

UNITED STATES FOOD AND DRUG ADMINISTRATION

BLOOD PRODUCTS ADVISORY COMMITTEE MEETING

Tuesday, December 2, 2014

FDA White Oak Campus

Great Room (Rooms B&C), Building 31

10903 New Hampshire Avenue

Silver Spring, Maryland, 20993

The meeting was convened at 8:30 a.m.,

JAY BROOKS JACKSON, M.D., MBA, Chairman, presiding.

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MEMBERS PRESENT:

JAY BROOKS JACKSON, M.D., MBA, CHAIRMAN, PRESIDING

SRIDHAR V. BASAVARAJU, M.D., FACEP

FRANCISCO A. BONILLA, M.D., Ph.D.

VALERIE DURKALSKI-MAULDIN, Ph.D., MPH

JOHN B. HOLCOMB, M.D., FACS

SUSAN F. LEITMAN, M.D.

NORMA B. LERNER, M.D., MPH

MARGARET V. RAGNI, M.D., MPH

PETER RHEE, M.D. MPH, FACS, FCCM

SONJA SANDBERG, S.B. Ph.D.

KATHERINE I. SCHEXNEIDER, M.D., CDR MC, USN

CHRISTOPHER P. STOWELL, M.D., Ph.D.

INDUSTRY REPRESENTATIVE:

TOBY L. SIMON, M.D.

CONSUMER REPRESENTATIVE:

COREY S. DUBIN

TEMPORARY VOTING MEMBERS:

JAMES ALLEN, M.D., MPH

LORI KNOWLES, LLB, BCL, MA, LLM

JOHN KNIGHT, Ph.D.

KENRAD NELSON, M.D.

MATTHEW KUEHNERT, M.D., FACP

MARK SKINNER

MONIQUE TURNER, Ph.D., M.A.

WILLIAM WARD, Ph.D., D(ABHI)

INVITED SPEAKERS:

JAMES BERGER, M.S., M.T., (ASCP), SBB

DONALD J. BRAMBILLA, Ph.D.

SIMONE GLYNN, M.D., MSc, MPH

S. MICHELE OWEN, Ph.D.

ALSO PRESENT:

BRYAN EMERY, R.N., LCDR, USPHS

Designated Federal Official

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PROCEEDINGS

(8:30 a.m.)

CALL TO ORDER AND OPENING REMARKS

INTRODUCTION OF COMMITTEE

CHAIRMAN JACKSON: Okay. Welcome, everyone. Good morning. I'm Brooks Jackson. I'm the chair of the Blood Products Advisory Committee. This is the 111th meeting of the Blood Products Advisory Committee under CBER as part of the Food and Drug Administration. We have a two-day agenda. But first, I'd like to go around the table here and do introductions. If I could start -- maybe Bryan, do you want to start off?

MR. EMERY: My name is Bryan Emery. I'm the Designated Federal Official for this meeting, and there are -- to use the microphone, just push the talk button. And you can move it side to side to share the microphone, as well. And so we'll start to my right. Dr. Bonilla.

DR. BONILLA: I'm Francisco Bonilla. I'm a clinical allergist/immunologist at Boston Children's Hospital.

MS. KNOWLES: I'm Lori Knowles, University of Alberta, Department of Public Health, and Health Law Institute.

DR. LERNER: I'm Norma Lerner, pediatric hematologist, NHLBI.

DR. RHEE: Peter Rhee, University of Arizona, Department of Surgery.

DR. SIMON: Good morning. I'm Toby Simon, the Senior Medical Director with CSL Behring, and the industry representative.

DR. SCHEXNEIDER: Katherine Schexneider. I'm a pathologist and transfusion medicine physician at Walter Reed, Bethesda.

DR. SANDBERG: Good morning. I'm Sonja Sandberg. I'm a professor of mathematics at Framingham State University.

MR. DUBIN: Corey Dubin, the President of the Committee of Ten Thousand. I represent people with what we like to say, "An arm in the game."

DR. NELSON: I'm Kenrad Nelson. I'm Professor of Epidemiology, International Health, and Medicine at Johns Hopkins University.

MR. SKINNER: Mark Skinner. I'm a consumer representative, patient living with severe hemophilia.

DR. ALLEN: Jim Allen. Former BPAC committee member and chair. Retired and doing consulting work. Raleigh, North Carolina.

DR. KUEHNERT: Matt Kuehnert. CDC.

DR. STOWELL: Chris Stowell. I'm the Director of the Blood Transfusion Service at Mass General Hospital.

DR. RAGNI: Margaret Ragni. I'm a hematologist and Director of the Hemophilia Center at the University of Pittsburgh.

DR. DURKALSKI-MAULDIN: Hi. I'm Valerie Durkalski. I'm a professor of biostatistics at the Medical University of South

Carolina.

DR. BASAVARAJU: I'm Sridhar Basuvaraju, Medical Officer at CDC, Office of Blood, Organ, and Other Tissue Safety.

CHAIRMAN JACKSON: And I'm Brooks Jackson, transfusion medicine physician, as well as Dean of the Medical School and Vice President for Health Sciences at the University of Minnesota. So thank you all for coming on this rainy, dreary day, but it beats four below in Minneapolis. So we'll get started here with our first topic, which is scientific -- oh, before we start, Bryan needs to read the conflict of interest statement.

CONFLICT OF INTEREST STATEMENT

MR. EMERY: Before I read the conflict of interest statement, I'm just going to have a couple of little general announcements. Dr. John Holcomb and Dr. Monique Turner will not present today. They were on the -- they had other reasons to not be here today. Please remember to place your cell phones on mute. And if you need to go to the restroom, the restrooms are out to the right, through the lobby, and down the hall. And now I will start with the conflict of interest statement.

The Food and Drug Administration is convening the December 2nd and 3rd, 2014 for a meeting of the Blood Products Advisory Committee under the authority for 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 208 are being provided to participants at this meeting and to the public.

FDA has determined that all members of the advisory committee are in compliance with federal ethics and conflict of interest laws under 18 U.S. Code 208. Congress has authorized

FDA to grant waivers to special government employees and regular government employees who have financial conflicts when it is determined that the agency's need for a particular individual's service outweighs his or her potential financial conflict of interest. Related to the discussions at this meeting, members and consultants of this committee have been screened for potential financial conflict of interest of their own, as well as those imputed to them, including those of their spouse or minor children, and for the purposes of 18 U.S. Code 208, their employers. These interests may include investments, consulting, expert witness testimony, contract and grants, creatives, teaching, speaking, writing, patents, and royalties, and primary employment.

For Topic I on December 2nd, 2014, the committee will discuss scientific considerations related to reconsideration of the current blood donor deferral policy for men who have had sex with another man even one time since 1977. For Topic II, on December 3rd, 2014, the committee will discuss classification of Blood Establishment Computer Software, BECS, and accessories to BECS. In addition to the committee discussions, the committee will hear updates on one, Ebola virus, and potential implications for blood safety; two, the emergence of Chikungunya virus infections in the western hemisphere, and potential implications for blood transfusion safety; and three, the survey

of the rapid donor surveillance project on Middle Eastern Respiratory Syndrome, MERS.

Based on the agenda and all financial interests reported by members and consultants, no conflicts of interest waivers were issued under 18 U.S. Code 208. Dr. Toby Simon will serve as the industry representative. Dr. Simon is employed by CSL Behring in King of Prussia, Pennsylvania. Industry representatives act on behalf of all related industry. Industry representatives are not special government employees, and do not vote.

There may be regulated industry speakers and other outside organization speakers making presentations. These speakers may have financial interests associated with their employer and with their 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.

This conflict of interest statement will be available for review at the registration table. We would like to remind members, consultants, and participants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement; and their exclusion will be noted for the record.

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

TOPIC I: SCIENTIFIC CONSIDERATIONS RELATED TO RECONSIDERATIONS
OF THE CURRENT BLOOD DONOR DEFERRAL POLICY FOR MEN WHO HAVE HAD
SEX WITH ANOTHER MAN (MSM) EVEN ONE TIME SINCE 1977

INTRODUCTION AND OVERVIEW OF DATA PRESENTED AT THE
NOVEMBER 13, 2014 HHS ADVISORY COMMITTEE ON BLOOD
AND TISSUE SAFETY AND AVAILABILITY (ACBTSA)

CHAIRMAN JACKSON: Thank you, Bryan. It's -- Bryan said the first topic for today will be scientific considerations related to the reconsideration of the current blood donor deferral policy for men who have had sex with another man (MSM) even one time since 1977. And he will be presenting an overview of the data presented at the November 13th, 2014 HHS Advisory Committee on Blood and Tissue Safety and Availability. This topic will take up most of today, as you see on your agenda. And we will have several presentations first, and then time for questions, an open public hearing, and discussion on this. If you do want to speak for any reason, though, please use the microphone and identify yourself. And so, Alan Williams will be our first speaker from OBRR, FDA. Go ahead, Alan.

DR. WILLIAMS: Thank you, Dr. Jackson. Thank you all for coming, and welcome to FDA's White Oak Campus, which became CBER's new home this year; and we love it. I'm going to start with a couple of opening remarks on behalf of the agency, if I

can get the switcher. Okay. Sorry. The on switch hadn't been pushed. Okay.

FDA is actively reconsidering the current deferral policy for men who have had sex with other men (MSM), and we take seriously our responsibility to assure blood safety through science-based decision making. In this regard, we are mindful of the results of the studies recommended by the HHS Advisory Committee for Blood Safety and Availability -- Blood and Tissue Safety and Availability -- that were undertaken by the PHS agencies since 2010 to inform a possible change to the current donor deferral policy for MSM.

We are also mindful of the December 2013 and November 2014 recommendations of the HHS Advisory Committee for Blood and Tissue Safety and Availability, or ACBTSA. We look forward to today's discussions, and we're committed to moving forward in a timely manner with the policy reconsideration. Additionally, we are establishing a general program of blood safety monitoring, and look forward to hearing committee recommendations regarding the use of HIV recency testing as part of blood safety monitoring. Furthermore, we intend to engage in public discussions of related issues, such as enhancements to public and donor education about safe blood donation, and the potential for further optimization of the Donor History Questionnaire.

Regarding today's agenda, discussions regarding a

reconsideration of MSM blood donation deferral policy have to date been taking place at the level of PHS agencies and the Department of Health and Human Services. While we are not bringing the policy question to this BPAC as a decisional topic, we felt that it was important to brief the committee on the deliberations of the Advisory Committee for Blood and Tissue Safety and Availability at their November 13th meeting. The Blood and -- Advisory Committee for Blood and Tissue Safety and Availability at that meeting discussed largely the results of studies that they had recommended at their June 2010 meeting.

Following the overview of the ACBTSA meeting, I will present some of the considerations related to a general blood safety monitoring system based on donor markers of transfusion-transmissible infection and risk factors that will be stood up by FDA in collaboration with the National Heart, Lung, and Blood Institute. This will then lead us into a discussion of markers useful for incidence monitoring in donors, and HIV recency testing, which is a scientific discussion and a formal question for the committee.

Following this presentation, Dr. Jim Berger will present the actual recommendations that came out of the November 2014 ACBTSA meeting. Following that talk, Dr. Simone Glynn from the National Heart, Lung, and Blood Institute will present the U.S. Donor Marker and Risk Factor Monitoring Program: Building on the

REDS-II Transfusion-Transmitted Retrovirus and Hepatitis Virus Rates and Risk Factors Study; and she'll be presenting this from a perspective of the design and foundation that we could leverage to monitor a subsequent, longer term monitoring program.

Following this will be several talks on serological tests, which can help predict recency in HIV-infected individuals. The first talk will be by Dr. Don Brambilla of Research Triangle Institute International, who also has been a -- principle investigator for the REDS Data Center. His talk will be entitled "Estimation of HIV Incidence in Blood Donors." And following Don will be Dr. Michele Owen from the Centers for Disease Control and Prevention, discussing assays to determine recent HIV infection.

The program following that will include questions for speakers, the open public hearing, a period for lunch, and then the question for the committee and open committee discussion. So the actual questions for the BPAC is -- please comment whether serological tests for recency of HIV infection and HIV antibody-positive donors are sufficiently accurate to be useful for blood safety monitoring.

So at this point, I'm going to go ahead and discuss some of the key observations from the November 13th ACBTSA meeting. And then, from there, go into a discussion of some of the core

design issues related to a future transfusion-transmissible infections monitoring system. The meeting was held November 13th, and if you look at the link up at the top, this is a link to the actual webcast for the meeting. There should also, if not already, shortly be a transcript available for the meeting. Necessarily, my presentation will be high points, so for details of the data and the discussions of the committee, I would refer you to either the webcast or the transcript.

One of the presentations at the meeting was by Dr. Harvey Alter from NIH representing the HHS BOTS Safety Working Group on the MSM deferral. This safety working group was put together by the Assistant Secretary for Health following the June 2010 meeting of the advisory committee with the charge of reviewing and acting on the recommendations from that advisory committee, particularly in terms of conceptualizing and implementing studies to produce additional research data which would help inform a policy decision. That group put together and helped coordinate three major research studies which were described at the HHS meeting, will also be described in summary today. It also considered a pilot operational study, various policy options, and design of a monitoring program.

The first presentation will be some key points from the talk that I gave at that meeting on the origin, evolution, and effectiveness of MSM donor deferral policy. Clearly, a large

consideration in this whole discussion is the effectiveness and value of donor history screening to present a layer of protection for donors who present to donate blood before the testing occurs.

I think this is a classic slide that Dr. Michael Bush first developed representing the risk of HIV transmission by blood transfusions in the San Francisco area before the implementation of HIV-1 screening. And you can see the progression of estimated risk of HIV per unit, which grew from 1978, '79, and peaked in 1982. The first AIDS case reports were in June 1981. And at the peak -- coincided with the first -- recognition of the first transfusion AIDS case, which was an infant in San Francisco. Upon recognition of that case, blood center staff in San Francisco began to interface with the gay community in San Francisco, encouraged them to refrain from blood donation until it was fully understood just what was going on in terms of AIDS transmission.

And you can see from the curve, the major part of the curve began to come down, and when HIV was discovered and anti-HIV screening finally implemented in April 1985, there was a 90 percent risk reduction due to donor history screening. If you see the fine line going up, that's a projection of how that curve would have tracked in the absence of history screening. So clearly, when there's a known risk to the blood supply and an

absence of testing, donor screening can make a huge difference.

Of course, simultaneously with some of these activities, there was a regulatory response. And from 1983 to 1990, FDA issued recommendations regarding MSM screening, which started as exclusion of sexually-active homosexual or bisexual men with multiple partners; then evolved to men who had sex with another male since 1977 even one time; and to, finally, men who have had sex with another man even one time since 1977.

And in this evolution, I think, there are some important concepts. There was a change from, you know, a membership in a particular subgroup of individuals to an actual behavior, which constitutes the current question. There was a change in, you know, multiple partners to contact with a single male, and then even one time since 1977. So a progression of recommendations, but that has been stable until the current time reflected in a 1992 guidance. The current question on the standard donor questionnaire is from 1997 to the present. "Have you," for male donors, "had sexual contact with another male even once?"

Of course, in parallel, there were really some amazing advances in HIV testing following discovery and growth of the virus. In 1984 was AIDS virus discovery, and virus and antibody detection was detected in both hemophiliacs and blood recipients; and it began the development of blood donor screening tests, which were then approved for use in 1985,

implemented in blood banks about one year following HIV discovery, and were useful for detecting antibody with a pre-seroconversion window period. That is a period of antibody negativity when a donor could be potentially infective to a recipient. That period was 42 days.

Tests were improved from the late 1980s to the mid '90s, resulting in a reduced pre-seroconversion window period of about 22 days. And then from 1996 to 1999, p24 testing was added, which reduced the window period to 16 days. And then, finally, in 1999, which reflects current practice, nucleic acid detection technology was added in mini-pools, which reduces the current seronegative window period to about 10 days. It's important to recognize that that is current practice, and there is a -- currently a 10 day window period from exposure and being infected with the virus to being detected when someone donates blood.

Shown here are actual observed cases, numbers of cases of transfusion-transmitted HIV from contaminated blood products. This was published by the CDC and MMWR showing data from 1985 to 2008. This was actually simultaneously with the reporting of the last case that occurred in 2008. There been a total of 48 cases: 30 going back to the early 1985 to 1997 days, and then a distribution after that, and then really no cases from 2003 up to the one case in 2008. So cases are still recognized, but

clearly at a lower frequency.

However, I think it's important to recognize that there are some limitations to surveillance for transfusion-transmitted cases. The current estimate is one post-transfusion case of HIV exposure for 1.86 million donations. Based on 2011 data, there are 20.9 million transfused components per year. So doing the math, you would expect about 11 post-transfusion HIV exposures per year, but because it's felt that probably only about 90 percent of exposures result in infections, one might expect to see roughly 10 infections.

However, from the observations, clearly that's -- that figure is much lower for actual observed cases. There could be a lot of reasons for that. There is no -- currently no active blood recipient surveillance in place in the U.S. And there are significant barriers to recognizing cases and fully characterize them, including lack of testing of someone who is transfused because someone may well left the hospital after transfusion, and other barriers to characterizing cases. So the actual observed cases is much lower, but potentially for reasons.

Moving to a few slides talking about donor history screening and what is known about it. It's known that it's important to have donor history screening be very accurate for several reasons. One is to maximize blood safety, both for known agents that have a laboratory screen because of the potential

for window period testing errors or quarantine release errors, but also for agents for which there is known to be infection potential, but no test available. So unknown threats with no laboratory screen, donor history screening may be the only protection. Of course, there are some screens in place right now related to travel that reflect the level of protection that is in place in blood centers for some known agents.

It's also important to minimize donor loss due to inappropriate deferral. Like a test kit, if you have a non-specific question, you can lose perfectly safe donors due to the non-specificity of the screening method. It's also important to minimize negative operational impact, and that could be reflected in post-donation information, which can result in a potential recall of a unit. Minimize staff exposure to infectious donations and minimize blood center quarantine hold of infectious donations.

But there are unsolved issues related to donor history screening performance. One particular to this topic is the ability of donor history screening alone to distinguish at-risk versus low-risk sexual behavior among donors with adequate sensitivity and specificity for use in a blood center. And an example would be identifying at-risk heterosexual behavior versus low-risk subsets of MSM behavior. Still work to be done to identify appropriate questioning and history strategies that

could accurately identify such subsets.

A second unsolved issue is to understand and reduce noncompliance with the donor history; that is, the failure of a donor to appropriately self-defer. That's reported with a range of 0.7 to 2.6 percent of males being ineligible for donation, but still appearing for blood donation. And it's estimated through extrapolation that if the deferral period for MSM was changed to one year, there would still be potentially 1 percent of male donors giving blood in the U.S. who had had sexual contact within one year. So the goal for this, and it's really a behavioral challenge to solve, is -- if there were 100 percent MSM compliance with time-based deferral, there'd be 100 percent safety from MSM HIV-risk. Is that feasible to obtain? Can this compliance rate be diminished? Non-compliance rate.

