmindful to the cost to the blood community. We are also supportive in our work on the Hill. We discuss with Congress regularly the need to full-fund reimbursement, not just for our own community but for those of you in the blood community and elsewhere, community clinics, DISH hospitals who are all having trouble surviving.

But FDA's task is not cost. It is safety. And the last time it was cost, we had heard. And we want to remind you that this is also a period when what we were told for years as a theoretical risk in terms of transmission is now a probably risk, vCJD. And we are waiting for more information from the British case to understand the ambiguity and how to weigh that risk and what it means.

But there is no question the community is nervous about that. So I think it is important to understand, we know better than zero risk. There is no such thing, and to try and attain it would probably break the bank for many of these people sitting in the room.

The precautionary principle is something different. So I think it is most important that we remind you of that and that you all, as I began my statement, remember us. We are not all gone yet. There are enough of us still here to know what happened and understand the importance of the precautionary principle.

And I would say, even more important for me, personally, having sat on this committee two terms, is the relationships we all built. We learned from each other and the committee had a connection to what my friend calls "those with an arm in the game." We have an arm in the game. You make recommendations that impact us 24/7 every day. And I am using the larger "us," not just hemophilia--von Willibrand's--but even the neonates I mentioned, those with HIV and other immune-compromised disorders like primary immune deficiency and others.

Those are the people we all must remember because,

when I hear the numbers are low, and I understand they are, I still know the families who get hit, who shoulder this. Remember, even if they are low numbers, there is a family out there that is going to shoulder this. Can we prevent it? Not always. Can we do our best to contain risk? We believe we can, and you can.

And so we would remind you of that and, as always, thank you for the opportunity to address you.

MR. FREAS: Thank you for your comments, Mr. Dubin.

DR. SIEGAL: Let's proceed with the knowledge that the cafeteria closes at 2 o'clock and so we should be as judicious as we can.

Open Committee Discussion

DR. SIEGAL: We are now going to open the committee discussion concerning blood-donor screening for Hepatitis B by NAT. We will take questions for the committee first and then the discussion.

DR. BISWAS: Thanks, Bill. Question No. 1; does the committee agree with FDA that units from donors with apparent vaccine breakthrough HBV infections, HBV NAT-positive and anti-HBs-positive, should be presumed

infectious pending further studies?

Question 2; please comment on the value and design of candidate studies using animal models to assess the infectious potential of units from Hepatitis B-vaccinated donors with breakthrough Hepatitis B infections.

Question 3; considering the estimated yield of HBV infection, infected window-period donations and the answers to Question 1, please comment on the benefit of routine screening of blood donors for HBV NAT if testing were performed using available licensed tests on minipools assuming a sensitivity of at least 100 IU/ml for individual samples.

DR. SIEGAL: So, commentary? Questions? Discussion on Point 1?

DR. NELSON: It seems like only one of those are questions. There is a yes or no, and then there are two comments. I am confused.

DR. SIEGAL: Dr. Epstein.

DR. EPSTEIN: Kenrad, you are not confused. That would be rare. No; Question 1, we want a yes/no answer and the other two are essay questions. [Laughter.]

DR. SIEGAL: Maureen.

DR. FINNEGAN: I would like to suggest that we don't have enough information to answer Question No. 1. I don't think anybody has enough information to answer Question No. 1 because nobody has looked at the recipients of this blood to see what is going on.

The other thing I would say is that number of non-vaccinated personnel in North America is decreasing with time and so, actually, the question you are going to be asking in ten years is breakthrough infection in a vaccinated donor, what does it do in a vaccinated recipient.

DR. HOLLINGER: I think, also, if you look at that first question, I agree with you. I think, in this particular case, there is not much data to look at that particular issue. The only one was that study by Gerlich in which there was a vaccinate individual who was vaccinated with regular vaccine after three years seroconverted to anticore with a different genotype, a different genotype to the vaccine, one which is an AYW3 subtype, not the ADW2 which makes up the vaccine.

That platelet-pheresis donor ran from 3 to about 20 genomic equivalents per ml over a period of time. And then they did a lookback of 65 recipients, none of whom had

infection. That is the only one we have there. We have several other studies which, at least in my opinion, has clearly not shown any clinically relevant disease, if any disease at all, in patients who were anti-HBs-positive either in the absence of anticore and, in some cases, in the presence of anticore.

So we do have that data also. The other ones that were brought out that may have had some relevance were people--were donors who were anticore and anti-HBs-positive and, therefore, would be eliminated, or the recipients of those were immunocompromised individuals, stem-cell recipients, that may have had an occult infection underneath and were not tested. So we don't know whether that one individual in the WHI [ph] study might have been an occult infected patient who, then, generated infection.

So, anyway, I think those are the issues we have when we come to answer this question about relevance in this case.

DR. SIEGAL: Dr. Colvin.

DR. COLVIN: I keep thinking about the first question again. We also have to consider, including it was an interesting point, I think, about the recipients who

will all be vaccinated in the future. However, when you start thinking about who are the bulk of the population who will be receiving blood or blood products, even if they were, first of all, vaccinated, many of them will be immune-compromised for other reasons, so we don't know how well their immunity will hold up against HBV.

Second of all, a lot of recipients that we will be thinking about in this case, of course, the pediatricians will think of all the neonates who will not have been vaccinated yet. And I think they are, again, in a particular high risk to progressing to chronic Hepatitis B infection.

DR. HOLLINGER: Let me just ask the question, why wouldn't they be vaccinated?

DR. COLVIN: The neonates?

DR. HOLLINGER: Yes.

DR. COLVIN: Well, they wouldn't have an immune response yet in the time that, say, they are perinatally getting transfused.

DR. HOLLINGER: But they would be vaccinated, in this country.

DR. COLVIN: Well, the question is, I don't--not

being a pediatrician, myself, but in the NICU, is it normal practice, then, to vaccinate on Day 1 of life?

DR. HOLLINGER: It is practiced in this country for universal immunization with a birth dose in the vast majority of cases; yes.

DR. COLVIN: But just having gone through this again recently, I can tell you that, at least a lot of times they are putting it off within the hospital because the local pediatricians now are giving them multivalent vaccines for multiple things. So they are not sure what the primary-care doc is going to do with them. So, a lot of times, it is actually put off from the birth dose as well.

If you are thinking about the immune response, well, how long is it going to take this other immune response to develop after a vaccination especially in a neonate who may be in the NICU who may also require blood products.

DR. SIEGAL: Dr. Alter, first. Then Dr. Kulkarni.

DR. ALTER: I just want to remind you that, if we knew the answer to this question, there wouldn't be a question. So we have to make a presumption at this time

and we could presume that the units are infectious or we could presume that the units are not infectious. But, to presume that they are not infectious is a risky presumption in case they turn out to be infectious.

To assume they are infectious obviates the risk but it means that, at some point, you may have to renege what decision you make today. But, the precautionary principle, again, would say, the presumption that the units are infectious is the safest way to go until we find the answer. And the second question would be how can we find the answer.

So that is my perspective.

DR. SIEGAL: Dr. Kulkarni and Dr. Cryer.

DR. KULKARNI: As a pediatric hematologist, I think I can address some of the issues which come up. As far as neonates are concerned, you are assuming that these are full-term neonates. A lot of them are premature neonates. If I have a baby with intracranial hemorrhage as a result of a bleeding disorder or whatever it is, that neonate is going to get blood and blood products before any vaccination is even considered. So a lot of them are at risk.

The other thing I worry about is patients who receive repeated transfusions so, in their own lifetime--for example, patients with sickle-cell disease, every three weeks they get a transfusion. And I don't think we have an answer, is there an additive effect of repeated transfusion or repeated dosing of this particles.

I think, having worked with the CDC and still working with them--I think an ounce of prevention is better than any cure.

DR. SIEGAL: Henry.

DR. CRYER: I am very comfortable with the precautionary principle. I will just comment that, in my hospital, the vast majority of people who get blood transfusions are, in some way, impaired immunologically. So, I wouldn't know if they were pre-vaccinated, whether that would do them any good or not. I really don't know.

The data would seem to at least suggest that, if you can get breakthrough here, that those people would be even more sustainable to breakthrough. So I think the precautionary principle makes sense. The problem I have with it is you are never going to know because, if we remove all those units from the blood supply, we don't have

the ability to go back and find out what happened to people who might have gotten units like that before.

We are never going to really know whether this was a real problem or not, at least from anything I heard today. I didn't hear any experiments that would give us the answer. DR. SIEGAL: Any other comments on the great unknown? Jay?

DR. HOOFNAGLE: Why do you just propose it, and those with vaccine breakthrough opposed to everyone who is NAT-positive surface-antigen-negative? And I kind of agree with Harvey. You have to presume they are positive. But I have to admit that you haven't presented any data yet that they are, and that is the problem and it leads to the second question, and is--chimeric mouse models are perfect and will answer to the study the some extent.

Of course, if they are negative, we won't answer it completely but if you can transmit Hepatitis B to the chimeric mice or chimpanzees with one of these units that occurs 1 in 200,000, very rare, then it is reasonable to say, yes, these are infectious and press forward. But that clearly needs to be done.

DR. SIEGAL: And the chimeric mouse model is more

reflect of the immunocompromised host, probably, than--the chimeric mouse model is closer to the compromised host than the immuno-competent chimp.

DR. HOOFNAGLE: As Harvey points out, it is just a transmission model. You are not going to get antibodies or immune responses.

DR. SIEGAL: That's right.

DR. HOOFNAGLE: But you will show that something is infectious.

DR. SIEGAL8: Yes; in a SCID mouse.

DR. HOOFNAGLE: You don't have a good tissue-culture model that you can screen this blood and that blood for.

DR. ALTER: I have to agree with Jay agreeing with me.

DR. SIEGAL: So we have a consensus. Any other commentary?

DR. BALLOW: I just wanted to ask my colleague at the end of the table, what is the data on sickle-cell patients? Do they have an increased incidence of hepatitis through blood transfusions, Hepatitis B?

DR. KULKARNI: I don't think we know that.

DR. BALLOW: Wouldn't that come to light, though? Wouldn't that data come out just from those patients acquiring the infection?

DR. KULKARNI: I have no idea. I mean, clearly, for thalassemia and for sickle cell, for multiply transfused patients, that is the risk and I think that is what the CDC study is trying to determine as we speak on the thalassemia patients. And we are working with NHLBI to do a similar surveillance on the sickle-cell population.

DR. HOOFNAGLE: Among 88 sickle patients that we saw who were adults, one had chronic Hepatitis B and about three had chronic Hepatitis C. So, yes; they get these infections.

DR. BALLOW: But do we know how they acquired it? Did they acquire it through the transfusion or did they acquire it by some other means? It is probably not known.

DR. HOOFNAGLE: Well, I assume it is transfusions from a long--these are adults, so transfusion from a long time ago. They are now vaccinated, of course.

DR. SIEGAL: Dr. Finnegan.

DR. FINNEGAN: I recognize this is not part of the FDA's mandate, but I am wondering--I think Dr.

Hollinger brought up that this may be a public-health issue with the vaccination of Hepatitis B and perhaps this information should be passed on to the CDC so that it could, in fact, be looked at because I think that is the question that we have brought up today, is not so much the blood supply as it is, perhaps, the issue of the vaccination.

DR. SIEGAL: All right. Any other commentary before we vote on Question 1? Will you please explain to us all what we are supposed to do with these little buttons.

DR. FREAS: I have never voted as a group before. However, we will push simultaneously No. 1 if the answer is yes, No. 2 if you believe the answer is no, and No. 3 if you want to abstain. And would you make sure you have picked your remote. It should have your initials on the back.

We are ready to call for the vote.

[Simultaneous voting.]

DR. FREAS: Can we see what modern technology can do for us? For the record, we have: Dr. Nelson voted yes; Dr. Colvin, yes; Dr. Glynn, yes; Dr. Hoofnagle, yes; Dr. Trunkey, yes; Dr. Zimrin, yes; Dr. Hollinger abstained; Dr. Bower, yes; Dr. Siegal, yes; Dr. Ballow, no; Dr.

Blackwelder, McComas, Cryer, Kulkarni, all voted yes; Dr. Di Bisceglie voted no; Dr. Rentas voted yes; and Dr. Finnegan abstained.

Are those votes correct? I've lost faith in technology for being simpler, but--

DR. SIEGAL: Well, I guess it worked. Let's proceed to Question 2 which is commentary, and this doesn't require a vote, I understand. So who would like to comment on Question 2.

DR. FREAS: Could we have the tally of that vote? There were 13 yes votes, there were 2 no votes and 2 abstained.

DR. SIEGAL: Okay. Let's proceed. Commentary on Question 2. Dr. Cryer.

DR. CRYER: I mean, I think it is a fascinating experimental model but I just don't see any way that you can equate a knockout mouse to a human being. Even if you put human-being cells in it, it really becomes nothing more than a really fancy tissue culture prep. So, yes; it is an incredible model and I would love to use it in some research that I do, too, but I don't know that that--that alone is not going to give us an answer.

DR. ALTER: It does give you an answer. It is not the same as humans, but your question is are there infectious virions in these units. And it will answer that question. You can say whether these livers become infected and that is all you can say, is that they become infected. You can't say anything about the clinical course, the severity or whether the same would happen in humans. You just say there are infectious particles in that material.

DR. HOLLINGER: I guess I would have to take an exception to that because, again, in a human model, even with all the other things, you can get uptake of virus. You can get eclipsing but you may not have any replication at all for a variety of reasons. And you don't know that that is going to happen in these chimeric mice.

Certainly, you could say in the chimeric mouse model, it did, but I am not sure you can make that conclusion outside the human model. And I take, for example, one example would be Prince's study in which he did use a chimpanzee model. Chimpanzees are, what, 99.99 percent similar to humans. And, in that model, he gave 260 to 2,098, I believe it was, genomic equivalents to three chimpanzees none of which developed Hepatitis B.

So I do think there may be some differences. So you take that, and then you take your chimeric mouse model and you say, which one is right. Maybe Prince didn't do all the things that should have been done or maybe there were some differences in that material.

But I am not sure we are able to take this mouse model, this chimeric mouse model in which you have taken some human tissue, you have altered it in a variety of ways to make it replicate or grow in these animals.

DR. Di BISCEGLIE: But, Blaine, don't you think that if you can demonstrate replication in the mouse, the positive means something. A negative experiment doesn't necessarily mean anything; right?

DR. HOLLINGER: No, because I don't think necessarily that you might have full replication in a human model for whatever reasons, molecularly or otherwise. As I said, there are a variety of steps in which this virus gets into a cell and is processed and is eliminated from the cell. It may not be eliminated from a--

DR. Di BISCEGLIE: Yes. Again, that is a negative experiment. A positive experiment would be fine.

DR. HOLLINGER: Positive in the chimeric mouse

model but I am not sure it is equivalent.

DR. ALTER: It is not equivalent and a chimpanzee would be better and a human would be still better if you want to volunteer for that experiment.

DR. HOLLINGER: You have already sent me to Bolivia. [Laughter.] That is an inside joke.

DR. HOOFNAGLE: I agree with Harvey on that one.

DR. ALTER: But the thing is, Blaine, if you take one of these units, or ten of these units, and you put it into a sufficient number of mice, have positive controls and negative controls, which you can do in mice, and you show that it is--you have infectious particles in there.

Maybe you wouldn't do the same in the human, but at least you know there are infectious particles and that makes you pause and consider that it could be risky. It is not the perfect experiment. If you do a sufficient number and you don't see any infectious particles, it tells you something, too. It is not absolute. But if you have the right control who says, well, we don't find any infectious particles in this model.

So I think it gives you information. It is not perfect information.

DR. HOLLINGER: No; I agree with that. But I think I would like to see it at least in a couple of chimps.

DR. ALTER: Yes; if you get chimps, it's better.

DR. HOLLINGER: To at least document that this model has some equivalence in that regard.

DR. ALTER: It is just that they are very hard to come by right now.

DR. HOLLINGER: Yes; I understand.

DR. BIANCO: I would like to know if Dr. Alter were sitting here in this meeting a year from now and people told him that 50 of these chimeric mice received an injury and they were negative, if you would recommend that the requirement for testing for HBV would be eliminated.

DR. ALTER: Assuming that we implemented it and then--the tests were all--yes; I mean, I would. I would. I would go back. I think the FDA has to be flexible and I think if you say we want to get more data and then the data is contrary to your decision, I think you need to go back.

I think we need to get rid of syphilis testing. There are a lot of things that are in place that I think we could get rid of. I think we need to go to pathogen inactivation and then I would take all this away. So, yes;

we can change in the future. But, right now, we are in the unknown and it is better to go on the safe side, do the experiments and, if they prove to the contrary, then go back.

DR. HOOFNAGLE: I have a few comments. It is an easy experiment to inoculate the mice. No problem. There is another issue which I guess Blaine is getting to is that the infection in humans may not be kind of typical Hepatitis B because it is a low-level virus. You may get a mild infection. That is going to be very hard to show one way or another because, even if it is--let's say we can find one or two people, it's mild, that doesn't mean anything.

You have to do 100 people before you can decide--because Hepatitis B is usually mild. It is only like a third of cases that are even jaundiced. So it is almost an impossible thing unless you find one good case of an immune-competent person who gets one of these units and gets a good solid case of Hepatitis B. Otherwise, we will be perplexed.

I think it is kind of a no-brainer that these are probably infectious. But what kind of disease they cause

in humans and how frequently you see a problem, that is going to be very difficult.

DR. NELSON: It is very complicated because the genotype issue, I think, is relevant. We know that certain genotypes of Hepatitis B have a worse natural history than others. You might find, if you injected mice with hepatitis genotype A, you know, that they didn't get infected. But if it was C--or you wouldn't answer the question necessarily. And it is pretty complicated, I think, to answer this question with a few mice. It might require quite a few mice.

DR. BLACKWELDER: One comment relative to that, if you got a negative result and a sense of no infections and you had 50 mice or even 100 or even more, you could never prove that there is zero probability of infection. There is always a confidence interval around that zero that allows the possibility of some infection.

DR. HOOFNAGLE: You include positive and negative controls in something like that, of course, so the samples that are surface-antigen-positive are causing infection but that is without--the other thing is that the HBV DNA that is detected in serum is not floating around in serum as

free HBV DNA. It is encased in surface antigen.

So, if we had a more sensitive test for that protein, if protein detection was as good as nucleic-acid detection, then we wouldn't have to bother with this. We could just improve our test for surface antigen. So that's another way that this could be reversed if one of the companies came out with a surface-antigen test that was 20 or 100 times more sensitive.

DR. ALTER: I don't want to leave the false impression that these mouse studies are easy to do. They are actually very expensive. It is a difficult model. And so you are not going to get 100 mice in the study. But you might get 10 or 15 or 20. So it is not perfect and it is not cheap. We might get somebody who is--some company who is generous to allow this happen without cost is what I am hoping.

DR. HOLLINGER: It will be interesting if they use the mouse model, the chimeric mouse model, in the individuals that were--the vaccinated individuals that had HBV DNA in their blood and anti-HBs at certain levels. The ones that were done, if I am right, were ones from Yoshizawa's study which was acute plasma that did not have

any anti-HBs in it. So it would be interesting to see that later.

DR. ALTER: If I could make one more comment. There are also early HBV culture systems out there. That is another alternative--or preferably do both. But I would suggest that, if we can find access to the model, that we then have a committee, subcommittee, to design this experiment so that you don't do it and then go back and say, we should have done something else. So they are really carefully designed, the specimens are there, but which specimens to use, which controls to use, I think that is needed.

DR. HOOFNAGLE: I think we should pursue attempting to show this in humans, too. And, in this regard, because Hepatitis B is so rare in this country, we have to look like--you know, we get all of our drugs made in India and China. We will have to do some of our research in China where Hepatitis B is much more common.

These types of things could be found out if done appropriately and so forth. I don't think you will be able to show it in the United States. For one thing, it is a foregone conclusion you are not going to use those units.

But, with a little forward thinking, you might be able--like you showed in Thailand. There is a much higher rate of this problem in Thailand.

DR. ZIMRIN: I hope you weren't suggesting that it would be ethical to transfuse--I mean, if studies designed in this country--

DR. HOOFNAGLE: A lookback study.

DR. ZIMRIN: Oh; a lookback study. Okay. Thank you.

DR. SIEGAL: Dr. Alter, again.

DR. ALTER: In that study, you would have to prearrange that samples are saved from huge numbers of recipients. But I agree, the likelihood of something happening there is much higher and you could retrospectively find out who got just DNA-positive, anti-HBs-positive, units.

DR. NELSON: I did a study in Thailand that actually showed even a much greater risk than the one that is in press in Transfusion. It was published in Transfusion about a year ago. We screened 5,200 surface-antigen-negative donors and found six that were NAT-positive using the Chiron assay. One was a window period.

The others weren't.

DR. SIEGAL: Let's proceed to Question 3; considering the estimated yield or HBV-infected window-period donations and the answers to Question 1, please comment on the benefit of routine screening of blood donors by HBV NAT if testing were performed using available licensed tests on minipools assuming a sensitivity of at least 100 IU/ml for individual samples.

Comments? Questions? Thoughts?

DR. Di BISCEGLIE: Just a clarifying question, perhaps. Did I understand correctly that the use of minipools and a sensitivity of 100 IUs are sort of conflicting goals. It is not really--if you dilute them out in minipools, you can't really achieve a sensitivity of 100. Did I understand that right? No? Can somebody maybe help?

DR. BISWAS: The issue is if you are using pools of 16, the Ultrio test 16, the limit would be--the sensitivity there is 166 IUs per ml. If you were using smaller pools, 8 pools of Ultrio in all the other assays that were shown, they would be under the limit of 100 IU/ml.

Is that clear?

DR. NAKHASI: May I speak? A clarification. It is minipools, and, because we have minipools, as Robin said, with different sensitivities. So 100, below 100, would be like 8, 6. Those are the minipools which are below 100 IU.

DR. CRYER: I still don't understand the reason for the question. Who benefits if we answer yes or no. I don't quite get it.

DR. BISWAS: If you vote yes for the 100 IU/ml, then that would rule out the pools of 16 using Ultrio assay. And Sue Stramer has indicated that she wouldn't like that.

DR. FINNEGAN: But, Mr. Chairman, can you separate this into two questions?

DR. SIEGAL: Would you like to make a suggestion, Maureen, as to how we do that?

DR. FINNEGAN: Yes. I would like to see us vote on the minipools and then vote on the 100 IU.

DR. McCOMAS: But it doesn't look like we are asked to vote. It looks like we are asked to comment.

DR. SIEGAL: Are we asked to vote or comment?

DR. EPSTEIN: No; to comment. And we appreciate that there are two levels of commentary. One is whether there should be a recommendation and two is what is the

appropriate sensitivity level. And we are looking for discussion here.

DR. FINNEGAN: Okay. Well, I get to be the dumb person here because I am the orthopod and I don't understand any of this. But it seems to me that the data that was put up said that the 16 minipool is basically equivalent to the others. So I am not sure why the 100 IU is up there. I think the minipools is an obvious yes. I am not sure about the other.

DR. EPSTEIN: Okay. I will give you a moment, Richard, but you have heard two conflicting pieces of data. You have heard empirical data where eight of nine cases in the Red Cross system were found with minipools of 16 Ultrio. But you have also seen analytical data showing that there is a projected added benefit with smaller minipools and, in particular, the MPX with a minipool of 6 has a substantially better analytical sensitivity.

Why FDA converged on a suggestion of 100 IU is because the stand-alone test, the COBAS AmpliScreen, with minipools of 24, has a sensitivity of about 105. The Ultrio, in pools of 16, was at 166. If you drop it to pools of 8, it is at 88 which is back in that region of 100.

And the MPX is still better but the question is whether you would set it to the point where there is only one viable test on the market which is not the predominant in use.