There's been a lot of work on the donor history questionnaire. I'll just go through this quickly. The early donor questionnaire goes back to about 1953, largely based on hepatitis questions, was not validated for many years, but was added to periodically as new concerns became known. In the early 1990s, FDA sponsored contracts with the American Institutes for Research, which started looking at, you know, what language were used and would be most effective for questions and use of computer-based systems. The AABB Donor History Questionnaire Task Force was formed in 2000, and it still works hard to the

present time to keep this questionnaire streamlined and keep the questions as relevant as possible. And there have been two cognitive assessments there to study. In year 2000, NCHS did a cognitive assessment; and just recently, the National Center for Health Statistics did a further assessment using some newer methodologies.

This cognitive assessment, the latest one was presented at the ACBTSA meeting. And again, the link at the top is for the webcast. It was presented by Drs. Kristen Miller and Stephanie Wilson, entitled, "The Cognitive Interviewing Evaluation of the UDHQ: Results and Next Steps." So this was an assessment based on a new conceptual framework, based on comprehension, data information retrieval, judgment, and response, and that drove the type of interviewing that was done with the donors.

The study involved 166 respondents from five geographic areas. It was a non-random community sample, 63 percent male, 37 percent female, and 36 percent MSM. And the methodology was to have the donor read the educational materials under observation, complete the DHQ as if donating blood, and then there were a series of interviewing questions by trained interviewers which produced qualitative data for the study.

The results were that pretty uniformly that individuals understood that the purpose of the questionnaire was to preserve blood safety. But interestingly, the donor history screening

questionnaire's questions were often not taken at face value. Rather, they were answered based on an overall self-perception of the safety of their individual blood donation. That is, the whole questionnaire was interpreted and answered as "Is my blood safe?"

The presenters introduced possible next steps. One is to shorten the educational materials, because people just don't like to read often, so shortening might help gain individual's attention. Use language to de-emphasize that the questions are screening tools for safe blood. And include "Don't know" as a response option, which could be challenging.

An additional presentation at the meeting was "The Current Epidemiology of HIV Infection in the United States." This was by Dr. Amy Lansky from the CDC. HIV infection in the U.S. includes greater than one million individuals currently living with HIV, and this is based on 2010 data. But there's a particularly high burden of HIV infection among men who've had sex with other men. MSM represent about 4 to 7 percent of the male population, but accounted for 78 percent of the new HIV infections among males in 2010. 19 percent of HIV-positive MSM were undiagnosed, and this was similar to the proportion of undiagnosed heterosexual HIV-positives in 2010.

The percent of undiagnosed prevalent infections was markedly higher in younger-aged donors: 58.3 percent among males

13 to 24, and 25.9 percent among males 25 to 34. This is particularly important because many donors tend to be younger. There is increased HIV transmission potential among these younger donors. Individuals who are unaware of their infection may donate blood, and HIV-positive units in quarantine within the blood center create an unnecessary risk of quarantine release errors and staff exposure.

Additionally, there's concern that there's rising incidence among MSM. While the incidence of new HIV infection in most U.S. population subsets at increased HIV risk is stable or falling each year, the incidence of new HIV infection among MSM has risen 12 percent. There were 26,700 cases in 2008, to 29,800 in 2010. New infection rose 22 percent among MSM age 13 to 24, and rose from 7,200 cases to 8,800 cases from 2008 to 2010.

Another talk at the ACBTSA meeting was by Dr. Simone Glynn, who will also speak today. Simone's topic was the REDS-II transfusion-transmitted retrovirus and hepatitis virus rates and risk factors study with data collected between 2011, to 2013. This study is particularly important because -- as we consider about a monitoring effort moving forward to help fulfill a need for epidemiologic data among blood donors, this serves as a useful model for setting up such a system. This is important because hemovigilance of transfusion recipients in the U.S. is not yet established. It can be done, but it's both difficult and

costly.

Marker rates among blood donors, particularly levels of incidence in donors, can be used to estimate the overall level of blood safety. And as discussed at the 2010 ACBTSA meeting, until 2011, the epidemiology of transmissible infection markers and associated behavioral risk factors was really unknown for the previous 15 years after the earlier study sponsored by the NIH and CDC had been conducted. So quite a gap in data about our own blood system.

The REDS-II Transfusion-Transmitted Retrovirus and Hepatitis Virus Rates and Risk Factors Study produced a standardized collection of donor-confirmed marker rates and risk factors across the five large REDS-II blood collection sites, and represented more than 50 percent of the U.S. blood supply. Marker rates presented within that study, which will also, I think, be shown by Dr. Glynn today, but not discussed in detail. Hepatitis B rates per 10,000 were 0.757 per 10,000. HCD, 2 per 10,000. HIV, 0.282 per 10,000. And there was also a NAT yield rate.

NAT yield rate, by definition, is serological testing where a donor is in the early phase of infection, has developed a circulating virus detectable by nucleic acid technology, but has not yet developed antibody. So NAT yields for hepatitis B are shown; there were 13 HPV, 0.009 per 10,000; HCV, 60 identified,

0.041 per 10,000; and HIV, 14 cases recognized, 0.009 per 10,000. That 14 rate is particularly interesting because there'll be discussions throughout the day of, you know, the power provided by that finding, particularly given the variance that can occur year to year, and how useful it can be for predicting a statistically different change in that rate per year.

Additionally, this study also produced an estimate of MSM risk reported among HIV-positive male donors compared to controls. Among HIV-positive donors, 62 percent reported MSM or sexual contact with an MSM ever; and controls, 2 percent of controls who were uninfected, obviously, produced the same risk factor for a highly significant difference.

The next talk was by Brian Custer from Blood Systems in San Francisco. Also a REDS study, this from the REDS-III study, and these are results of the Recipient Epidemiology and Donor Evaluation Study, Blood Donation Rules Opinion Study, or Blood DROPS. So the goals of Blood DROPS were to determine motivations for non-compliance --

[inaudible commentary]

DR. WILLIAMS: Yeah.

[inaudible commentary]

DR. WILLIAMS: No. It's okay. Also, to gather community opinions about potential MSM deferral policy changes; the

percent of male donors with unreported MSM history since 1977; donor opinions about possible MSM deferral policy changes, which was collected in donors; and the likelihood of compliance with self-deferral under revised eligibility criteria. Blood DROPS was conducted at five REDS-III sites, comprising focus groups, community surveys, and blood donor surveys, and also interviews with recent donors identified as having deferral MSM risk. Really a hard-to-identify population, but there are quite a few identified within the study, so a good set of interviews.

Conclusions are that 88 percent of individuals are aware of the MSM deferral policy from community surveys; 67 percent are clear about who can give blood; 59 percent of the MSM community members reported they would follow a change to a one-year deferral. However, non-compliance with the current MSM policy is evident, and may be increasing compared to earlier time periods. It's hard to say definitively where there's an increase over time because different methodology is used; but the earliest report in 1993 was 0.7 percent, the latest report, 2.6 percent. So there has been an observation of increased noncompliance.

Opinions about changing the policy are mixed, with noncompliant donors much more likely than compliant donors to support a policy change. I mentioned the telephone interviews with donors with MSM deferral risk. Between 30 to 50 percent of noncompliant MSM are likely to remain so, even if the policy is

changed for various reasons, including their own self-determination of risk; the value of the donation to help others outweighs risk concerns; a belief that HIV testing will identify all infected blood; belief that the current MSM deferral policy is not scientifically-based; a donation that is done in protest for various reasons; and a fear that disclosure of MSM is linked to coming out, i.e., a fear of stigma or discrimination that could present disclosure.

Overall conclusions of the study were that the estimated prevalence of HIV among MSM who attempt to donate blood is lower than the HIV prevalence among MSM overall, and lower than has been previously modeled. That's a particular interest which indicates that there is some self-selection for individuals with MSM risk who are appearing for donation. However, MSM who do not comply with the current MSM donation policy still have a much higher risk of being HIV-positive than non-MSM donors.

There was discussion at the meeting about suggested stakeholder outreach. This includes recommendations from Blood DROPS, as well as discussions. There's interest in proactively establishing communication channels with stakeholders and advocacy leaders in the community. Also, listening to consolidated stakeholder concerns, and acknowledge and address their concerns where possible, and offering transparent and compelling scientific rationale for current and future policy

development. And then seek proactive leadership support to help encourage compliance with current policy, given that background of transparent scientific rationale.

An additional talk at the meeting was the Australian experience, or "Data-Driven Policy Changes for the Australian MSM Blood Donor Deferral Experience" presented by Dr. Richard Benjamin from the American Red Cross. The Australian Red Cross deferral experience is potentially relevant for the U.S. Dr. Clive Seed in Australia has published several publications that are relevant. One discusses the implementation of a 12-month deferral for male-to-male sex which occurred in the year 2000. It resulted in comparable numbers of incoming HIV-positive donors for five years pre- and post-policy change, so no difference with the change in policy. However, noncompliance with the deferral policy was determined to be the factor most likely to influence overall risk, rather than the duration of the deferral itself.

There had been discussions between the blood collection community and the regulatory agency seeking a six-month MSM deferral period. This request was reviewed, was not approved so far by the Therapeutic Goods Administration, the regulatory authority for Australia. In part, this was tied to concern about national data in Australia that have shown a 10 percent increase in newly diagnosed cases of HIV in Australia in 2012. This was

the largest increase in 20 years and predominantly occurred among MSM.

To address the issue of donor compliance, Dr. Seed also headed a web-based study to assess compliance and MSM behavior among 100,000 recent successful male donors. And this study found a noncompliance rate of 0.23 percent, with no difference between first-time and repeat donors. This Australian estimate of noncompliance is lower than estimates from other countries, even when corrected for differences in deferral policy.

Without being able to make any attribution, I think it's of interest that the Australian Red Cross, since 1984, has maintained a policy of requiring all blood donors to initial and then sign the blood donor questionnaire form in the presence of a witness. And on that form includes a statement which literally reads, "I declare that I have understood the information on this form and answered the questions in the declaration honestly and to the best of my knowledge. I understand that there are penalties, including fines and imprisonment, for providing false or misleading information." We spoke with Dr. Seed, and evidently, there have been no structured studies of this statement, or how often it's been tested or implemented, but the statement does remain in the current questionnaire.

I'm going to switch gears a little bit now and set the stage for discussion of a donor-based monitoring system. There

have been recommendations for establishment of a transfusion-transmissible infections monitoring system, which has been abbreviated here as TTIMS. This has happened several times, including HHS advisory committee meetings in August 2006, June 2010, December 2013, and November 2014. And then in 2009, HHS, based on the August 2006 recommendations, conducted a pretty comprehensive gap analysis for biovigilance in the U.S.; and that report also recommended establishment of a donor-based monitoring program.

So, as mentioned earlier, FDA, working with the National Heart, Lung, and Blood Institute, will build on the REDS-II transfusion market rates and risk factor studies, leveraging the opportunity -- leveraging the progress that was made by the REDS-II program so as to design and implement a long-term blood safety monitoring effort that will be representative of blood donations in the U.S.

As part of its oversight of regulated products, FDA is committed to collect and analyze infectious disease marker rates in a representative sample, and establish a potential to assess newly emergent or re-emergent transfusion-transmissible infections of concern. This'll include accurate tracking of data to identify meaningful changes over time in donor marker incidence, prevalence, or risk factors, provide signals at predetermined levels when intervention is needed, and provide

ongoing data availability to objectively assess the value of new blood safety initiatives.

Now, clearly there's a model for doing this. And prevalence data in donors is relatively simple to collect, but marker-positive blood is not used, so it's not a particularly sound measure of blood safety. Incident infection, however, is the most important measure to obtain. It relates directly to potential recipient risk related to the window period, but it's also the most difficult parameter to measure due to its very low frequency and variation over time.

There are various methods for assessing incidence in donors. The first, which has been used for some time, is derived from seroconversion of repeat blood donors with a calculated inter-donation interval for overall repeat donors. That method is accurate and effective, but limited to repeat donors and use of sophisticated blood center databases, which can produce the inter-donation interval data. The second method, which you'll hear more about, is observation of confirmed nucleic acid testing activity in the absence of HIV antibodies, this is called NAT yield cases, which reflects the presence of early HIV infection that must have occurred within the past 22 days, the window period for detection of antibodies.

And then, method three, which is -- been in use for some time internationally for predicting population incidence.

Serological tests may be able to demonstrate recent HIV infection as a predictor of incidence for surveillance purposes. Considerable work is going on internationally to characterize the performance of these and additionally modified incidence assays, such as multi-analyte assay combinations. Examples -- experiences with each of these assay types and algorithms have varied in different laboratories. And there are factors, such as the nature of the population testing, the infecting virus strain, the baseline level of HIV pre-prevalence; all are important, including the population tested. These are all important to influencing the results of those tests.

So as a topic for discussion today, in the interest of trying to improve the power related to new infection data in a monitoring system, FDA wishes to obtain the advice of the BPAC on the feasibility of applying currently available HIV recency tests to cross-sectional samples from HIV antibody seropositive blood donors that might be obtained in conjunction with a monitoring effort. So the specific question for the committee is, please comment whether serological tests for recency of HIV infection and HIV antibody-positive donors are sufficiently accurate to be useful for blood safety monitoring.

That's the end of my presentation. So I look forward to the discussion, particularly related to the use of recency testing. But we also, of course, invite your comments on the other data

that were presented and the other issues at hand. So thank you very much. I look forward to a successful meeting.

CHAIRMAN JACKSON: Thank you, Dr. Williams. We do have about five minutes, so maybe we could take some questions. If that's okay, Dr. Williams? Can I just start though by just clarifying about the definition of serological test? Is this -- specifically would include NAT yield tests, or we're just talking about the antibody detuned assay type test?

DR. WILLIAMS: Came across a little muffled to me. You're asking about the definition of a serological test. Is that correct?

CHAIRMAN JACKSON: In terms of the question, is this limited to antibody tests? We're talking about recency tests looking at the level of antibody, or are we also including things like NAT yield tests as part of this?

DR. WILLIAMS: Well, I think we welcome comments on all of them, but I think the think the question was specifically targeted to antibody-based recency tests. But, you know, certainly, we'd welcome comments on a NAT yield, as well. But they all basically derive from some serums, so they're all serological tests.

CHAIRMAN JACKSON: Yes. Other -- Dr. Nelson?

DR. NELSON: Yeah. I -- as I recall, there -- at one point, the blood banks had a procedure wherein if someone did the

questionnaire and answered it, and blood was taken, but, in fact, they didn't want to disclose that they were MSM, or that they were in a risk group, that they could then call back later and say, confidentially, "Don't use my blood." So this would protect someone against disclosing, and a possibly stigmatizing or embarrassing situation. But I just wonder is that still a policy? And then, secondly, are there any data on how often this has happened -- been implemented, either in the U.S. or Australia, or other blood banks?

DR. WILLIAMS: You're referring to a procedure known as confidential unit exclusion, or CUE. This was in place pretty broadly, I would say, probably 15 years ago, where a donor could make a donation, confidentially indicate whether their blood should be used for transfusion, or in many cases, the blood center said for research. I think the observations overall is that you can find association of markers with those donors had used -- who had used the CUE. But in the large, there was also a very high rate of non-specificity, so many donors indicated that their blood should not be used for transfusion or used for research. And it was felt not to provide a great deal of protection overall, although there was some, I think, elevated relative risk associated with markers in the CUE group. It is not currently used, I believe, anywhere in the U.S. right now.

DR. NELSON: The concern is that people -- that a certain

proportion of donors won't answer the questionnaire correctly, and there are a variety of reasons for this. And this is one reason that might be dealt with, and I don't know why it isn't still available.

DR. ALLEN: I don't work with a blood bank, but I believe that many blood centers still do have the option for donors to call back and report any information. I mean, quite apart from HIV, I think it's more often used for malaria-risk from international travel. Donors can call back if they've got information they want to update. Obviously, if you've got an infectious unit, or an infectious donor, or person who's given a unit of blood, you don't want to keep that. You've collected the unit. You've got to then, you know, exclude it, destroy it, or whatever. So it's preferred, obviously, not to have that unit collected. But I believe the option is still there for a donor to call back to a blood center and update the information.

DR. BASAVARAJU: Yeah. I just wanted to clarify something, Allan. You said there's no active blood recipient surveillance in the United States. So, just to clarify for other members of the committee, CDC does operate a recipient hemovigilance system in the United States. I mean, there are limitations with the ability to detect HIV, but it does exist. CDC also has an HIV/AIDS reporting system, so HIV's mandatorily nationally notifiable. It also includes questions on transfusion history;

of course, there are limitations to that, as well. And CDC does follow cohorts of frequently transfused populations, as well, where HIV could potentially be detected, as well.

CHAIRMAN JACKSON: Thank you, Sridhar. Toby?

DR. SIMON: Yes. I'd like to ask a question and try to simplify the issue of the exclusion. Typically, we've had two types of exclusion for risk activity. One has been the "Have you ever" or the permanent exclusion. For example, someone who ever had hepatitis or AIDS, someone who ever injected drugs. And then we have the exclusions for other risk activities, such as if you've had sex with a prostitute, where we have 12 months and we basically trust the test to be adequate with that level of risk. Has the FDA now come to a decision that the MSM belongs with the type of risk of having sex with a prostitute rather than having ever injected drugs?

CHAIRMAN JACKSON: I think part of that may be addressed by our next speaker on some of the recommendations that the ACBTSA just --

DR. WILLIAMS: Yeah --

CHAIRMAN JACKSON: And so maybe we could wait, Toby, on that question.

DR. WILLIAMS: I think that's probably a good idea. I mean, a one-year deferral -- what I can comment, a one-year deferral would clearly harmonize with other sexually-related risk factors

that result in deferral of donors, so it harmonizes with that. IDU is, you know, indefinite deferral. So in terms of timeframe, yes.

CHAIRMAN JACKSON: Okay. Corey. Then we're going to have to move on, I think.

MR. DUBIN: Alan, I want to come in behind CDC. I wonder strongly, because for us, recipient surveillance is really important, and yet, we've been raising it since the late '80s, early '90s, and it's almost like it's under the rug, if you will. It's not something that people seem to want to look at and really deal with. And I wonder if you have anything to say about that.

DR. WILLIAMS: I think, you know, picking up on Sridhar's comment, it's not that it isn't taking place. It's that it's being done in more, you know, select groups and certain studies, rather than a nationally representative program. The issue is the rarity of outcome measures, and it -- you know, it's logistically difficult. You need a -- generally a pre-transfusion sample, a post-transfusion sample, the ability to, you know, obtain the testing via consent, and so forth. So -- and I'm aware that NHLBI ran a recipient monitoring study, I believe it was called the FACTS Study, some years ago -- 10, 15 years ago. And it produced some positive findings, but it was just, you know, a large study which had limited outcome measures

because it is such a rare event, you know, thankfully, but it makes it difficult to study accurately over time.

DR. NELSON: Yeah. I was the P.I. of the FACTS Study. We found two HIV transmissions in 100,000 exposures -- 100,000 units. But this was before NAT testing, so it's much more now I'm sure.

CHAIRMAN JACKSON: Okay. Thank you, Dr. Williams.

RECOMMENDATIONS OF THE NOVEMBER 13, 2014 MEETING
OF THE HHS ACBTSA

CHAIRMAN JACKSON: Our next speaker is Mr. James Berger from the Office of the Assistant Secretary for Health, who will give us a presentation on the recommendations of the November 13th, 2014 meeting of the HHS ACBTSA meeting.

MR. BERGER: Good morning. I'd like to extend my appreciation to Dr. Jackson and the other distinguished members of the BPAC for inviting me this morning to address the committee. This presentation will cover the following three issues. The first issue will be -- I'll address the topics that occurred during the November 13th and 14th Advisory Committee on Blood and Tissue Safety and Availability. The second issue will be to provide the previous steps in the MSM policy discussion. And the last issue will be to give you what the Advisory Committee on Blood and Tissue Safety and Availability provided as far as recommendations.

So the main topics of that meeting were the following four: the MSM blood donor deferral policy; hemoglobin S testing, which I will not be discussing today, but just giving you the topics; the blood system issues in addressing babesia; and the fourth one was the subcommittee report on informed consent. And then following that, there was recommendations that were made on two of the major topics -- was the -- of course, the MSM blood donor

deferral policy, and the last one was on the hemoglobin S testing.

This slide presents -- provides the previous steps in -- where we started out in 1983 and where we are today. It started out with -- in 1983 with the deferral that the FDA established for sexually-active homosexual or bisexual men with multiple partners. That was further refined in 1984 with the deferral policy of MSM contact even once since 1979. And then in 1985, that 1979 was changed to deferral of even one MSM contact since 1977.

In 1992, the FDA provided the current guidance on deferrals for the increased risks of HIV. In 2010, the Advisory Committee on Blood and Tissue Safety and Availability voted nine to six that the policy would remain the same. They, however, called it suboptimal, and they felt that additional studies that would lead to informed scientific decision making need to be done before any changes. And then, along with that, the -- with the recommendations from that advisory committee, HHS put together an operational assessment in three studies.

The first issue that was put together for the operational assessment was a Quarantine Release Error. This is the operational assessment that addressed why do blood product release errors occur. The first major study was the Uniform Donor History Questionnaire; and that study was based on -- do

donors understand and interpret the questions that they're asked when they donate blood? The second major study was the Retrovirus Epidemiology Donor Study II, also known as the REDS-II Study, for transfusion-transmitted viral infection, marker prevalence, and risk factor study. This study addressed the issue, what are the current rates of major transfusion-transmitted infections? And then the last major study that was completed was the REDS-III, which is the Recipient Epidemiology and Donor Evaluation Study, Blood Donation Rules Opinion Study, also referred to as Blood DROPS, and basically, this study summarized what are MSM attitudes towards blood donation.

And then, last month, in 2014, the ACBTSA recommends a change in the MSM blood donor policy to one year. The questions that were provided to the committee to address -- was the first one, "Do the completed HHS MSM blood donor deferral studies, along with other additional studies and data, provide the Advisory Committee for Blood and Tissue Safety and Availability with sufficient information to support a change from the current MSM deferral policy; that is, deferral for MSM even once since 1977, to an alternative policy that would permit blood donations by some MSM?" The committee voted 16 in favor, and two against.

The second question that was addressed to this committee was, "After hearing the MSM study results, if the committee determines that a policy change is supported by the evidence,

what deferral timeframes does the committee recommend for change to the MSM blood donor deferral policy recommendations?" The committee voted for a one-year deferral, and that vote was 16 in favor and two against.

And then, the third question was, "Based on the donor history questionnaire study performed by CDC's National Center for Health Statistics and the data from the REDS-III Blood DROPS Study, what approaches does the ACBTSA recommend for exploration of potential enhancements to the donor history questionnaire format and associated public health education and outreach to blood donors and public stakeholders?"

With that information, the committee made the following recommendations to go forward to the secretary in regards to the recommended change in the MSM policy. The first was to -- implementation of the recommendations made during the December 2013 Advisory Committee for Blood and Tissue Safety and Availability meeting, especially those regarding surveillance of transmissible diseases. The next one was to develop and implement a coordinated communication plan regarding a change in MSM deferral policy focused on all relevant stakeholders. In addition, the advisory committee recommends for all donations that the secretary, one, undertake studies to evaluate the effectiveness of the administration of the donor history questionnaire; two, take steps to improve transparent

communication to recipients of the relative risks and benefits of blood, organs, cells, and tissues; three, evaluate and revise the donor education material in order to improve its uptake, comprehension, and utility to promote accurate disclosures of risk; and four, improve the sensitivity and specificity of the donor selection criteria to identify donors at increased risk of transmissible diseases.

That concludes the presentation. Open to any questions.

CHAIRMAN JACKSON: Yeah, we have a couple minutes. Dr. Stowell?

DR. STOWELL: Could you clarify how the question two was posed? Was -- were they given a choice between, say, five-year, one-year, six-month deferral? Or was it one-year deferral versus no change?

MR. BERGER: There was background given on what studies had looked at as far as possibilities, and the committee decided to go with the one-year deferral. They certainly had the option to explore other recommendations.

CHAIRMAN JACKSON: Mr. Skinner.

MR. SKINNER: Hi. Thank you. Mark Skinner. The secretary received recommendations from ACBTSA, December 2013, and again just a couple weeks ago, particularly regarding hemovigilance. Other than the secretary's acknowledgment of receipt of the December recommendation, I haven't seen a substantive response

in terms of her plans for implementation of the hemovigilance program. We've heard inklings today of what the FDA might do in conjunction with NHLBI, but does the secretary have a formal position, or does she have a formal response from the December recommendation, which was renewed this past November?

MR. BERGER: The secretary has been briefed on the recommendations and is deliberating those recommendations at this time. She's not made a decision.

CHAIRMAN JACKSON: Okay. Thank you.

U.S. DONOR MARKER AND RISK FACTOR MONITORING PROGRAM: BUILDING
ON THE REDS-II TRANSFUSION-TRANSMITTED RETROVIRUS AND HEPATITIS
VIRUS RATES AND RISK FACTORS STUDY

CHAIRMAN JACKSON: Our next speaker will be Simone Glynn. Dr. Glynn will be talking on donor marker and risk factor monitoring program from the REDS-II Transfusion-Transmitted Retrovirus and Hepatitis Virus Rates and Risk Factor Study. Dr. Glynn?

DR. GLYNN: So, good morning. It's a pleasure to be here, and I'm going to talk to you about U.S. donor marker and risk factor monitoring program as it relates to transfusion-transmissible infections. I'm going to call those TTIs. And also, talk to you about potentially building on the study design that was done for the REDS-II Transfusion-Transmitted Retrovirus and Hepatitis Virus Rates and Risk Factor Study.

So first, the question is why do we need the monitoring system? Because a monitoring system would allow us to evaluate and monitor data related to transfusion-transmissible infection rates, and that can help us ensure a safe blood supply for transfusion recipients. So it really is to be considered a public health tool, if we can have a comprehensive system. And the fact that comprehensive monitoring systems can be very useful has been demonstrated by other countries that do have such systems in place, such as Australia or Canada.

So first of all, it's quite a complex system that we want to evaluate. So we start with a potential blood donor who may decide to self-defer; then if the person decides to donate, they have to be screened through a donor history questionnaire. Both of these layers of protection, the self-deferral and the donor history questionnaire, are known to be very effective, at least 90 to 95 percent effective. And we know that from looking at the prevalence in first-time donors as compared to the prevalence in the general population. Once the donor has provided a donation, that donation is screened by very sensitive assays so that the risk of having a donation with a potentially infectious component in it released into a blood supply is quite small. That risk is called a residual risk, and as Dr. Williams said before, it's of the order of about 1 in 1.5 to 2 million for HIV and HCV.

Then, of course, if you have a donation that has an infectious component in it, that doesn't mean that it's going to cause a transfusion-transmission in the recipient. You first need to have a component that also has enough of that infectious agent in it to be able to cause an infection. The component needs to be transfused, and then the recipient needs to be susceptible to actually get the infection.

So when we think about monitoring the transfusion-transmissible infections, we can essentially look at it from two

angles. We can look at it from the recipient side of things, and we can look at it from the donor donation side of things, and both are important. So what I'm going to try to do in this presentation is give you a little bit of background about what kind of monitoring components we have in place already, both on the recipient side and on the donor/donation side of things. And then, after that, we'll go through potential options to how we could improve this system.

So if we first think about the recipient side of things, if we had 100 percent comprehensive transfusion recipient monitoring system for TTI, so if we were able to have active surveillance of 100 percent of the hospitals in the U.S., we could use that to investigate and evaluate if transfusion transmission occurred; and we could accurately measure the number of recipients with a transfusion-transmitted infection, and therefore, blood supply safety vis-a-vis transmission-transmitted infections.

If we then look at the donor/donation side of things, monitoring of risk factors and the TTI marker risk among donors and donations can be used to evaluate the effectiveness of a donor screening process. And again, that has been done in other countries that do have a system in place. Evaluator change in the donor screening process and also estimate the residual risk, or the risk of releasing a potentially infectious donation into

the blood supply, and that serves as a surrogate measure to assess blood supply safety.

So what is the current status in the -- both the recipient and blood donor/donation sides? Overall, there are no single comprehensive donor/donation or recipient transfusion surveillance systems which include all facilities and population in the U.S. And the current data collection efforts that we have are often not coordinated nor complete.

On the recipient side, and these -- this information for the recipient surveillance components that we have in place comes thanks to Dr. Basavaraju and Dr. Kuehnert, who are here today. So in terms of the transfusion recipient surveillance monitoring system that we have in place, we have reporting of transfusion-transmitted infections that is done through either public health reporting of nationally notifiable infection systems. And I'll talk to you about the HIV and the HCV/HBV components that are in place, and then I'll also mention the National Healthcare Safety Network, NHSN, Hemovigilance Module.

So in terms of public health reporting for HIV, we have an electronic reporting system that is set up in all states and jurisdictions in the U.S., whereby new HIV diagnoses that are reported by clinicians or clinical labs to the state or local public health departments are then entered into that system. And that -- when you enter that, there is a form, and you can

complete a question on whether a transfusion occurred since 1985; but this is not required so it's often left blank. The other issue with the system right now is that if you provide another risk factor, the infection will be attributed to that risk factor first, rather than to transfusion. So the likelihood of recognizing that an HIV infection is attributable to transfusion in the current system is small.

For HBV and HCV, there are two types of reporting in the U.S. There is a passive reporting surveillance system by state and local health departments; so new cases are reported by clinicians or the clinical lab to the health department. And the health department may decide to investigate further; they don't have to, and it really is based primarily on funding limitations. There is also an enhanced surveillance system at seven sites, which is really very thorough, I think, funded by CDC. And in this case, the cases would be, you know, investigated quite thoroughly. The enhanced surveillance site, however, it's only seven of them, and they may change every three to five years, depending on funding. Okay.

Finally, in terms of the last piece for the transfusion recipient surveillance system that we have in place, we have a National Healthcare Safety Net for Hemovigilance Module, which was launched by CDC in 2010 with important support from ABB. And it's put in place to capture data on transfusion-associated

adverse events in the hospital settings. So participating hospitals report on those adverse transfusion reactions if they are recognized, and they would include viral bloodborne pathogen, again, if they are recognized. The limitation included is that currently, only 5 percent of the transfusions are under surveillance, and underreporting, especially for viral bloodborne pathogens, are unlikely to actually be recognized and identified in the hospital setting. It's more likely that they would be recognized later.

All right, so then going on to the blood donor and blood supply side of things. Although not all blood collection organizations compile a donor/donation database with sufficient information to evaluate marker rates and characterize their demographic, geographical, and temporal trends, some organizations actually do have those systems in place. However, none of the existing databases that we have include information on more than 50 percent of the U.S. blood donors and their donations. And we know that each blood collection organization is unique with respect to its geography and other donor factors.

We also know that there are data quality limitations that are inherent to many data collection efforts, but that is true for both the recipient and the blood donor side. The existing databases that we have do not automatically talk to one another. The other two components that we have, we have an evaluation of

risk factor data on TTI marker-positive donors that is done at the time of notification, but it's not elicited and compiled in a consistent manner or in any kind of database. Also, we do have a big effort concerning look-back investigations for HIV and HCV; but again, those data are not collected and compiled in a consistent manner by the organizations.

So as we think about what we have and where we could go, what kind of steps can we take to try to enhance the monitoring system that we have in place? And the proposal in front of you is that we should first concentrate on the donor and donation monitoring system, trying to get a more comprehensive system there, because it's easier to implement logistically and cost-wise. We know that it would provide sufficient monitoring capabilities to evaluate if a new donor screening approach could have a major impact on infectious marker risks and for risk factors of the TTI marker-positive donors. And we can also hopefully use what we've learned from the NHLBI REDS-II TTI rate and risk factor study to assess the feasibility of obtaining data on more than 50 percent of a blood supply, and also assess for risk factors consistently among the TTI-positive donors.

So what was the REDS-II study? This was a collaboration between American Red Cross, Blood Systems, and New York Blood Center to achieve broadly representative coverage of a little bit more than 50 percent of the blood supply. And this study had

two components; it had a rate component and a risk factor component. And for the risk factor component, OneBlood in Florida also participated in this effort. The aims of the study was to provide contemporary baseline TTVI marker rate and risk factor data, and also to hopefully serve as a model for a future ongoing more comprehensive blood donor monitoring effort for donor transfusion-transmissible infections and associated risk factors, if we found that it was feasible. It takes a village to do this kind of study, and I want to thank all of the participants. And this particular study was led by Dr. Custer at Blood Systems.

So as I mentioned, there are two components to that study, so I'll start with the TTVI rate study component. Again, participating were the Red Cross Blood System and New York Blood Center. The goals of that particular component was to assess the feasibility of designing and implementing a multi-center donor and donation database capable of being used for infectious disease surveillance, including the ability to define positives for the numerator and total number of relevant donations for the denominator. We also wanted to accurately characterize and define testing algorithms from each center for HIV, HCV, HBV and HTLV, so these were the four infections we looked at. We want to implement a secure and encrypted method for data delivery; set up quality control programs for triage review and reporting back

to regions on any issues related to data submissions and our data; and finally, actually see if this worked by estimating marker rates for 2011 and 2012 across the three participating organizations for the first time.

So the database construction process was very long and arduous process, and I want to specifically thank Anne Noterry [spelled phonetically] and Diane Nelson for their work on this database. We first needed to define virus testing algorithms for the testing services, so there is one for Red Cross and one for Blood System and New York Blood Center, which is CTS. We needed to develop algorithm-based consensus data dictionaries defining fields, variables, and formats; establish file-naming conventions and set up secure file transfer mechanisms; write extraction programs; extract center data transfer files; review data for format errors, blanks, mismatches, illogical results, interpretation errors. We then resolve those issues at the centers by asking them to provide additional data and doing some code updates in terms of a program. And then repeat all of that until you have clean data files that then you can put together and analyze.

So I don't want to bore you with all these details, but this is just to demonstrate that this is actually quite an important effort, and if we can build on it, I think it might be quite useful. As I mentioned, you needed to come up with

definition categories for what you defined as a positive HIV, HCV, HBV, and HTLV donation. And we had two definitions for this particular study, one related to NAT yield positive and another one that was defined as seropositive and NAT positive.

So I'm going to show you some tables with some data, but I'm not going to go into depth into any of them. I presented those last month at the advisory committee. But this is just to demonstrate to you that we could actually get those rates and that they actually made sense, as well. So for the total positive rate, as Dr. Williams said before, for the highest rate was for HCV, then followed by HBV, and then the two retroviruses were a little bit lower. The NAT positive yield rate, I'll just mention, that as you can see for HCV was the highest with 60 cases two years, and for HIV, we had 14, and HBV, 13 in two years. So these numbers are small.

This is to demonstrate that we can calculate those rates by demographics. We can calculate them by gender, and, as illustrated here, by age. We can calculate those rates by geographical region. For HIV, you can see that the highest rate for -- in the southeast. We can look at temporal trends in these rates; and we can look at temporal trends in the numbers, actually, so looking at the NAT yield numbers, look at those.

Now going onto the risk factor interview study component of that study. This was actually a case control study where we

identified between 200 to 300 cases for each of the infection we looked at. These were defined as donors who had passed the donor history questionnaire, so they answered negatively to all the questions, but then they were found to be reactive on the screening test, and then they confirmed positive. The controls, we had about 1,600 of them, were negative. Participants: Red Cross, New York Blood Center, Blood System, and OneBlood. And the major thing to note on this particular component is that we're able to administer a common risk factor questionnaire to donors by donor counselors at each organization between July 2011 and April 2014; and most of those we were able to do by phone, usually about a couple of weeks after notification.

So the risk factor interview domains are here. We had the sections -- questions, if you want, on expanded donor demographics, like questions on education, income, that kind of thing. We had questions on motivations and reasons for donating, such as test seeking, response to donation appeals; and then we had questions on the potential risk factors for infection: sexual history and behaviors, drug use, sexual partner risks, medical exposures, and other factors.

So I'm just, again, going to show you just some representative results for HIV. We found that the cases were more likely than controls to be younger, male, first-time donor, foreign-born, non-Caucasian, single, have a lower education

level, and have a lower income. For males, looking at behavioral risk factors for HIV, we found that they were two major risk factors. 62 percent of the HIV-positive males reported MSM, or sex with an MSM, as compared to 2 percent of the controls. And the other major one was having sex with an HIV-positive partner. That was reported by 26 percent of the HIV-positive males, as compared to 0 percent of the controls. So when we look at the odds ratio adjusted for a variety of factors, those two factors are the major ones that come up.

So, in conclusion, for each major viral infection, the primary behavioral risk factors were consistent with the known epidemiology for each infection and validate the current deferral criteria we use for blood donors. And also, they are donors who, as we've seen, are not disclosing a range of deferrable risk behaviors, and, in particular, sex with an HIV-positive partner and a history of MSM remain the two leading independent risk factors for HIV, as was originally observed back in the 1990s in CDC-funded studies. And we also know that, of course, non-disclosure has the potential to place recipients at risk.

For the database piece of things, although requiring significant effort to design, set up, and implement, a common database approach across the main blood center organization was developed successfully. And we were able to evaluate marker

rates for more than 50 percent of the blood supply for the first time by demographics, by region, and temporally. And we therefore believe that this effort demonstrates the feasibility of a coordinated representative donor surveillance efforts for TTVI markers and risk factors, and that -- the study provides a current baseline for marker rates and associated risk factors.

So finally, a word about the possible infrastructure that we could use, based again on the REDS-II study for a donor and donation monitoring system, what Dr. Williams referred to as TTIMS. So we would have data provided by the blood center organizations, the ones that have comprehensive databases for their organization being provided, and we would need two components. We need a donation database component and a TTVI marker-positive donor component. If we look at the donation database one, we would need to consolidate donation demographic and marker data cross the participating centers. It's very important to use consistent definitions across centers using the information that is available. And then, of course, you need to manage the data and conduct the analysis. And we hope from that exercise we would be able to get marker prevalence and incidence for known TTIs, again, in at least 50 percent or more of the blood supply to get as much comprehensive coverage as we can.