So what we were trying to do was harmonize the available systems. We were essentially saying, okay, we have got three systems out there. Maybe, over time, it will only be two. I don't know. The point was made earlier by someone that we didn't want necessarily to drive the system toward the multiplex assays. That may be the evolution but should we be forcing it.

So, right now, you don't have the use the multiplex assay. You can use the COBAS AmpliScreen which has sensitivity of 105. So, it was an attempt to harmonize a standard that recognized the existing systems that could practically be used.

Now, what you have also heard, though, is that, obviously, if you go from pools of 16 to pools of 8, you have to do twice as many pools.

DR. FINNEGAN: But my problem, too, is twofold. One, not modeling but finite element analysis was used in orthopedics and the relationship between the finite element analysis and reality is huge. So the modeling is--I have a

little skepticism. But, more importantly, you haven't shown us there is a disease. So we are talking about toys, but we are not actually talking about a disease.

So I find it a little difficult to put pressure on the system when we are not sure that we are treating anything.

DR. EPSTEIN: Well, yes. This comes back, I think, to Dr. Alter's point about looking at this in a precautionary way. If there are infectious units, there will be transmissions. Now, the estimate that was presented in 2004 at the Secretary's Advisory Committee was 0.16 qualies [ph] per transmission. We can go into all the details of where did you get that number.

We know that there is a high rate of transmission from an infectious unit. You have heard that it could be as few as 10 virions. You are talking about transfusing whole units so the likelihood of a transmission may be high. Putting aside the whole question about vaccinees, if we are just talking about the early window period, transmission rates are probably high.

Disease attack rates probably are low, but there will be disease. I mean, there are isolated case reports

of fatalities from fulminant Hepatitis B. Partly, we see that in immune-suppressed recipients. So we can't give you figures. We can't tell you how many cases of disease.

I think Blaine put up a chart where he tried to get at that in the Open Public Hearing that Dr. Hollinger showed his estimate for how much disease per annum and over 25 years. It is small. But the point here is that we do expect multiplex tests to come into general use and should we be setting and HBV NAT standard or leave that part of test use voluntary.

That is really what we are getting at. If they are used, should they meet a standard for HBV because they have a screening claim for HBV, but they are not the same as each other.

DR. BLACKWELDER: I still have a question about the 100. Does the FDA mean for that to be an absolute number? Or I think you mentioned an assay that had a sensitivity of 105. If we were in favor of 100, does that mean 105 is ruled out?

DR. EPSTEIN: You know, we are here to get comments and we were talking ballpark.

DR. BLACKWELDER: Ballpark; okay.

DR. EPSTEIN: I think there are three numbers that matter. The sensitivity of the Abbott PRISM, which is the predominant HBsAg test in use today is about 330 IU. And then we have the sensitivities of the minipool test which we have repeated several times. I am happy to say it again. But they span a range from 22 to 166. And we were trying to figure out where could we put a standard that would practical.

The point was also made earlier by Dr. Biswas that FDA was disinclined to propose a standard that would have no obvious benefit over the Abbott PRISM assay. Exactly, what would be the point? If we recommended routine use of HBV NAT at a sensitivity no better than antigen detection, it would moot the question.

DR. BUSCH: Jay, if I could, I think there is an apple-oranges issue here. These numbers that you are referring to with respect to the NAT assays are the 95 percent limits of detection of these assays. The Abbot PRISM sensitivity of 300 IUs or 1500 copies of the 50 percent limit of detection that, when we do these analyses, we are looking at the--this viral load at the cutoff they asked to see at a 50 percent level.

And there is about a 1-log difference between the 50 percent and the 95 percent limits. So the big point is that we will--with the current pool size of 16 with Ultrio, we will achieve a significant window-period reduction and we will pick up a fair number of these window-phase breakthrough infections that we can study.

So, personally, I think, again, this 100 versus 300 for antigen is not correct. You would have to multiply the 300 times 5 so it would be more like 1500 IUs for the 95 percent limit of detection.

Personally, I think if we move in with pools of 16, we will pick up these cases and can study them. We will pick up lots of them as we have seen, and we can characterize the dynamics and have the units to look at infectivity. To force the industry to reduce pool size for this limited incremental value, I think, is not reasonable.

DR. SIEGAL: I am going to call a break at this time because, if we don't take a break for lunch now, we are not going to have lunch. So, I would like this group to reconvene within half an hour if that is possible. Thank you.

[Luncheon recess from 1:30 p.m. to 2:00 p.m.]

A F T E R N O O N P R O C E E D I N G S

[2:00 p.m.]

DR. SIEGAL: Do we want to do some further discussion on Topic 1A before we proceed to Topic 1B? Would could return to Question 3 if there is anyone with any more comments.

DR. GLYNN: So one thing that I wanted to mention is it looks to me like the confidence intervals that were calculated for the theoretical model comparing the 16 minipool to the 8 minipool do appear to overlap. So, actually, this idea that there is a difference between what the theoretical model says and what the empirical data shows, I am not sure that is true, actually.

DR. SIEGAL: It seems to me that we should be addressing this with our biostatistician who is not back yet from lunch. So maybe we ought to come back to that question. Anybody else while we are waiting to reassemble?

DR. ZIMRIN: I think that is actually the critical point so I would like to address that as well.

DR. SIEGAL: Yes; I think that is a very good question, actually.

DR. COLVIN: We could almost think of this,

though, in terms of a biological question. What I was thinking about is if we make the assumption, which is not necessarily a good one, that the sensitivity per copy, whether you pool it as 8 or pool it at 16, it is the same. So the number of copies is the same. Now, that as an assumption that is not necessarily going to be fair.

Then, going from 16 to 8 should cut off, basically, one replication cycle of the virus, meaning approximately almost three days which is about 10 percent of the window period. So, in some respects, and whether or not--of course, there are going to be confidence intervals around it but the biology would suggest that, by doing this, we are going to cut three more days off the window period.

DR. SIEGAL: You could argue that it is intuitively obvious to the most casual observer. And I also think that the n is so small for all of these events--somebody else should comment on that, but it seems to me that it is very hard to make broad-brush judgments based on whether you pool or 16 or 8.

DR. COLVIN: But three days in the window period is not a--that means how many donors in the window period you would be picking up in a year--that is, in terms of

yield.

DR. COLVIN: It is approximately 10 percent of the window period; right? So the window period varies depending on who you are looking at and which study you look at from as low as 20-something days to 50-something days, if I recall the literature correctly. So it is almost approximately 10 percent of the window period. Do, if you cut down 10 percent of the window period, you are still 10 percent of the cases.

DR. SIEGAL: Okay. Anybody else? Dr. Stramer, do you want to comment on that at all, on this last discussion?

DR. STRAMER: You mean on the last comment that was made, that I should comment on that? Well, it is 2.56 and it is a 38-day window period. Well, yes. So it is about 7 percent. But I still go back to what we saw in yield and back to Simone's comment about you have to look at the statistical tests.

DR. KLEINMAN: It is 7 percent of the window-period cases but--in the non-vaccinated people and it is no effect in the vaccinated people. So that one doubling time gets even diluted out if half your yields are in vaccinated

donors. So, I think, the potential benefit of going from 16 to 8 is half of the percentage that you mentioned, so half of, Sue says, three days out of 38 days. So that is 7 percent, half of that. So it is really not a lot of benefit even from the theoretical model in going from 16 to 8.

DR. FORSHEE: Just to remind the committee, in my earlier presentation we did present our best estimate of the yield that would be achieved using the theoretical model for non-vaccinated. So, in my presentation, going from the Ultrio 16 to Ultrio 8 would yield about six cases going from that sensitivity. So that was the estimate that we had.

The incremental yield for all the tests is available in my presentation if there is ever any question about that.

DR. KLEINMAN: So six cases. But that is 1.7 components per--that is six components. So, really, it is three or four donor units per year that you are talking about if each one is made into 1.7.

DR. FORSHEE: Yes; that is correct.

DR. SIEGAL: Any further discussion of Question

3? Dr. Epstein, did we address this sufficiently well?

DR. EPSTEIN: I think we want specific comment on benefit and on an appropriate sensitivity level. I mean, what the FDA is interested in knowing is are we encouraged to discourage from going forward with a recommendation and to what extent does the committee feel we should be soft or firm about 100 IU.

So I am not sure that I have the sense of the committee. I think we have had a lot of comments about the strength of the data. But how about--

DR. CRYER: I don't think--I, for one, don't know.

DR. HOOFNAGLE: I think all the data in favor of it is just modeling. It is mathematics, that when we hear the data presented with actual samples, it looks like such a cutoff isn't necessary.

DR. FORSHEE: But, as I understand with the data in the sample, the data that Sue Stramer presented, we only had one case that was identified using the ID NAT. So determining what the relative yield would be of different sizes of minipools is just coming from that one donation at this time and so I just think we have limited information there.

DR. HOOFNAGLE: There was none that was picked up at the 1 to 8 that wasn't picked up at 1 to 16.

DR. SIEGAL: Ann?

DR. ZIMRIN: I agree with what several people have said that I don't think that we have seen data that suggests that moving from a minipool size of 16 to 8 is helpful. There is modeling, a suggestion from the models, but we did not see that confirmed. I think, in general, the concept of looking at HBV testing with NAT is certainly worth doing, I think, with the window period cases that would be picked up as well as this concerning issue of the breakthrough infections that I think we would all like to have more information.

So I think the concept is a good one, but I don't feel that we have seen enough information to suggest a change in the specific recommendations in terms of titer-level sensitivity.

DR. HOLLINGER: I think that we have seen evidence that you can get the limit of detection at 95 percent down to fairly low levels, less than 5, 6, something of that nature. So my feeling would be that the limit of detection of an individual minipool sample should

be something in the range of 50 or 60 IU/ml as a lower limit.

You might as well, then, get the most sensitivity that you can out of it. If you are not going to do individual donation NAT, then one should get the most sensitive detective levels on the minipools that you are going to be testing, whether 6, 8 or 16 or what.

So, if you are doing 8 and you have a limit of detection of 6, that means you could get down to 50 on the pool or 60 if you want to have a little bit of leeway on that. So I think that is it.

I will also just throw out a little novel thoughts to the blood-banking community. If you really wanted to do these things, what I think would be cheaper for you to do would be, since you have about 82 percent of your donors are repeat donors, that you start vaccinating your donors. You bring them in. They donate a unit of blood so you get the unit of blood. You give them the first dose of vaccine. Two months later, you have them come back in. They donate another unit of blood. You give them another vaccine. Six months later, you do the same thing.

You get three or four units that way out of the year, and you have vaccinated your repeat-donor population in doing so. It is a lot cheaper than doing these tests.

DR. KLEINMAN: Something I am not understanding about Recommendation 3 and really the question is directed to Jay. If the product already--if Ultrio already has a claim for HBV detection at a pool size of 16, and if you were to adopt 100 IU/ml as a requirement and Ultrio in pools of 16 would fail that requirement, is the consequence of putting that in to rescind the current claim that you gave on clinical grounds?

DR. EPSTEIN: Well, we would be recommending that it be used at pools of 8.

DR. KLEINMAN: Right. But you have already said it could be used in pools of 16. That is what is confusing me.

DR. EPSTEIN: What we have said in the approval is that it will detect HBV DNA in the absence of HBsAg and anticore. In other words, there has been proof of principle. But what we are now talking about is at what sensitivity level do we think there is a sufficient yield to warrant an FDA recommendation for routine use.

So, yes; it would have the practical effect of the change in the label for donor screening. Yes.

I think another perspective on this--I think what has been argued, at least in part, is that the current practice is adequate. But I think the way the FDA is looking at it, if it is a new standard, we are saying, what would you do completely de novo. In other words, it was put into place with pools of 16 because it was approved that way but now we are talking about an HBV NAT standard.

So, if you were doing it de novo, where would you put the limit?

DR. FINNEGAN: Jay, how can you justify--what data are you using to choose 100 over 166? I don't understand that and what is the urgency, or the significance, of going to 100 instead of 166?

DR. EPSTEIN: Well, you must understand. FDA is not wedded to that proposal. We put that out as a candidate because we saw it as a sensitivity limit that could harmonize continued use of the three available systems. In other words, we weren't intending to take the COBAS AmpliScreen out of the equation.

DR. FINNEGAN: But what is the scientific reason

for dropping down 66 IU?

DR. EPSTEIN: Okay. The question in FDA's mind was what is the most sensitive assay that is still practical to be implemented. It was sort of the same logic that Blaine was putting forward. Blaine was arguing for 50. We talked about 50.

The way we were looking at it is if we are going to make a recommendation for routine use of HBV NAT, what is the most sensitive test that we could recommend that still is practical--in other words, could be implemented with the available technologies, the things on the market. And we thought that that was a tolerable limit.

Why? Because Ultrio at 8 minipools isn't so different as MPX at 6 in terms of volume of testing and cost of testing. And, similarly, to Dr. Cryer's point, what would happen if we looked at the AmpliScreen at 24. It is 105 IU. Would you have to back off to 20? But the point is that those are systems that are practical and can be implemented.

I mean, even though it was done investigationally by the Red Cross, a very large-scale assessment was done with pools of 8. So it can be done. So, again, FDA's

perspective here, wherever you put the sensitivity limit, it is arbitrary. But the way we were trying to approach it, trying to balance what is feasible with what is beneficial, was what is the maximum sensitivity that we could set as the standard that is still achievable with the current technologies on the market. That is the way we were looking at it.

DR. Di BISCEGLIE: That sounds reasonable. But I must say, I think we are fooling ourselves if we think that there is a real difference between 166 and 100 in an analytic test like that. It is a theoretical construct.

DR. NELSON: I can see the reason for having some number because what is to stop somebody from marketing a minipool of 500 or 150, or something like that. There has to be--I mean, it seems to me maybe 100 is arbitrary. I agree. And I would be happy with 166. But it seems to me that, in addition to having a minipool NAT, there should be some mention of how sensitive it should be.

DR. SIEGAL: Dr. Zimrin.

DR. ZIMRIN: I could get a lot more excited about a cutoff of 100 if there was any proof that it actually picked up cases. I think, having a number--if you want to

have a number, having a number that is in accordance with the data would be very reasonable which would be, as I see it right now, at 166.

DR. GLYNN: I agree with what Ann just said. So, essentially, we don't have any data that shows that the 16 is any better or worse than the 8. So I would go with 166 to--actually, it is a little bit more than that. It is 166.4.

DR. SIEGAL: Anyone else wish to comment? Okay. Jay, any other--enough? Okay.

Let's proceed to Topic 1B, Testing Donors of Human Cells, Tissues and Cellular Tissue-Based Products, HCT/Ps for Hepatitis B Virus Infection by Nucleic Acid Testing.

The first question; please comment on the potential benefit for HBV NAT testing in the ID NAT format and in the small minipool format for living donors of hematopoietic stem/progenitor cells. These questions don't call for a vote. Any commentary?

DR. HOLLINGER: You mean, we only get to use these once?

DR. SIEGAL: It sounds that way.

DR. HOLLINGER: That is kind of fun.

DR. SIEGAL: We could do it anyway, even if we are not asked. Is there any commentary on this question?

COMMITTEE MEMBER: It seems reasonable to use the same standard.

DR. SIEGAL: Is that the sense of the committee? It is. Since, there is no further commentary, let's proceed to Question No. 2; please comment on the potential benefit of HBV NAT testing in the ID NAT format for other living donors and cadaveric donors.

DR. HOLLINGER: I would just maybe comment about the cadaveric donors. The blood that is obtained from cadaveric donors is often after a period of time and other things. I can't see how you could even begin to pool that and do a minipool of cadaveric donors. There are so many things you can't explain that is in the blood that is happening, proteases, a variety of other things. To pool it would just be disastrous, in my opinion. That has to be an individual NAT testing in my opinion. Living donors are a different story.

DR. SIEGAL: Dr. Finnegan.

DR. FINNEGAN: I would second that. I think that

the potential for a disease spread to way more people is also an important factor in that, so I would agree with that.

DR. SIEGAL: Is there anyone else who wishes to comment or is that the sense of the committee?

DR. BALLOW: I would agree as well. Since the instrumentation coming on line is multiplex, it is going to get done anyway from what I heard this morning.

DR. SIEGAL: Anyone else? Dr. Alter, do you have any comment?

DR. ALTER: No comment.

DR. SIEGAL: Okay. Then I think we have been through the questions. Dr. Epstein, is that sufficient? Okay. Thank you all very much.

DR. FREAS: Before we start Topic II, I would like to thank Dr. Alter and Dr. Hoofnagle for participating in Topic I and we appreciate your comments.

At this time, I would like to welcome a new temporary member, Dr. James Maguire to the table. He is Professor of Medicine, Harvard Medical School. Welcome.

Topic II

Potential Testing Strategies for T. cruzi Infection

in Blood Donors

DR. SIEGAL: So, Topic II, as you all know, is Potential Testing Strategies for T. cruzi Infection in Blood Donors. The Introduction will be given by Robert Duncan, Ph.D. of FDA.

Dr. Duncan. We seem to have lost Dr. Duncan.

Introduction

DR. DUNCAN: Good afternoon.

[Slide.]

I am Dr. Robert Duncan from the FDA. I am giving you some background and overview of the session on Potential Testing Strategies for Trypanosoma cruzi infection in blood donors.

[Slide.]

We have talked about this disease and this agent many times before at the advisory committee. But I would just, once again, like to give a couple of tidbits about the disease that particularly affect how we make decisions about its implementation.

Trypanosoma cruzi is a small protozoan parasite that, at one stage, lives freely in the blood. The disease that it causes is called Chagas disease. This is often a

chronic, asymptomatic infection that is very difficult or impossible to treat with severe symptoms occurring late in the infection in about 30 percent of the cases. It is primarily found in areas of Mexico, Central America, South America where there are estimated to be 16 to 20 million infected.

Transmission of the parasite is through the feces of a blood-sucking insect although it can also be transmitted by organ transplant, transfusion. It can be transmitted orally. The parasites can be rubbed into other areas like the conjunctiva of the eye or there could be laboratory accidents.

Blood transfusion transmission has been recognized as a problem in the endemic areas for a long time and, over time, it was estimated that an infected unit has about a 12 to 20 percent probability of transmitting that infection.

[Slide.]

After a process of evaluating the need for a test for T. cruzi in this country, one company came to the FDA and we licensed the test in December of 2006, an ELISA test. Since that time, the majority of blood centers have been

testing voluntarily, or at least the majority of blood donations have been tested, for the last two years.

Under that voluntary testing practice, repeatedly-reactive specimens are mostly retested with an unlicensed radioimmune precipitation assay or RIPA because there is no licensed supplemental test available.

[Slide.]

All of the repeatedly-reactive donors are indefinitely deferred and the RIPA-positive donors are counseled and prior donations are traced for quarantine and in order to contact and test the recipients of those prior donations. An FDA draft guidance recommending universal testing of blood donors and tissue donors was released just about a week ago, March 26, 2009.

So, in the context of that draft guidance, the discussion today can be seen as comments to the draft which later will be incorporated into a final guidance.

[Slide.]

The current issue for today begins, actually, back in 2007 when the committee noted that a period of universal testing of all donors would generate critical data on the prevalence of T. cruzi infections and that

strategies for selective donor testing needed to evaluated and validated.

Over the past two years, evaluation of the results of T. cruzi testing of donors has led to requests from some blood establishments that the FDA consider recommending selective testing of donors. All the proposals that have come to us and that we have considered include testing all donors at least once. Selective testing, the question of how to implement selective testing, revolve around how to evaluate a returning donor who has a prior negative test.

[Slide.]

So, in the session this afternoon, we will go over the background, which I am doing now, epidemiology of Chagas disease and T. cruzi infection, a summary of the results of testing of the past two years, evaluation of risk questions as a means of selective testing. There will be several proposals for approaches to selective testing mentioned. The FDA will present a risk analysis of the effect on potential new transfusion transmissions of different selective testing strategies and there will be several questions and committee votes at the end.

[Slide.]

I'd just like to highlight what we think are the key factors that should be affecting our decision on how to move forward with selective testing, the first being prevalence of T. cruzi infection among blood donors; is the prevalence of the infection rare enough that we can consider reducing the amount of testing.

What is the rate of transmission from a presumed seropositive unit? This will be a critical question as we move forward with less testing. If there is a very high rate of transmission, that would be a problem. Another key factor in evaluating selective testing is the ability of risk questions to identify the confirmed positive donors or newly acquired infection, how effective could questions be.

[Slide.]

Another key factor is the evidence that has come forward on endemic vector-borne transmission in the United States, what is referred to as autochthonous cases. It means that we are not just looking at travel to endemic areas.--to some extent, the United States has endemic areas--and an evaluation of how frequent those infections are.

And then, in general, the frequency of incidence of T. cruzi infections. Any selective-testing strategy will have to consider the risk of newly acquired infections that may occur after a person is qualified with a prior negative test.

Finally, I would like to mention the problem of test sensitivity. We need to look at the prevalence of confirmed positive donors that have had prior negative test results. And this change from a prior negative to current positive is not because of incident infections but because of low signal-to-cutoff values that exist among a number of the infected individuals that occasionally fall below the cutoff affecting the real test sensitivity in the clinical setting as opposed to the analytical sensitivity.

[Slide.]

So there will be a number of presentations that will have data that bear on these key factors. The American Red Cross survey and follow-up study will be presented by Dr. Susan Stramer where they have asked detailed history questions of repeatedly-reactive donors, where they have complied the results of recipient tracing and testing and quite a few other things that bear on these

questions.

There will also be information that comes from a study by the Blood Systems Research Institute that specifically evaluated risk questions for Chagas infection and their ability to identify the confirmed-positive donors.

We have also had input from a survey of the America's Blood Centers that was given to us by Dr. Celso Bianco. There won't be a separate presentation on this b ut some of that data appears in various presentations.

[Slide.]

I am going to just give a quick overview of a few data points. A much more detailed presentation will follow. But, on the question of prevalence, from the study by the American Red Cross combined with the Blood Systems data, up until January of 2009, 19.3 million donations tested. Among those donations, 2,775 were found repeatedly-reactive on the blood screening test, 677 confirmed-positive by the RIPA. So, using the RIPA as our confirmed seropositivity, that computes as a prevalence of confirmed-positives of 1 in 28,508.

From the ABC survey, 9.2 million donations, 1,425 repeatedly-reactive, 436 confirmed-positive for a prevalent

of 1 in 21,000. Overall, it seems to me these are good estimates. They are actually the best estimates that we have of the prevalence among blood donors.

But an important thing to keep in mind, this is nationwide. There are high prevalence areas. California and Florida from the Red Cross study, 1 in 3,800 in California, 1 in 7,800 in Florida.

[Slide.]

One of the ways of evaluating the risk of transfusion transmission from a seropositive unit is the lookback study. In this case, donors that are confirmed-positive with the RIPA test who have had prior donations, the recipients of those prior donations are followed up and tested.

In the American Red Cross study, 95 recipients were tested. One of those 95 was positive and turned out to have been born in El Salvador. So, based on the potential for a prior infection--I am not including that in this count--so just among the 94 recipients, none of them were consistently positive on various RIPA, ELISA and PCR testing. So that would estimate a very low rate, near zero, of transfusion transmission by a seropositive, potentially

seropositive, unit.

Among those 94, there were 11, however, that were not positive on the Ortho ELISA but had positivity on one or more of the other tests, the RIPA test, the PCR test. Some of the cases could easily be discounted as false-positives. But if we were to take the worst-case scenario, that all 11 of those were actual transmissions, then that would suggest an estimate of transfusion transmission from a potentially seropositive unit of 11.7 percent.

That would be a high estimate but, compared to the historical estimate from the endemic areas of South and Central America, that is even below those. So it is clear that there is a lower rate of transmission from a potentially seropositive unit in the country and there are various reasons why. But I am just going to continue to move on.

From the ABC lookback study, there were 147 recipients that were tested. Two of 147 tested positive by an immunofluorescence assay and further study is continuing on those to verify. But if we assume that those represent transfusion transmissions, that suggests a rate of 1.36 percent.