Then, for the TTVI marker-positive donor component, we think it would be important to evaluate the risk factors for all

the HIV-positive donors, and for the incident HBV- and HCV-positive donors, and follow that. It probably would be important to get some follow-up testing, and it would be nice to have biospecimens being collected to allow for further research. There's a question about whether it would be important to get recency testing of HIV antibody-positive donations to evaluate whether some of these are recently-acquired infections, and you're going to hear about that in the next couple of presentations.

And finally, research-wise, we think it would be really important to sequence HIV and the incident HCV and HBV infections, do some drug resistance for HIV, as well, to understand the evolving molecular epidemiology of these viruses in the donor population, and then help optimize donor screening assays. And then, the idea is that both of those components would be overseen by a steering and monitoring committee with representatives from both government and participating blood collection centers organization. The nature and the frequency of the data reports would be established by this committee, as well as the signals and the thresholds that would trigger further investigations. These reports would be -- and results of investigations would be reviewed by the committee, and, of course, the information that needs to go to the relevant federal agencies would be provided. Is of the French Alps. Very nice.

CHAIRMAN JACKSON: Okay. Thank you very much, Dr. Glynn. Maybe we have time for one question or two before we take the break. Are there questions on this? Toby?

DR. SIMON: What's the funding status of what you presented?

DR. GLYNN: I'm sorry?

DR. SIMON: The funding status?

DR. GLYNN: The founding --

CHAIRMAN JACKSON: Funding.

DR. GLYNN: Oh, the funding status. This is under evaluation.

[laughter]

CHAIRMAN JACKSON: Corey Dubin.

MR. DUBIN: [inaudible] --

CHAIRMAN JACKSON: Right --

DR. SIMON: I'm sorry, and -- maybe a definitional question. You've used words like "comprehensive", "national", "complete." But in terms of the donor surveillance program, we're talking about a representative sample, and so your definition of "comprehensive" or "national" really is something greater than 50 percent, but not national the way I think of it in terms of 100 percent or all blood donors.

DR. GLYNN: Right. I think the hope would be that you start -- so right now, we have a very disjointed, I think, piecemeal kind of system. So the idea is at least to start building a

system, starting maybe with 55 percent, and then gradually build this higher so that we gradually, you know, include as much data as we can. But we need to start somewhere, so that's the idea.

CHAIRMAN JACKSON: Dr. Epstein.

[inaudible commentary]

CHAIRMAN JACKSON: Yes, one more. Susan Leitman.

DR. LEITMAN: Data -- is this on? Oh. Data that covers 51 percent of the blood supply in the U.S. is pretty good, actually, and likely to be highly representative. So I just -- I'm not quite sure I understand why you need -- you'll never get 100 percent. But if you approach 90 percent, how is that better than 51 percent, if 51 percent covers all the regions, high-risk regions, low-risk regions? It's an extremely rare event. Is that why? Transmission? So you might miss it if you cover 51 percent?

DR. GLYNN: No. I think the idea would be to definitively, as you say, get at least 55 percent. And then, after that, the way to look at things, I think, is to look where the participating organizations are located, and then see what pieces of the U.S. you might be missing, and then try to get representation from these states where you might not have as much representation from the participating organization. Now, if we find that the 55 percent that we have cover the entire U.S., then I agree with you. There is no reason to think that we -- you know, we're missing something. But we need to check that --

that representation.

CHAIRMAN JACKSON: Okay. We're going to take a 15 minute break, and come back in 15 minutes, and we'll have a couple more presentations. Thank you.

STRATEGIES TO MONITOR HIV INCIDENCE AND RECENCY
IN BLOOD DISORDERS

CHAIRMAN JACKSON: Could people, please, take their seats and we'll get started. Our next speakers will be Dr. Don Brambilla from Research Triangle Institute International and Dr. Michele Owen from the CDC who will be talking about strategies to monitor HIV incidence and recency in blood donors. So, Dr. Brambilla, feel free to start.

DR. BRAMBILLA: Thanks Brooks, and thanks for inviting me to speak today. It's -- I am actually the -- I'm here, I think, because I am a statistician and the P.I. for the REDS-III Coordinating Center, which is now housed at RTI. How are we advancing? Ah, there we go. Okay.

What I want to do is speak about incidence estimation -- I want to speak about incidence estimation in general first, and then, how it applies to blood donors -- the special challenges that we face with that. Common approach to estimation is really quite straightforward. Just follow a cohort, which is -- often you follow them for a defined period of time -- sorry about the typo -- exclude prevalent cases, and then record new infections during the follow-up interval. And the incidence calculation is simply the number of cases divided by the total follow-up time, often expressed as something like cases per 100,000 patient years or person years. The denominator is -- if a person goes

all the way through the follow-up period with no disease, then it's the total follow-up within the interval for that person. It may be to a censoring point, person drops out of the study, but it's that person's total follow-up time. For cases, it's beginning of follow-up for that person to the point of infection. Very simple.

Now, that equation, cases over total follow-up time, is actually the equation for estimating the parameter of an exponential distribution, if one of two things is true: either you know the event times for all subjects or the event times are known for some and all others are uninfected at the end of the study, so -- right -- censored. Then we say that "I" is an estimate of the parameter theta. And that's -- I think, the last equation that's in here. I was told to take the equations out by my reviewers for the talk.

[laughter]

DR. BRAMBILLA: It's the trouble with a statistician getting a -- you know, I'm a statistician, everybody else who was advising me on this talk is not, so I was told to take the equations out. But, theta -- whoops, wrong button. So theta is the parameter of the exponential distributions, just the base of natural logarithms. "T", time. So it's -- this is just the equation for the probability that the infection has happened by time, "T". And, as I said, "I" are incidence estimate -- is an

estimate of the parameter θ , so for the exponential.

Now, this has some consequences for what we do. First thing it tells us, is that over the follow-up interval for which we are estimating incidence we are assuming that the risk of the event is constant. Risk actually has more than one definition, so let's get more specific here. The first thing is that the incidence parameter doesn't change over time. We are also, basically, tacitly assuming that the population is homogenous with respect to the risk of disease. And one consequence of this assumption that things are constant is that the conditional probability of disease in an interval, among those with no disease at the start of the interval, depends on the length of the interval, but does not depend on when the interval starts.

So to illustrate that, consider a two-year study and consider the probability of disease in Year 2 among those who get all the way through Year 1 without disease. Well, then the conditional probability of disease in Year 2 is the same as the probability of disease was in Year 1 for all subjects. That's one consequence of the constant risk.

Now, these are the assumptions we make. In fact, risk does -- risk of disease does vary among individuals, which violates the assumption of homogeneity, and risk of disease often varies over time. So what this really means is that incidence, these two together, really mean that incidence -- this approach to

estimating incidence works best if we do it over short time intervals; over short time interval, then the assumptions hold approximately and we're fine.

So studies of incidence in blood donors, if you look at published studies, they usually talk about incidence over one year or two years. There's one large study, which I'll quote later, where -- like, I think it's about a ten-year interval, was actually broken up into two-year subintervals with a separate incidence estimate in each of the two-year intervals -- is the approach to getting around these departures from our assumptions.

Now, there's some good news here. The standard error for incidence is very easy to calculate. It's just the incidence estimate divided by the square root of the number of cases. The not so good news for rare disease is the number of cases is usually small. That's the problem we've been talking about all morning. And that means that standard error can be relatively large, leading to wide confidence intervals and limited power to detect changes and differences.

To illustrate that, suppose we have an estimated incidence of 100 cases per 100,000 person years, and we follow the subjects in a study for one year. Here, I've said -- looked at three different studies: one of 10,000 subjects, one 100,000, and one of a million subjects, and then just -- with the same

incidence rate we're going from -- whoops, I did it again. Ten cases to 100 cases to 1,000 cases, all to get us an incidence rate of about 100 per 100,000 person years; and you can see how the standard error drops as the number of cases goes up. We're holding the incidence rate constant. And the confidence limits - - here we've got 100 plus or minus 62; now we're down to 100 plus or minus about 20; and now down to 100 plus or minus 6.3 by the time we're up to a million subjects. So that's one of the problems that we face, is that we need a large number of persons followed to generate enough cases to have reasonably narrow confidence limits around an estimate.

Here are some estimates for HIV from the literature. The first two are from a paper by Shimian Zou. It was in transmission in 2010, these are data from the American Red Cross. And there actually are, I think, five intervals in the paper that -- incidence estimates for five intervals. I just picked two to illustrate the situation here. And we had was 1.56 for 100,000 person years, and there's the confidence limits. Next to it, then, 2.16 per -- in the 2007-2008 period per 100,000 patient years. The first one is based on 67 cases, the second on 92 cases. And the first one is 67 cases in 4.3 million person years of follow-up. Now that's 4.3 million person years in a two-year span, so we're talking about in excess of 2 million people followed, which is what was required to get these

confidence limits that Shimian's got here.

Steve Kleinman and his colleagues, going back to a paper from the early '90s -- you have an estimate of 4 per 100,000 patient years and wider confidence limits because this is based on only 33 subjects -- 33 cases in 800,000 person years of follow-up. And so there's the large cohort is needed to generate reasonable confidence limits, that's the message.

I said the statistical power may be limited and what I wanted -- to illustrate that by showing -- consider a two-year study to compare a disease incidence in two groups. And let's just assume that in the -- what we'll call the reference group, that the incidence rate is 10 per 100,000 person years. The sample size required to get 80 percent power to look at -- again -- just starting at the top, a 50 percent increase in incidence versus 40 percent, down to 10 percent. Here's the sample size per group for our two groups that you need in order to be able to have 80 percent power to detect that much of a difference. So even at 50 percent -- a 50 percent difference, so 10 per 100,000 versus 15 per 100,000, you still need almost 400,000 subjects per group or 800,000 total to be able to detect a 50 percent increase. If you really care about detecting smaller increases, like 30 percent or 20 percent, then you're up in the one to two million per group range.

Now you can think of this as not just comparing two groups

that are running at the same time, but you could think of this as something like -- what do I need to do to look at what the incidence rate is before policy change compared to after a policy change? You have the same problem. So when we design -- when we think about surveillance and looking at policy changes, these are the things we have to take into account. Okay.

So let's talk specifically about blood donors. You've heard earlier that there are basically two general approaches. One method is based on repeated observations of the same subjects, and for that you need repeat donors. It's a widely used approach. It's probably -- it is the classical approach. It does required repeated observations on the same donors. The other approach, which we've also heard about, is -- that can be applied to both to first time and repeat donors -- is to look at identifying recent infections and basing incidence estimates on the number of recent infections identified.

So let's talk about repeat donors briefly. Usually, we define a follow-up period, as I said earlier of one to two years. We identify all the donors with at least two determinations of infection status within the interval that we're interested in. So we might say in 2012 and 2013 find everybody who's got at least two determinations of infection status in that interval, where the first one is that the person was not infected, may or may not be infected at the last one in

the interval. And then all new infections identified in the interval go in the numerator of our incidence estimation. The denominator, if there's no infection, follow the person from the first observation in that interval to the last observation within that interval. That's that person's contribution to the denominator.

If there -- what about if there is an -- if we have a person who is determined to have an infection. Well, we don't -- incidence estimation, if you look at the equation, it depends on knowing the time that the event -- that the infection actually occurred. But we don't know that. It's -- we have what statisticians call interval censored data. We know that the infection occurred during an interval, we don't know exactly when. And a widely used convention is to set the infection time halfway between the last observation with no infection and the observation with an infection.

Other approaches have been tried. You could do -- cut-off follow-up at the visit before infection. You could carry follow-up all the way out to the time point where infection is identified, which is after it occurred, or at some random point in between. For rare infections, it turns out that this doesn't matter. For example, suppose we have 10 infections identified in 100,000 donors with an average follow-up of one year. The total follow-up for non-cases is 99,990 person years. The total

follow-up for cases is less than 10 person years. So take your pick. If you put it at the midpoint, you might put it -- say that that's five years of total-follow-up, compared to 99,990, or it might be 10 or it might be -- depending on where you put it. And it's really such a small fraction of the total that the choice is irrelevant.

This just illustrates what I was just talking about, just a little picture to do this quickly. A 24-month study, here's the 24-month point, 24 months before this -- start of the study, so from Month 24 to Month 0. The arrows indicate the beginning and end of follow-up for each hypothetical person illustrated here. The closed symbols indicate an infection was detected, open symbols no infections. So you see from first observation in the interval, even though this person had one beforehand, and then halfway between the last two. Now, here, we just are going halfway between the only two observations we have of the second person. This case would be excluded because the first time that person was examined within the interval there was an infection. And so on. So the first to last, here, because no infection was detected. So that's just to illustrate what we're doing. Okay.

Now, there are problems. As has been said earlier, we need to exclude first-time donors and those with only one observation within the interval when we do this estimation. And that creates a problem if incidence is different in the people who are

excluded, especially if they're a large fraction -- a reasonable fraction of the total. So the other problem is that methods based on repeat donors may not be sensitive to the effects of policy changes, if the policy changes result in people deciding to donate, because they'll be first-time donors. So that's where we get into using the methods for detecting recent infections, because we can apply those methods to all donors. We only need one determination per subject if the person isn't -- basically, this should make these methods more sensitive to policy changes.

So, basically, the approach for HIV, test all HIV-positive samples to separate recent infections from long-standing infections. You heard about NAT yield cases and this involves people -- again, I did that. This involves -- the NAT yield cases basically involve donors who are positive on nucleic acid tests but negative on serological tests, so they're in the window before an immune response develops to HIV. The other way to do this is with serological tests for recent infections, which distinguish recent serological responses to infection from longer-standing serological responses to infection. I think Michele is going to talk more about these in the next talk.

We still base our incidence estimate on cases over follow-up time, so we have to determine a follow-up time contributions to this calculation. What we do is we -- the people who contribute to the incidence estimate are the recent infections

and the -- and people who are determined not to be infected. The long-standing infections are excluded as prevalent cases. We need to know the duration of the interval during which an infection would be called recent in order to do the calculation. I've got nine days here for HIV, I think some people might -- I think that -- I'm not quite sure if I've got the exact -- the correct number there. It might be off by a few days for the NAT yield window. The serological tests, I've see values of up to six months, as, you know, some of you can say the infection occurred sometime in the last six months.

The follow-up time then for non-cases is that -- if somebody who's not infected, take that full window and that's that person's contribution to the denominator of the incidence calculation. For cases, by convention, people tend to put this at half the window value. Again, with rare events, where you put it in that window really doesn't have a material impact on the estimate -- so still doing something along the same lines.

Comparison of the NAT yield approach and the serological approach, the serological approach has a longer window for calling something -- a longer time interval over which you would consider something a recent infection. I think I just said up to six months versus a matter of days or a week or two. That means that with the serological approach, in theory, you should have more cases in the numerator, when you use this approach, which

means you should get smaller standard errors and narrower confidence intervals and greater statistical power for doing the comparison. We're near the end here.

So, possible problems, some infections are falsely classified as recent. I don't want to spend a lot of time talking about this because I think Michele is going to talk about it more. There are statistical methods for dealing with this, if you can estimate the proportion of cases that are classified -- recent cases that are actually falsely recent, then you can simply exclude that proportion from the numerator of the calculation -- straightforward. But I gather there's some laboratory methods and further data that can be applied to the problem, as well, to exclude the cases on an individual basis.

So let me just sum up here. HIV is rare and it creates problems with incidence estimation. We have a tension here because we need large sample sizes to get precise estimates of incidence and reasonable statistical power, but we don't want to do estimation over long time intervals because of the problems that creates with shifting incidence rates and changing donor populations and the like. So that's a problem we have to confront going forward. Incidence estimation, repeat donors, is, as I said, straightforward but we basically are excluding groups that we need to include in the calculations, especially if we're evaluating policy changes. And the methods based on recent

infection can include both repeat and first-time donors. Serologically-based methods should have greater power than the NAT yield methods and we -- but then the last thing I said -- need to adjust for false positives. Okay.

We have an incidence committee in REDS-III, which is charged with determining -- standardizing the methods we will use in REDS for estimating disease incidence in our studies. Here are my partners in this exercise: Mike Busch and Brian Custer from Blood Systems, Roger Dodd from the American Red Cross. Steve Kleinman who's also the chair of our domestic steering committee for REDS-III. Emily Liu and Hua Shan are both from Johns Hopkins, part of the China contingent on REDS. Liliana Preiss is a statistician at RTI. Ester is the head of the Brazil component of REDS. Marion is in the -- SANBS is the South African National Blood Service. She's in South Africa. And Shimian is at NHLBI. So they contributed quite a bit to this presentation. I'm very happy that they did. Anyway, thank you very much.

CHAIRMAN JACKSON: Thank you, Dr. Brambilla. Maybe we'll have Dr. Owen speak next, and then, maybe take a couple questions --

DR. BRAMBILLA: Sure.

CHAIRMAN JACKSON: -- if we do that. So, Dr. Owen.

DR. OWEN: Yay, my slides. And I want to thank everyone for

inviting me to talk. And I think I have a tall order here. I think I'm supposed to describe what recency assays do, and I'm hopefully going to give a fair and accurate description of what they can do and what they can't do, at least at the moment.

So a little bit of background, lab assays were designed quite a few years ago to measure biological analytes in cross-sectional samples to classify infection as either recent or long-term. There are really two potential uses for these assays that distinguish recent from long-term HIV infection, and there's one -- is population-based incidence estimates. And this is, like, the classic equations that came out of the first Janssen paper. And then, possibly, the prediction of recent infection on an individual level, but this is definitely in its infancy as far as on the individual level.

So some additional background for you guys. Most all research to date has focused on the use of these assays in large populations. Primarily, in cross-sectional situations where you have no additional information about the person, you just have -- they're tested -- and the result on the recency assay. But, like, in the U.S., it can also be combined with case-based surveillance. So all those numbers you heard earlier about HIV incidence in the U.S., those calculations, it was actually done that way. A recency assay was used, but it was actually combined with case-based surveillance information, like, when they were

tested previously, et cetera.

So there are quite a few critical parameters for assays when you want to use them in cross-sectional population-based incidence measurements. One is the mean duration of recency; it's also known as the window period. That's what it was called in the early days. The statisticians tell me the better term is actually "mean duration of recency". And, no, I am not a statistician; I'm a laboratorian. Multiple papers have been published about the approaches for MDR calculations. And, actually, this is one of the areas that's added to some of the confusion in the field -- is because of the different approaches for calculating that mean duration of recency.

The other critical parameter is the false recent rate. So it's actually the rate at which the assay misclassifies a person as recent when they're not actually recent. Until recently, all measures were done by antibody measurements, and that's been the foundation of all the assays until recently. They're evolving to possibly include some nucleic acid characterization. There is more interest in determining if these assays can be used on the individual level.

So what are the biological considerations for these assays and how they were developed? So, basically, during the course of HIV infection certain things happen. This happens not just in HIV but other infections as well. Antibody titers rise, antibody

maturation occurs, and I'm going to talk a fair bit about this. Avidity and affinity increases, so for you, non-chemists, basically, it's how tightly an antibody binds to its antigen. Temporal antibody responses occur to HIV proteins; so we know that they antibody response changes over time. So, first, you may get a response to the p24 of the virus, then the envelope of the virus, et cetera.