[Slide.]

So this just gives you an idea of the kind of data that is used to estimate the rate of transfusion transmission. The risk analysis that the FDA is going to present uses a range of values in this spot and these estimates are within that range--well, they are not within the range. 11 is outside the range. That study which Richard Forshee will explain much more in detail later used an estimate between 1 percent and 5 percent.

[Slide.]

So we might want to look just a little deeper. If we are really trying to probe this question of transfusion transmission, can we tease apart from those 11 potentially positive donors, are there any with a little bit higher index of concern.

One way to assign a slightly higher index of concern would be to look at the donors that donated the blood and had more indication of parasitemia. So, in that follow-up study, both PCR testing and hemaculture testing were performed on the RIPA-positive donors.

So, of the donors that were involved in lookback studies, 23 of them were positive by PCR but not by

hemaculture. Six of them were positive by hemaculture but not by PCR and four were positive by both. Each of these tests would indicate that that donor had a higher index of concern so then the recipient, we might have a higher index of concern.

From among these 23, three recipients were tested. Only one of them were among the 11. It had one single RIPA assay-positive that was not reproducible. From among the hemaculture-positive donors, nine recipients were tested. From among those nine, two of them were positive by PRC by not by RIPA. Dr. Stramer will elaborate a little bit more on these cases.

And then, from the ones that were hemaculture- and PCR-positive, three follow ups were done and none of them were positive. So that just gives us a little bit more feel for what is underneath the question of what is the true rate of transfusion transmission from a seropositive unit.

[Slide.]

So just some other brief presentations on how to compare different selective testing strategies. One would be universal testing. That is the current recommendation.

And the best estimate we could make for that for its effectiveness is the analytical sensitivity of the test. The Ortho T. cruzi ELISA test system has a 99.88 percent sensitivity.

From the American Red Cross study, there was an evaluation of questions that were able to distinguish the true positive donors and born in the endemic area was the question with the best record, and you will see more details on that. But even that was only 75 percent effective at identifying the confirmed-positive donors.

From the Blood Systems study of a combined risk question, only 64 percent sensitive at identifying the confirmed-positive donors.

[Slide.]

I want to go a little bit into detail about how we have calculated sensitivity of the one-test versus two-test strategy. This arises from the American Red Cross study in which 17.8 million donors, up through November 30th, were tested. From within those tests, 394 were confirmed positive. While evaluating those 394, it was found that 16 of them had been previously tested and tested negative. So that represents a prior false-positive test.

We can use that 16 false-positives. All the prior tests were high negatives, many close to the cutoff. There was no evidence of newly acquired infections so the presumption is that the prior test was a false-negative. Therefore, we could take 16 away from 394, or 378. And, if we were to test only once, then we would miss people at that rate. 378 out of 394 is a 95.94 sensitivity of a test-once strategy based on this dataset.

[Slide.]

In a similar way, if we were to use a two-test strategy where each donor is tested first when they come for the first time. When they come at some other subsequent donation, they are tested again. If they are negative on both of those tests, then they would be qualified to be tested again indefinitely. Who would we miss on that?

From the same study, there were five cases that had been tested at least two times prior, some more than two times, with negative tests. Likewise, there was no evidence of a newly acquired infection. These are probably false-negative prior tests. So, by that analysis, 394 minus 5, or 389, divided by 394 is 98.73.

[Slide.]

So that leads to this combined table where you see the sensitivity of universal testing, the range of sensitivities of using risk questions as a screen, the sensitivity of testing one time and then no testing after that or testing two times. You will see later how these sensitivities are worked up in a risk analysis to the potential for new transfusion transmission based on different testing strategies.

[Slide.]

So I thought I would read the questions just once through now to help focus your minds on what we want you to address as you listen to the other presentations this afternoon.

Question No. 1; does the committee agree with the FDA that scientific data on effectiveness of risk questions in general do not support a selective testing strategy in which donors who previously tested negative for antibodies to T. cruzi are tested again only if their answers to risk questions indicate they have a risk of a newly acquired infection? So that is the risk strategy question.

[Slide.]

Question 2. We have just put in two parts; do the combined scientific data on risk of transfusion transmission of T. cruzi support a selective testing strategy in which, A, one negative test would qualify a donor for all future donations without future testing or questions regarding risk of a newly acquired infection or, B, if the answer in 2A is no, would negative tests on two independent donations qualify a donor for all future donations without further testing or questions regarding risk of a newly acquired infection?

[Slide.]

And then we have a third question asking for comment; please provide any additional comments on considerations for selective testing for antibodies to T. cruzi in repeat donors.

So, with that, I would like to go to our first speaker in the series, Dr. Susan Montgomery from the Centers for Disease Control in Atlanta who will talk about epidemiology of Chagas disease and T. cruzi in general.

Chagas Disease in the United States.

DR. MONTGOMERY: Thank you. Good afternoon.

[Slide.]

I was asked to speak specifically to the risks of acquiring infection in the U.S. and also what we know about the epidemiology of the disease here.

[Slide.]

I just wanted to highlight some points about the life cycle of this parasite. This is a zoonotic disease. It is vector-borne, but humans are not necessary to the cycle and there are more than 100 domestic and wild mammal species that have been found to be infected with T. cruzi. Common hosts include possums, wood rats, raccoons, dogs and cats. And that is the in peridomestic setting.

Infection of host and vector is lifelong. Once a bug picks up the T. cruzi parasite, it is infected for life and can transmit to whoever it feeds and defecates on. And, similarly, there are enormous reservoirs of non-human infected animals.

[Slide.]

This map shows you the areas that are endemic for human Chagas disease in red and then the areas that are, I would say, en-zootic for infected vectors and non-human mammals in gray. You can see that the range actually extends very far north into North America.

[Slide.]

I wanted to briefly touch on the programs for Chagas disease control worldwide. The programs in Latin America are focusing on controlling transmission, in particular vector control. However, there is also a strong emphasis on blood safety and the screening of blood donors.

In 2007, the World Health Organization initiated a global network for Chagas disease because of concern of not only in facilitating this control in the endemic countries but also, given the immigration patterns in the last 20, 30 years, non-endemic countries are also dealing with Chagas disease now. In particular, the situation in the U.S. is unique in that we are what could be considered both endemic and non-endemic for this disease.

Also, we have had recently the treatment drug donated to WHO which means that there is now a free supply of drug to countries wishing to treat patients.

[Slide.]

This diagram is to emphasis the course of Chagas disease in the human host. Initial infections are mostly asymptomatic. More than 90 percent of the acute infections pass unnoticed and the acute phase lasts from one to two

months, typically. Then an infected person moves into the chronic phase of this disease and they are asymptomatic, which we are calling the indeterminate form, for years to decades. So someone is unaware of the acute infection and now is indeterminate, asymptomatic, has no idea they have Chagas disease until if they are within the 20 to 40 percent of patients when then progress to clinical disease, typically heart manifestations.

The gastrointestinal disease seems to have somewhat of a geographic distribution in that people who acquire their infections in the southern cone are perhaps more likely to have mega-colon or mega-esophagus. And then a certain proportion of infected people remain asymptomatic for life.

Although there is some controversy, some researchers feel that, if we were able to follow people into their 70s or 80s or beyond, that we would end up finding some manifestation of Chagas disease. It is just that most people's lifespans are not that long.

[Slide.]

I also wanted to highlight some of the clinical challenges with testing. There is no gold-standard test

for diagnosis. Serologic tests are varied. They all have limitations in sensitivity and specificity. For parasitological diagnosis, and by that I mean identifying the parasite on a blood smear, this requires specific skills and this is especially important in cases of acute infection or reactivation of these, someone who had Chagas is indeterminate and, for whatever reason, has a reactivation of their acute disease.

There is no test to identify which of the patients who are infected are the ones who are going to go on to develop clinical disease, I would say within their 40s or 50s, typically. We have no way of telling who that will be and we also have no test to determine cure after treatment with antiparasitic drugs.

[Slide.]

So the risk of it in the U.S. We have more than 300,000 infected immigrants likely living in the U.S. These are people who acquired their infections when they were back home in their home countries in the endemic areas of Central and South America and Mexico. But there is also risk of acquiring the infection in the U.S.

Certainly people are exposed to infected vector

and/or reservoirs and this could be within the U.S., itself, or potentially during travel to other areas; children of infected mothers; transplant recipients, transfusion recipients; and then there have been several cases of laboratory-acquired infections. I am going to go into each of these categories in a little more detail.

[Slide.]

I also wanted to highlight the history of T. cruzi and the vector bugs in the U.S. I think most people are unaware of this but the vectors have been identified in the U.S. since the mid-1800s. The discovery of the association between parasite and disease in Brazil by Dr. Chagas was in 1909. We are now in the centennial.

However, the parasite was first identified in California just a few years later. And the first human autochthonous case of vector-born disease here in the U.S. was reported in 1955. So we actually have a very extensive history with this disease.

[Slide.]

This map illustrates the states where T. cruzi vectors have been found. So the states in yellow, which is essentially the whole southern part of the country, is

where one or more of the 11 vector species have been identified. Texas is the state that has had the largest number of reported species. They have seven different species in that state. The other states may have one or more.

I would argue that some of that is associated with the efforts put into identifying the bugs in those states. For instance, West Virginia is probably only white because no one has looked in that state.

[Slide.]

Now, I have overlaid on the same map, the states where infected reservoir animal species have been found. And those are shown in green. So the states that remain yellow are where just the vector species were found but now, in green, are where infected mammals have been reported.

I have also put red stars on states where human autochthonous cases have been reported from. We have had more than 18 different animal species identified as infected with T. cruzi.

[Slide.]

This is from a recent study that was published looking at the prevalence of infection and vectors in the

State of Texas. And you will see that there are actually wide distribution of the bug and the infection in Texas. Overall, in this study, all of the bugs tested, 50 percent of them were found to be positive for T. cruzi. The photograph just illustrates two of the most common species in this part of the U.S. We often get calls from the public who have identified similar bugs or, in fact, this species of bug in their house or their garden.

[Slide.]

These are the published cases of autochthonous transmission in the U.S. You will note the first one, again, is from 1955. More recently, cases have been reported from Louisiana and Texas. Most of the infected people are infants. However, there are two older individuals who were found to be infected.

[Slide.]

I am going to go into a little more detail by describing the age range, again, two weeks to 84 years. Four of these patients were male. Four actually presented with acute symptoms of disease. In one case, it was myocarditis. In another, it was a pericardial effusion. But most of them were a nonspecific febrile illness.

Two cases out of the seven had a primary complaint of bug bites and, in one of those two, there was a fever reported within 48 hours of the bug identification. In one of the seven, there was an unclear clinical history.

The vector bugs were found on the property of five cases during the resulting investigations and, on four of the cases' properties, they found infected reservoir animals suggesting that transmission was local.

[Slide.]

You are going to hear more about the blood-donor screening having turned up autochthonous cases but I wanted to mention two blood donors in Mississippi that CDC was involved in the investigation of these two cases with State of Mississippi Health Department. Both were individuals who had never left the U.S. save one who had gone across the border apparently for margaritas but never spent the night.

On the premises of one of those blood donors, we were actually able to find a triatomine bug stuck in the screen of his home that was positive for T. cruzi. However, we have no indication that these infections were recent. Both of them were serologically positive but negative for a

circulating parasite.

I wanted also the highlight that we have initiated a study to try and understand the risk for autochthonous transmission better taking advantage of the blood-donor screening and the identification of numerous--up to now, I think it is about 50 blood donors who are suspect autochthonous cases. We are performing that in collaboration with Red Cross and Blood Systems.

[Slide.]

Because of the question of travel-associated infection, we don't have much data at all, just these two anecdotal cases to describe. The first is a case that was reported to the Geosentinal system in travel clinics. It is a 26-year-old Canadian woman who spent six months in the Yucatan in rural Mexico and returned home with a sign--symptom, sign--of acute Chagas disease, Romana's sign, which is a swelling of the orbit.

The second is a 56-year-old man from California, Northern California, who was identified through blood-donor screening, asymptomatic, normal EKG, no evidence of clinical disease. His only international exposure was three trips, each less than two weeks, two of those to

Mexico and one to a non-endemic area of Argentina. This man is a hunter. Those trips were hunting trips and so he was in, I would argue, rural areas of those countries.

[Slide.]

Congenital transmission is important to consider. Although there have been no confirmed cases in the U.S., I think in terms of the questions about country of birth, this may be an issue. It certainly has been reported from other non-endemic countries such as Switzerland where mothers, immigrant mothers, have delivered infected babies.

The congenital transmission rate in endemic countries is estimated to be between 1 and 10 percent. These children are, again, asymptomatic typically, although there can be some non-specific findings at birth, which I have listed there. Based on our estimate of the prevalence of infection in immigrant population in the U.S., we have calculated between 63 to 315 infected infants may be born per year. This is using a transmission rate of 1 or 5 percent that has generated the range.

[Slide.]

For transfusion transmission, there have been five published cases although CDC has been involved in the

investigation of 24 recipients of solid organs from seropositive donors and those organs include heart, liver, kidney and then a combination of pancreas/kidney, liver/kidney or pancreatic islet transplant. Seven, or 41 percent of 19 recipients that we were able to complete investigations of became infected.

[Slide.]

I think this information is probably familiar to you. These are the same seven transfusion cases that have been reported in the literature, five from the U.S. and two from Canada. But I would argue that this is largely under-recognized and under-reported. Again, thinking of the way this disease presents in the acute phase, typically asymptomatic and then, as people move into the indeterminate form, they are, by definition, asymptomatic.

[Slide.]

These are the laboratory-associated cases that have been identified in the U.S. The kinds of exposures that people working in labs get are through handling the infected bugs, handing cultures, either from people or animals. These are hemacultures. Needle-stick injuries. There have been mucus-membrane exposures and potentially

inhaling of aerosolized organisms.

There were eight cases reported in the U.S. Three were associated with needle sticks. Three, contact with infectious material in someone who had a break in their skin, and then, for two, the actual exposure is undefined.

[Slide.]

We have been saying, for several years now, that we think that most physicians in the U.S. are unfamiliar with Chagas disease and I am happy to say that we now actually have data to support that statement. Completed a survey of the American College of Obstetricians and Gynecologists, concerned that congenital transmission has not been recognized and maybe one reason for that was that obstetricians/gynecologists were not aware of this disease. In fact, that is true based on our survey results.

MedScape recently completed surveys of different specialty--they have websites that are geared for particular specialties in the medical profession and, based on their surveys, the ID physicians are coming out ahead but essentially all specialties are not familiar with this disease.

Then we also have worked with community-based organizations conducting focus groups trying to reach out to the healthcare provider at the level where an immigrant with this infection might actually receive care at the health-clinic level and, even at that level, the healthcare providers are not familiar with Chagas.

We have also been involved in a clinical study where patients with cardiac disease, the EKGs that came into a cardiology service are screened for typical EKG changes associated with Chagas. In subsequent testing of those individuals, 14 percent were positive for Chagas. And their infections had previously been unrecognized. So, even the clinical cardiac manifestations of this disease are not recognized in the U.S.

[Slide.]

One important limitation to our ability to gather this information and to quantify the risk is that Chagas is not a nationally notifiable disease and is reportable only in one state, Arizona, so far, although Massachusetts is working to make it reportable in that jurisdiction as well. We have no systematic public-health surveillance. We are benefitting greatly from the AABB's Chagas Biovigalence

System.

There are competing priorities at the public-health level that often impede our ability to collect this information and there is a lack of public-health testing capacity. At this point, none of the state public-health labs have testing for Chagas in their facilities and all testing is forwarded to CDC.

[Slide.]

I wanted to give you another example of where we think there may be barriers to our ability to understand this disease better in the U.S. and that is consultations at CDC. The drugs for treatment of Chagas disease are not available outside of CDC in the U.S. because they are not FDA-approved and we have them under investigational new drug IRB-approved protocols.

At this point of the 765 RIPA-positive blood donors that were reported in 2007, 2008 on the AABB website, we have only heard from physicians treating 115 of those donors. Of those, we were only able to release treatment drug for 45. And, granted, some of the patients were not eligible for treatment but, in many cases, the patient would become lost-to-follow-up. The physician would see

them once, call CDC and then the patient never returned. So, clearly, there are many other barriers at work here.

[Slide.]

This graph just demonstrates that there has been definitely a change since the introduction of blood-donor screening. In the past, starting in 1997, and actually before that but I am only presenting that data from '97 to 2009 here, the releases were largely associated with reactivation in people receiving organ transplants who already had Chagas but it was unknown until they got their transplant and were immunosuppressed and developed an acute parasitemia and illness.

However, starting in 2007, we have seen an increase in the number of releases and most of them are associated with blood-donor infections. The increase in clinical patient releases is largely associated with that study I mentioned of cardiac patients with EKG changes compatible with Chagas.

[Slide.]

So, to conclude, certainly we have important challenges to address and improving healthcare-provider awareness is right at the top of our list in particular in

improving the awareness and, hence, diagnosis of clinical disease, recognizing transfusion transmission which is complicated because typically patients who are receiving transfusions have comorbidities that may make the recognition less than optimum.

And we are working closely now with the transplant community to improve their awareness and ability to screen transplant recipients and transplant donors for this disease. We would very much like to quantify the burden of clinical disease in the U.S., not only the cardiac but also gastrointestinal disease burden.

[Slide.]

Then, finally, I wanted to make it very clear that we have no estimates for the risks of transmission in the U.S. because of insufficient data and what we need is studies to investigate the risk of T. cruzi infection by these various modes of transmission, in particular autochthonous but also travel-associated infections, transfusion-associated and the concern with congenital transmission.

[Slide.]

I wanted to recognize these three individuals who

gave me slides and also contributed to content of the presentation. Thank you.

DR. SIEGAL: Thank you very much, Dr. Montgomery.

We will next hear from the American Red Cross experience with blood-donor screening for T. cruzi with Dr. Stramer.

ARC Experience with Blood Donor Screening for T. cruzi

DR. STRAMER: Good afternoon. I am going to tell you, as introduced, about our experience with screening donors for T. cruzi antibody. Again, I would like to thank my collaborators from the Red Cross and Blood Systems. I am sorry that these don't project very well, but I will read them to you and you will understand what I am going to cover.

[Slide.]

So what is going to be covered in my presentation are the number of positive donors and donations identified by universal testing; that is, testing every donor every time during the 22-month experiment of the Red Cross. I also will include an earlier time period that we were screening in Southern California under IND.

The algorithm that we used for all of our studies

included the Ortho Chagas ELISA. Repeated reactives were then tested on radioimmuno-precipitation assay, or RIPA. And a confirmed positive was considered so if they were RIPA-positive on index or follow up.

I am also going to present the results of additional tests to determine the donor questioning and identification of risk factors in positive donors, test performance characteristics, and our lookback or recipient tracing experience and its significance.

[Slide.]

So, before I go through that data, let me tell you what have we learned in support of a selective testing strategy. We know the donor prevalence is quite high. It is about 1 in 30,000 which is the same rate that we see HIV antibody-positive donors. Exposure in an endemic area is the most common risk factor associated with positive donors but it does not explain all positivity.

Infections have been acquired in all cases many years ago when the donors lived in an endemic area and are not related to recent travel during the time of us of the licensed test. Positive donors with possible autochthonous case--that is U.S. acquired infections--occur, as Sue

Montgomery has already mentioned.

Again, however, when we have identified a potential source of infection, it has been remote in time. We also see, as has been referenced by Rob, positive donors who have a seronegative donation and then come back and are repeat-reactive and RIPA-confirmed positive. So these represent ELISA variability and also I will show you that there is also RIPA variability around the assay cutoff.

Again, these cases do not represent incident infection. I will present our lookback data which, to date, does indicate a lower than expected rate of transmission. And donor qualification by having tested negative should be able to replace universal testing.

[Slide.]

So, let me first start with donor and donation prevalence in our donors with parasitemia. This is a map following the 22-month experience that was reported on the AABB website. The red dots are the zip code of residents of where RIPA-positive donors lived. You can see the high concentrations in New York that really reflects prevalence in New York City, actually, in the Maryland and Virginia area where we are now, in Florida, Texas and certainly many

positive donors in California.

So, during the 22 months, there were 735 donors reported on the AABB website from 41 states.

[Slide.]

If you now look at the Red Cross donor experience and the states highlighted in pink show you were we have seen RIPA-confirmed positives. Those in green are repeat-reactives but not RIPA-confirmed. And the numbers on the states just indicate the numbers of repeat-reactives. So we have screened 12.8 million donations with a repeat-reactive rate of 0.14 percent. That is actually the lowest repeat-reactive rate of all serological tests that we perform. So the test performs very well.

We have seen repeat-reactives from 42 states although not all of those have confirmed-positive. And, as mentioned earlier, 60 percent, or the highest rates that we see, are from Florida and California and the positive predictive value of the ELISA based on RIPA is about 20 percent.

[Slide.]

Now, if we add Blood Systems data to the data from the Red Cross, this increases the number of donations

screened to 17.8 million. The repeat-reactive rate is consistent and we see an overall prevalence, then, of 1 in 27,000. So this includes 362 confirmed-positive from the Red Cross. This is during the licensed period. The 394 that I will talk about includes 32 donors that we identified during IND period plus 277 donors that are listed here on the map from Blood Systems.

[Slide.]

So, now, if you look at our prevalence by donors only, and you look at the different types of collections that we have, our total donor prevalence is 1 in 23,000. But it ranges from directed whole blood in 1 in 6700 to pheresis or plasma or leukophersis or double REDs of 1 in 245,000. So, again, this is by donor.

And then these are the same categories by donations. Obviously, the numbers are lower because a donor can donate multiple times in the database. So it ranges from 1 in 9,000 in directed whole blood to 1 in almost a half million in some of the pheresis product donations.

[Slide.]

Now, I am going to talk to you about PCR. This

is a summary of results of a study that David Leiby has published with Barbara Herwald in JID. It documented about a 63 percent rate of PCR positivity. But what was important in the study is that PRC-positive donors can be negative on the next time they are tested on follow up, then again be positive on a subsequent follow-up sample.

So, just like I have already alluded to for ELISA and RIPA, we also have variability in PCR testing. So all of these tests have a certain degree of variability.

[Slide.]

What have we seen, and Rob has already shown some of these data--but what have we seen for PCR positivity or hemaculture-positive, and these donors are not necessarily positive by both. In fact, only four of these 33 donors were positive by both PCR and hemaculture. But we see 14 percent of our donors, a lower number than David published of 63 percent, only 14 percent were PCR-positive and 4 percent hemaculture-positive.

[Slide.]

Let's talk about donor risk factors. Now, I am considering our entire dataset of 394 RIPA-positives. What we used as our control are other on the other side of the

table here, 1490 repeat-reactives but RIPA-unconfirmed. So you can compare their characteristics.

63 percent of our RIPA-positives are first-time donors. It is about an even split of males to females. In contrast, in the false-positive donors, three-quarters of them are repeat donors because these are false-positives and they are hitting our repeat donors since those are our most frequent donors. Males and females are about the same split as in the RIPA-positives.

Now, if you look at country of birth and this comes from the detailed questionnaire that Rob referenced, we have 157 RIPA-positives from which we have gotten detailed information about demographics and risk factors. In comparison, in our control group, we have 456. The countries of our RIPA-positives include Mexico, El Salvador, Bolivia, Honduras, Columbia, Argentina, Guatemala, Brazil, Ecuador, Nicaragua, Chile, Paraguay and Somalia which isn't exactly an endemic area but we have one from Somalia.

But important here so note that 40 came from the United States in contrast to the other site here where these are really not endemic areas with the exception of one from Venezuela and two from Columbia. Of interest, the

two that we have from Columbia that were RIPA-unconfirmed, they did, in questionnaires, say that they did have some cardiac and GI irregularities. But then, again, don't we all.

[Slide.]