And we also know that there are differential classes or subclasses of antibodies that are made. Mostly, the response people are measuring is IgG; and, in particular, in early infection, there is a certain class called IgG3. And then we also know that genetic diversity increases of the virus when a person's infected over a period of time. So this particular slide is classic. And the one at the bottom basically is describing what I just told you in words. So, person gets infected, they have RNA, it occurs, p24 occurs, it can be detected, and then, antibodies occur. And people use the time in this period, that's in that gray block, to describe more specifically what's happening with the antibody response. Is it becoming higher? Is it binding tighter? Is there a different type of antibody being produced? Et cetera.

So the early assays were all titer-based assays, so basically looking at the concentration of antibody to HIV. The first one was the detuned assay by Rob Janssen. The next assay

that came along was the BED capture assay; it measures the proportion of a specific -- HIV-specific IgG. Recently, modification of the vitros assay was done in Dr. Busch's lab.

But there are a lot of challenges for titer-based assays. So there's a decreased antibody production when antigen simulation decreases; and this could either be because someone's a natural suppresser or because of therapy. There's also, sometimes, decreased antibody concentrations in late stage disease, primarily because the cells that support antibody production are being destroyed, in the case of HIV. And then, also, if you look outside the U.S., the diversity of other clades causes a problem for some of these titer-based assays because it's only subtype B antigens that were used in most of the assays.

So because of this and because of some of the -- what people would consider to be the early failures of -- particularly, the BED or the less sensitive approach, many investigators, including myself, started looking at avidity. And, like I said, avidity is, basically, just the combined strength or binding to the antigen. And, in theory, the idea is that low-avidity antibodies occur early in an infection, and later in an infection you have higher-avidity antibodies. And that would equate with long-term infection.

There's been multiple avidity assays that's been developed

in the past few years, and this is not all of them. This is not an extensive list. But I included these because these are the ones that have been most rigorously [spelled phonetically] evaluated in an independent evaluation. So we developed one at CDC, Bio-Rad avidity assay. Collaborators at Hopkins took this assay and they modified it slightly. It's the same assay with slightly different incubation times and likely different cut-offs. There's a limiting antigen avidity, also known as LAg, that was developed at CDC by Bharat Parekh after he developed BED. And then, there's a -- vitros avidity that was also developed at BSRI in Mike Busch's lab.

So, just some principles for avidity assays. I like pictures, so on the left part of the screen, this is the classic avidity type measurement where you have antibodies binding, both low and high avidity antibodies. You add some sort of chemical, this is to disassociate the antibodies that don't bind tightly and they are washed away. And then you measure those two wells and you compare them. That's the idea behind the Bio-Rad avidity assay.

With limiting antigen, they took a slightly different approach. They lowered the concentration of antigen. And the theory is that if you have a lower concentration of antigen -- because of the way antibodies bind -- and a single antibody can bind to two sites, lower avidity antibodies would be less likely

to bind. So here's some -- just some data about the Bio-Rad avidity assay and some characterization about it that we've done in-house at CDC. And if you look at the bottom right, you can actually see these are 165 people followed over time and what their response is in this assay. And, as you can see, it's a bunch of squiggly lines, but, hopefully, you get the idea that they do go up over time, so that the avidity does go up over time.

We actually looked at false recent rates in some -- in an MSM population, where we have archived samples. These were people that were completely ART-naïve, and we know this because these were individuals that were collected in the early days of the epidemic before there were actually any ART available. And we had a very low false recent rate. We did the estimation of MDR calculations, and we arrived at a 30 percent cut-off. That's our final; we will not change that. And that's shown in green. Is -- if you look at it, you will see that there's various days there, depending on the method used for the MDR calculation, but, luckily, they don't vary greatly. So, in this case, it's 242 to about a 256 days -- is the mean duration of recency with this assay according to CDC.

The limiting antigen assay, there's -- that was also developed at CDC, but in a different lab. It's the -- I showed you the principle before, the current package insert for this

assay says that the MDR is 130 days, so you can see its considerably shorter than the Bio-Rad. The false recent rate is a very low. And they're in the process of doing multiple MDR calculation comparison, kind of like what we have done with the Bio-Rad.

So, because of the field and the fact that a lot of the published information about incidence assays were not consistent, people use different populations, people did different -- testing was done in different labs, et cetera, there was an effort, a few years ago, to standardize the evaluation of incidence assays. So a consortium was set up, and it was funded by Gates. And it's -- we refer to it as CEPHIA. And, basically, the whole idea was to develop a specimen repository to evaluate these assays independently. The institutions that were granted -- given the grant was HPA in London, Blood Systems, Mike Busch in San Francisco, Chris Pilcher in San Francisco, and all of statistical analysis was done by Alex Welte in South Africa. And they have a great web page if anyone wants to look at the equations of how they say you should measure cross-sectional incidence, et cetera.

The CEPHIA approach was to come up with three panels: one that developers could use; then a qualification panel that a person had to pass to have their assay evaluated; and an evaluation panel. All of the assays -- all of this that had

assays, sent the -- transferred our technology to them and they did blinded testing of the assays. And so, these are the assays -- some of the first that were tested: the original BED, the limiting antigen that I talked about, the Bio-Rad avidity that was developed at CDC, the vitros less-sensitive, and the vitros avidity.

And just recently the paper came out looking at this evaluation. And once again you're going to see these lovely spaghetti plots, as they call them. But as you can see, in all these assays -- hopefully, you see that over time responses go up and you can actually evaluate that. The middle block there is actually another way of looking at this, it's the box and whisker plots, and it's actually showing the percentage of people that are recent or non-recent over time. And, in each case, the solid line there indicates the cut-off of the assay. So -- and then it's time going forward. So, as you can see, all the assays -- more people are -- are considered recent at the beginning and it's over time fewer and fewer look recent.

And the very far one on the right, is actually just a distribution of the sampling. And as you'll see, one thing that's very different about the Bio-Rad is that once people get up there the -- they do plateau and they reach 100, whereas, with the other assays there seems to be a distribution of the actual values you get.

Once again, this is the same type of thing. But this is looking at over time percent -- recent over time. In this case, it's shown based on clades. I realize in the U.S. we're primarily interested in the -- uh oh, what did I do, what did I do -- subtype B, which is the second one there, they just did them in alphabetical order. And you will see, the top is a limiting antigen and the bottom is the Bio-Rad, and there's various ones in between. I will tell you, absolutely for sure, that the Bio-Rad assay does not work with subtype D but, hopefully, we don't have too much subtype D in the U.S.

This is just some other information about this, and it's a very busy table, but I just want to highlight a couple of things. So if you look at these -- all of these assays, the limiting antigen basically had the lowest false recent rate of any assay. Overall, if you looked at all clades, it was 1.3 percent. The Bio-Rad had the second lowest, it was at 6.2. But the other thing that's really interesting is, if you look at the limiting antigen, the mean duration of recency was considerably shorter, it's 188 days, and the mean duration of recency for the Bio-Rad was 333 days.

At the end -- and then, if you look at this by subtype -- it actually puts the window period and the false recent rate based on subtype. The previous one was all samples. And if you look at subtype B, for example, the LAg becomes 153 days for the

mean duration of recency, but once again has a very low false recent rate of about 0.05. If you look at the Bio-Rad, it's 330 -- 300 and -- 299 days for subtype B and it's a false recent rate of 2.1 percent. After this analysis was done, because it was all doing blinded, we at CDC we're still changing the cut-off. And that's -- all this slide shows is that for the Bio-Rad, if we actually used the cut-off that we now recommend for the assay instead of 40 percent, where all that analysis was done, that the mean duration of recency goes down slightly and so does the FDR.

I wanted to show some other data from other investigators, basically, that have also been evaluating the assay. And this is -- good collaborators at Hopkins: Tom Quinn, obviously, has been in the field of HIV incidence for a long time, and Oliver Laeyendecker. And, basically, this is a very busy slide for the next two -- but, basically, all it shows is that the reason you get the false recents with limiting antigen primarily is people that are older -- and that's probably related to time of infection, actually, which is also related to year collected, so, actually, when the samples were collected. And if a person has decreased viral load or on antiretroviral therapy, the odds ratio for misclassification goes up; which is basically the exact same thing that the CEPHIA people showed. Those are the types of factors that affect whether an assay has a higher false

recent rate.

Another group -- and I found this interesting, this is actually a group in Germany that compared the three assays. And, basically, they had a well characterized seroconverters and no long-term infections. And this is just a scatter plot of the data they actually saw with this group of people. And the interesting thing to point out here is the Bio-Rad has -- the BED probably has the greatest scatter. The Bio-Rad and the limiting antigen have considerably less scatter.

But if you look at the very bottom of the limiting antigen -- this was the concern that they raised with limiting antigen in this paper, is that there were a fair amount of people, if you look at the people on the far left of the plot, that actually looked false long-term. So they actually had a high limiting antigen value, but were very early in their infection. And in the case of the blood donors -- I'm guessing this might be something that people might want to take into consideration. And this is the same data just shown graphically, and it's the same type of thing. There's the bar graph. So those people are all recent, and it's showing the percentage of them that were classified as recent. So if you look at the Bio-Rad, it was -- the highest one that was accurate at predicting the ones that were recent, whereas, more of the recent people were misclassified as long-term. And then, if you look at the long-

term people or the people on therapy, the limiting antigen and Bio-Rad were pretty comparable in those cases, the limiting antigen was probably slightly better.

So to try to fix all of these issues with the assays and them not being exactly perfect, it was decided to look at algorithms. And this isn't a real leap for anyone that's worked in diagnostics. We -- particularly for HIV, how do we diagnose HIV? We use an algorithm to increase the accuracy. So the idea was to do the same thing with assays. And this is also from Tom Quinn and Oliver Laeyendecker. And all these are trying to show you is -- is that -- that the ones on the left is just using the assay, the ones on the right it's actually combing a bunch of assays, and the whole point is you want to approach zero. You want that line to approach zero far out. So those are people that would be misclassified.

So all this slide is really showing you is that if you do an algorithm, you're accuracy is improved as far as classification. Now, whether -- how you combine the assays makes a difference. And this -- and the MAA 1 that was on that previous slide, they actually used the Bio-Rad avidity modification from Hopkins and limiting antigen and that predicted recency. Any time you do the algorithms, you have to create a new mean duration of recency, so in that one it was 119 days. Whereas, if you did the MAA 2, which is extremely

complicated, you'd have to do CD4 counts, Bio-Rad avidity, limiting antigen avidity, viral load, and you get a different MAA. Probably, it's not worth it.

At CDC, we knew that algorithms were working, so we're actually in the process of trying to develop an assay that takes this approach but does it in one assay. And this was actually published last year. So we take a large number of epitopes, and we do both titer and avidity, we combine them together. And the whole point of this slide is -- we showed that we can sort of do the same thing with one assay that has multiple components. And this was a simulation study; it was samples that we knew were recent, long-term, et cetera, and we made a population to do the calculations. And, if you can see, the estimated -- the actual incidence was 1 percent, and if you did the various combinations you got closer to that with a relatively long mean duration of recency and a relatively low false recent rate. So the ones highlighted in bold there are examples of a long MDR and a short false recent rate.

I just want to mention, in the U.S. population, how HIV incidence estimates are done. And I mentioned this at the beginning of my talk. Previously, it combined data with the assay with case surveillance data. Up until this year, the assay that was used, at least since 2008, was the BED. This year, it was -- the decision was made to actually transition to the Bio-

Rad avidity, so incidence estimates going forward will be used -
- at least for this year, will be using the Bio-Rad avidity as
the assay component. But it also uses a lot of information that
is collected on those case surveillance reports for HIV, the
[unintelligible], that was mentioned previously. You can get
information about previous testing history, viral load, et
cetera. And all these parameters are put together to come up
with a probability of being recently infected.

These two papers at the bottom. The bottom one is a very
heavy statistics paper that I cannot begin to understand. The
other makes a little bit more sense to me; it's more of an
epidemiology paper of how the incidence estimates are done. But
the idea is you have probabilities of being infected and you can
use this and extrapolate, even though you cannot get data from
everyone in the population.

Like I said, prediction at the individual level, there's
interest in this, but there are more data needed for divining
assay cut-offs. You have to know the observed dynamics of
assays. And the data, if you look at it from a pure diagnostic
sense, it does look possible; but we have to define what we
would consider to be the minimal acceptable sensitivity and
specificity. I can give you, for an example, some of the cut-
offs we've done with the Bio-Rad avidity. We probably think we
can get to a sensitivity of about 85 percent, 90, maybe,

specificity of about the same, about 85 to 90. Is that okay for defining if someone is recently infected? Well, it's still better than a lot of assays for other diseases, so, maybe. But it's certainly not as good as actual HIV diagnostic tests.

We need to know what is the optimum period of prediction. So what do you want to use this individual data for? What is -- you're trying to use it for? Is it to do contact tracing? Is it to look at individuals donating blood, whatever? And -- but therapy is still going to be a limitation, but as long as you have a way to get an accurate indication of whether therapy is involved is probably possible.

So, my summary, no perfect assays, but assays have definitely improved over time. Current lab assays have been developed for population-based testing. And the CEPHIA work is very encouraging in the fact that we have almost met the target product profile that was set out to start with. There is additional work required for accurate prediction at the individual level. We would have to define parameters. We would have to do additional testing of very frequently sampled seroconverters to help really refine that cut-off for an individual level.

We know from past history titer-based assays have higher false recent rates. Most new antibody assays utilize avidity maturation for improved false recent rate. Testing algorithms

further decrease false recent rate and likely improved estimates in cross-sectional testing. As you might have noticed going through this, there is some -- still variation in the MDR and false recent rate calculations. Some of that -- is it the methods? There's been a group of people trying to work on this to find the optimal method for calculating MDRs; and I think there's a paper coming out soon. And, when -- how you define a person's infected -- in the early days, is you always defined them as infected by being -- Western blot. And then, populations is -- are there but not being disclosed, and we actually have some evidence that happens in some situations. And then the collection parameters of the samples that are used for doing the MDR.

So, my final thoughts, incidence assays would likely be useful tool in blood donor setting to extend that mean duration compared to NAT. So, as the previous speaker talked about, you actually have more time you can actually put in to get a more accurate estimate if you want to look at trends and incidence over time. So, my understanding of this question -- and I can be totally wrong, this is my own personal understanding, is that the reason you want to add this to the testing of HIV-positive donations by serology is to actually look over time -- if the regulations were changed is incidence in blood donors changing over time? In that case, employing the serological assays might

be helpful. You will still have to determine the exact assay you want to use, or if you want to use an algorithm, which is probably the best approach, and reconcile the parameters for MDR and false recent rate and the statistical considerations for sample size. And there's a lot of people that helped with this and did a lot of the work, so they get a lot of credit. And that's it.

CHAIRMAN JACKSON: Okay. Thank you Dr. Owen and Dr. Brambilla.

QUESTIONS FOR SPEAKERS

CHAIRMAN JACKSON: We have some time for questions of the speakers. So -- for either Dr. Owen or Dr. Brambilla. Dr. Williams?

DR. WILLIAMS: Thanks. Very nice, Michele. Alan Williams, CBER. So, one fairly simple question, for the assays, what is the coefficient of variation for a given assay? Do you run multiple assays and take a mean or is one single assay reproducible?

DR. OWEN: So, the coefficient variation isn't extremely high. It is relatively reproducible from sample to sample, if that's what you're asking. So are you saying run the same sample? It does vary with the assays. And that's actually some of the data that's in the CEPHIA paper, is they actually talk about the coefficient of variation. It's not considerably higher than other HIV tests.

CHAIRMAN JACKSON: Mr. Dubin.

MR. DUBIN: I'm curious about trends, because for us that's a big issue in the change in the policy. We know about HIV, HPV, HCV, it's that emergent horizon, if you will, that we're very interested in on the recipient side. And it's the question we get the most within our circles at the Committee of Ten Thousand. So maybe you could say a little more about that.

DR. OWEN: Well, I can say a little bit as far as -- that

is, I think the reason for wanting to do the assay, is to actually look at trends over time and something that hasn't necessarily been done. And by using the assays you have more data time to actually sample in. So I'll let you answer from the statistical approach.

DR. BRAMBILLA: Yeah, couple things. First of all, one of the papers that I quoted showing incidence estimates in blood donors, I had two estimates from Shimian Zou's paper, there are actually, I think, five in the paper for five successive two-year intervals. And that's what you would need as a baseline against which -- so I wouldn't use the last two years before a policy change in order to look for trends. I'd want to use all five of those. The first question I'd want to know is there any kind of a trend going on in those five or am I looking at what appears to be random variation over time in those five. And if it's random variation, then I actually have five observations against which to measure a policy change. Okay.

MR. DUBIN: Thank you.

DR. BRAMBILLA: You're welcome.

CHAIRMAN JACKSON: Dr. Stowell.

DR. STOWELL: I'm having a little trouble grasping this MDR concept. Do I gather correctly that what the MDR is measuring, essentially, is the time to appearance of the high affinity antibodies?

DR. OWEN: Yes. It's the mean duration of all of those people that are put into that calculation -- it is the mean duration at which a person will reach that threshold of -- whichever it is, if it's an O.D., or a percentage, et cetera.

DR. STOWELL: Okay. Then my follow-up question is, so, why is it better for that to be longer rather than shorter? I mean, is it --

DR. OWEN: Well, what I am told is the longer you have -- it's once again, it increases your time that you can actually do the measurements. So, you actually capture more people that are recent by using a longer one, so you actually have more data points to actually get a more accurate estimate. You can agree or disagree. [laughs]

DR. BRAMBILLA: I agree completely. I mean, the advantage is this, if I have a -- say, a one month window that -- calling somebody recent, then those are the people who are going to end up in the numerator of the incidence calculation. And -- but if I got a six-month window, then I'm going to pick up more people. Now, I'll have more time in the denominator, but remember that the standard error is the incidence estimate divided by the square root of the number of cases. So the longer window gives us more in the denominator, which gives us a narrower or smaller standard error and narrower confidence limits.

CHAIRMAN JACKSON: Dr. Nelson.

DR. NELSON: All right. Are any of these assays significantly affected by how samples are stored, or for how long, or under what conditions?

DR. OWEN: Oh, actually, I can answer that -- I think there was actually a paper in the reading package. Actually, we worked with Oliver Laeyendecker at Hopkins and we actually did that. And, really no. We subjected them to multiple freeze thaws, up to, like, 15. We did it at 4 degrees for, like, up to two weeks. We did it at 37 degrees. We did it at room temperature. And the only thing that really affects it is if you leave a sample out at 37 degrees or body temperature for a week, then it starts to go down. But we really shouldn't be storing samples that way, anyway. So.

CHAIRMAN JACKSON: Yes, Dr. Basavaraju.