Anyway, so now looking at univariate analysis of all of the risk factors for 394 donors and looking at odds ratios, so what this asks is the likelihood of a RIPA-positive having one of these variables versus a RIPA-negative. So, for example, born in an endemic country, a RIPA-positive is 256 times more likely to be born in an endemic than a RIPA-negative donor. And so you have, for all our significant variables, most of those related to endemic exposure.

We have some other risk factors as well. But, then, when we did the multivariate analysis to see what came out significant, born in an endemic area is strongly significant. Other factors have borderline significance. But, clearly, we are talking about born in an endemic country. That is our highest significance.

But, again, I remind you that not all donors are endemic born. 40 of our donors were born in the U.S. and

possible autochthonous of which five are parasitemic.

[Slide.]

So, Sue Montgomery went through vectors and reservoirs. So I will skip this.

[Slide.]

But similarly to the way Sue plotted the documented autochthonous cases on the vector map.

[Slide.]

Here I have plotted all of our autochthonous cases from blood donors. So you can see that not all of them came from areas where insects and mammalian reservoirs exist. But I will tell you that some of these donors were exposed to T. cruzi and are infected.

For example, this Montana donor who grew up in Texas and camped frequently as a boy scout when he was a child, did have primary Chagas and Ramona's sign which a whole slew of physicians could not properly diagnose.

[Slide.]

So, now looking at more detail of our 40 autochthonous cases, 13 do have some identified risk, six being congenital, three of those with rural residence in Mexico, four of those being PCR-positive. We did have a

veterinarian who practiced in Mexico and we believe got infected during her practice there.

One donor lived for six years in endemic areas including being bitten by a reduviid bug and receiving blood transfusion in Argentina. Five with significant outdoor activities in the United States including camping, as I mentioned, hunting, as Sue Montgomery mentioned, and one individual who lives in an area where she sees the triatomine insects daily. She is a frequent gardener so we believe that was her risk factor.

One of these five donors was PCR-positive. Another was hemaculture-positive. So, if you look at all of the tests that we have done on these 40 potential autochthonous cases, five, as I mentioned, or 40, or 12 percent were parasitemic. If you look at multiple RIPA-positivity, because we do repeat the RIPA on the index, we repeat it on the retreat plasma unit. We have got follow-up samples from these donors. So we look at the ones that are really hot, if you will, that have multiple positive RIPAs--that is about half of them, 48 percent.

And then we did some South American tests--that is, Silvano Wendell did these tests for us. Looking at

other tests using a different strains of the T. cruzi parasite, you can see percentages of 37 and 60 percent for two ELISAs and 9 percent for IFA.

[Slide.]

So now let's look at the ELISA and RIPA test performance. This is a histogram showing you the distribution by signal-to-cutoff ratio.

[Slide.]

This is the readout for the test of those who have tested RIPA-negative. So these traditionally have low signal-to-cutoff ratios and then those that have tested RIPA-positive.

If we were looking at HIV or HCV, the positives would all show exactly the opposite type of distribution as we see for the negatives. But, for T. cruzi, we don't. We get what I call a smear--well, not a blood smear but a smear of EIA reactivity starting from low signal-to-cutoff ratios all the way through the dynamic range of the assay.

Looking at the positive predictive value of signal-to-cutoff ratios, if the value is equal to or over 3.8, 95 percent of those will confirm by RIPA.

[Slide.]

Now, looking at the stability or I should say the variability of these signals, first these are the individuals who have high signal-to-cutoff ratios and have been followed. So you can see--I mean, within the range of reason, these are fairly stable as far as their signals.

[Slide.]

Looking at mid-level, and you can see how long we followed some of these donors, the ELISA signal is relatively stable.

[Slide.]

Looking at low-level individuals, clearly some people do drop below the cutoff but this is fairly consistent. These were all, now--the three graphs I just showed you were for RIPA-concordant positives.

[Slide.]

We also see donors who go from RIPA-positive to RIPA-unconfirmed. Does that mean that they have changed their serological profile or is this just variability in the testing? Well, I think it is variability in the testing. Their signal-to-cutoff ratios, with the example of this individual, had been fairly consistent.

[Slide.]

Similarly, from going to RIPA-positive to RIPA-unconfirmed, you can go from RIPA-unconfirmed to RIPA-positive. Similarly, you see relative stability in the signal-to-cutoff ratios when these donors are followed.

[Slide.]

So, now, what about RIPA-positive donors who go from ELISA-negative to ELISA-positive. So we have seen 16 donors, as Rob mentioned. So this actually is the limitation of a 1X strategy would be the 16 donors because they did have a prior seronegative donation followed by a seropositive donation that was ELISA-repeat-reactive and RIPA-positive.

Ten of these 16 had one RIPA-positive result when you look at multiple samples collected. Their signal-to-cutoff ratios were right around the cutoff, as Rob already mentioned, and these ten were all PCR- and hemaculture-positive.

Then, of the 16, we had six. I put this in red because, when I go through calculations of test sensitivity, I will do it both for the 16 and then for the six because these six now had two RIPA-positive results. So, if you believe maybe some of these are false-positive, here we

have two RIPA-positive results from two independent samples, two different laboratories. So those would be more reliable test results.

Then we have five of 16 who had multiple prior seronegative donations. So this is where even a 2X strategy would miss these five of 16 donors. But only one of five had two RIPA-positive test results, so that will weigh in again when we do the calculations of selective testing.

Then, if you look at follow up of these 16 donors, 13 of 16 were followed and 9 of 13, their seroreactivity persisted up to almost 300 days.

[Slide.]

And those are shown in this graph. These are the 13 of the 16 positives who were followed. These is signal-to-cutoff ratios of their seronegative donation. These are their index donation. And these are follow up. So, just like I showed you on the other graphs, these are fairly stable and, therefore, probably do not represent incident infection.

[Slide.]

So, speaking of incidence, let's talk about the

absence of donor incidence during our IND and 22-month experience. We have looked at 2.5 million donors with two or more donations who have contributed 2.3 million person years of observation during the 22-month experience. Only intervals between donations that were tested were counted and the mean interval between the two donations was 0.9 years.

So we now combine this with the Blood Systems, or the data from United Blood Services, this now totals to about 3 million, or 2.788 million donors, with two or more donations that contributed about 2.6 million person years of observation. So we see no seroconversions from these donors over these periods of time.

[Slide.]

So now what additional evidence do we have against incident infections. I have talked to you about our 394 RIPA-positive donors, 157 of those who were interviewed and, in all of those, infection was remote in time and related to endemic risk. And they all had consistent signal-to-cutoff ratios.

The 40 autochthonous cases for whom recent risk can be identified, risk was, again, remote in time and

either related to endemic occupation or childhood risk and not related to recent travel. And they, too, had consistent signal-to-cutoff ratios. I talked to you about the 13 donors who we followed. None of them showed serological progression. These were the individuals who were seronegative followed by seropositivity.

Then I mentioned to you our 2.6 million person years of observation in which we failed to see any incident infection.

[Slide.]

So now let's talk about recipient tracing or lookback.

[Slide.]

For our 22-plus-month experience plus the IND period, we have had 70 repeat-reactive RIPA-positive donors. I should say RIPA-positive donors who were repeat donors. 33 of those were parasitemic. We have had 372 prior donations from which 791 components were made. 334 were transfused into 119 living recipients of which we tested 80 percent of our living recipients, or 95.

They come from 71 percent of the positive donors that I described. The known transfused components include

the majority of which were red cells, 63, eight platelets, ten plasma, two whole blood, five cryo and we are still pending component results from seven cases.

We have seen 12 reactive test results one of which was a whole-blood derived platelet but, as Rob said, this was an El Salvadoran so he believed this individual had risk factors--well, this individual did have risk factors--and then we had 11 unexplained test results. Of the 11, four were ELISA-negative but RIPA-positive and one of those--and they went into four positive recipients--well, four recipients. One of two came from a positive, PRC-positive, donor. Then we had 70 ELISA-negative PCR-positive recipients, one of five with repeat PCR positivity and two from a hemaculture-positive donor. Two actually came from two PCR-positives--came from the same hemaculture-positive donor.

[Slide.]

And that I am going to show you in this slide. I am not exactly sure how you make a final interpretation of this but these are the results that we have. This is the index, the retreat plasma unit and the follow-up sample, high signal-to-cutoff ratios, all RIPA-positive, PCR-

negative but hemaculture-positive. So products from this donor were transfused, two independent donations, into two recipients both of which were PCR-positive. So, again, it could these both be false positivity? Yes, but certainly there seems to be a linkage from a hemaculture-positive to h have two independent donations yield two PCR-positive recipients.

[Slide.]

So, now, again, you look at all of our lookback data together, the number of transfused components, we have had 289. 73, or 22 percent, were actually tested. Of the isolated test results, we had, if you look at red cells versus platelets in whole blood and do an odds ratio to see what is the likelihood of platelets in whole blood, which are the components that have been associated with transmission, what is the rate of those relative to the RBCs, we see an eight-fold increase in the likelihood of finding a positive test result in these components versus this.

Now, are these all false-positives? It is possible, but there is the strange statistical association that is difficult to explain.

Then this is the one from random-donor platelets that was ELISA-positive and RIPA-positive.

[Slide.]

So, if you combine our lookback experience, or 95, with that of the ABC that is lookback on 147 and consider only those ELISA RIPA-positive donors minus those with other risk factors--Rob mentioned there were two. These are both apheresis platelets. If you put this together, all of the lookback experience, for 242 components and two likely positives, we have only seen a transmission rate of 0.8 percent.

[Slide.]

What about the limitations of lookback. We know that many of the positive results that I have described are likely false-positives. There certainly is an uncertain specificity of RIPA or PCR that hasn't been validated to the extent that the ELISA has. Similarly, many donors triggering lookback may have been false-positives. So this reduces the number of recipients who actually would provide valuable lookback data.

We have only tested a small number of platelets in all of the combined studies, 32 of 242, with three total

positives or two which was 0.8 percent which was the transmission rate, as I previously said. However, we have only tested 22 percent of our recipients. So was there survivor bias; that is the recipients who may have likely succumbed to Chagas infection with acute disease and died or have comorbid factors that caused their death? We will never know--we don't know that.

So that is certainly a limitation. Even if we have zero-positive findings of 95, statistically, that doesn't exclude the possibility that about three recipients should have tested positive.

[Slide.]

So, in summary, the prevalence of T. cruzi antibody-positive donations in the U.S. is approximately 1 in 30,000. Endemic-born is the only significant risk factor identified from multivariate analysis. These risks are remote in time and do not represent incident infection. Autochthonous cases occur in limited selective testing strategy based on questioning.

Risks, when identified, again, were remote in time and do not represent incident infection. RIPA-positive donors may have reactivity at the assay cutoff.

No incident cases were identified in 2.6 million person years of observation, however. Our lookback experience is actually limited but it does suggest very infrequent transmissions. And a selective testing strategy could be pursued based on a prior donation test-negative model.

[Slide.]

So now I am going to show you a couple of slides on what we did. Rob already presented what the universal testing sensitivity is. If you look at born in an endemic area, it is about 74 percent based on removal of our 40 autochthonous cases. We have the 16 donors who hit a prior seronegative donation, so that yields 95.94 percent sensitivity.

If we look at the five who have multiple prior seronegative donations, the sensitivity of a two-times screen is 98.73 percent. Now, if you restrict this to only those RIPA-positives who have had multiple RIPA-positivity that is more than 1, then you increase the sensitivity of one-times testing to 98.5 percent and two-times testing with only one donor who would not be detected of 99.75 percent.

[Slide.]

So if you look at, again, at all of these strategies put together, questioning one-time screen-neg an two-times screen-neg, I have listed the ranges of sensitivities that I have just described and I added the yield. So questioning would yield about 1 in 20,000 donors, 1X screen would yield about 1 in 15,000 donors, and a two-times screen would, on top of this, give you an incremental yield of only about 1-and-a-half million depending on which numbers you use to 1 in 2-and-a-half million.

[Slide.]

So the FDA did ask us to comment about the validity of selective testing in the cGMP environment.

[Slide.]

So I will just show you one possible model. You can have software that creates what is called a donor assertion for test-negative donors so that they can be easily identified in your computer system. This computer system can communicate with laboratory information systems such as those donors without an assertion would be flagged for testing.

Then, finally, the release of results would be prevented from donors lacking in assertion if the required

non-reactive test was missing.

So that concludes what I have to say. Thank you.

DR. SIEGAL: Thank you, Dr. Stramer. We will next hear from Mike Busch from Blood Systems reflecting their experience with risk questions and testing for T. cruzi.

Blood Systems, Inc. Experience with Risk Questions and Testing for T. cruzi

DR. BUSCH: Thank you.

[Slide.]

I want to acknowledge the folks at Blood Systems who have been involved in this work, particularly Brian Custer and Maria Agapova and Hany Kamel who have really done most of the analyses, and then Sally Caglioti at BSL and Peter Tomasulo of the medical office.

[Slide.]

So Blood Systems, like Red Cross, implemented universal T. cruzi antibody screening at the end of January, 2007 with a routine EIA screening followed by RIPA of repeat-reactive donations. From the outset, we wanted to evaluate alternative screening strategies and this actually was discussed and we sort of followed the guidance of BPAC

a couple of years ago following that initial implementation.

We added additional questions to all donations. So, unlike some of the analyses that Sue has shown where she has assessed risk factor, et cetera, after the donors were identified and counseled, in our case, we really implemented these questions up front and asked the question of how sensitive would routine donor questions, additional questions regarding country of birth and other Chagas risk-related activities, be with respect to identifying infected donors.

[Slide.]

So, actually, we routinely ask all of our donors regarding race, ethnicity and country of birth. And that had been going on for several years prior to Chagas screening. But then, in February of '07, we implemented three additional questions that are indicated here. The first question asks, with respect to the donor's prolonged residence, three or four months in Mexico, Central America or South America.

The second question referred to the donor's mother's prolonged residence in these three regions. And the fourth question focused on travel since the last

donation, so whether the donor had traveled to these three regions. For each question, the donor was asked to respond with respect to whether they had solely been resident in or their mothers resident in or traveled to Mexico or Central and/or South America or both areas, Mexico as well as Central or South America, particularly given that there is a very high proportion of our donors who come from or have traveled to Mexico. We wanted to separately be able to ask the questions with respect to travel or residence in these differential regions which have quite different T. cruzi risks.

Now, these were not absolutely mandatory questions so a donor could not answer these questions and still proceed to give blood.

[Slide.]

In addition, then, when donors were identified as repeat-reactive in actual--prior to obtaining RIPA results, the donors were notified by telephone and counseled and a risk-factor interview was conducted. Follow-up samples were collected from all donors, again prior to obtaining the RIPA results from the index donation and those follow-up samples were further tested by ELISA, RIPA and PCR. The

confirmed RIPA-positive donors have been offered clinical assessments including EKG and echocardiograms.

[Slide.]

So the key questions that I want to address with the data as I present it are, do donors answer these additional donor record at the time of donation questions. Do the positive answers, with respect to the country residence or travel, et cetera, do they predict confirmed positive infections? Are the answers to these questions accurate and reproducible and do the correct answers detect the majority or all of the positive donors? What is the sensitivity of this pre-donation questioning with respect to interdiction or potential targeting of testing to confirmed infected donors.

Slide.]

So this slide summarizes the data from Blood Systems specifically. So, in the 220 months of testing, the basis for the analysis, we identified a total of 223 repeat-reactive donors 61 of whom confirmed RIPA-positive. Now, what is important here is the distinction--Blood Systems actually has three, and more recently, four affiliated blood-center programs.

So the United Blood Service's network of blood centers represent probably three-quarters-plus of all donations. And those were the centers on a single computer system that implemented these additional questions. So, in addition, there is blood center on the coast of California at Santa Barbara/San Luis Obispo called Central Coast. Then the San Francisco called Blood Centers of the Pacific, which are part of Blood Systems but did not implement these additional questions into that computer system.

So this is important because the further data that I will focus on will be the UVS donor data which yielded 34 RIPA-confirmed positive donors. So it is really these 34 donors where we will be asking how good were the questions at identifying these infected donors.

[Slide.]

So, as we looked at those 34 donors and we asked first of all what was the yield of RIPA-positive donors relative to the country of birth, what we see is the majority, 77 percent, of donors were born in the in the U.S. We did identify 10 RIPA-confirmed probable autochthonous infections for a yield in 1 in 56,000 amongst donors born in the U.S.

For donors who were born in Mexico, identified 10, a yield of 1 about 2,000. And, for donors born in Central or South America, only 2,000-plus donors, 8 positives so a yield of about 1 in 280. So you see a dramatically higher yield of T. cruzi seropositivity from the more endemic regions of Central and South America relative to Mexico and a much lower yield in donors born in the U.S.

[Slide.]

With respect to the responses to the specific new questions that were added, the first question about the donors prolonged residence, three or more months, again focusing on separately--just to give you a sense of the extent to which donors indicate such prolonged residence, we see that, overall, a total of about 2-and-a-half percent of our repeat donors are indicating that they had residence in T. cruzi-endemic countries whereas, among first-time donors, this is about 5 percent of all first-time donors have indicated in their responses that they had prolonged residence within these countries.

[Slide.]

In terms of travel, amongst our repeat donors--these are questions focused on travel since last donation

so this is relevant only for repeat donors, you can see that 8 percent of our donors had traveled to Mexico since their last donation and an additional approximate 1 percent had traveled to Central or South America or both Mexico and Central or South America. So this is the magnitude of donors who would theoretically be subjected to selective testing if we were to use these questions to target that selective question.

[Slide.]

Then, if we begin to ask more specifically how sensitive are these responses to these pre-donation questions, if we look at the country of birth relative to the true status, so, of the 34 donors who were confirmed as RIPA-positive, 19 of these donors indicated a country of birth in response at the time of donation that would have identified them as infected. So we had only about a 55, 60 percent detection rate based on country of birth.

[Slide.]

In terms of responses to the questions of prolonged residence or mother's prolonged residence or travel to these countries in persons who were not born in these endemic countries. So, excluding those who indicated

they were born in these endemic countries, we did have a total of two donors with overlap here in the responses who were RIPA-confirmed who had indicated that they were not born in these countries but had traveled to, or their mother had prolonged residence in, or they had prolonged residence in. So there was some additional yield beyond country of birth based on these questions in repeat donors--I'm sorry; that as first-time donors.

[Slide.]

Likewise in repeat donors, some additional yield with three additional questions.

[Slide.]

But this is really the key table which is sort of taking a composite of all the responses from the donors prior to donation, both their response to country of birth that was a required field as well as this prolonged residence of themselves, their mothers. What we found here was that, overall, of the 34 donors, 26 of them, or 76 percent acknowledged one of these risk exposures prior to donation. So this is kind of the sensitivity, the sort of rolled-up-sensitivity, or pre-donation risk questions with respect to identification of the T. cruzi confirmed-

positive donors.

[Slide.]

One of the concerns we had was the consistency with which these donors were acknowledging risk at the time of donation relative to responses given subsequent to donation when they were told they were positive. And what we are referring to here is discordant responses, again at the time of donation relative to when the donors were interviewed subsequent.

What we see here is there were, amongst the RIPA-positives, 10 of the 34 gave discrepant results from the index donation responses to the responses when they were interviewed subsequent to being informed that they were RIPA-confirmed positive.

[Slide.]

Specifically, I just want to highlight, without detail, this group in purple here which are donors who completely denied risk at the time of the index donation. But, when they were then informed that they were repeat-reactive, they admitted to themselves residing, or their mother residing, in Central America or South America. So these were discrepancies amongst donors who were RIPA-

confirmed positive.

So this made us concerned that the predonation question responses were not accurately soliciting exposures that, in fact, existed in these donors.

[Slide.]

We also asked what is the background rate of discordant responses amongst our donors who answered these questions on multiple occasions. So what we looked at was, for this 11 months of 2008, we had 184,000 donors who gave 514,000 donations and we focused on only the allogeneic donors. What we discovered was, in terms of responses to these Chagas questions, that there was about a 3 percent discordancy in individuals' responses over time to the very same question. These were donors who were completely negative. So there is simply a background rate at which donors are not answering these questions consistently over time that raises further concerns about the appropriateness of a selective testing strategy based on responses to questions.

[Slide.]

As Sue indicated, for Red Cross, we compiled our data as well with respect to overt seroconversions. So in

the approximately 18-year-and-three-quarters time period, we had zero donors go from EIA nonreactive to EIA reactive and RIPA-confirmed in the UVS centers. During this period, there were 305,000 donors who gave two or more donations and, subsequent to seronegative donations, there were 267,000 person years of observation to assess an incidence rate or a zero observation of incident cases in that denominator. Each of these donors contributed, on average, 0.87 person years of observation.

So, as with Red Cross, there have been no observed frank seroconversions in our donors.

[Slide.]

In terms of travel responses, amongst donors who were negative and then responded with respect to travel since their prior negative donation, we had 13,680 donors who were repeat donors who had tested negative on a prior donation, on subsequent donations by these donors, there were two repeat-reactive but they were not RIPA-confirmed. So the travel question did not identify any additional infected donors.

[Slide.]

As presented by Sue, but just on one slide, I

just wanted to show we have enrolled these donors over time and these are the donors who were RIPA-confirmed--EIA repeat-reactive, RIPA-confirmed--at index donation. You are seeing here the results of the EIA on the follow-up donation for the donors who were not only RIPA-positive on index but also RIPA-positive on the follow-up donation.

You do see some of these examples where it looks as if the EIA reactivity is increasing suggesting that some of these might have been recent seroconverters. However, we have retested these samples side-by-side, the index and follow-up results, and there is no change in the signal-to-cutoff results when the samples are tested within the same run side-by-side.

There have also been donors who were initially RIPA-negative and then converted to RIPA-positive. I think that group is actually up here. So these would be apparent incident infections. They were EIA-reactive on both samples. Again, it looks as if there is some single intensity increasing by side-by-side testing showed no change. So these are simply the same kind of borderline reactives that are erratically scoring as RIPA-positive or negative over time, what I personally believe are resolved

infections from individuals who just have waning antibody after they have spontaneously eradicated the organization.

[Slide.]

Just in terms of the follow-up interview information, so, in the larger system, because donors at our blood centers in San Francisco and California are eligible. So we have enrolled 48 RIPA-confirmed donors and 171 controls that were EIA-reactive, RIPA-negative. And you can see very highly significant associations between residents in Latin America living in houses with thatched roof, et cetera. The classic exposures that are associated with T. cruzi infection are clearly correlating in our infected donors as well.

[Slide.]

Interestingly, in terms of symptoms, there is no difference in the rate of reporting of various symptoms that might be attributable to T. cruzi, cardiac disease, swelling, shortness of breath, EKG abnormalities, et cetera, between the RIPA-positive and the controls. So, although these donors are infected, they are obviously healthy enough to give blood and, when interviewed and questioned about T. cruzi-related symptoms, there is no significant

difference in the rate of symptoms in these infected donors versus a control group.

[Slide.]

So, back to the question that I posed earlier; do the donors answer these questions "yes," but not all the time. So these were voluntary questions and we did see a moderate rate of non-response. Clearly, that would be changed if this were mandatory and would drive testing decisions.

Do the answers predict infection? Yes, and particularly the country of birth is highly predictive. We saw a ten-fold higher rate of infections in persons born in Central America relative to Mexico and a ten-fold higher rate there relative to those born in the U.S. So, asking questions would clearly dramatically increase the yield and the predictive value. Unfortunately, though, they don't detect a substantial fraction of the infected donors.

Are the answers accurate and reproducible? Unfortunately, no. What we observed was that about 30 percent of the RIPA-confirmed donors changed their answers after they were told they were infected relative to what they said at the time of donation, and we also documented a

3 to 5 percent change or discordancy in responses of the control donors and the negative donors. So, really, these questions, like all questions of donors, are subject to variance.

And then do the correct answers accurately detect all the positives? No. Our composite analysis of all the predonation questions demonstrated only about a 75 percent sensitivity.

[Slide.]

So this table, which Brian Custer developed, really, then, sort of takes the Blood Systems data and applies various selective testing options to ask how many donors would need to be tested according to different testing strategies and what proportions of the infections would be missed, what the sensitivity of a risk-reduction capacity of different selective testing strategies would be, the rate of identification of infected donors and the residual risk if you used that selective strategy.

So sort of the extremes are if we didn't test at all, we would have released these 34 units and the risk to recipients would have been about 1 in 41,000 recipient units would have been from T. cruzi seropositive donors.

These were all interdicted by universal testing but that required testing 1.4 million donations and that universal testing strategy, we think would have left us with essentially a zero-residual risk or close to zero residual risk.

For us, one-time testing identified all of the infected donors so, whether you do one-time or two-time, no incremental gain by doing two-time testing, so it would have reduced the number of tests from 1.4 million to about 700,000 tests would have been performed had we tested donors only once and, based on this analysis, we wouldn't have missed any infected donors in the UBS system.

If you focus on alternatives such as donor's country of birth, we would have tested a much smaller fraction of the donors, only 200,000, but we only would have picked up about 53 percent and the composite of all the questions, again, would have only picked up 74 percent of the infections. So we would have been left with the residual risk had we employed those selective strategies of still a moderate residual risk of exposure to T. cruzi seropositive blood of 1 in 200,000.

[Slide.]

This is a new table not in your handout that Brian just developed. Essentially, it is doing somewhat the same thing, looking at different testing strategies. But now we are building in the numbers that you saw Sue present and earlier Rob that looked at potential alternative sensitivities based on larger data. So the 1X testing based on a analysis Sue presented has about a 95 percent sensitivity, 2X testing, 97 percent. But even universal testing, the assay, itself, has false-negatives that are not able to be detected with 100 percent accuracy particularly these very low-level antibody reactives that may represent resolved infections.

So, as we apply these sensitivity rates and risk-factor question-based sensitivity, for example, to the actual--the rate of T. cruzi-positive donations that would be missed by these different strategies, and then estimate the residual risk assuming a 1.45 components per positive unit, and then assuming a 10 percent transmission efficiency, we can estimate the residual risk of actual acquisition of T. cruzi infection according to different screening scenarios.

It is really that last point I want to make here

which is really, in the absence of any screening, the risk of actual transmission, given the observed probably over estimate of about 10 percent would be about 1 in 200,000. With universal testing, we are probably down in the range of 1 in 10 million residual risk and 1X testing, which we feel is sufficient, would leave us with residual risks of about 1 in 4 million of possible acquisition. And that assumes the 10 percent transmission rate.

[Slide.]

Then just one final slide which is to emphasize how important that transmission rate is on the final sort of determination of the value of this screening. This is an actual output of a cost-effective analysis. For this group, we are not supposed to get into the cost, but I just want to emphasize that, if we are dealing with transmission rates in the range of 10 percent, then the testing that we are doing is not really too far out of the ballpark of reasonable cost-effectiveness for blood-screening assays, in the range of a half a million dollars per quality-adjusted life year with clearly the more selected testing strategies being more cost-effective than universal screening.

But, if the risk drops below 10 percent down to 5 or 1 percent, you can see the cost-effectiveness ratio is increased exponentially. So, if the transmission rate is as low as has been documented with only the two transmissions, really unequivocal transmissions, confirmed, we are down at a 1 or 2 percent transmission rate, then we are going to be dealing with cost-effectiveness ratios of universal testing up in the 1 in 5 million and some of the selective testing strategies down in the 1 in approximately 1 million, so just to emphasize how important that transmission rate parameter is in the assessment of the utility of this screening program.

Thank you.

DR. SIEGAL: Thank you, Dr. Busch. Now we will hear the FDA Perspective on the Risk Analysis from Dr. Forshee.

FDA Perspective on Risk Analysis

DR. FORSHEE: Good afternoon, everyone. Once again, I am Rich Forshee. I am with the Risk Assessment Team in the Office of Biostatistics and Epidemiology at the Center for Biologics Evaluation and Research.

[Slide.]

What I am going to be presenting is the probabilistic quantitative risk assessment that we have developed at our office, and I have been working closely with my colleagues, in particular Dr. Steve Anderson has been working on these issues for years now.

I just want to remind people what the purpose of a risk assessment is. Our goal here is to try and integrate a lot of the information that we have already been hearing today and put it in a format that is going to help you figure out which factors make a difference and what the overall impacts of some of these different approaches are.

It is not to try and tell you what the particular right answer is but, rather, to give you the information you need to make an informed decision.

And I also want to thank all the previous presenters today for really setting the stage very well. They have gotten a lot of the issues on the table so I will be able to jump right into how we put it together.

[Slide.]

So what we have done is we have built a probabilistic mathematical model of the major factors

affecting transfusion-transmitted T. cruzi in the United States. For all of the uncertainty, uncertain inputs in the model, we chose a probability distribution. So, for example, with the probability of transmission, we have chosen a uniform distribution between 1 and 5 percent and, again, all of the uncertain inputs have specific distributions.

Then, based on these distributions, we have simulated 10,000 hypothetical years in which there was a possibility of transfusion-transmitted T. cruzi. In each one of those years, a separate value was drawn from each one of the uncertain distributions that let us see what the possible range of outcome is going to be.

One of the real advantages of this kind of risk-assessment approach is that it allows us to pursue "what if" scenarios to compare different risk-management strategies and also to see which factors have the biggest input on change in the final outcomes of the model.

[Slide.]

Just to remind people what we have focused on in our risk assessment are the issues being discussed here today and that is, in particular, whether selective testing

using a one-time or two-time strategy would be an adequate approach compare to universal testing. Again, just to remind people, there are at least two additional sources of increased risk that could come from selective testing. We could have a donor who was infected and has been screened one or two times become infected sometime after the tests, or we could have a repeat donor who was infected but had a false-negative ELISA result on the first or second test.

[Slide.]

In terms of the probability of a risk of infection after previous negative results, we are not aware of data on the probability that this could happen. We know that it must be greater than zero. We think that the probability is low because of the nature of the disease cycle, but, given some of the data that we have seen about the possible transmission within the United States, we certainly can't eliminate this is a possible risk factor.

[Slide.]

Also, with regard to the risk of repeat false-negatives, the approved test that is being used for this does have a very high sensitivity of 99.88 percent. So the risk of multiple false-negatives is going to be relatively

low but, nevertheless, multiple tests are going to reduce the risk of the false-negative result compared to a single test.

[Slide.]

The way that we built this information into the model was to use the data that was presented by Dr. Stramer earlier to estimate the number of transfusion-transmitted cases we would get under four different scenarios.

[Slide.]

So we have a baseline scenario which uses the seroprevalence data that has been developed in the last couple of years but assumes that there is no testing or no other screening to eliminate the infected donors from blood supply. Then we test the strategies of test-once, test-twice, or universal testing using the sensitivities that have been developed based on the results that were presented earlier today.

I want to emphasize that these are hypothetical options at this time. They don't reflect current practice or guidelines but we are using the best data that is available to try and make these estimates.

[Slide.]

Again, just to remind people, for calculating the test-once and test-twice strategies--this is based on 394 individuals for the test-once and test-twice and 861 for the universal scenario.

[Slide.]

In terms of the model, we developed a process model that considers the reported seroprevalence of T. cruzi in the U.S. blood supply. We were using a average value of 1 in 22,000 units as our seroprevalence in the model that I will be presented. We looked at key aspects of the U.S. blood donation system. In particular, we looked at the number of annual donations estimated as an average of about 16 million based on the 2000 National Blood Collection and Utilization Survey.

We looked at the probability of acquiring a T. cruzi infection from a blood unit that is donated by someone who is infected. Again, we used a range of 1 to 5 percent as our best estimate of this. This is considerably lower than the range that had been estimated in international models and it includes the upper limit of 3 percent that Dr. Stramer mentioned. There is so little data and there are such limitations on the lookback data

that we have in the United States that we wanted to include a slightly wider range which is why we went up to 5 percent.

Finally, we looked at the risk-mitigation options that are being considered today. I should also mention that there has been a recent change in the draft guidance that is being provided by the FDA and, just a few days ago, the FDA released a draft guidance that is recommending universal testing, and that is available on the CBER website.

[Slide.]

Major elements of the model; we began by looking at the seroprevalence of T. cruzi in U.S. blood donors. We looked at aspects of the blood-donation system in the U.S. and then we looked at the estimated number of transfusion-transmitted T. cruzi infections under the four scenarios discussed, the baseline, test-once, test-twice, and universal testing.

[Slide.]

Key results.

[Slide.]

Our model estimates that, based on the recent seroprevalence data that we have, is that, with no testing,

we would have a baseline number of about 44 cases of transfusion-transmitted T. cruzi in the United States in a given year. This is considerably higher than the reported cases that we have right now. However, we believe that because of the under-reporting issues that have been discussed already today that this is still a reasonable estimate of what the baseline transmission rate would be in the absence of testing.

All of the testing strategies are going to significantly reduce the number of transfusion-transmitted cases. However, there is still a difference that universal testing is still safer than the other models.

[Slide.]

This same information can be presented in graphic form. Again, this is the baseline looking at 44 transfusion-transmitted cases with a relatively wide range going from the 2-and-a-half percentile to the 97.5 percentile. All of the testing strategies are significantly reduced from the baseline.

[Slide.]

But there are differences. Going from the test-once strategy, we estimate that there would be about two

transfusion-transmitted cases of T. cruzi a year, perhaps ranging up to about 7 cases at the upper 95th percentile. If you go to universal testing, we are going to see about one case every ten years, so we are going to dramatically reduce the possibility of transfusion-transmitted T. cruzi.

[Slide.]

One of the advantages of using probabilistic simulation model such as this is that you can explore how sensitive the model is to the uncertain inputs that you are looking at. So, what we are going to present next is the sensitivity testing that we did to see how much the results of the model would change if certain key inputs were always set at a very low or a very high value.

[Slide.]

This is what is called a tornado graph, called a tornado graph because it has the rough shape of a tornado. What this is telling us it that, at the middle, we have the mean estimate for the test-once scenario. So, at the middle, we are at that 1.9 cases of transfusion-transmitted T. cruzi.

Then we have the different uncertain parameters in the model which have been set to either a high or low

value. So, for the sensitivity of the test, when the sensitivity of the test is very high, at 99.99 percent sensitivity, that practically eliminates transmission even in the test-once scenario. So, if we always had a 99.99 percent sensitivity in all 10,000 years, that would be enough, even with test-once, to eliminate almost all cases of transfusion-transmitted T. cruzi.

On other hand, if the sensitivity was only 93.5 percent, we would have slightly more cases. We would be getting up close to three cases per year as opposed to the 1.9 when we are using the entire distribution for sensitivity. The only other points that I want to make on this graph are that the other inputs, in declining order of importance, are the probability of transmission. Here, as a low value, we went all the way down to 0.8 percent. As a maximum value, we went up to 5 percent.

The exposures per donation, whether a given donation causes exposure for one, two, or three recipients, the seroprevalence of the model, and, finally, the annual donations of the U.S. had the least impact on the predicted cases in this model.

[Slide.]

As with any modeling, there are limitation strategies, in particular the estimates of seroprevalence of antibodies to T. cruzi to U.S. blood donors are uncertain. But those estimates are much better than they were two years ago. Two years ago, we knew very little about what this value is. We know a lot more today.

Another issue, as has been highlighted by the other speakers, is the limited data that we have an the probability of transmission as a result of a blood unit from an infected donor. Here, again, we are using 1 to 5 percent as our best estimate at this time. I fully expect this to change as we get more data and more experience and to see this part of the model refined.

Another issue that we didn't even try to incorporate into the model is the processing of blood units. We have almost no data on how processing of blood units may affect the probability of transmission. That is something that it would be very useful to know more about and to be able to incorporate into a model.

Finally, validating this model is challenging because of the under-reporting that was discussed earlier. We think that there is significant under-reporting of

Chagas disease in the United States and I think most of the speakers today have mentioned that. So it makes it difficult to determine just how accurate, in particular, our baseline estimate is using these figures.

[Slide.]

So the final point for discussion is that, first of all, any of the testing strategies that we are talking about are going to have a significant reduction from the baseline risk that we talked about but, among the choices of selective testing or universal testing, selective testing would slightly increase the mean estimated risk of transfusion-transmitted T. cruzi infections, but there is substantial overlap between those confidence intervals.

Also, I hadn't seen until just a few moments ago Dr. Busch's estimates of the residual risk. I think that those are not going to be far off from the numbers that I am presenting here. We would have to sit down and work out the exactly details, but I don't think that these two models are discordant from one another.

[Slide.]

A lot of people helped me while I was working on this. Dr. Rob Duncan, Dr. Jay Epstein and Dr. Hira

Nakhashi all assisted me from OBRR. And my colleagues in the Risk Assessment Group including Mark Walderhaug, Steve Anderson and Hong Yang have contributed as I developed these models.

So thanks for allowing us to share these results with you and we will be happy to answer any questions or comments that you may have.

DR. SIEGAL: Thank you, Dr. Forshee. Do we want to ask some questions before the break, or take our break?

DR. TRUNKEY: I have a question for Dr. Montgomery and this has to do with her Slide 18 transplant transmission in the United States. You said there were five published cases, but we don't have the denominator for the cases during this period of time. But the transmission rate seems very, very high which suggests, to me, that immunosuppression affects the transmission rate and, if it does, can you get a mathematical model for that and should this be mandatory testing for all potential donor recipients?

DR. FORSHEE: I'm sorry; was this addressed to me or Dr. Montgomery?

DR. TRUNKEY: It was Dr. Montgomery. I don't

know if she has the data or not. But she is gone. I guess that answers that.

DR. FORSHEE: Can anyone else from our group provide any insight on that?

DR. DUNCAN: I could comment in one regard. There is no question that immunosuppression makes a difference. Whether we want to have some sort of policy for differentiating blood for immunosuppressed patients--

DR. TRUNKEY: Well, blood and organs.

DR. DUNCAN: --and organs, testing not being our purview. That is sort of a larger question. But it is no question that it is an issue.

DR. KLEINMAN: At least two of those transmissions from organs, and maybe three, were from transplanted hearts. The parasite is known to infect hearts, so it may not be a immunosuppression question in those cases. It may also be that they got a larger dose of the parasite.

MR. MAGUIRE: The experiment in Latin America is most of the transplant-associated transmissions have actually been from other organs. Those two heart cases were the first ever reported.

DR. NELSON: I am interested in--there are quite a few EIA positives that end up being RIPA-negative and I think some strongly reactive. I wondered about the specificity of this assay. Many parasitic assays cross-react with other species. I wondered if this Roche assay is specific for, really specific for, Chagas or does it cross-react with Leishmania or other species and, therefore, have a negative RIPA but the donor may have had an infection with another agent that could be transfusion-transmitted.

I wonder, is that an issue?

DR. FORSHEE: First of all, I can tell you that we did estimate the number of false-positives that would be generated under the universal testing scenario. For that, we used a specificity of 99.997 percent which is the published specificity of the test.

Dr. Duncan, do you have anything else to contribute to that?

DR. DUNCAN: No. You may remember that the issue of cross-reactivity with a number of other parasitic species, Leishmania as well as a little bit with malaria, were picked up in the clinical trial and, based on that, we

recommended, and it is in the package insert, that a situation as you describe that is strongly reactive on the ELISA test but not positive on a further confirmatory test be looked at for other parasites.

And the American Red Cross did a tremendous amount follow-up testing for antibodies to Leishmania until they had--they never found a positive in all of their testing. So, at this point, we would not even recommend further testing for other parasites unless the donor had a history or some other indicator that they were in an area that exposed them to another parasite.

DR. BIANCO: Dr. Forshee, you used, as a sensitivity of the assay, the maximum sensitivity the package-insert sensitivity. That was done with donors in Bolivia, Chile, Argentina, very high prevalence areas. Is that applicable? Are we comparing apples and oranges or how would that influence the results.

DR. FORSHEE: First of all, I want to emphasize that, for the main results of the model, we were using the sensitivity results that are the same results that were presented by Dr. Stramer earlier today. And so, for the main results that we presented, we were using these ranges

for our estimates.

The point of the sensitivity test was to determine what would happen if we were always on an extreme end of some of the whole distribution that we were looking at. Personally, I would think it would be very unlikely for the test-one scenario to always be coming in at a sensitivity of 99.99 percent, but the goal of the sensitivity test is to see what these extreme differences would have on the results of the model.

It is designed to help tell you if your model would diverge wildly from your base results if one or your key assumptions was at an extreme end. I am not sure; did that completely address your question?

DR. HOLLINGER: I have a question for Dr. Busch. It is an interesting study, I think, the one about the questions that they asked. I wanted to check about the travel history if I could, a little bit, Mike. Apparently, there have not been very many tourists who have come back to the United States who have been found to have Chagas. I think there are three reports in the European literature. One was an Italian who was a tour guide on a ecotour who came back with acute Chagas. Another was a woman in Paris,

60 years old or so, who spent some time in a dig in Columbia that developed acute Chagas. But I don't think anything, in terms of a tourist, as we look at tourists, maybe a week or two somewhere.

So you had a question about three months. Was that question asked that, essentially, since your last donation--I know you didn't have any seroconversions, anybody who apparently went from positive to negative. So the answer is pretty clear. But was the question asked that, since your last visit, or since your last donation, have you traveled south of the U.S.-Mexico border, excluding the Caribbean, for example, for three months or more or two months or more or something like this because that is really the critical question that I have.

There is really not much data about people who have had extended time periods of travel to areas like Mexico or Bolivia or Paraguay and come back. The data should be there. I mean, one could sample, for example, Peace Corps volunteers. There have been thousands of them who have spent time in rural areas or urban areas. I don't think they have ever been sampled to look at the prevalence of Chagas in that population. But there are certainly lots

of them around to look at.

So could you help me a little bit about your questions in regards to--because one of the issues that we have here is should there be a risk question, if you just do single testing--I think that is reasonable. But should there be a risk question about people who have been gone for a period of time and spent time in these areas?

DR. BUSCH: There were separate questions. There were the questions about the donor, themselves. One is, there is a question, where were you born. Then there are questions separately; have you resided for greater than three months in these regions ever in your life. Has your mother resided in these regions for more than three months, ever. And then, have you traveled to these regions subsequent to your last donation for any period of time, but not specifying a prolonged period of time.

I think the most important is for donors who came in and were negative on the screening test since we implemented, we had 13,680 donors who came back and donated again who said, yes, I have traveled since my last donation to a Chagas-risk, south-of-the-U.S.-border, country and no infected donations detected exclusively in those traveling

donors.

If you go further and you say, amongst the positive donors that we have picked up on their first donation, have we detected donors whose sole exposure was prolonged travel where they didn't have country of birth within these endemic regions and yet they had traveled to these at-risk regions. There were small numbers of donors who indicated they weren't born in these countries but they had prolonged residence in these countries. So there are a very small number of donors who probably acquired the infection after being born here but then lived for very prolonged periods.

They were all identified the first time we screened, in the first, if you will, culling of the donor pool. So we haven't seen any examples of donors who have acquired the infection but, as you point out, we haven't been testing donors for ten years so we can't say that the donor that was tested negative and then went away and lived in these countries for five, seven, years couldn't acquire the infection.

DR. HOLLINGER: Were the donor demographics--because you said not everybody answered the question. They

had the option. It didn't matter. You would take their blood anyway. Was the donor demographics of those that answered that question similar to the donor demographics of the population in general?

DR. BUSCH: I don't know. That is a good question and we haven't looked at that.

DR. HOLLINGER: The issue about the travel is really interesting. I had an opportunity to talk to Dr. Kirchoff at the University and we discussed a little bit about the travel because most of his work has been in Mexico in the Jalisco area in which the prevalence is about a half to 1 percent. They had shown some transmission in that area. They had four cases of transfusion-transmitted Chagas from his group there.

But the issue is that we don't have much information about the risk of somebody spending some time, a prolonged period of time, whether that is a month or two weeks or what, in an area, a rural area particularly, and acquiring the disease and coming back.

The issue did come up and his feeling was that people who come back with acute disease are probably more likely to be able to transmit than somebody who has had the

disease for many years; that is, the probability of seeing the parasite in the blood is probably greater in the early course of the disease than it is as time goes on. The same with, I guess, hemacult positivity and so on later.

But, anyway, I think are issues that come down to the point about whether a question should be asked if you just do single selective testing once.

DR. GLYNN: Along the same lines, did you do any modeling with that kind of targeted strategy where you would do testing once and then you would have a question after that?

DR. FORSHEE: We have not done that modeling yet. It is something that could be incorporated into what we have done here. But, at the moment, the sensitivity estimates that we have really bundle all of those issues together because the sensitivity could be because of a false-negative earlier on or it could be because it was acquired later. So, at the moment, the data that we have on the sensitivity sort of captures both those possibilities. And so we haven't disentangled it at this point.

DR. GLYNN: I had another question related to the

feasibility of these various strategies that we are discussing. Could someone address, what can be operationally feasible. Of course, universal testing, that is doable since you do it now. But if you went to a different strategy, how difficult are some or how easy are they?

DR. BUSCH: I was going to mention this later in the public session but, at least for Blood Systems, a strategy that would involved one-time donor testing could be implemented tomorrow. Our computer systems are capable of tracking and verifying that a donor was tested once as negative and the systems could be put into place such that untested donor samples are designated for screening and, most important, that you could not label a unit that did not come from a donor who has previously been tested as negative.

Going beyond that, a system that would require documenting multiple negative results or incorporating an additional travel-related response, driving additional testing or a requirement that you test every three years or five years, these would require substantial modifications to the I.T. programs and expensive and potentially

problematic with respect to accuracy and error events.

So the one-time strategy is one that is completely viable and implementable whereas the more complex two-time or interval or question based additional testing options would be much more difficult.

DR. BIANCO: I want to add to the comments from Dr. Busch. Most of the computer systems, they all have approvals by FDA. It is not that we go home and switch one thing to the other. That takes a lot of time, a lot of validation, a lot of work. Most of the computer systems in use that have 510K approval are able to do a one-time test.

I don't know any that could be now switched to be able to produce the type of results that the other models, the twice-testing or testing with a question, all that, would be applicable. And that is something that is very important; that is, selective testing, at this scale, requires a lot of computation of power. We are limited in that at this point.

DR. BLACKWELDER: I don't understand what it would be that difficult to, say, pick our donors who have been tested twice, who have been negative twice.

DR. BIANCO: Because the systems, in general, are

modular. So you have a donor module and a laboratory module, for instance, and a recruitment model. Essentially, what you want is, at the time that you are going to label the unit, for you to consult each one of modules to be able to tell you if the unit was cleared by all the tests, by the donor-deferral files and by all the activities.

So, in general, if you make one modification in one of them, you are going to affect the most important step in the software--that is, the accuracy of labeling. And any modification in that requires extensive validation, resubmission to FDA for an amendment to the 510K and then the application.

DR. CRYER: In your models, is the increase in effectiveness between testing twice and universal just because of the sensitivity number you plugged in?

DR. FORSHEE: Yes.

DR. CRYER: All right. So then one of the questions, or actually two of the questions, that we are eventually going to have to answer have to do with, you test once and then you get asked some questions, and is that enough to not test again. So did you plug in any of the data regarding the accuracy of the answers to the

questions that we heard earlier into your model?

DR. FORSHEE: No; that is not incorporated into this model. All of the information about the sensitivity of the test comes from the empirical data that has been gathered so far and that was reported by Dr. Stramer earlier today.

So the cases that we have in the missed-once category could be from any sorts of error including an original false-negative or acquiring the disease later. And, at this point in time, we don't have any way of sorting that out.

DR. CRYER: Then I have one other question and that is your model, again, depends--one of the factors that it did depend on was what the true incidence of the prevalence in the community actually is. Do we have an idea of how big that might be? Could it be ten times higher than the number you used, or is it only likely to be maybe one-and-a-half or two? Or do we not have any idea?