DR. BASAVARAJU: So, I guess to me it would seem that "incident" and "recent" would have different definitions based on the population that you care about. So, for example, in a general population, it's reasonable to say that incident or recent would be six months, because the goal there is to identify whether your control and prevention plans are working. So six months seems like a fine time or whatever.

But in blood donors, the idea is not -- has the person been infected in six months? The consideration is safety. So, are you going to have an infection that's not detected by NAT? So in

that situation, it would seem that incident would actually be, you know, a much shorter time. Right? Because you're trying to find people who may not be detected by NAT. So, whether a person got detected -- infected four to six months versus whether they got infected within 10 days is a much more important consideration. Right? So I guess I don't understand how identifying a person who got infected at four or five months or 180 days is that valuable when you know, you know, that they are NAT positive and antibody negative.

DR. OWEN: My understanding of the reason for this is not to necessarily look at the safety so much of the donation that's happened, but to actually look to see if the population is changing over time that is donating because of a change. That's my understanding of the question; in which case, then, yes, you could, but it has nothing to do with whether or not the person you identify, just then, was the issue.

DR. BASAVARAJU: But can't that also be just by -- done by quantifying the number of people who are NAT-positive and antibody negative and seeing if there are changes in that, those numbers, and statistically comparing those pre- and post-deferral change?

DR. BRAMBILLA: You mean the NAT -- the NAT yield cases, NAT-positive and serologically-negative?

DR. BASAVARAJU: Right.

DR. BRAMBILLA: Yeah. You can do that. But the problem is that the window for that is so narrow that the number of people you're going to find is much smaller than what you'll find with a larger -- with a broader window, wider window, time window. And that's really what the issue is -- the nice thing about these assays is they give us more statistical power for detecting changes. Remember, the other thing is that what we're doing here is -- as I understand it, is -- you're not applying the recency assay to every blood donor. You're applying it to blood donors who are already tested positive for HIV. So it's not for detecting HIV cases, it's for looking at incidence, specifically.

CHAIRMAN JACKSON: Dr. Epstein.

DR. EPSTEIN: Yes, thank you. And, also, thank you, Michele, for a very clear presentation. Could you come back to the slide where you showed us the multi-assay algorithm, 1 and 2?

DR. OWEN: [affirmative]

DR. EPSTEIN: And my question is, can you give us the false recency rate for MAA 1? MAA 1 kind of looks promising. And in the previous graph, when you looked at MAA 1, at least for greater than one year, false recency looked pretty low. I mean, it's hard to know what the actual number is. And then, on the next slide, you also have something called shadow; and you didn't explain what shadow is. And should we be worried it's

shadow? So, my first question is, for MAA 1, which would be the use of the Bio-Rad avidity and the limiting antigen avidity test, what is the false recency rate?

DR. OWEN: If I remember correctly from the paper, it was very low. It was less than 1 percent. I don't remember the exact number, but it was extremely low. I can look for you but it is low. It is extremely low. It's lower than limiting antigen alone, I can absolutely tell you that. And the shadowing, my understanding is it has to do with -- I'm not a statistician -- is the curve, and it's actually where it's approaching zero. How you see on -- without the MAA, how it goes on -- it starts to approach the line and then it starts to go back up. I believe that's what he was calling the shadow. Whereas, with the MAA, as you can see how it approaches the intercept, but then it doesn't go back up. So the shadow is less with the MAA.

DR. EPSTEIN: Okay. So if the combined algorithm has better false recency than the limiting antigen alone -- that was 0.5 percent. So we think the combined algorithm is even better than 0.5 percent?

DR. OWEN: Yes. That's always been the case any time the MAAs are done effectively.

DR. EPSTEIN: Subtype B.

DR. OWEN: Yes.

DR. EPSTEIN: So, it's for subtype B. Okay. And then one

other question relating to Dr. Basavaraju's point about incidence versus recency. Can we derive an incidence estimate for NAT window period from a recency estimate, since we know the median time to recency for either the NAT, or the algorithm, or whatever else we might choose for recency? Can you derive the one from the other? Because again it would let us get to, sort of, the finish line which is estimating change in residual risk.

DR. BRAMBILLA: If you start with the -- one of the, you know, recency assays, the serologically-based recency assays, and -- so you've got, let's say a six-month window just to use a number and you know that -- and if you say that the window for being NAT-positive, serologically-negative is nine days, that's going to -- you can express that as a fraction of the total window. But the thing is, you're reducing the follow-up time in the denominator of the calculation at the same time that you're doing that. So you're going to end up with the same estimate of the incidence, but you're going to end up with a larger standard error when you -- because you've reduced the number of cases in the denominator -- in the numerator, excuse me.

CHAIRMAN JACKSON: My question is, in terms of this particularly study, for example, were the algorithms derived or formulated to fit the data? Or were these all pre-set and then you did it? Because, in my experience -- I've had a lot of experience with these assays -- that everybody keeps changing

the algorithms to fit the data. And then, of course, as the underlying population changes, whether because of the viral strain, or the immune deficiency -- degree of immune deficiency, or the age of the population, the amount of immune stimulation, and other factors, these algorithms fall apart when these populations change underneath.

DR. OWEN: So, my understanding is, is this actually occurred after the analysis was done with what was causing, you know, false recency, et cetera. And, in this case, my understanding, the way Oliver approached this MAA was that -- no, he didn't try to take the assays and fit them to make them look better. He, actually, did have several algorithms that he established upfront and then tried them to decide which ones worked best.

But -- I understand your point because, yes, it has been the case where that has changed over time. But I think the CEPHIA data really has told us now what causes assays to fail, which is what was missing in the early days. In the early days, when BED was done and the less sensitive assay, the assumption was that it wouldn't change over time, that once you crossed over that threshold you would never go back. And I think that's what the CEPHIA evaluation has actually taught us, that we know that there are situations where the assays fail and as -- you have to eliminate those situations to actually use the assays.

So -- and that's what adding viral load is for here in MAA 2, is the -- adding the viral load is the surrogate to eliminate people that are on therapy or elite controllers, which are the people that we know make the assays fail.

CHAIRMAN JACKSON: I guess, as you said -- I mean, if you take several algorithms and you see then which one works best with that particular dataset, then, you know, if it does change underneath that population then that algorithm may not work. The other thing is it does seem fairly complicated. I mean, we're having a difficult time enough trying to get blood centers to get samples for NAT yield, which is pretty simple. And if you've got to do viral loads and CD4s and various other things, it gets very complicated. But --

DR. OWEN: Right. And I think that's -- oh, sorry -- something to take in consideration. I mean, there is a balance there of what you can actually feasibly do. MAA 1 probably is pretty feasible to do -- two EIAs basically on a sample that you already have collected. Whereas, doing CD4 counts is very unrealistic, and such -- so.

CHAIRMAN JACKSON: Yes, Dr. Schexneider.

DR. SCHEXNEIDER: Schexneider. Thank you. I want to just go back to a comment that Dr. Owen made a few minutes ago. And I think we've circled around this, but I just want to make sure that I'm clear and we're on the same page. The question before

the BPAC here today is to think about serologic tests so that we can describe HIV-positive blood donors in terms of the recency of their infection so that we can better estimate the residual yield. That -- I'm -- I think I've captured what you said more eloquently, but that's what's before us today. Is -- Dr. Epstein, can you comment on that? Thank you.

DR. EPSTEIN: The goal of a monitoring system for markers in donors, as a surrogate for risk in recipients, is to be able to see change over time. Now, we're interested in change over time that might be a consequence of policy change, but it could also be a change in just epidemiology in the donor population. So the crux of the matter is how best to look for changes over time that can be translated into changes in risk. And so the question is, can we use HIV recency testing to improve our ability to estimate change in risk of HIV in the donor base above and beyond what we now do, which is -- we use the seroconversion rate and the NAT-only rate to derive estimates. And, you know, the issue in a nutshell is -- well, we could increase the numbers if we have accurate tests for recency that would reduce the uncertainty. But what I thought I heard Dr. Brambilla say is if translate that into the estimate of a change in incidence, we will still have a larger uncertainty.

CHAIRMAN JACKSON: Dr. Bonilla.

DR. BONILLA: If you take a fixed cohort of individuals and

you follow them serially over a very long period of time, decades, and you use either the NAT or the serological study to measure incidence, do you get essentially the same answer?

DR. OWEN: Sorry, I didn't hear the question.

DR. BONILLA: If you take a fixed cohort of individuals and you follow them prospectively over very long periods of time, say decades, and you measure incidence either with NAT or with the serological assay, do you get the same answer?

DR. OWEN: I would say in the early days, absolutely not. It's -- the whole idea of the false recent rate was the issue that people never took into consideration. There's actually been studies -- there's been a study with limiting antigen that I think is about to be published. It was actually done in Swaziland where they did that, and the estimates are very close. I will also tell you there is currently a study going on in Zimbabwe, where they are using both the Bio-Rad avidity and the limiting antigen in a previously characterized, the [unintelligible] cohort, where they do no incidence. And those studies, hopefully, are going to be published in about six months or so. And so far the data does look promising that -- yes, likely, they are going to get incidence estimates that are very close as the cohort estimate. But there is only limited data to actually show that.

DR. BONILLA: So the real difference that we're looking at

between the performance of these assays has to do with the time-limited nature of the studies that have been done thus far. That's where the whole issue of the false recency rate comes up; because you're only measuring incidence over a couple years and it's a rare event. And that's where your definition of incidence changes and that's where the whole concept of false recency arises. Is that not correct?

DR. BRAMBILLA: Well, I think you have to take into consideration, when you say follow a cohort for a long period of time, this is not like looking at heart attacks or strokes where you know when they occur. Presumably, what you're doing is following a cohort over a long period of time and periodically testing people to determine whether they are infected or not. If you are looking at this from the point of view of detecting recent infections, then the number of people who go into the numerator of the incidence calculation will, with that approach, still be larger with the recency assay than it will be with the NAT yield assay. So you're going to have the same problem with the standard error difference all over again, even if you have the same estimate of incidence.

CHAIRMAN JACKSON: Dr. Durkalski-Mauldin.

DR. DURKALSKI-MAULDIN: So the first speaker talked about the challenges of the large sample size, and he gave us that statistical power table. And so when I was looking at it -- so

let's say you want to do a pre/post policy and look at the incidence changed. So you gave us what we could detect statistically, but clinically what would be the relevant change you're looking for when you're looking at incidence over time. Is it any change? So it could go even lower than even 10 percent? Or have you talked about what you want to see?

DR. BRAMBILLA: The way these conversations usually work is the statisticians ask what change do you want to be able to detect and then we tell you what sample size you need to get there.

DR. DURKALSKI-MAULDIN: [affirmative]

DR. BRAMBILLA: So that's -- what you're asking for is something that -- we tend to shy away from telling you here's what you ought to be looking for. We want you to tell us that.

DR. DURKALSKI-MAULDIN: Right.

DR. BRAMBILLA: That's why I had small numbers up there: a 10 percent increase, a 20 percent increase. Because I had the feeling, just from conversations I've had with the REDS-III group and others, that people care about, in this arena, relatively small changes if we're talking about an increase in incidence. So.

DR. DURKALSKI-MAULDIN: And then with the sample sizes you showed us, could you tell me -- so what's not feasible?

DR. BRAMBILLA: Well --

DR. DURKALSKI-MAULDIN: How large does it have to be before it's just not feasible to do?

DR. BRAMBILLA: The total population of blood donors in the United States would be your upper limit. But -- and that's not as facetious as it sounds. It would be difficult to get there, we've already talked about that. But, you know, Shimian's paper from the American Red Cross that -- there were -- in those two-years windows that he had -- he had on the order of 4.5 million person years of follow-up in each of those two-year windows, which means he's got an excess of 2 million people in each of those estimates, 2 million donors. It's doable because it's been done. And those numbers are in the ballpark of the 10 to 20 percent increase that I was talking about -- at least, if you're starting with 10 per 100,000, if you start with a different reference number then we have to do the calculations all over again.

CHAIRMAN JACKSON: Dr. Williams?

DR. WILLIAMS: Just one other brief comment with respect to the purpose of the question. There's an additional parameter that you really haven't heard about yet, and I think that's going to come when Dr. Stramer presents her open public hearing. And that is, there's a lot of variation over time in a lot of these markers in the donor population, so that adds additional complexities. So I think to the extent that we can, you know,

maximize the power of whatever's being measured, it gives us a reasonable chance of being able to detect a trend change within, you know, a reasonable time that we could interpret it and make a, you know, potential intervention. Otherwise, we might find ourselves with huge periods of time necessary to have a meaningful result.

CHAIRMAN JACKSON: Okay. I think we'll now move to the open public hearing.

OPEN PUBLIC HEARING

CHAIRMAN JACKSON: And before we start, I will need to read the announcement for particular matters involving specific parties meeting. So both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing, a session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance of the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

So we can start with our first -- okay -- Bryan -- Mr. Emery has an announcement.

MR. EMERY: Before we call the individuals up one at a time

for the open public hearing, would the public please use the microphone to my right in the front? Because we had a microphone problem earlier. And so, if each person, as they're called, can come down and speak into the right microphone, your left, that would be great -- I would be grateful. Thank you.

CHAIRMAN JACKSON: Okay. Our first speaker is Ms. Andrea Levario from Human Rights Campaign.

MS. WARBELOW: I apologize. It seems like my colleague was listed. I'm actually Sarah Warbelow. I'm the Legal Director for the Human Rights Campaign. I'll be speaking on behalf of the organization. The Human Rights Campaign is the nation's largest lesbian, gay, bisexual, and transgender advocacy organization with over 1.5 million members and supporters nationwide.

I'm here today to first thank you for taking the time to consider changing and revising the current policy banning donations of blood permanently by men who have sex with men. This particular policy, as you are aware, not only is outdated, it no longer reflects sound scientific judgment and unnecessarily harms the LGBT community by further stigmatizing HIV/AIDS, and by not recognizing the vast majority of individuals, and treating as a problem sexual orientation as opposed to individual behaviors.

We deeply respect the duty of the FDA to protect the safety and security of the blood supply. What we would like to see is

that men who have sex with men are treated identically to every other category that is donating for the blood supply. So instead of having a categorical ban, looking at risk factors and treating men who have sex with men the same as other individuals. So if individuals are purchasing sex for money, using that instead as the category for assessment; looking at individuals who are engaging in intravenous drug use, other types of risk factors.

We really want to encourage that a policy is not based on prejudice but rather on sound science. We strongly urge you to consider all of the science and end the discriminatory outdated policy that has a negative impact on gay and bisexual men. Thank you.

CHAIRMAN JACKSON: Thank you. Next is Mr. Timothy Rinehart for the University Park Undergraduate Association

MR. WORTMAN: Good afternoon everyone. My name is John Wortman and I serve as the Speaker of the Assembly of the University Park Undergraduate Association, which is the undergraduate student government at the Pennsylvania State University. Today we're here to present a resolution that was passed by our body regarding the current lifetime ban by MSM donors. And we would like to lay out the reasons of why we feel that this policy should be changed.

So, as you know, in 1983, the Food and Drug Administration

implemented a policy which banned the ability of men who engage in sexual activity with other men to participate in blood donation efforts. Since 1992 no significant modification to this policy has been made to reflect the availability of new scientific data that attests to the greatly reduced risk of disease transmission from blood donation and subsequent transfusion.

In conjunction with the recommendations made by several scientific associations, including the American Medical Association and the American Osteopathic Association, as well as those sustained by a significant portion of the Pennsylvania State University student body, gay and straight alike, the undergraduate student government passed a resolution urging the FDA to amend its blood donor policy to reflect these recommendations. This resolution urging the FDA to act will be considered at the January conference of the association of Big Ten schools, in order to garner the support of all fourteen student governments in the Big Ten. And my colleague, Tim Rinehart, will be talking about some of the statistics and, kind of, the situations that we're running into on campuses that led us to pass this resolution.

MR. RINEHART: Thank you. Thank you for having us here. My name is Tim Rinehart as my colleague, John Wortman, said. On behalf of the 40,000 students at the Penn State University Park,

we wish to address the Blood Products Advisory Committee on how this policy negatively impacts blood donation efforts on the university level.

According to estimates provided by the American Red Cross, roughly 20 percent of the millions of blood donations made each year come from high school and college campuses. At the Penn State University Park campus alone, nearly 120 blood donation efforts are conducted every year resulting in nearly 7,000 units of blood. According to the Williams Institute study, approximately 1.7 percent of the male population in the United States identifies as homosexual. Now, if this percentage were applied broadly to Penn State's male student population of approximately 49,000 individuals, out of a total population of 98,000 across the Commonwealth of Pennsylvania, we can reasonable estimate that this standing policy prohibits the donation of blood from 833 undergraduate male students.

Using the same metric, applied broadly to other institutions in the Big Ten, it can be estimated that an approximate 6,134 students across the Big Ten identify as homosexual males and have engaged in sexual activity with other males -- are therefore banned from donating blood. Now, according to the Red Cross, a single donation can save up to three lives. Therefore, if the 6,134 Big Ten students who are currently barred from donating blood were able to donate via an

amendment to the standing FDA policy, 18,402 more lives could be saved annually per donation due to the increase in the availability of the blood.

Another point I'd like to make real quickly is the majority of student-run Red Cross organizations across the nation derive a portion of their funding from a student activity fee paid for by all students in order to conduct blood drives on campus. Students are often mandated by the university to pay into this fee on a per annum basis. So, therefore, students who identify as homosexual males pay into a fee pool that goes directly towards events that they are barred from participating in. Now, on a university level, this is discriminatory.

So, therefore, let me just say, I think -- let us change this policy, let us catch up with the rest of the developed world and amend this policy to reflect a one-year deferral for all MSM donors. It is a necessary change, it is a prudent change, and it is one that is definitely common sense step in the right direction. Thank you all for having us here.

CHAIRMAN JACKSON: Thank you. Our next speaker is Dr. Jesse Joad for the Gay and Lesbian Medical Association: Health Professionals Advancing LGBT Equality.

DR. JOAD: I have no financial disclosures. Thank you for the opportunity to address the committee. And please also see the letter we have provided you. My name is Dr. Jesse Joad. I am

President-Elect of GLMA: Health Professionals Advancing LGBT Equality, a membership or association of healthcare professionals whose mission is to ensure equality in healthcare for LGBT individuals and healthcare professionals.

GLMA believes policies governing blood donation should be based in science, promote adequate supplies of safe blood products, and ensure stigma is not perpetuated among MSM. Based on these principals, GLMA respectfully requests the committee fully consider a paradigm shift in policy that would eliminate categorically restricting MSM from donating blood and replace it with a policy addressing specific at-risk sexual behaviors, regardless of sexual orientation or gender. Given present day testing technology, the deferral period from the time of this specific at-risk behavior should be substantially less than one year.

GLMA has long been concerned about the stigmatizing effects of the blood donation deferral policy. With the scientific rationale -- what is the scientific rationale behind preventing an HIV-negative man who is in a long-term, monogamous relationship with an HIV-negative partner from donating blood? In a time when young MSM continue to be at disproportionate risk of suicide, bullying, and mental distress due to sexual orientation, what message is sent when a young gay man is told by policy of his government that he cannot participate in an act of compassion

and civic responsibility based on the gender of who he is having sex with, rather than the kind of sexual behavior he is engaged in? Thank you.