DR. FORSHEE: Well, I think that the numbers that we have on seroprevalence are now much, much stronger than they were two years ago. The data that has been collected now, I believe we are at approximately 14 million donors

who have been tested at this point. And so we are getting a good body of evidence on seroprevalence now. Those numbers certainly could change, but that number is not a small sample number at this point.

DR. KLEINMAN: It is 28 million from Dr. Stramer's presentation but also it is likely to go down because, if there really are no infections in repeat donors and you continue to test your repeat donors again and again, you are going to have a bigger denominator and a lower numerator, or the same--well, lower numerator from the first-time donors will be the only ones who test positive.

So if you looked at the prevalence in two years, I bet it wouldn't be 1 in 28,000 if we continued with universal testing. It would probably be half that, on a per-donation level, anyway.

DR. FORSHEE: And that is certainly something that would be re-evaluated as new data came in and the model would be updated.

DR. NELSON: I wonder, though, to what extent the infections in repeat donors might have been somewhat underestimated by the exclusion, the geographic exclusion, of donors for malaria exposure who might have visited an

area that is also endemic for T. cruzi but weren't tested because they were already excluded because they had a malaria risk.

Is that an issue?

DR. FORSHEE: Well, I think the seroprevalence that we are looking at now is among blood donors who are currently passing the screening questionnaire. Now, if the screening questionnaire was later changed in some way to be more liberal in terms of allowing people from areas where potential donors may have been exposed, I could imagine that affecting the seroprevalence. But my first thought on your question is that so long as the questionnaire remains the same, that shouldn't affect the seroprevalence among blood donors. And that is what we were looking at in this model. We weren't looking at the seroprevalence in the general population but within the blood-donor population as currently screened.

DR. NELSON: I guess there is some concern about the efficacy, effectiveness, of geographic exclusion for malaria risk, and I have heard some interest in doing screening for this so that--to actually document an exposure because a lot of them--exclusions are for cruise

ships to the Caribbean and what have you.

But I suspect that there could have been an underestimate of the real recurrent risk because of the exclusion of visitor to malaria.

DR. BIANCO: Ken, the exclusion for malaria is a temporary exclusion.

DR. NELSON: I know, but it is still for a year.

DR. BIANCO: It is one year.

DR. NELSON: And if somebody had visited Paraguay, Mexico, et cetera, in the past year and acquired T. cruzi and they admitted, they wouldn't be screened for T. cruzi because they would be excluded. I mean, we are not transmitting, but I suspect that the data on recurrent infections may be underestimated.

DR. BIANCO: But the donor population does not reflect the general population. You have about ten-fold less than one log.

DR. SIEGAL: Dr. McComas.

DR. McCOMAS: Thanks. This question is for Dr. Busch and it is in relation to the question to the questionnaire strategy. When you did the follow up to try to understand the discrepancy between those who had

answered the questions one way and then were later found to be positive, I am wondering if you did any systematic collection or questioning about why they answered the questions wrong in the first place.

DR. BUSCH: No, is the answer. The follow-up question was actually administered at the time the donors were notified several days after and they were told they were reactive, but there wasn't any subsequent sort of effort to understand the reason why they changed their responses from the original donation.

DR. MAGUIRE: I want to make a few comments about the change in epidemiology of Chagas disease both in Latin America and the United States. Since 1990, particularly in the southernmost part of South America, there has been a tremendous control program. And the overall prevalence of the infection has probably dropped from about 18 million down to 10 million or less.

So when we talk about risk of travel, a lot of the areas we are calling endemic are really not endemic anymore. In fact, when you look at some of the data, for instance, from Brazil where they have knocked out transmission from the major vector, the cases that are seen

now are almost accidental cases in which bugs fly into the fruit juice or they are ground up and so it is oral transmission, very unusual transmission. I think there is one case of a German tourist who was infected in one of these outbreaks of oral transmission.

To get infected with T. cruzi, if you live in an endemic area with invested houses--for instance, when we worked in Brazil some years ago where people who live in infested houses, the maximum prevalence of infection took about 20 years. So, a night, a week, a month, in a heavily infested house is still fairly low-risk exposure.

I think, more and more, the real exposures are going to be people who are camping and going out in the environment. In the United States, also, I think we have seen a little change in the ecology. After Katrina, one of the autochthonous cases occurred in New Orleans. And there was a big change both in the ecology of armadillos which are probably the major reservoir host, and the finding of large numbers of bugs in the house of the person who was infected.

There has been some modeling done of warming, change in climate, and what may happen to the distribution

of the bugs in the United States. I think the cases we are going to see in the United States will be, again, among people who are camping or kind of these freakish accidents in which bugs get into the food supply somehow.

DR. FINNEGAN: Actually, my question is to ask Dr. Epstein if he could explain to us what the cost or what the difficulty would be in changing the software so that they could do two instead of one. The reason for that is that the statistics shown for two selective testing as compared to universal are pretty close whereas there is a difference between one and universal.

So I am wondering what the cost to the system is or what the difficulty would be.

DR. EPSTEIN: I can't answer that with respect to cost. And also the issue has not been explored. We would have to get applications. Dr. Bianco is correct that we would not just allow changes within the organizations without submission of software modifications.

That said, there is at least one model which is the anticore test where you have to have two reactives to defer a donor. And so the systems do keep track of the number of reactive tests. I don't know how adaptable those

systems would be. So I really can't answer your question because it has been unexplored.

Since I have the mike, and happen to be here, I wanted to raise a couple of points that I hope would get discussed. One is about the fact that there were borderline reactives, high negatives, that had positive RIPA and positive EA on retest. This is, of course, concerning. It is one thing, if you will, to have sins of omission. If we accept sensitivity at a certain level and you never see a reactive, then that's that.

It is another to have sins of commission. And, in this case, what I am getting at is the borderline reactives because some of them are real. And so one question is, was there a strategy ever to look at the high negatives by RIPA. I know that this was done in the Ortho clinical trial but I just wonder whether you have thought about that and that would lead, potentially, to a consideration of a strategy where you might not use the unit.

You might not defer the donor at that point because it is negative but you might not use the unit. That is what is done right now with anticore. Likewise, it

used to be done with ALT. So, that is one question, is whether we should consider a different way to use the EIA in order to address the high negatives. The scientific way to frame the question is what proportion of high negatives have positive RIPAs. I don't know if you have that from your study.

The second question I would like to ask is really directed--well, I guess Mike or Sue. The finding of no seroconverters in roughly 3 million person years, I think is a little confounded because there was no individual that was in the observational period more than 22 months. We do know autochthonous cases can occur. We do know that they can occur at any age at any time.

So it leads me to wonder whether a sort of belt-and-suspenders strategy would be to test each donor once every five years or every ten years because then you have a chance to pick that up even though you didn't see it in 3 million person years, but no single observation. I mean, I am sort or reminded of when we do drug toxicity. It is not the same thing to say a million people were exposed one year as it is to say that we had X number of people, each exposed ten years, because there can be cumulative effect.

I think it is the same thing. If there is a time-related risk of getting an autochthonous infection, you might want to consider the retest for that reason. And then, one third point I would like to raise. All of the risk estimates have been framed in terms of the national average. In other words, you take 1 in 29,000 average prevalence and you model everything based on that.

But you know, and I know, that there are hot spots. And you showed it on your slides in Florida or in California, particularly the Los Angeles area, can be as high as approximately 1 in 3,000 or even sometimes a little higher. And so one question in my mind is, well, should we really be generalizing or should we be looking at the range of safety.

I know that we have considered the question of geographic-based testing and that is sort of non-flyer because you found positives all over the country. So that is out. But it shouldn't, I don't think, prevent us from thinking about the range of risk because the range of risk is really quite remarkably different, as much, potentially, as a factor of 10, depending where you go.

And so I kind of whether we shouldn't factor that

into our thinking instead of simply looking at a national average. So, simply stated, Sue, since you are at the mike, would you want borderline reactive blood transfused?

DR. STRAMER: Let me answer the question maybe--okay. So, when we did the clinical trial, there was a gray zone used during the clinical trial. And we saw gray-zone reactives, three during clinical trial, that were RIPA-positive. So, when we implemented the licensed test, we continued with the gray zone until the manufacturer had their cutoff changed.

So, in addition to those three during the clinical trials, we found another three during the interval of time between when the test was licensed and the cutoff was changed. Do we still see samples that rest right at the cutoff? Yes. But one can ask the question, how many times can the cutoff be changed. It was changed once prior to our doing the clinical trial, once post-licensure. So, at some point in time--you can't just keep changing the cutoff.

I showed the signal-to-cutoff ratio of RIPA-positives that ranged from 1 all the way to 8. And there were significant numbers of each of those bars. I don't

know, Jay, if I answered your question, but certainly cutoff reactivity is something that we are going to live with with this test always.

DR. EPSTEIN: The other way to look at it, though, is that there is wiggle room. There is a tradeoff between sensitivity and specificity. At its current sensitivity, the test has remarkably high specificity.

DR. STRAMER: Yes.

DR. EPSTEIN: Could you live with a little less specificity for a little more sensitivity? In other words, how far below cutoff are the borderlines with positive RIPAs? If they down to an signal-to-cutoff of 0.5, what proportion of test is that? In other words, how badly would it affect specificity?

And the other way to look at it would be, and this is a little bit out of the box because we don't usually do this, but discard the unit and see if it happens again with the donor.

DR. STRAMER: It would be like anticore.

DR. EPSTEIN: Or routinely do RIPAs below the cutoff. So I just think that there is wiggle room here because the test, as it has been developed, has remarkable

specificity. But maybe we want more sensitivity because you have a significant proportion of true positives near the cutoff.

DR. STRAMER: Yes. And one other thing that I didn't really highlight. We have had some PCR-positives that have rested right at the cutoff as well as RIPA-positives. We have two that have signal-to-cutoffs of 1.1 and were PCR and RIPA-positive. So some of these positives certainly are real.

Regarding the decrease in specificity for an increase in sensitivity by another cutoff reduction, certainly, of 16 that I showed, that will help. But we would have to do a 20 percent cutoff reduction to get a significant number and we remind you and the committee that we still have no donor re-entry test. So, to have an increase in number of deferred donors with doing a research RIPA and no way to capture them is a burden and a stress to those donors. So, for me, I wouldn't favor another cutoff reduction.

DR. BUSCH: Two points. One, the borderline reactives that were detected, the sort of flip-flops, the ones that Sue showed that required two-times or even three-

times testing to pick them up as relative, those were all PCR-negative. If you look at the relationship, although there are a few examples of PCR-positive low reactives, that there is a strong relationship with the signal-to-cutoff of the assay and the probability of parasitemia.

So these low reactives, to my mind, for the most part, represent remote and probably resolved infections or non-parasitemic donations. I think, in the model, you assumed the same transmissibility of donations that were detected on the first time versus the second time, et cetera. I would argue that there is probably a much lower risk with the donations that might be missed on a first time and only picked up on a second time.

As to the incidence analysis, I agree with you that the donors who contributed person time to that zero incidence rate, on average, only contributed ten months and couldn't have contributed more than two years. That actually led to the suggestion by Rob Duncan that we look at the serial data from all of our RIPA-confirmed and other donors, as both Sue and I showed, for whom we had follow up to ask whether there was any evidence of any incident infections that would be evidence of seroconversion in the

donors who we had picked up as positive.

And the answer was no, that we didn't see any identified donors who evolved from the index donation to the follow up. So that added--to me, it was a great idea and it added a lot of weight to the fact that we are not seeing incident T. cruzi infected donors coming into the system. So I don't know exactly how to factor that into the person time, but it was certainly reassuring to not see seroconversions amongst the RIPA-positive donors.

DR. BIANCO: The other point that is important here is that the discussion is based on the assumption that all RIPA-positives are true positives which we know is not true and RIPA is an assay that uses--the RIPA assay--uses exactly the same antigen that is in the ELISA test. It is just on a strip in a different way. So I assume that some of those have the same non-specificity that led to an ELISA that is reactive leads to a RIPA that is positive.

Regarding the question from Dr. Epstein, I have got a lot of untested blood, Jay.

DR. HOLLINGER: For Dr. Stramer, a question about the PCR. Are you assuming the PCR blood is also infectious? I mean, you made a comment that they are PCR

and therefore they are infectious. So, could you comment a little bit about that and then also why you think there is so little transmission to individuals. Does it have to do with the kind of blood that they receive where it is whole blood or platelets or things like this? And then the third one is about the autochthonous donors, if you could maybe go in a little bit more about where you think they acquired their infection and so on..

DR. STRAMER: Regarding PCR positivity, your first question was--I never used the word "infectivity." I said "parasitemic." So we don't know if PCR positivity has a relationship to infectivity. We know they are potentially parasitemic. Certainly, ones that are hemaculture-positive that demonstrate circulating parasites, those would certainly, if the parasites survive our component manufacture, those certainly would be the ones that would be highly infectious.

PCR; you know, we don't know yet if there is correlation with infectivity or even if there is correlation with parasitemia. But we know there is presence of something that triggers a positive PCR result which is different than growing out the parasite.

And then your second question, Blaine, was--autochthonous was the third one.

DR. HOLLINGER: 40 autochthonous cases in the U.S.

DR. STRAMER: Where did they acquire their infection?

DR. HOLLINGER: Where do you think--I mean, of those, and just sort of summarize it a little bit, fudge it if you want to, how many do you think were really infected or seem to have acquired their infection that you believe in, and then where do you think they acquired--how do you think they acquired their infection here?

DR. STRAMER: Well, of the 40 I showed, 50 percent of them had reproducible RIPA results, two different samples by two different laboratories. So it is hard to say those are false-positives. 60 percent of them reacted on another test using another strain of T. cruzi. So, again, it is hard to discount those.

Where have they gotten infected? Sue Montgomery mentioned the fact that we are going to do a more detailed study with these donors where additional testing will be done and a very in-depth questionnaire will be provided to these donors with responses. This is part of the USTC,

U.S.-derived, T. cruzi transmission study.

So, in that, we ask many, many detailed questions about outdoor activities, animal exposures, housing, what your hobbies are, do you garden, do you camp, do you hunt, so trying to identify risk factors. In our donors, and many of them I have talked to myself, we know some are hunters. During hunting in areas of the United States where there are vectors and reservoirs, they spend a lot of time outside in contact with reservoir animals, vector insects. Many of them have seen rejuviid bugs. They are familiar with them. I mentioned the individual in Montana, the young man, who actually did have, in retrospective review of his clinical records, Ramona's sign when he was a young boy and camped in Texas. So you have to have contact with either the reservoir animal or vector insect. So it is going to relate likely to outdoor activities or the type of housing that you live in.

Right now, we haven't done enough detailed questionnaires to be able to understand the risk factors in these individuals other than they have to be in contact with either infected blood from another infected human, a reservoir animal or the vector.

DR. HOLLINGER: Sorry, Fred. Just one other question to Dr. Maguire.

DR. STRAMER: Oh, and then you asked about transmission, differential transmission. Certainly, and this has been discussed at other BPAC meetings, the organism, the agent, seems to segregate with the platelets. And when you store platelets aerated at room temperature, that, again, would encourage survival of platelets versus red blood cells that are stored for longer periods of time under refrigerated conditions or certainly plasma that is frozen. And we know, in the absence of cryoprotective agent, the parasites won't survive.

So one theory is, because the parasites, when you process platelets, will comigrate with the platelets and will, perhaps, survive for that five-day period of time. That is why platelets pose the greatest risk. But, because we don't use fresh whole blood, our blood is stored and the parasites certainly will die off quickly over a period of time.

One reason for the lower rates of transmission that have been documented in the Central and South American literature is that we no longer transfuse fresh whole blood

and we do highly manufactured components that are stored over longer periods of time.

DR. HOLLINGER: I was going to ask either Dr. Maguire or Celso or Kenrad or anybody else here, you mentioned--I thought it was an interesting comment about the fact that people usually have to be in an area often for long periods of time. I didn't hear anybody talk about age-specific attack rates in various countries. I know the prevalence is low in many countries, but in Bolivia, Paraguay, it is very high although I understand it is getting lower.

So could somebody just tell me a little bit about age-specific attack rates, how rapidly they go up and so on in populations.

DR. MAGUIRE: First of all, the exposure that is really the high-risk exposure is living in a house that has become colonized which means the bug has set up its life-cycle. It is very different than a house in which a bug flies in and temporarily visits. So, again, you have to think of the way it is transmitted which is not through injection of the parasite. It is through defecation with the parasite in the feces and the parasite has to get in

through the wound.

So you look at data from areas that have high prevalence of Chagas disease from the vector, most of the transmission that is going to occur occurs in childhood and early adolescence. I think what you will see in the heavy areas is that people who are at risk because of their housing, in this ten-, 15-, 20-year period of time, will get infected. If it is a lower force of transmission, then that peak age is going to be greater.

DR. SIEGAL: If there are no more questions or discussion for now, let's take our break and then we can come back and have the Open Public Hearing and proceed. Thank you.

[Break.]

Open Public Hearing

DR. SIEGAL: Again, both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

For example, the financial information may include the company's or a group's 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 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.

DR. FREAS: The first Open Public Hearing speaker we have is Dr. Michael Busch making comments on behalf of American Red Cross and Blood Systems, Incorporated.

DR. BUSCH: Thank you. And I work for Blood Systems.

I have five points. The first is that, as you have seen, the Red Cross and Blood Systems have

collaborated closely with FDA to characterize the yield of T. cruzi antibody screening and to analyze the predictive value and sensitivities of potential selective-testing options.

In January of 2009, the Red Cross and Blood Systems medical and scientific leadership met and reviewed all of the data that had been accrued through November, 2008, essentially the data you have seen today. And this analysis included assessment of the very low transmission rate demonstrated by lookback and the absence if seroconversion or of recently infected incident-infected donors.

Based on that review, we concluded that transitioning from universal to selective testing, specifically one-time testing, would afford essentially equivalent safety to universal testing and would be significantly more cost-effective than universal screening. The specimen handling, testing and I.T. systems to support one-time testing already exists at Blood Systems and could be developed and established at the American Red Cross. Alternative selective testing options such as two-times, travel-driven or temporal retesting options would be more

difficult to implement and would require expensive and delayed implementation of I.T. systems to be able to manage those systems and could be prone to errors.

The American Red Cross and Blood Systems strongly endorse the development of selective testing strategies not only for T. cruzi but as a more general approach to more rational and cost-effective screening not only for infectious agents such as West Nile, malaria and Babesia, but as well for non-infectious screening such as for TRALI.

We formerly communicated, a letter from the CEOs and chief medical officers at both organizations to FDA to Drs. Goodman and Epstein, this position in late 2009 and expressed the intent that we would convert to one-time testing pending the outcome of this BPAC discussion.

DR. FREAS: Thank you. Our next Open Public Hearing speaker is Dr. Steve Kleinman.

DR. KLEINMAN: Good afternoon. As I mentioned before, I am a paid staff for AABB. This is a joint statement from AABB and also American Red Cross. So I will just read it.

An antibody test for T. cruzi was licensed by FDA in December of 2006 following clinical trials showing yield

of positive donors in the West and Southwestern areas of the U.S. A voluntary implementation of the licensed test occurred starting in January, 2007. Through the end of 2008--that is 22 months--approximately 75 to 90 percent of blood centers have implemented the licensed test.

In 2006, prior to any FDA guidance, AABB Association Bulletin 0608 was released to provide assistance for how to manage donors and components for those centers that chose to implement the test. To date, only one test has been licensed--and this is incorrect in the statement--FDA has now issued a guidance for the use of the test.

The algorithm being used by most collection facilities includes the Ortho T. cruzi ELISA test system followed by a more specific RIPA that is unlicensed but is commercially available through Quest Diagnostics. During the 22-month period through the end of November, 2008, as the data have been reported at today's meeting, there have been 2,989 EIA repeat-reactive donors on which 735 from 41 states have confirmed positive.

The performance of the screening assay has been excellent with the repeat-reactive rate of 0.015 percent

and a positive predictive value of 20 to 30 percent which is comparable to other screening confirmatory assay systems. However, even with the use of a licensed screening test with excellent specificity and a research RIPA as a supplemental test for donor counseling, there is still the need for an FDA-licensed supplemental test that could be used for re-entry of donors with false-positive screening reactivity.

During the screening experience with the Ortho EIA, we have learned the following; U.S. autochthonous cases, presumably insect-derived, of T. cruzi infection have occurred primarily associated with rural outdoor activities in states where infected insect vectors and animal reservoirs are present. As we have heard, no overt seroconversion in a donor has been documented after approximately 3 million person years of observation in the Red Cross and BSI experience.

RIPA-positive donors have been identified with EIA reactivity close to the assay cutoff with the EIA results from these donors varying between reactive and non-reactive on sequential donations, but these do not represent incident cases of infection. In fact, there is

no evidence of an incident infection--that is, an unequivocal seroconversion--or results from serial testing of index donation and follow-up specimens consistent with the increases one might expect in O.D. values in recent seroconversion, no evidence of this in any U.S. blood donor in this dataset or any other dataset past or present.

Lookback data published in the literature and ongoing investigations triggered from the use of the licensed screening test suggest that an infectivity of components from RIPA-confirmed U.S. blood donors is probably no greater than 10 percent. It is difficult to calculate a more precise percentage because of the uncertainty of some recipient test results and because the majority of recipients were not available for testing.

For example, as we have heard today, in the Red Cross studies, only 22 percent of the total recipients were available for testing and, although 80 percent of living recipients were tested, these recipients could not, obviously, be tested to confirm if transfusion transmission had occurred. Confirmed or probable transmissions have only been observed from either whole blood or platelets including leuko-reduced units and/or irradiated whole-

blood-derived and platelets and apheresis platelets. No confirmed transmissions have resulted from packed red cells or from any frozen product.

Low infectivity is likely due to limited survival of the parasite under contemporary blood-banking conditions and the use of manipulated such as leuko-reduced blood components that are transfused being the survival time of the organism. Perhaps more important is that not all antibody-positive units contain parasites. This low risk should be taken into account in FDA's deliberation of testing strategies and mandates.

Based on the above, continued universal testing is not medically appropriate and we know that blood collectors who did voluntarily initiate universal testing in 2007 are now looking at various other options. We believe we should focus on selective testing strategies that adequately protect recipient safety and have been used successfully for multiple agents include T. cruzi outside of the U.S.

A precedent for selective testing is particularly important as we consider other emerging infectious diseases for which it may be impractical or unnecessary to perform

universal testing. Examples include babesiosis and Dengue.

The blood community must invest substantially in the I.T. systems required to support a selective strategy in a cGMP environment and FDA endorsement of a selective-testing option for T. cruzi for which ample data supports such a policy will incentivize blood centers to invest in this I.T. capacity.

Of the selective-testing measures reviewed, data from BSI suggests that donor interviewing to identify risk based on birth or residence or maternal birth or residence or donor travel to endemic area cannot be recommended due to inadequate sensitivity and reproducibility of responses to endemic-country exposure questions administered during the routine donation process.

We recommend that if the FDA requires--again, this was written before the guidance so we recommend now that the FDA is requiring testing of donors for antibodies to T. cruzi, that a selective donor-based testing approach and the I.T. systems to support such testing be used. Our favored strategy for selective testing at this time is donor qualification using a single negative licensed screening test result.

The excellent performance characteristics of the current licensed screening test, the lack of observed incident donor infections and the rarity of transfusion transmission demonstrated by lookback support the conclusion that the approach is acceptable with respect to recipient safety. One-time donor screening to qualify donors as T. cruzi antibody-negative is also practical from I.T. and operational perspectives. Two-time testing is a less desirable option as is testing only donations from which platelets will be manufactured.

We would like to re-emphasize to the committee the importance of taking this opportunity to shift the testing paradigm so that we can achieve maximum safety while avoiding unnecessary testing and be able to focus on other issues related to drug and patient safety.

Thank you.

DR. FREAS: Thank you, Dr. Kleinman. Our next speaker, Glenn Mones from the National Hemophilia Foundation.

MR. MONES: Glenn Mones, National Hemophilia Foundation. I am going to make a very brief statement. In my comments earlier today, I described the attitude of NHF

as one of erring on the side of maximum safety with regard to blood and blood products and their potential to transmit infections.

Decisions affecting the safety in blood products must focus on safety far and above any other consideration. This approach applies to the current discussion on testing for T. cruzi as much as it applied to the earlier discussion on NAT testing for HBV.

Universal testing, we believe, is the best method to minimize transmission of the infection and we see no clear evidence that alternative strategies will not results in an increased risk of transmission. We believe the focus should be on improved testing and elimination, not on deciding to test less based on considerations other than just safety. Let's stay with what seems to be working until we have something that genuinely improves safety rather than potentially reducing it.

Thank you.

MR. FREAS: Thank you, Glenn. Our next speaker, Dr. Merlyn Sayers from the Carter Blood Care.

DR. SAYERS: Many thanks. My name is Merlyn Sayers and I am the Chief Executive Officer at Carter Blood

Care which is a community independent blood program for North Central Texas. Those of you that were listening to the earlier presentations will have heard that Texas is that state which has seven species of the reduviid bug 50 percent of which are infected. So my comments come against the background of a warm and cordial relationship with disease vectors.

So I am on the faculty of the University of Texas Southwest Medical Center and also the faculty of University of North Texas, and I serve in an advisory capacity to Caridian BCT, Paul Byer [ph] Medical and to Turuma [ph]. Having listened to the presentations this morning and this afternoon without wanting to sound melodramatic, I really have to say that we are at a crossroads.

There is a question at this particular crossroad and the question is can we afford to continue making decisions about donor testing's role in promoting transfusion safety as we have made those decisions in the past or is it reasonable to try considering a different approach.

There are a number of aspects of the draft guidance for serological tests to reduce the risk of

transmission of T. cruzi that do argue for at least some consideration of a slightly different approach. In the first place, we can't assume, as we did with transfusion-transmitted Chagas, that experience elsewhere, namely South America, will pertain in the North Americas.

As has been pointed out, transfusion-transmitted Chagas disease did not present against a background of epidemic as West Nile virus and HIV. Consequently, it was premature to refer to transfusion-transmitted Chagas as an unsolved problem. But, once it was characterized like that, and once there was encouragement to manufacturers to develop a screening assay, and once there were recommendations from the American Association of Blood Banks on Chagas testing, it is not surprising that we are looking at draft guidelines to intercept a disease characterized by infrequent, if any, transmissions in North America.

I am sure that there are differing opinions as to how we got to this point, but we would have been much better served if we had had evidence of what the risks of transfusion transmission were. We would have been much better served if we had had a licensed confirmatory test.

We would even have been better served if we understood better the role of RIPA in the understanding of individuals who have fluctuating test results.

So, while there may be different opinions as to how we got here, I think there is one opinion that we might share without any confusion and that is this. There really has not been much public debate about risk analysis, risk management or risk communication. And, without the debate about the role of risk in public-policy making, we have an exaggerated attitude to that risk and I suspect that policy makers could be under pressure to eliminate risk in the way that this is disproportionate to any potential damage.

In 1996, in an interview with the Philadelphia Inquirer, Dr. Philip Lee, who was then the U.S. Assistant Health Secretary and the Blood Safety Director, was reported as saying, "When it comes to blood, you have got to make it as safe as you can. You can't put a dollar value on public confidence.

Well, those days are over. And, rather than strategies which pursue the illusory goal of a zero-risk blood supply, what might be required is a standard against which the need for safety interventions can be measured.

And, ideally, an infectious-disease transmission threshold should be reached before decisions are made that additional safety is, indeed, justified.

In the U.K., such standards are contemplated by organizations like the National Institute for Clinical Health and Excellence and also by the Select Committee on Science and Technology. I think that, in this country, the Institute of Medicine had been approached in the past to help develop safety standards but I believe they demurred. Without such standards, we are going to be confronted, as we are with Chagas disease, by the prospect of additional tests whose benefit is difficult, if not impossible, to measure and whose justifications require no more than the demonstration of the remote possibility of transmission.

There is a well-developed science around safety decision-making and I think we could be well-served if elements of risk/benefit analysis became tools in our trade before the implementation of additional and new testing.

These comments shouldn't be taken as criticism of the addition of new tests and a brief history of the contributions that serological testing have made to transfusion safety recognize that many of those

contributions are major. But, what is different now is that transfusion safety is not just a reflection of how much testing can be applied. Transfusion safety now includes consideration of the availability of blood and components and, unless decisions are made differently about which tests to add, and when to add them, cost is also going to be a major influence in transfusion safety. There are limits, especially in these economic times, to the extent to which additional costly interventions can be added.

A word about the precautionary principle. And it has been invoked today from both sides of this plastic divide. And it was gratifying to see that something emerged as a unifying concept, albeit it was the precautionary principle. If the precautionary principle is more than a philosophically appealing maxim and if it is edging its way into regulatory policy, then it needs to be defined along with the circumstances under which it should be applied and it should have guidelines for its use.

And then, finally, comments about the need for risk/benefit analyses in the development of public policy, comments about the need for safety thresholds and comments

about the need for clarification of any regulatory role for the precautionary principle should not be regarded as cynicism or insensitivity on the part of the speaker. I really do value a safe blood-transfusion supply as much as anybody else, but additional testing must not be a low-yield economic burden when the investment could pay significant dividend if it was applied elsewhere.

Thanks.

MR. FREAS: Thank you, Dr. Sayers. The final request to speak in the Open Public Hearing is from Dr. Susan Rossman, Gulf Coast Regional Blood Centers, representing ABC.

DR. ROSSMAN: Thank you. I am representing the 74 members of America's Blood Centers, ABC. We provide about half of the volunteer blood supply in the United States. Our U.S. members are not-for-profit community-based organizations that are licensed and regulated by the U.S. Food and Drug Administration. Hema-Quebec, our Canadian member, is regulated by Health Canada.

We thank FDA and BPAC for the opportunity to comment on potential testing strategies for T. cruzi infection in blood donors. The FDA briefing document, the

AABB statement and the presentations made before the committee, describe the results of screening for antibodies to T. cruzi between January 29th, 2007 and November 30, 2008. As opposed to the universal screening approach being used by many centers in the past two years, AABB's statement suggests a selective approach because of the limited number of positive donors identified in more than 15 million donations screened, the lack of seroconversions on observation of more than 3 million person years, and the very few transmissions of infection by a positive component detected by lookback investigation.

In addition, AABB is recommending that, since FDA requires screening for antibodies to T. cruzi, donors be qualified by the one-time performance of a single licensed donor screening test. The AABB statement and presentation by Dr. Michael Busch suggested that sensitivity of selective screening testing triggered only by a history of residence or birth in an endemic area was not fully adequate.

As mentioned in our statement about HBV NAT presented this morning, the potential recommendation for the screening of blood donors for antibodies to T. cruzi

can also be interpreted as new paradigm in dose screening for infectious disease. We are being asked to screen blood donors because one test was licensed, not because the country is confronting an epidemic with substantial risk of transmission of the disease to blood recipients.

Initial considerations about screening for antibodies to T. cruzi were based on limited epidemiological studies that conveyed the impression that a large proportion of U.S. donors were infected with the parasite and that T. cruzi represented a public-health problem.

Chagas was the subject of several discussions at BPAC and, based on historical information about the high risk of transmission by transfusion in observational studies carried out in Argentina and Brazil in the 1950s, FDA indicated that when an adequate screening assay became available, it would be recommended for adoption. Unfortunately, reviews of the historical information did not consider the evolution of component preparation and transfusion during the last half century.

In the 1950s, physicians in South America transfused fresh whole blood collected in glass bottles

using latex tubing instead of stored blood components. We also, in our eagerness to improve blood safety by reducing a perceived risk, missed the fact that the first clinical trial of the currently licensed assay included 40,000 specimens from U.S. donors without a single positive specimen detected. Positive donors were detected in subsequent trials performed by the American Red Cross. Those trials focused on areas rich in immigrants from Central and South America and did not necessarily represent the entire country.

Finally, we should acknowledge that, as noted in the FDA briefing document, one ABC member identified two antibody-positive recipients on lookback. These recipients had no apparent risk of exposure other than the platelet transfusions. They received apheresis platelets from two separate donations made by the same donor. The cases are under investigation and confirmatory tests are being performed.

There is substantial diversity of opinion about a recommendation for implementation of donor screening for T. cruzi among ABC members. So far, our positions have been developed by each blood center in concert with their boards

and local medical communities. Essentially, several members support to AABB of one-time screening for antibodies to T. cruzi using the licensed assay. Others would prefer a delay in such recommendation until a second assay, currently under development, is licensed. This would avoid the errors, complexity and cost of implementation of dual technologies in many donor-screening laboratories or the need for outsourcing the test with consequent delays in product release.

Others would prefer selective screening based on questions about birthplace of donor or mother. The data suggest a marked enrichment of positive donors selected by these questions. Others feel that only donors of platelets, both by apheresis or separated from whole blood, need to be screened because the vast majority, if not all, of the recorded transmissions have occurred after transfusions of platelets from infected donors.

A few ABC members feel that the implementation of serological screening for antibodies to T. cruzi is premature and favor the performance of regular surveillance studies to assess changes in prevalence of antibodies over time. We want to remind the committee that the

implementation of costly new assays changes the allocation of healthcare resources in every community. Testing all donors all the time for T. cruzi consumes over $100 million annually. A proposal to test all donors once will still take millions out of hospital budgets at a time when many are struggling to survive and are forced to make difficult choices in patient care.

In conclusion, as in our HBV statement, ABC members suggest that, if T. cruzi testing is recommended, blood centers be allowed to determine the optimal screening strategy for their community.

We thank the committee and the FDA for the opportunity to present these comments.

DR. FREAS: Thank you, Dr. Rossman. That ends the Open Public Hearing Session.

Open Committee Discussion

Questions for the Committee

DR. SIEGAL: We are ready for the questions for the committee and additional committee discussion.

DR. DUNCAN: So, Question No. 1 is on the board. Does the committee agree with the FDA that scientific data on effectiveness of risk questions in general do not

support a selective-testing strategy in which donors who previously tested negative for antibodies to T. cruzi are tested again only if their answers to risk questions indicate they have a risk of a newly acquired infection.

DR. SIEGAL: Any discussion on this point?

DR. ZIMRIN: Yes. It is a very narrow question, I guess. I would agree that it didn't sound like that using questions to determine risk was particularly helpful. Does the FDA think it has a good idea of the committee's feeling about selective testing in general. Actually, I haven't read through all the questions--or can we comment more generally about a selective-testing strategy other than the one you mentioned.

DR. DUNCAN: Question 2, Parts A and B, will ask about selective-testing strategies. So you could favor one of those.

DR. ZIMRIN: Okay.

DR. DUNCAN: Then Question 3 is open for any other suggestions.

DR. ZIMRIN: Okay. Got it. Sorry; I should have read through this first. We have heard a lot of very interesting material today. I think that we know a lot

more than we knew a couple of years ago. Its sounds like there are still a lot of questions that are unanswered at this point.

I am sure that there is more research that is planning to be done in this area, but I guess I am a little hesitant--maybe this is answering a question that is coming down later--to recommend universal testing at this point where there is so much that is up in the air. I would not, however--much as I would like the idea of questioning to bring out the people most at risk, it doesn't sound to me like that is a feasible approach given the inaccuracy with which people answer questions.

DR. DUNCAN: Well, you are right in one sense that our perception is that the questions would not be an adequate way of identifying the people at risk. But, keep in mind, that all the selective-testing strategies that we are seriously considering will follow one negative test. Everyone who comes in for the first to donate will be tested. And the issue of selective testing will be what happens when they come back again. Will they be asked questions to determine whether they are at risk? Will they be tested again, or will they not be tested again? Or will

they be tested again every time they come?

DR. CRYER: So the answer to No. 1 is really moot. What we are really talking about is No. 2. Is that right?

DR. DUNCAN: What do you mean? There is no 2 up there yet. We want to get this one answered and then move on to 2.

DR. CRYER: But the question doesn't make sense because you are already--No. 2 already presupposes that everybody is going to get one test, as does this. What you are asking in No. 2 is--

DR. DUNCAN: No. 2 would be testing once with no questions asked. That is the difference between this and No. 2.

DR. NAKHASI: You have to take this question in its own right to say what you heard from the data presented whether the questioning is one of the viable options or not.

DR. Di BISCEGLIE: I would say, based on what we heard today, we heard no evidence that newly acquired infection is, indeed, a problem. It takes years to become infected living in an infested house. Reasonably casual travel doesn't seem to represent a risk factor. So it is not quite directly aimed at the question of whether

questions are sufficient, but the general issue of newly acquired infection is a problem.

I did have a question for Dr. Forshee, though, which is somewhat related that I didn't get a chance to ask. In the modeling that you did, looking at test-once, test-twice, and universal, and you didn't really factor questions in. You said that. But you said that the difference between universal and test-twice, there is a numerical difference, that it didn't matter whether you factored newly acquired cases in or not. That didn't quite make sense to me. How could the number come out the same whether you did or didn't factor in newly acquired infection? Maybe I misunderstood.

DR. FORSHEE: Because the differences between those scenarios were based on the empirical sensitivity estimates that had been provided in Dr. Stramer's estimates. So our question there wasn't, how did the case get missed but, rather, just what percentage of cases would be missed under the alternative testing strategies of test-once, test-twice or use universal testing.

So, simply based on the empirical estimates of what the sensitivity was under those three estimates, we

used those sensitivities to estimate the models and those were the differences that we found.

DR. ZIMRIN: So you are saying the autochthonous numbers are so low that it doesn't change the risk as compared to the other causes of positivity?

DR. FORSHEE: I'm sorry; could you repeat.

DR. ZIMRIN: Are you saying that the autochthonous are so low it is not going to change the risk estimate comparatively?

DR. FORSHEE: I am saying that the estimates in our model, to the extent that the autochthonous are in our model, they are in some of the cases that were missed in the test-once or test-twice strategy in the, I believe, it was 394 individuals who were looked at under the test-once and test-twice strategy. So, at this point, we didn't have sufficient data to sort out what those newly generated cases would be. So, instead, we relied on the estimates of sensitivity that were coming from the American Red Cross.

DR. EPSTEIN: If I could help shed some light on this. There are no accurate data, and really no data, to tell us how likely it is that a donor will acquire Chagas in the U.S. What Susan Montgomery showed you is it does

happen. What we also saw from the cumulative testing by the blood organizations is that you will pick up autochthonous cases. However, what we are getting at is whether either additional testing or additional questioning could help us decide how much more testing to do in order to pick up newly emerged infections.

So what the survey found is that, over a 22-month observation period with an average 8 months per donor, per repeat donor, we didn't see an incident infections. Does that mean they don't occur? No; of course not. But do we believe that retesting donors based on a history of, say, camping or traveling south of the border, or, did you ever see a reduviid bug on your wall. We have no evidence that that would be of benefit.

Now, what I think is confusing about the question is we made the presumption that no one is going to advocate that you only test people based on a questionnaire history because the sensitivity of that methodology was low. It was 75 percent at best. So we presumed that there will be testing if there is intervention at all.

Now what we are talking about is, okay, you are already tested once. Is there an added value of

questionnaires. That is really what we are trying to get at. And, unfortunately--and you asked the right question but, unfortunately, there are no data to tell us how often, or with what likelihood, we would pick up a recent infection. We just know it happens. But we don't know how often and we didn't see it.

DR. FORSHEE: And if I may say just one more thing about the modeling. Some of you have a very good intuition there are other ways the model could have been set up to look at process of doing a questionnaire, following them up for repeated testing. There are other ways the model could have been set up. But what we decided to do was to use the empirical data that we had showing the relative sensitivity of test-once, test-twice and universal. We decided that, out of all the choices we had about tradeoffs between the quality of data, we decided that that was the best data that we had at this moment to show the relative effectiveness of the three strategies.

DR. SIEGAL: Dr. Cryer.

DR. CRYER: Unfortunately, that doesn't help us answer Question No. 1. But we also do have data here--I mean, real data--that says that if you ask people the first

time, before you tested them, that they get it wrong; right? So one would presume that there would be no different pressures involved or any different insights involved when they answered the question again. So it is an assumption, a supposition. But at least we have data for the first half.

So it seemed to me that this question for me is pretty simple. I mean, they are going to answer wrong again.

DR. McCOMAS: If I may follow up on that just to confirm that research, on-survey research, indeed shows that there is a self-report bias so, from other studies, people are going to get it wrong, not necessarily that they mean to lie but they misunderstand the question or they don't really understand the reason behind the question.

So, whereas, I don't think that questioning is necessarily a bad thing to do, I think that these questions appear not to be the right ones to ask or they are not being asked in the right way. And, if the FDA or the blood industry wants to have questions, and I perceive that they might, that they really ought to invest in a little bit of analysis to understand why people were systematically answering it wrong and what are some of the built-in

procedures that might be influencing those wrong answers.

DR. Di BISCEGLIE: I would suspect that the real meat, the real discussion, will be in Question No. 2. I have a sense that the committee knows what the answer is to Question No. 1 and we might want to get on to Question No. 2.

DR. SIEGAL: I think that is maybe a good suggestion and, perhaps, we ought to take a vote on this. Are people willing at this moment to do that? Dr. Hollinger?

DR. HOLLINGER: I still have a problem with this question, also. And it also is tied into the others. I think this is what the issue is. You are presented with two or three alternatives, the optimal of which is universal testing. And then we talked about one-time testing, two-times testing, and we talked about testing once and then maybe five years later which is probably a very difficult thing to do.

And then we talked about the question and so on. But, I think there is a lot of good data, it seems like here, that selective testing can be very useful. However, under the circumstance of not knowing for sure about

incident cases, both in this country as well as abroad--I think Dr. Stramer's data was that only about a quarter--about a quarter of the RIPA-positives were autochthonous, or may be autochthonous. The majority were from outside. I think it was 40 of the 157.

So most of the others were presumably from acquisition outside the United States. So the question that was not asked, to my satisfaction, was, since your last donation, has this happened. Now, granted, there are not very many incident cases in that 22 months, which is a short period of time. I am much more comfortable, personally much more comfortable, until we know this data and this data is available to us, to have a question like that asked of some sort, particularly the one about, have you been out, say, for more than a month south of the border, south of the U.S.-Mexico border, any travels down through Latin America or South America including the Caribbean.

Until we are sure that, with the data, that there are no incident cases occurring in this group that we were going to let--that would not test. After several years, we would have that data and then we could make a better

decision about how to proceed in there. I just think it has been too short to come to the conclusion that just selective testing once is sufficient.

DR. BIANCO: I think, Blaine, that this is proportional to the size of the population of positive donors that we are finding in this experience of two years. How much are you going to wait by that strategy in terms of pickup.

The issue I think that we are all having--I don't have to answer the question--but that we are all having with this question is, really, does the committee agree with FDA that questions are an inadequate method to select donors for testing. This is a little bit round-about and, if it were direct and just applied to the data that we heard here, that is the answer. No.

DR. ZIMRIN: I think there are two issues. One is that questions are not a particularly good way, it seems, of getting accurate data. And the second is we don't actually really know. It is not as if, if they answered yes, we would know 100 percent sure that they would, therefore, be at risk. We don't even really know what the risk factors are. So not only is the method not good, but

we are probably not even asking questions that are going to give us a reasonable answer.

So I would suggest that, until we have data that suggests that questioning really does some good, it would not be a good idea to mandate its use.

DR. SIEGAL: Dr. Colvin.

DR. COLVIN: It seemed like there was one question that was a problem and that was the question as to where somebody was born. There could be many reasons why that question could be answered incorrectly that would probably be purposeful by the person answering that question. In this case, a lot of times, they may be afraid of immigration status and what somebody might say or suggest about their immigration status depending on where they were born.

The other questions, it didn't seem like they were that far off. There weren't different answers every time they were answered. So it seemed like one particular question. Now, the question you would ask on secondary testing would not be where you were born anymore, because there was already a negative test. The secondary question would be, since the last time you donated, have you spent a

month overseas or in Mexico or in South America, which is a very different thing, I think.

Obviously, it is a hypothesis that I cannot prove that it has something to do with immigration, but it is one possibility.

DR. BIANCO: I think that you are correct, that this has biased many of the questions. But Dr. Maguire just told us that people have to live in those houses for years in order to develop an infection. It is not something, except for the couple of weird incidences of oral transmission that happened in the last few years because they ingested the bugs, the mashed bugs, as they prepared juices and all that.

The possibility of getting infected just by the housing and all that is minuscule in travel.

DR. MAGUIRE: [Off mike] --an area where the transmission--you have got the control measure. I mean, there are still parts of Central American, northern South America, where control measures aren't that far. But, still, the risk of getting infected--let's say you spend a week in such a house--is tiny.

DR. SIEGAL: Anyone else? Then let's proceed to

a vote on this question.

DR. FREAS: Before you vote, please double-check to make sure you picked up your correct remote. There are 17 voting people at the table. The industry rep is not voting. When everybody has voted, please show the results.

[Simultaneous voting.]

DR. FREAS: Dr. Nelson, Dr. Colvin, Dr. Glynn, Dr. Maguire, Dr. Trunkey, Dr. Zimrin all voted yes. Dr. Hollinger voted no. Dr. Bower voted yes. Dr. Siegal, Dr. Ballow, Dr. Blackwelder, Dr. McComas, Dr. Cryer all voted yes. Dr. Kulkarni, Dr. Di Bisceglie, Dr. Rentas and Dr. Finnegan all voted yes. So it was all yes with 1 no. That is 16 yesses and 1 no.

DR. SIEGAL: So let's proceed to Question 2A, which also requires a vote. I can read the question; do the combined scientific data on risk of transfusion transmission of T. cruzi support a selective-testing strategy in which, A, one negative test would qualify a donor for all future donations without further testing or questions regarding risk of a newly acquired infection? Discussion?

DR. TRUNKEY: I would ask Dr. Epstein a question

in regards to the immune-incompetent individual. Would you use a one-test or two-test if you identified a potential donor for solid organ or tissue?

DR. EPSTEIN: Well, I don't know the answer. We are here to be advised. I think you did bring up earlier the question of whether you would want a more scrupulously tested donor pool for your most immune-compromised recipients. I don't think that we have really had a full deliberation. I think that the general framework is that we set a safety standard and we screen donors according to that standard.

Now, there is the model for CMV where we do not have a routine requirement to test but where we do have approved screening tests and where discretion is exercised by blood banks to provide CMV-negative blood for at-risk recipients. So I think we could think in those terms if we believe that additional testing adds value.

And, anyway, even if we recommended one-time testing routinely, it could still be a industry practice voluntarily to screen twice for an immune-compromised recipient if there weren't otherwise a consensus.

DR. TRUNKEY: I am not sure I have the knowledge

to ask this question, but it seems to me there is some value in using two tests which increases the rate, if you will, of knowing whether a person has this particular antigen; is that correct?

DR. EPSTEIN: Yes; the data do indicate that at least two-times testing improves sensitivity about 95 percent up to the 98 percent range.

DR. TRUNKEY: But, unfortunately, Dr. Montgomery did not give us the denominator of the people. But, it seems to me, if there were five cases of Chagas in donors and it went to 19 people who got infected, that seems to me an increased risk factor. I may be all wet on this. I don't know.

DR. BIANCO: Are we discussing--I think the question from Dr. Trunkey is very important, but are we discussing blood donors or are we discussing organ donors and recipients. They are very different.

DR. EPSTEIN: That's true. But I think if I understand Dr. Trunkey correctly, and you can rephrase it if I am wrong, you are asking whether we should entertain a concept of a twice-tested donor selectively for an at-risk recipient for an immune-compromised recipient, especially

an organ recipient but perhaps others as well.