CHAIRMAN JACKSON: Thank you. Our next speaker is Mr. Scott Schoettes, HIV Project, Lambda Legal.

MR. SCHOETTES: Good morning. My name is Scott Schoettes, and I'm the HIV Project Director at Lambda Legal and a member of the Presidential Advisory Council on HIV/AIDS. As the oldest national organization committed to achieving the full recognition of the civil rights of the LGBT community and people living with HIV, Lambda Legal has been advocating on the MSM blood donation ban since its implementation. And I appreciate the opportunity to address the committee regarding this important subject.

Lambda Legal supports the recommendation of the Advisory Committee on Blood and Tissue Safety and Availability to reduce to one year the deferral period for blood donations from gay and bisexual men as an important first step in a more comprehensive review and revision of the blood donation policies. However, changing the parameters of this discriminatory policy does not alter its essential nature, eliminate its negative and stigmatizing effects, nor transform it into a policy that is based on current, scientific, and medical knowledge. To accomplish those things, the policy must be changed to one that

is based entirely on the conduct of the potential donor and not on sexual orientation, gender identity, or the perceived health status or risk factors of the donor's sexual partners. With these things in mind, Lambda Legal recommends a policy based on two things: one, the sensitivity of the current test for bloodborne pathogens; and two, deferrals based on donor self-report of activities involving a significant risk of transmission during the relatively short window period for these more sensitive tests.

First, the current length of the deferral period is arbitrary and is untethered from the sensitivity of current testing technologies. Because the deferral policies work in conjunction with the primary method of protecting the blood supply, the testing of all blood donations, the deferral policies should be targeted at and tailored to the existence of bloodborne pathogens that those tests may not detect. And the commonly used current tests detect HIV within 9 to 11 days of contact, and detect hepatitis B, which has the longest window period, within 20 to 25 days. These more sensitive tests justify, at most, a two-month deferral period.

Second, to eliminate the discriminatory, stigmatizing, and anti-prevention aspects of this policy, of current donation policies, deferrals should be based entirely on the potential donors' conduct during that dramatically shortened window

period. We now know the relative risks of HIV transmission. For instance, receptive anal sex is approximately 10 times riskier than either insertive anal sex or receptive vaginal sex.

Therefore, the department need only to determine the point along the risk spectrum that it deems tolerable. And perhaps it is the significant jump in risk associated with receptive anal sex and implement a deferral based on engaging in that conduct without regard to the donor's sex, sexual orientation, or gender identity. Similarly, the deferral period could be eliminated by the use of effective prevention methods such as condoms or pre-exposure prophylaxis, which we now know is as effective as condoms when taken at least four times a week during the deferral period.

In any event, at whichever point on the spectrum the department determines is a tolerable level of risk for pathogen acquisition within the deferral period, the policy should be applied equally to everyone and based on information within the personal knowledge and control of the potential donor. A woman does not necessarily know if she is having sex with a man who has sex with men; and no one knows if they are in a completely monogamous relationship. If the committee is serious about implementing a truly non-discriminatory policy that is most protective of the blood supply, it will treat all donors the same and base any deferrals on the conduct of those individuals

within a scientifically-justified period prior to donation.

Thank you.

CHAIRMAN JACKSON: Thank you. Next speaker is Ms. Johanna Gray, National Hemophilia Foundation.

MS. GRAY: Hi, good morning. My name is Johanna Gray, and I am a federal policy advisor for the National Hemophilia Foundation. NHF is the oldest and largest organization for people with hemophilia, Von Willebrand disease, and other bleeding disorders. I'm very pleased to be here today to share a statement on behalf of NHF and the bleeding disorders community.

As a result of the devastating effects that tainted blood products has had on our community, we are acutely interested in policies to ensure safe blood supply. First, we'd like to thank HHS for the thoughtful and deliberative process you have followed in initiating and conducting the research that we requested with our colleagues in A-PLUS, the plasma users community, in 2010. You should have the A-PLUS statement, and we join with those colleagues in asserting that the results of the recently conducted research provide an opportunity to revise the current lifetime deferral to one year, provided that a robust and comprehensive hemovigilance program is implemented at the same time. This policy reflects a balance of respecting donors and protecting patients.

We fully support the December 2013 recommendations made by

ACBTSA, that were reaffirmed by the committee last month, calling for the establishment of a transfusion-transmitted infections monitoring program. The one year gives us a margin of safety, but further data collection will be key to taking any corrective action and considering any further policy changes. We also take note of and support the additional recommendations made by ACBTSA last month regarding the need for coordinated communications to all relevant stakeholders as part of implementing any policy revision. Thank you.

CHAIRMAN JACKSON: Thank you. Next Ryan James Yezak, advocate.

MR. YEZAK: Hi. There's no podium; I thought there was. Good afternoon committee members, I'm here today to share my experience with the FDA's lifetime deferral and what I learned from the HHS committee meeting I attended in November.

The first and only time I've ever donated blood was in high school. I was surrounded by a group of my peers when I came across the MSM question. In fear of being outed, I answered no and donated blood. I spent the next several weeks paranoid that the donation center would be able to tell from my blood that I was gay.

Several years later, I was working for a TV network when a tornado struck one of our offices. There was an emergency call for blood donations and my boss asked me to donate with her. As

I gathered my things I realized that I might not be allowed to donate now that I was an openly gay man. For the first time in my life I had found a reason to give blood, a way that I could help save lives. That is, until I found out that I couldn't. Not because I wasn't feeling well, or because of my travel history, or a tattoo, but because I had had sexual contact with another male even once since 1977, because I am gay.

There are many ways you can still legally be discriminated against for being gay here in the United States. However, none of them come directly from our government like the MSM lifetime deferral does. Are you aware of the negative stereotypes and stigmas this ban perpetuates and the consequences it has on gay and bisexual men?

During the epidemiology presentation at the HHS meeting, Dr. Amy Lansky provided data that showed a majority of new HIV diagnoses in 2011 were attributed to MSM. The data also showed that blacks or African Americans made up the largest proportion in terms of ethnicity. Dr. Brian Custer later pointed out that the REDS-II data showed there are HIV-positive donors now, and one quarter of them are female who aren't affected by the MSM policy. If there are other groups that are at an increased risk for contracting HIV, why are we only banning this one?

Dr. Alan Williams informed us that most international MSM donors screening policies include a time-based deferral that

greatly exceeds the longest known HIV testing window period. Dr. Richard Benjamin showed how Australia introduced a one-year MSM deferral with no significant increase in HIV risk. If there are other countries who have changed their MSM policies without any increased risk, why are we incapable of doing the same?

Dr. Williams highlighted the unsolved issues with donor history questionnaire sensitivity. Number one, better screening mechanisms are still needed that will distinguish at-risk versus low-risk. Dr. Custer presented findings from the REDS-III Blood DROPS study that speak to the emerging differences in the nature of MSM donors versus the broader community of MSM. He calculated that a substantial number of recipients are already receiving blood from MSM donors. Dr. Kristen Miller found in the donor questionnaire study that gay men were so much more likely to have an HIV test than any other group; and so, you can, sort of, surmise that this group of people probably knows more than any other group of people that their blood is safe.

Number two, need to understand and reduce noncompliance. Dr. Williams noted that noncompliance is now recognized internationally as a major contributor to the low residual HIV risk that remains in the blood supply. Dr. Custer suggested in the REDS-III Blood DROPS presentation that noncompliance probably is increasing more specifically with respect to self-assessment of risk. Dr. Stephanie Wilson found in the donor

history questionnaire study that the issue of compliance or self-deferral problems are not unique to MSM. The pattern they see among MSM is no different than any group of potential donors; people don't walk into a center unless they already think their blood is safe.

There seems to be a connection between noncompliance and self-assessment of risk. However, individual risk assessment, which could potentially remove discrimination against sexual orientation from the deferral process, was rejected as a deferral option at the HHS meeting. One of the reasons being that further studies would be needed to determine practicality and safety. Why not make a recommendation to begin those studies?

HHS Committee Chair Dr. Jay Menitove put it best when he said, "To maintain the trust and compliance on the part of the public, it is time to modernize based on what has happened since the early 1980s and make a change." The FDA has said repeatedly it is open to changing the lifetime ban and has been awaiting the results of the HHS research to provide additional evidence. We have the research. The evidence has been presented. Now it's time to take the first step in bringing an end to this lifetime ban. Thank you.

CHAIRMAN JACKSON: Thank you. Next is Ms. Kimberly Haugstad, Hemophilia Federation of America.

MR. BRAYSHAW: This is Paul Brayshaw [inaudible].

CHAIRMAN JACKSON: Okay, Paul Brayshaw, I'm sorry.

MR. BRAYSHAW: Hi, thank you. My name is Paul Brayshaw, and I'll be here in place of Kimberly Haugstad. And I'm speaking on behalf of the Hemophilia Federation of America, as the former president of the board. HFA is a non-profit organization that assists and advocates for those with bleeding disorders. And I'd like to thank the committee for the opportunity to provide the patients' perspective on the proposed revision of the MSM donor deferral policy.

As end users of blood products and plasma protein therapies, it is vital to the health of those with bleeding disorders that all policies concerning the blood supply take patient issues into account first and foremost. That being said, HFA does not support inherent discriminatory policies and feels that there is an opportunity to revise the current deferral policy provided that a robust, comprehensive, hemovigilance program is also implemented.

Those with hemophilia experience firsthand the devastating effects of a tainted blood supply and many remain leery of the ability of those charged with protecting them to do so adequately. In conjunction with our A-PLUS coalition partners, we would like to stress the critical importance of a robust hemovigilance program as a component of any policy change.

Without this system, it will be impossible to track and counter known and emerging infectious threats to the blood supply, whether they arise from a change in the MSM policy or occur more broadly.

In December 2013, and again in November of this year, the ACBTSA recommended the establishment of a transfusion-transmitted infections monitoring program or TTI. We fully support this recommendation. The benefits of the TTI include, but are not limited to, the monitoring of a modified or new deferral criteria, the monitoring of the impact of changes to the donor history questionnaire, the monitoring of the impact of new screening strategies, the comparison of TTI marker rates and risk factors, as well as the pre- and post-implementation of policy changes, and the scientific foundation for the consideration of any future revisions.

We urge HHS to fully fund a robust TTI monitoring program to ensure that the ramifications of all present and future policy changes are tracked and based on sound scientific evidence. And while we support a revision of the current deferral policy for MSM donors, we believe that a comprehensive hemovigilance program must be implemented concurrent with such a change. Thank you.

CHAIRMAN JACKSON: Thank you. Next is Mr. Jason Cianciotto, Gay Men's Health Crisis Group.

Mr. CIANCIOOTTO: Good morning, thank you. I'm Jason Cianciotto, the Director of Public Policy at Gay Men's Health Crisis or GMHC. Our mission is to end the AIDS epidemic and uplift the lives of all affected.

GMHC is committed to partnering with the FDA to ensure that U.S. blood donation policy not only prevents transmission-related infections, but also stops perpetuating the stigma and discrimination driving the HIV epidemic, particularly among gay and bisexual men and transgender people. This is why we advocate for a system that screens all donors, gay or straight, based on high-risk practices that could lead to HIV infection, implemented along with a robust transfusion-transmissible infections monitoring system.

While the proposed change from a lifetime ban to a twelve-month deferral is a step forward, it does not go far enough. Any deferral based on a sexual orientation label, MSM, gay, or bisexual, still perpetuates the harmful and unscientific notion that HIV is transmitted because of who you are rather than what you do.

For the overwhelming majority of gay and bisexual men, donation policy that requires twelve months of abstinence is a de facto lifetime ban. Do you require heterosexuals to be abstinent for one year, regardless of assessing their risk for HIV? This step forward still bans gay and bisexual men who

routinely engage in low-risk behavior, men who would otherwise be eligible to donate if they happened to be heterosexual. For example, my husband and I had been monogamous for 11 years, legally married for seven. Yet under the proposed policy we are still banned for life. If I happened to be heterosexual and married to a woman, we would be ideal donors.

Earlier in the conversation today someone made a comment suggesting that the switch to a twelve-month deferral for someone in my situation put it on par with the kind of deferral that is applied to someone who has sex with a prostitute. Just let that sit for a minute. While data presented on Australia's donor policy -- I'm sorry -- of course, the FDA does not require marriage or monogamy from heterosexual donors, yet a gay man who routinely uses condoms and has not had sexual contact for someone who is HIV-positive, another example of low-risk behavior, is still banned for life.

While the Australia data presented on November 13th support the proposed twelve-month deferral in the U.S., neither the FDA or HHS has acknowledged that you're considering a policy already implemented for 14 years in Australia. One that has also already been implemented in Argentina, Brazil, the Czech Republic, Hungary, Sweden, Japan, and the U.K. Italy and several other countries have even implemented a risk-based assessment similar to what GMHC advocates; and we now have good data from Italy

showing that its number of HIV-positive donors did not increase disproportionately.

What does this say about HIV stigma and discrimination against gay and bisexual men in the U.S.? Does America's commitment to human rights exclude being a world leader in scientifically advanced safe and non-discriminatory public health policy? GMHC recognizes that the United States has a unique history and experience with HIV, which includes the tragedy of transfusion-related HIV infections in the early days of the epidemic. Every hot and nutritious meal we serve, every mental health counseling session we provide, every person we connect to life-saving antiretrovirals, and so many other critical life-saving programs supported by funding named for Ryan White reminds us that HIV prevention includes ensuring that our blood supply and blood products are safe.

Likewise, every day we see the growing concentration of new infections among gay and bisexual and transgender youth, particularly youth of color. The CBC recently announced that from 2002 to 2011 new infections among MSM ages 13 to 24 grew by 133 percent. This also is a reminder to us and this committee that we must support policy that addresses the complex ideology of HIV transmission including the stigma and discrimination driving new infections.

With respect and gratitude for the work you have supported

so far, we urge that a shift of blood donation policy that requires twelve months of abstinence for gay and bisexual men be just one, albeit an important, more step in the journey to a risk-based donor screening system. One that is focused on behavior that can lead to HIV transmission and that is blind to the sexual orientation label of the donor. We must stop reacting to HIV like it's the early 1980s when our country assumed it was a gay disease. With your help we can keep our blood supply safe through policy and practice rooted in science without perpetuating the stigma and discrimination still driving the epidemic. Thank you.

CHAIRMAN JACKSON: Thank you. Our next speaker is Mr. Nicholas Taylor from the AIDS Institute. No? Okay. Then Ms. Kimberly Miller from the HIV Medicine Association. Is she here?

MS. MILLER: Hello. I have no financial disclosures. And my name is Kimberly Miller. I'm a Policy Officer with the HIV Medicine Association, speaking here on behalf of our board chair, Dr. Adaora Adimora of UNC Chapel Hill. And you can also see the letter we submitted for the record.

The HIV Medicine Association appreciates the opportunity to provide public comments to the committee in support of your work to advance evidenced-based blood donation policy. We represent more than 5,000 medical providers and researchers working on the frontlines of the HIV epidemic across the United States. And we

are housed within the Infectious Disease Society of America, with a membership of 10,000.

Since 2004, the HIVMA has strongly supported changes to the blood donor deferral criteria. And we urge the committee, today, to at minimum adopt the ACBTSA recommendation to reduce the exclusion of men who have sex with men, MSM, to one year. However, we urge broader changes to the criteria to reflect advances in blood testing technology and scientific knowledge regarding the transmission of HIV disease. Specifically, HIVMA recommends that blood donor screening procedures be revised to ask all potential donors to exclude themselves based on risk behavior regardless of sexual orientation.

We remain very concerned that requiring a one-year abstinence period for MSM, regardless of risk behavior, is not grounded in the science regarding both transmission behavior, and risk behavior, as well as today's diagnostics for detection of HIV infection and other bloodborne pathogens. And we see some -- we would point out the focus on HIV alone, just -- itself, speaks to the discrimination, because we know there are so many other bloodborne pathogens, like HCV, that are going undetected at much higher rates in the general population than HIV. And in addition, we note that a one-year exclusion period will still unjustly exclude most HIV-negative MSM from donating blood, unless they are sexually inactive, which makes no sense.

We hope that there will be ongoing work on the blood donor exclusion policy to focus the deferral criteria on risk behavior rather than sexual orientation. We strongly support the additional studies recommended by the ACBTSA to work toward blood donation deferral criteria that will protect the blood supply, while also reducing discriminatory overexclusion of HIV-negative MSM. Thank you.

CHAIRMAN JACKSON: Thank you. Next is Mr. Peter Sprigg, Family Research Council.

MR. SPRIGG: Good morning. My name is Peter Sprigg and I am a Senior Fellow for Policy Studies at the Family Research Council in Washington D.C. And I have no financial interest at stake regarding this policy.

I urge you to oppose any change in the current lifetime deferral as blood donors of men who have sex with men, unless it can be scientifically proven that a revised policy would result in no increase in risk to the blood supply. Even a small increase in risk is unacceptable. Let us not forget the dramatic magnitude of the increased HIV risk in this population. The Centers for Disease Control reported in May, quote, "Gay, bisexual, and other men who have sex with men, represent approximately 2 percent of the United States population. Yet, in 2010, gay and bisexual men accounted for 63 percent of estimated new HIV infections in the United States and 78 percent of

infections among all newly infected men." Close quote.

As the FDA website says, a revised policy would have to identify a subset of this group, quote, "who do not still have a substantially increased rate of HIV infection compared to the general population or currently accepted blood donors."

The very small size of this population means that any potential benefit to the quantity of blood supplies would be marginal. Claims like that of one group that such a policy change, quote, "could be used to help save the lives of more than 1.8 million people", close quote, give the impression that currently 1.8 million Americans per year die due to the current policy. This is completely false.

Political and social considerations should play no role in your advice or decision-making on this issue. It should instead be based first, last, and only upon your obligation to maximize the protection of public health. Thank you.

CHAIRMAN JACKSON: Thank you. Next, we have Mr. Larry LaMotte from the American Plasma Users Coalition and Immune Deficiency Foundation.

MR. LAMOTTE: Hi, I'm Larry LaMotte. I'm Vice President of Public Policy with the Immune Deficiency Foundation, and I'm here also representing the American Plasma Users Coalition, of which you have a statement that I think that was distributed to you all. And I have no financial interests at all.

American Plasma Users Coalition, or A-PLUS for short, is -- you've heard from the hemophilia part of that -- of our coalition. It's also people who are using -- patients who are using blood plasma products in one form or another. The Primary Immunodeficiency community, which is the organization that I work with, the patient organization that I work with. CIDP, Alpha-1, ITP, hereditary angioedema, these are all different kinds of conditions that use blood products in order to live normal -- as normal as possible lives in their day-to-day lives. So we thank you very much for the opportunity to talk to you today.

And we, first off, A-PLUS, if you look at our statement, is based on the recent scientific work that has come forth at the ACBTSA meeting in the last month. We are supportive of the reduction to the one-year period. And we want to really emphasize though that this -- all these issues really relate to our constituency patients. They're the bottom line as to what is going to happen and how healthy they can be and how they can trust the blood supply; and that is the most important part of all of these issues.