We are talking about screening blood donors. We are not talking about screening organ donors although the same concepts might apply.

DR. BIANCO: Dr. Epstein, these may apply very well for, for instance, cadaveric specimens. They are much more difficult to test. But you don't have two specimens in a cadaveric donor to test. You have one.

DR. CRYER: I think it is more about the recipient. So, in other words, a bone-marrow transplant patient is going to be getting a lot of blood in our institutions as are all the other transplant populations. So the blood supply that is coming in for that group of patients potentially would need to be safer than it is for people who are not immune-compromised that are going to receive blood. So it is about the recipient, not the donor, not the donor of the organ that we are testing. It is the donor of the blood for blood that is going to be transfused into immune-compromised--

DR. BIANCO: Yes, but it will create, Dr. Cryer, a complexity that is very--requires serious thought because you will have to create a population of donors that you

maintain an inventory on the shelf that have been tested twice to be provided to those recipients. So you have to balance the complexity, the possibilities of error and the fact that people may not be necessarily--the physician may not necessarily request that unit at that time.

DR. ZIMRIN: I just wanted to say that I thought the doctor from Texas, who spoke to us, made an excellent point. I think that one thing we sort of lose track of is that we have moved, over the years, from a discussion about HIV and hepatitis, which caused a lot of mortality and certainly a lot of morbidity, to West Nile where there was clearly an infectious disease that caused morbidity and some mortality as well to something where we don't know the clinical implications, where I think there is a lot of uncertainty.

I think this is, again, a test that we have available but trying to make decisions as to how much resources to commit to this, trying to make a risk/benefit analysis when we don't really seem to have a good handle on the risk, or we at least don't know the lower level--well, we really don't seem to have a good idea of what it is. It certainly doesn't seem to be as high as some of the other

diseases that we are comparing it to.

So I just think we need to keep that in mind as part of this discussion when we are thinking about what kind of mandates we are going to recommend.

DR. BALLOW: To test once seems to pick up the individuals that were born elsewhere. And we get a 95 percent exclusion of those donors. Doing two tests increases it to 98 percent which is pretty close to universal testing so I think probably people around the table would say there is no sense doing universal, that testing twice gets us almost at the same point.

But the real black box is the autochthonous individuals who acquired this disease, or at least acquired infectivity, who were not born in South America or Mexico. That is the information we don't know. Apparently, the CDC is looking into further--trying to get some further information about those individuals and how they acquired the infectivity and what the clinical consequences are.

So, without that data, it is really difficult to decide whether we should test once or test twice since we don't know what the clinical outcome of those individuals are. So I don't know whether we would be conservative and

just say, okay, let's test twice and, hopefully, in two years, we may come back and we will have that data about those individuals that acquired the disease in the United States and then may have to change our policy. I mean, that would be a conservative approach with those individuals.

DR. SIEGAL: Dr. Cryer.

DR. CRYER: I see it a little bit differently. So, if I do the math right, if you test once, you are going to have 20 patients left in ten years that are going to get the disease from the blood transfusion. If you test twice, you get rid of 12 of those, so you are down to seven. And then, if you do universal, you knock it down another six, down to just one. So, if you are going to spend the money to knock it down 12, then it ought to be worth the money to knock it down another 6.

The trouble is, if I heard the math right, the cost of that at $100 million a year over ten years for knocking 19 patients out of the pool is $1 billion.

DR. GLYNN: I think I agree that the issue is the incidence because we only have data for about 10 months on the incidence, so the incidence is zero over 10 months.

But we don't know what is going to happen over the next few years. And the way those questions are phrased, it looks like you test once or twice and then, after that, you don't ever test them again. So is that correct? Or is there another alternative?

DR. DUNCAN: That is the correct formulation of the strategies that are in these questions. The concept has been raised of testing again after two years, five years, and we would entertain comments from the committee on Question 3 for those kind of suggestions.

DR. EPSTEIN: I just want to clarify one point which may or may not be clear to everyone. A two-times testing strategies is not the same thing as saying retest in five years or retest in ten years. A two-times testing strategy could be that the second test happens at the next donation in 56 days, or it could be it happens in 48 hours at the next platelet donation. It is simply twice-tested. It is not an interval test inherently.

Now, on average it is, because, on average a repeat donor gives twice in three years--I'm sorry; three times in two years, 1.5 times per year. But, bear in mind, that is a short interval. In the actual study, the average

was about 8 months. So, just to be clear, when we talk about a two-times test, we could be talking about two different things. We could be talking about a retest at some fixed interval or we are simply talking about test-twice.

Now, the test-twice argument had nothing to do with picking up incident infections. It only had to do with picking up some proportion of the true positives that are fluctuating near the assay cutoff because the antibody titers are low. So think of that more as replicate testing then interval testing. They are really two completely different ideas.

DR. GLYNN: But, Jay, just to clarify, the one we are asking to vote on is that one, the second one, the repeat testing.

DR. EPSTEIN: Well, yes. Replicate testing. In other words, on more than one occasion but without any specified interval. And that concept is targeted toward picking up again some proportion of the low-level reactives that are true positive but might be missed on any one-time assay because they are so near the cutoff, just outside variation.

DR. Di BISCEGLIE: So that is useful, Jay. I mean, there are these two thoughts, picking up new cases, incident cases but I think, more important, trying to confirm the negativity by basically repeat testing. It seems to me like the science is a little bit in evolution I mean, this is firstly a new--I am not sure of the right work, mandate recommendation, from the agency.

The test is fairly new and we really don't have adequate confidence intervals around that rate of incident cases of zero. So I wonder if a suitable strategy may not be to say we have done a good thing by doing one test and now we need to study it further to look at incident cases, whether questions can identify them, what interval it might take for new cases to appear. Nine months may not be enough. It may be five years, and isn't it likely that a newer and better test will emerge. It is the nature of things, compared with competition, that newer and better tests tend to emerge.

DR. BIANCO: And adding to the points that Dr. Di Bisceglie made and Dr. Epstein, maybe we should consider the consequences of another change in cutoff. I don't know. I know Dr. Stramer would hate that. But, in a certain way,

if the impact is small, or tolerable--I wouldn't say small--it may be easier to deal with than repeat tests.

DR. STRAMER: Let me just say it is a slippery slope. It is never going to end because of the dynamics of the test. We will always find, then, other samples that are below the cutoff, so it will never end and we will negate all the work that Ortho did in design of experiments to make this test highly specific. We will chew away at all of the confidence that we have that the test is specific.

DR. BIANCO: Aren't you going to have the same problem multiplied by 2 if you test twice?

DR. STRAMER: No.

DR. CRYER: That question for me is not so important as it is how many--if you went universal. So the difference how many tests you would decrease by doing it twice from doing it universally. Do we have an estimate of what that might be? It is easy from 1 to 2. It is half. But what is not so clear is what the difference between doing it twice and doing it universally is, because that depends on how many times people come back.

DR. BIANCO: Dr. Busch has some estimate.

DR. BUSCH: I showed those numbers for the first year and a half of testing. If we went to, I think the last page of the handout--right; so in the period where we did universal testing on 1.4 million, if we went to one-time testing, it would drop to 700,000. If we required two-times testing of those donors, it would be 1 million, 4 thousand. But that will evolve over time as the repeat donors get tested once or twice.

So, eventually, theoretically, with a one-time donor strategy, we should settle out continuing to need to test about 22, 23 percent of donations because these are the first-time donors coming in. If you have to test all donors twice, you know, it would probably settle out at 25 to 30 percent of donations will be need to be tested on an ongoing basis.

DR. NAKHASI: Hira Nakhasi. I just wanted to emphasize the point there that Celso was sort of suggesting and I guess Sue answered to some extent, it is not only reducing the specificity and increasing the sensitivity, you will increase the false-positives and we do not have a supplemental test. Therefore, you are going to increase more people false-positives which are varied well, and that

is another consequence of that.

DR. ZIMRIN: It seems to me the most clear improvement we can make over the strategy of doing nothing is to test once. After that, the improvements are relatively small and the gain is relatively ill-defined. So why not recommend something that seems likely to be a positive and continue to investigate until we actually know more about what are recommending.

DR. DUNCAN: One of the points I wanted to make about the question of incident infections, whether it is from travel or whether it is from autochthonous transmission, is, if that is still a concern and we still need to do more study, then what testing strategy we propose will affect that greatly because, at this point, the only testing strategy that will capture true seroconversions, true new infections, would be universal testing or maybe some sort of time-dependent multiple testing short of universal testing.

Whether we test once or twice, anything else would be a study that would be outside of the standard blood-donor screening.

DR. ZIMRIN: Are you saying we can't study this

unless we mandate it. That is the only way to get the information.

DR. DUNCAN: I would not say we can't study it, obviously. There could be ways, but the kind of studies that the Red Cross has done, that Blood Systems, Incorporated, have done, where they are doing the study in the context of donor screening are just more productive because of the sample size they are able to marshall.

DR. BUSCH: I would suggest a study could be done. And, because we are so in favor of moving to selective testing, that, if a kind of postmarket--so, let's say you guys approved one-time testing but with the understanding that a study would be conducted perhaps in two or three years where we would retest, perhaps, in some of the higher prevalence regions, the regions in which there are higher rates of persons from those countries.

We could test 200,000 additional donations from donors who had been tested once before who have come back now, two, three, four years later, so some kind of postmarketing study could be conducted in a few years to just verify that we haven't seen incident infections. We could also continue to enroll and follow and get serial

data from the positives which is, again, a very good approach to identifying recent seroconverters.

So I think some sort of post-selective testing studies could be designed and we would make the commitment to conduct those downstream to verify absence of seroconversion.

DR. GLYNN: I agree that that makes a lot of sense to me. It is more reassuring to know that later on you would have data that hopefully would confirm your original decision because, otherwise, again, the way it is worded right now it is like you do it once and you are done forever. So I think we would have a Choice 3. I don't like A and B, myself.

DR. Di BISCEGLIE: So something that Dr. Busch said that we haven't explored very much is this question of regional variation. We did have a big discussion about sensitivity and specificity and, of course, those are very much affected by the actual prevalence of whatever it is you are testing in the particular population. So, part of further study might be the need for regional variation in the retesting strategy, perhaps, because, again, sensitivity and specificity will be different in California

and Texas than it might be in Minnesota.

DR. HOLLINGER: And I think Dr. Busch's suggestion is a good one. I think you do need some additional data and it sounds like this is a disease you could probably get that in. So, doing this several years down the line, or a few years down the line, to look at-- but I would also just include it over the whole group because we still want to know about incident infections in a population. That would help us a little bit understand that after several years. So, to me, that would be a better approach.

DR. SIEGAL: Are we ready to vote on Question 2A?

DR. GLYNN: Can we add that question, then, as a choice, what we just proposed?

DR. ZIMRIN: I think there is some support for that.

DR. DUNCAN: You mean the suggestion about later studies? I would suggest that we put that into Question 3.

DR. SIEGAL: There is room for it there and we can discuss that again. But let's vote on 2A.

DR. ZIMRIN: I am not clear on Question 2A. So this is regarding a mandate, not regarding a recommendation

for further studies or further research. Okay. Thank you.

DR. SIEGAL: This is one negative test that would qualify a donor for all future donations without further testing or questions regarding risk of the newly acquired infection.

DR. DUNCAN: But the place it would fit in--

DR. ZIMRIN: There would be no postmarketing?

DR. HOLLINGER: According to this.

DR. NAKHASI: But then, in Question 3, you are going to [off mike].

DR. ZIMRIN: Wait, wait. Let this get real clear for me. So, if I like the postmarketing idea, I should vote yes or no for this?

DR. HOLLINGER: No.

DR. DUNCAN: If you think one test is a good idea, vote yes. You can then say postmarketing in Question 3.

DR. ZIMRIN: Okay. Thank you.

DR. GLYNN: But that is different. That is different from--the question you are asking is can you do the testing once and then, afterward, you do nothing ever again on the repeat donors. That is how I understand that question.

DR. SIEGAL: That is the question.

DR. GLYNN: That means no studies, no postmarketing studies.

DR. ZIMRIN: No; we are supposed to vote yes for this and then vote--include postmarketing in the next question.

DR. HOLLINGER: But if you answer it that way, and if you answer it the way you just stated that, that is not what it says. It says one negative test would qualify a donor for all future donations. You are not saying you could do something different. You would have to vote no on this question and then add something in the comment section about it.

DR. DUNCAN: Could I suggest we look at it this way, that this is a policy that would be applied in general to blood donors.

DR. ZIMRIN: Okay.

DR. DUNCAN: The question of another study, a subsequent study, a postmarket study, that is going to be done as a subset of people anyway. It is not something that will be applied to all donors. And the outcome of that study might change the policy that we would then apply

to all donors.

DR. ZIMRIN: Okay. So this is a policy question. Okay. Got it.

DR. CRYER: Can I clarify one thing because it seems to me that, if the data model is correct, that you would have to test the entire pool of donors in a year to have a chance of just finding 1--0.7 patients--0.7 patients--that the first test was wrong in. So you are not going to do any post tests that are going to mean anything. You would have to play this out for ten years to find out whether it was working or not. And the answer to that really depends on how you would answer No. 1.

DR. DUNCAN: I would suggest that is not exactly the right interpretation. The model that says if we test once, there will be 1.9 new transmissions in the next year is based on transfusion transmissions. This postmarket study that Mike Busch has just suggested would be to try to capture incident infections that could come from vectorial transmission, that could come from travel, or other sources.

DR. BUSCH: But I think the concern is that 22 months is only less than a year in a modest number of donors. A study could be designed that would implement a

question to donors who have been repeat donors and were screened negative three or four years ago, and now we are going to target donors who may have traveled outside the country, so we could add a special question, or donors who live in the high autochthonous zones, and test half a million.

I mean, it sounds like a big number, but, for blood screening, that is trivial. And the amount of money that we will save over the course of three or four years of single-donation testing, it is well worth a large study to endorse and determine whether this strategy is safe.

DR. HOLLINGER: Jay, this is a stand-alone question.

DR. EPSTEIN: Yes.

DR. HOLLINGER: And, if voted on as a stand-alone question, it opens itself up to a lot of interpretations. And you just heard the discussion around the group here, because the way it is written is very clear. It doesn't say anything about doing something later on, considering something later on. It says, specifically, one-time testing. One negative test would qualify a donor for all future donations without further testing or questions

regarding risk. It doesn't say about any further testing down the line.

So either you have to add something at the end of this that says, "although something else will done," or, "we will consider other possibilities," or you leave the question like this. If you do, and somebody wants to do, or wants to consider, some repeat testing in a certain period of time later on, they would have to answer "no" to this question and then put it in the comments afterwards.

DR. GLYNN: I agree. That is my interpretation as well. I mean, I agree completely with what you said, Blaine. That is also what I understand from the question.

DR. EPSTEIN: I think that it is very clear that the sense of the committee, at least those who are outspoken on this point, would like to see further studies to clarify incident T. cruzi infections. I think the FDA gets that. That doesn't mean we can compel those studies. So what we are basically saying is, do you think that the data warrant a one-time testing strategy. And I think that Dr. Duncan correctly framed it. That would be the routine recommendation at present. We are not foreclosing other options in the future, but that would become the standard

of practice.

So we are really saying, should we at least test each donor once. Now, you can go on and say no, but we really ought to test them twice, or you could go on and say, test them once but test them again maybe in five years. All those options for the future would be fine to recommend. But the threshold question is should we at least test every donor once.

If you think there is no value in that because of the transmission rates being so low, tell us now. If you think it has value, then you really ought to say yes even though you may have much more to say.

DR. NELSON: So, Jay, then you say the obverse of this question is not testing every donor. Is that what you are saying?

DR. EPSTEIN: If you answer no to 1 and 2, you would be saying don't test--I'm sorry; to A and B, 2A and 2B, you would be saying don't test.

DR. FINNEGAN: But 2B gives you an improved statistic.

DR. EPSTEIN: Yes; 2B is, do the combined scientific data on risk of transfusion transmission of T.

cruzi support a selective testing strategy in which donors should be tested twice. But, bear in mind that that is not interval testing. It could be 48 hours later in the platelet donor. It is simply tested twice. Think of it as a repeat test.

DR. CRYER: The way I read A is it is saying is once enough, yes or no.

DR. EPSTEIN: That's correct.

DR. CRYER: Not whether you ought to do it at all, but is once enough.

DR. EPSTEIN: That's correct. But, if you answer no to A and B, you have recommended against testing unless there are other comments.

[Comments off mike.]

DR. CRYER: It seems to me that that is correct.

DR. EPSTEIN: Well, that could be the comment.

DR. BLACKWELDER: It seems to me that A is saying. is once sufficient. And B is saying, well, if you don't believe that, is twice sufficient. And if you say no to that, then--

DR. EPSTEIN: But Mike's point is correct. That is in lieu of universal testing because what we are talking

about is alternative testing strategies. The baseline presumption is FDA's current guidance which is universal testing--draft guidance. What we are debating is whether there ought to be an alternative for selective testing.

DR. BLACKWELDER: But I interpret it as saying, if you say no to A, no to B, then you still have universal testing.

DR. EPSTEIN: That's correct. Unless you comment, "don't test." I was just leaving Point 3 open. You can comment back to us anything you want to comment, but the way we have framed it it is universal testing unless you answer yes either to 2A or 2B as the committee recommendation. Again, that doesn't foreclose other advice. I think we have already had the sense of the committee that, because there is concern about incident infections, there is a need to continue to study that possibility.

But, short of recommending universal testing, it won't happen automatically. I mean, somebody has to want to do the study, I heard Mike was interested, but, you know, we can't mandate that.

DR. BOWER: It could also be what was mentioned before about testing every one to two or five years. I

mean, that could be part of the comment and that would be something that could look into incident infections outside of postmarket; correct?

DR. EPSTEIN: Yes.

DR. BOWER: Thank you.

DR. HOLLINGER: But, Jay, I think this is where the FDA has gotten in trouble before about not mandating postmarketing tests. I have said in these committees before about doing some postmarketing thing and then the company never follows through on it or often does not. And nobody sits down and says, you need to do this.

So I think that is a dangerous slope to be on. I think it has to have some follow up. I am a little concerned about that.

DR. EPSTEIN: Well, the problem here is whose responsibility. See, we have already licensed the test. And we didn't impost a postmarketing commitment at the time of licensure. So, generally speaking, unless there is a failure of a product, we don't go and mandate it after the fact. So the question is who carries the burden.

What we are talking about is the burden to the blood operators. And I am not sure what the regulatory

framework is by which we would mandate that. We could recommend the tests in three years or Q-three years or Q-five years as guidance. We could certainly do that. But I think it is outside the framework of what was the condition of licensure. That is all I am saying.

DR. ZIMRIN: One option would be to recommend one test, or to make policies that a single test--and we are operating under the assumption that a further study will take place that will clarify the issue. If, four years from now, the study hasn't taken place and there is no evidence that anyone is making any effort to make it take place, a future BCAP committee might, then, say that the committee did not get the results they expected, we no longer feel comfortable with continuing with one test because there is no follow-up data, so maybe they ought to now move to making it more formal, that an every-five-year or two tests, or whatever they want to do at that point so it is not that we don't have options or someone doesn't have options down the road.

DR. SIEGAL: I just don't see how we can vote yes on this because forever is a long, long time. And, if we agree to this per se, then we are stuck with it, it seems

to me.

DR. Di BISCEGLIE: I would suggest we are stuck with it until data emerge that would motivate for a change in policy, perhaps,

DR. SIEGAL: Yes, but where are those data going to come from?

DR. DUNCAN: I would like to interject, also, that, since I worded these questions, that the sense of the all-future donations without further testing was to make clear the nature of the testing, not the nature of the policy. The policy could change. We are not saying yes to this question. It doesn't mean you approve that policy forever. That just means you approve of that testing strategy now.

DR. EPSTEIN: Could I suggest that, if we reword the question, subject to the understanding that additional studies will be done to investigate the incidence of new infections in donors, would one test negative qualify a donor, da, da, da, da, because I think what the committee is reaching for is to link these two ideas and not very happy postponing it to Question 3.

So, if we simply link it, then I think we may

have a question that the committee is prepared to vote.

DR. SIEGAL: So, can you guys rephrase the question?

DR. EPSTEIN: Yes. Subject to continuation of studies on incident infections--well, that should be the first--well, either way; yes.

DR. DUNCAN: Subject to what?

DR. EPSTEIN: Subject to continuation of studies to define the incidence of new infections in donors--new infections in previously screened negative donors.

DR. SIEGAL: Thank you. Does that satisfy the group?

DR. BLACKWELDER: Well, I'm sorry; not quite.

DR. SIEGAL: Okay. Well, that is why I asked.

DR. BLACKWELDER: My understanding, and I am repeating, I believe, that the difference between one negative and two negatives, in the modeling anyway, was based strictly on sensitivity of the test. I had nothing to do with incidence of new infections.

DR. FINNEGAN: I would suggest that that same line needs to be added to B because we don't know enough about the disease. So it really needs to be added to both

of them.

DR. DUNCAN: Right; and that is absolutely what I was intending to do because, as Jay said earlier, the one-test/two-test strategy is about more sensitivity, not about capturing new infections at all.

DR. SIEGAL: All right. So, shall we vote? Yes. Let's proceed. There is a question in the back, a couple of questions in the back.

DR. BENJAMIN: Richard Benjamin, Chief Medical Officer for the American Red Cross. I work for the Red Cross. I don't have any conflicts. I wanted to speak for the American Red Cross. We strongly support the suggestion that has been put forward by Mike Busch that we have committed ourselves to going to single testing but we would need to sit down with the FDA before we actually implemented such as test anyway and, at that time, our organizations, and I believe Blood Systems will make the same commitment, would commit to doing a follow-up study at an agreed time with the FDA to look for incidence infections.

[Seconded.]

DR. SIEGAL: Thank you. Anybody else?

[Comments off mike.]

DR. FREAS: All votes are zeroed out. We are ready to vote. Go ahead and vote. We are voting on 2A at this time, only. I believe there are still 17 voting people at the table.

DR. SIEGAL: Where is 2A on this thing? There is 1A, 2B, 2C.

DR. FREAS: You are voting on Question 2A at this time. If you push 1, it means yes. If you push 2, it means no. If you push 3, it means abstain.

[Simultaneous voting.]

DR. FREAS: Dr. Nelson voted no. Dr. Colvin, Dr. Glynn, Dr. Maguire, Dr. Trunkey, Dr. Zimrin, Dr. Hollinger all voted yes. Dr. Bower voted no. Dr. Siegal, Dr. Ballow voted yes. Dr. Blackwelder, Dr. McComas voted no. Dr. Cryer, Dr. Kulkarni, Dr. Di Bisceglie, Dr. Rentas voted yes. And Dr. Finnegan voted no.

I count 5 nos, so, there are hopefully, 12 yeses.

DR. SIEGAL: All right. Then we need not vote on Question B. I think that is true, isn't it? Do you want us to vote on B also? No.

DR. SIEGAL: So let's proceed to any further

discussion on 3 for which there is no vote requested. Is there any further discussion?

DR. BOWER: I will go ahead and say that--what I think the committee has talked about is that, to look into the question of incident infection, that there should be some postmarketing test or that the FDA should require or recommend that they do testing every two, three, five years, some number to be determined, to look into the question of incident infection in the U.S.

DR. NELSON: I would also think that, as Dr. Di Bisceglie said, that we might focus some prospective studies on donors from California, Texas, Florida. And the other issue, very minor but theoretical issue, is that it isn't sensitivity and specificity that changes with prevalence but it is predictive value, positive and negative predictive is a fundamental epidemiologic concept.

DR. SIEGAL: Any other commentary? Well, with that in mind, we will call this session to a close and reconvene tomorrow morning.

[At 6:45 p.m., the meeting was recessed, to be resumed the following day at 8:00 a.m.]