Now, with that, we believe that it is absolutely imperative that there be a long going -- along with this policy, a very robust, national, fully-funded hemovigilance program that goes along with that. We've heard some positive things today with

regard -- from Dr. Epstein, with regard to funding for such a program. But it needs to be done and at the same time as any change in the donor deferral policy to make that effective. So that we can look for -- not only what kinds of things -- diseases that are happening today, but also what may be coming around the corner that we don't even know about. So the -- such a hemovigilance program is absolutely necessary to provide us the ability to look ahead and look at where we are and assess the kinds of risks.

And I would -- we suggest very strongly that in addition to the question that you have before you today -- which doesn't necessarily touch all these issues that we've been talking about, but we would recommend very strongly that you recommend to FDA and to the secretary that there be a very strong, robust, national, fully-funded hemovigilance monitoring system. We urge you to amend your statements, amend your recommendations, and make that happen on a policy level all the way up to the top. Then we will have a system in place that we have not had and we've wanted to have for a long time -- to look at what is coming down the pike, making sure that the blood supply is safe, not only today but also in the future. Thank you very much.

CHAIRMAN JACKSON: Thank you. Our next speaker is Ms. Susan -- Dr. Susan Stramer who actually -- we've asked her to present donor HIV marker variability over 16 years of Red Cross data.

Yeah.

DR. STRAMER: Thank you, good morning. As Dr. Jackson just mentioned, I'm going to talk about variability of donor HIV marker rates. We've heard a lot this morning about data; we haven't heard how to interpret those data, or how those data serve as triggers for policy changes, and how those would be monitored over time. So let me address those.

First, though, I want to address the recency question that came up that -- for recency assays, if we applied those in blood donor populations, we would only apply those to serologically-confirmed donors who were also RNA-positive. So they would have a tremendous impact on the false recency rates. We would control the population that we study. But, anyway, that's off topic. I just wanted to make that point.

So as far as background and outline, the -- I should have said, I'm an employee of the American Red Cross, and I paid my travel to get here this morning. The American Red Cross, along with the ABB and ABC, America's Blood Centers, support a change in the MSM policy to a one-year deferral.

Nationally representative data do exist from the American Red Cross and have been published for HIV and other agents, including emerging infectious disease agents. So for HIV, they include NAT yield, a [unintelligible] from seronegative individuals. These include -- this includes methods for a

consistent confirmation. We've also published on prevalence and incidence. The ARC, as mentioned, participated in the U.S. risk factor study. We coordinated the surveillance efforts and provided the majority of data.

We have also accumulated HIV data over the 16-year period that I will show, since the beginning of NAT. And I will demonstrate temporal variability in NAT yield. We will see increases in incidence, but relative stability in prevalence. So as we've been talking about this morning, monitoring will require analysis of high frequency occurrences or long time periods for low frequency events to detect meaningful change.

So this is the slide that Dr. Glynn showed from the U.S. risk factor study which covered two years. The data here is split by a quarter so that we could show tracking over time. So the numbers over each bar give you the number of cases, but what's important and relevant to what I'm going to be talking about is HIV. The HIV bars are in red. So these are NAT yield rates, again, with the numbers written over the bars in the little boxes. So for the two-year period of time, for HIV, in 2011, there were 12 cases. For HIV, in 2012, there were two. So those are recent NAT yield cases.

Looking at these data another way, or you can compress them, the way we originally looked at the data for the two-year period of time. Now, these are only the cases from the Red

Cross. Of the 14 cases that were included for NAT yield, 13 of the 14 came from the Red Cross based on confirmatory data and complete confirmation. So looking at these 13 cases, there were 12 in 2011 and one in 2012. How would one interpret these data? Would one say, "Oh my God. We've seen a tremendous increase in the safety of the blood supply."? Looking at the next two-year period of time, what would your conclusions now be? We've gone from one NAT yield case to eight. If this happened post-policy change, would we say, "Oh my God. Something drastic has happened."?

Let's look at the earlier period of time, starting from when we began NAT in 1999 to 2011. This is a significant increase; however, the population base or testing methods did not change. So how would you interpret these data?

These are now all the data put together for the 82 NAT yield cases we've had at the Red Cross the past 16 years. The published yields in the literature, starting from the period of time from 1999 to 2002, are 1 in 3.1 million. That's the frequency of seeing new HIV infections as detected by nucleic acid testing. And the last number we published using the NAT method we use today, Ultrio Plus, is 1 in 740,000. Again, significantly different.

This now puts the NAT yield cases in context with the other markers that we look at by NAT in a triplex assay, HCV in

turquoise and HBV in green. So the yield of HCV is about 1 in 200,000; the yield for HIV is about 1 in 740,000; and that for HPV is about 1 in 600,000.

So what can you interpret from these data? For 16 years of observation, we've seen a mean of 5 HIV NAT yield donors per year, giving you all the variability that I have shown you. The range was 1 to 12. The 95 percent confidence interval of that is 3.43 to 7. Thus, a mean of greater than 7 per year would be significant. That is, we compare two 16-year periods, however that's a pretty long duration to watch, and 7 still is part of the normal variability that we see in data with the range of 1 to 12.

So if use a single data point, for example, a given year, we still just see the same NAT mean yield rate, we still see the same range with a 95 percent confidence interval, which is really our range, 0 to 12. So if we assume that 12 per year is the maximum, or that is the observed maximum, the 95 percent confidence interval of that is 4 to 20. So now if we rely on 7 per year as a trigger, this then is not outside of the observed range. So it may be statistically significant, but it's not biologically significant. So should the trigger be 20 per year, corresponding to an upper 95 percent confidence interval of the maximum value? This preliminary analysis demonstrates the uncertainty of managing very rare events.

So now let's talk about data tracking. A lot has been said about incidence and prevalence and if or if not those are measured in the U.S. blood supply. What we have been doing so with the Red Cross -- we represent about 42 percent of collected blood in the U.S. and collect blood in 44 of the 48 contiguous United States -- contiguous states in the U.S.

So this was the paper that has been referenced earlier by Dr. Brambilla, from Zou and colleagues of the Red Cross. So this number now gives you, or this slide gives you, prevalence rates per 100,000 first-time donors. The bottom line, or the line with the circles, are female donors; the line in the middle are total donors; and the line on top are male donors. This now is over a ten-year period of time since NAT introduction. So the line with the diamonds in it are males, as I said, and they range from about 14 to 18 per 100,000.

So interestingly enough, if you look at the three centers and take the male first-time donors that participated in the U.S. risk factor study, acknowledging that their confirmation rates may have been a little bit lower than those for the Red Cross, we see about 13, so within the expected variability. So prevalence is stable and the U.S. risk factor study confirmed that the numbers going into the future are representative of what we've seen in the past.

Now let's look at incidence. These are now repeat donors.

In the dots on these bars, these are females; the vertical lines are total donors; and the horizontal lines are male donors. So what you can see over the five two-year periods of time, if you look at the bars with the horizontal lines there's an overall increase in trend, so we are seeing an increase in incidence.

What we did in this paper was -- looked at the two periods of time, the last two periods of time, to look for significant differences. And there were significant differences. And the significant differences were mostly attributable to 16 to 19 year old male donors, who were, again, responsible for about 60 percent of this increase. Again, this increase was significant.

In each of these two-year figures, the total number of incident donors observed was 62 to 97. Now if we look at incidence for the Red Cross, incidence was not measured in the U.S. risk factor study, but if we look at the same two-year period of time for the Red Cross donors, we see an incidence of 2.94, or 62 incident repeat male donors. So the 3 actually does kind of correspond or is relatively close to the figures we see for 2007-2008, which were just above 3. So, again, it's relatively stable. But over the long period of time we have seen incidence.

So thoughts regarding rare events, for example, HIV and blood donors. Long-term measurements of prevalence in two-year incidents, as I've shown you, are more stable than one-year

measurements, as I showed you for NAT yield rates. So measurements over short periods of time may be too insensitive to detect meaningful change. Using the available 16-year data as a baseline, what would be deemed acceptable? Should we look for a NAT yield of greater than 20? Should we look for prevalence in first-time male donors that is significantly greater than 13 per 100,000, or incidence in repeat male donors that is significantly greater than 3 per 100,000?

Should we use that in combination of other measures? We've talked about recency, but we really haven't focused on what we can call out of questionnaire data. What we saw for REDS-II, as far as noncompliance, we measured that 61 percent of MSM -- male -- HIV-positive male donors, 61.7 percent of those declared MSM, which is actually not too different than the incidence you've heard from CDC, as far as HIV and incident male donors who are MSM. But as far as a background, this is consistent with what other studies have demonstrated, about a 1 to 2 percent rate in control males of MSM. So with that, I can answer any questions. Thank you.

CHAIRMAN JACKSON: Okay. Thank you, Dr. Stramer. I think we'll go through -- we have two more. So next we have Ms. Mary Clare Kimber from PPTA.

MS. KIMBER: Thank you. My name is Mary Clare Kimber, I am a salaried employee of the Plasma Protein Therapeutics

Association. PPTA is the international trade association and standard-setting organization for the world's major producers of plasma-derived and recombinant analog therapies, collectively referred to as plasma protein therapies.

PPTA supports the use of science-based decision-making in determining whether there should be changes in FDA blood and plasma donor eligibility criteria for MSM. PPTA applauds HHS for undertaking studies that provided data for consideration. PPTA respects the recent recommendation from the ACBTSA to reduce the lifetime deferral to twelve months for MSM, providing any change in policy is accompanied by a robust monitoring system to evaluate the impact of such a change.

PPTA member companies are committed to providing safe and effective therapies. Patient populations who receive the therapies made from plasma have chronic and serious conditions. Donor selection is one of several layers of safety in the manufacturing of plasma protein therapies, and includes state of the art testing of individual plasma donations and manufacturing pools, followed by a robust manufacturing processes with dedicated safety steps. Plasma protein therapies are a distinct class of therapeutic products which undergo significant viral inactivation and product purification processes that provide plasma protein therapies with significant virus safety margins. Companies have made substantial investments in all of these

areas and in over two decades there have been no documented transmissions of HIV or hepatitis B or C.

PPTA's Voluntary Standards Program for collectors of source plasma and manufactures of plasma protein therapies contributes to safety of source plasma and plasma protein therapies. The standards include, among others, provisions for testing donations and manufacturing pools with both serology and nucleic acid amplification testing. Donations from one-time source plasma donors are not used in manufacturing. Donations undergo a 60-day inventory hold before pulled for manufacturing. PPTA members emphasize the importance of collecting plasma from a low-risk donor population, and one of the standards is the viral marker standard, which sets limits on the number of positive qualified donations for each collection center.

PPTA members operate in a global environment. As such, companies must adhere to often divergent regulatory requirements. For MSM, these requirements vary from continued lifetime deferral, five-year deferral, one-year deferral, to no specific MSM policies. As noted, PPTA supports the studies undertaken by the U.S. government, as the results of these studies are valuable to help inform decision makers around the world.

CHAIRMAN JACKSON: Thank you very much, Dr. Nair -- or -- I'm sorry. One more speaker. And because we don't have an open

public hearing in the afternoon when we have an Ebola update, we do have one speaker who'd like to say something about the Ebola update topic. So Dr. Hari Nair, are you here to give an update on that? No? Okay. Well, it's about 12:30 p.m. at this time. We will be taking a lunch break now and coming back at 1:30 p.m., and then this will be open for discussion. And we can also ask any speakers questions that presented, as well. So please be back here promptly at 1:30 p.m. so we can get started. Thank you.

[off the record]

[on the record]

CHAIRMAN JACKSON: Okay. If everyone could please take your seats, we'll get started. It turns out there were a couple more people who wanted to present at the open public hearing, so I'm going to extend that for a few more minutes. These presentations should be no more than two minutes long. I will have to read the open public hearing announcement for particular matters involving specific parties meeting again. So I will do that now.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

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

So we now have Ms. Miriam O'Day to speak for the Alpha-1 Foundation. If she could -- come on over here [inaudible] --

MS. O'DAY: Thank you very much.

CHAIRMAN JACKSON: So if you could -- two minutes or so.

MS. O'DAY: Great, thank you.

CHAIRMAN JACKSON: Thank you.

MS. O'DAY: I have no conflict of interest to report. And I'm Miriam O'Day, Senior Director of Public Policy for the Alpha-1 Foundation.

First of all, we want to commend all of the advocates here today. We, along with our colleagues who represent plasma recipients, have advocated for many years to ensure that the

discussion of blood safety focuses on the recipient and not on the donor. We hope that all present here today remember that donor deferral is but one component of blood safety.

This is not a political issue. If it were a political issue, the decision would be very easy. This is not about sexual orientation. It's about risk associated with behavior. This is not about civic responsibility of the act of compassion of donating blood. This is about ensuring safety. In fact, the recipients that I represent don't care if our donors are gay or straight, wear cowboy hats or baseball caps, are Democrats or Republicans. What they care about is the product that they're going to infuse on a weekly basis is as safe as possible, and that all of the fail-safe methods of testing, donor deferral, and safe manufacturing are in place to ensure that safety.

Individuals who have alpha-1 antitrypsin deficiency have a genetic defect; they're missing a protein. They receive a weekly infusion that replaces that protein. The cost is approximately \$100,000 to \$150,000 annually. And what it does for them is it sustains life, it -- in many cases, stops them from getting bad infections that causes additional lung function loss.

So we are members of A-PLUS and have worked in coalition with our other plasma consumers for quite some time. And we support the statement that's been submitted to the committee. We encourage a better understanding of known and emerging pathogens

in specific populations. We recommend the establishment of a framework for accelerated approval of pathogen reduction, removal, and/or inactivation technologies. And we demand that hemovigilance be a vital part of any change that's made in policy.

Thank you very much for letting us come forward and make our statement to the committee today. Again, we want to make sure that the focus is on the recipients and not on the donors when we have discussions of blood safety.

CHAIRMAN JACKSON: Thank you very much. Next, we have Dr. Edward John Alara [spelled phonetically] from PRIME Biologics who will -- wanted to present on the topic of our Ebola update, which we'll be talking about later. But please, go ahead.

DR. NAIR: Thank you. I'm Dr. Hari Nair, who's the Executive Vice Chairman. These are his remarks. He's in Singapore; I'm his American counsel, so I have a bias. We're just here to talk about the concerns that we see prospectively with Ebola: the need for separation technology that can be used in a hot zone, because we're all concerned about the potential risks; the inability of many countries to accept plasma that would come from convalescent patients.

So our goal is to help work with you to develop hyperimmune globulins and technology that works in situ, in that theatre. And it accomplishes two things: one's reduce the risks and

concern; and two, it provides you with a mechanism for a placebo arm control -- or a control arm that is ethical and local. And you can then use that as a mechanism for treating vaccines or experimental drugs. So I have written remarks, but thank you very much for your time.

CHAIRMAN JACKSON: Thank you very much Mr. Lara [spelled phonetically]. Is there anyone else from the audience who would like a couple minutes to address the committee, before we move to discussion of today's topic? One? Okay. Please just state your name and association.

MR. MCCALL: I'm William McCall. I am the Director of Health Policy for AIDS United. I don't have any conflicts of interest. We are a -- AIDS United is a grant-making technical assistance and advocacy organization working to end the HIV/AIDS epidemic. AIDS United supports the end of the FDA's policy indefinitely deferring men who have had sex with another man, even one time since 1977, from donating blood.

However, we also recommend that the FDA go further, to further research and, ultimately, implement a deferral system based on behavioral risks for all donors, regardless of their category. AIDS United, under our previous name of AIDS Action Council, has long recommended that the Department of Health and Human Services institute policies that carefully distinguish between high-risk and low-risk categories of behavior and

achieve better identification of risk categories.

In particular, we support a deferral policy that would include the identification of people at high-risk of donating blood infected with HIV or other transmissible diseases, allowing MSM at low- or no risk for HIV to make blood donations. As we have noted in the past, the current policy is discriminatory because it pertains only to MSM and is based on outdated information about what actually constitutes risky sexual behavior.

It is also of concern that the current system of screening does not distinguish between higher or lower risk behaviors for any at-risk group. We also remain concerned that the policy has become so discriminatory that some citizen groups have started to boycott blood drives. We don't support such a boycott, but that's happening and leading to a decreased pool of donors. AIDS United believes that the recommendation to end the lifetime deferral for MSM and replace it with a one-year ban is helpful in moving away from this highly discriminatory current ban, but does not reach the ultimate goal of distinguishing between people at high-risk of transmitting HIV and those at low-risk.

New York-based GMHC, which you've already heard from, which is a member of AIDS United's Public Policy Committee, issued a study of blood donation policies in 2010, "A Drive for Change: Reforming U.S. Blood Donation Policies." They recommend setting

and implementing an individualized risk-based assessment system. AIDS United continues to support this ultimate outcome. We, therefore, call for the FDA to support and fund the additional research that is needed to implement a comprehensive and effective risk-based deferral system for all donors. We agree with the many other speakers with the further recommendation to ensure that U.S. implements a strong hemovigilance system to reduce risk to the blood supply. We appreciate your willingness to review this policy and we look forward to engaging in the process. Please do not hesitate to contact us. And I'm going to pass these --

CHAIRMAN JACKSON: Thank you. Is there anyone else? All right.

OPEN COMMITTEE DISCUSSION

QUESTIONS FOR THE COMMITTEE

CHAIRMAN JACKSON: We will move to this part of the -- where we will be discussing the question at hand. But first, based on what you've heard today, and including the recommendation from the HHS Advisory Committee on Blood and Tissue Safety and Availability, are there general comments about the recommendation and the deferral period that's being recommended in general or the comments we heard in the open public hearing today, before we address this serological marker issue? So, Mr. Dubin.

MR. DUBIN: Thank you, Mr. Chairman. I think we got to look at the house of cards that we're talking about. And I pick my words carefully. But we have a situation where we heard some very good presentations. I think it was Dr. Brambilla -- did I get your name right? And Ms. Owen -- that I think were really wonderful and I think we've heard a lot of good discussion about recency testing and its importance. And yet it's built on a house of cards. Our good friend, Doc Holliday, over here got up and kind of saved the day in terms of funding, as Dr. Epstein does a lot.

But I think for us, in the hemophilia and the A-PLUS community, and especially at the Committee of Ten Thousand, because we had three calls this last week to discuss this --

Rich Colvin, M.D., Ph.D., who used to sit on this committee. And while we see the need for change -- no question, we see -- we were one of the earliest groups in the hemophilia community to call for that -- there is no support at the top. We see a secretary who seems to be out of touch with where we're talking about going. How long will FDA funding last? How do we put in place a longitudinal, realistic, long-term surveillance that's commensurate and is co-joined at the hip with the policy change? And I don't hear that. We don't hear that.

And, in fact, we've heard that the administration believes it should be decoupled or uncoupled, whatever the word may be. And that troubles us because we're about to make an important change that we should make. And yet, short of FDA stepping in to fund it, I would say short-term, unless Dr. Epstein has a different answer, we feel like we have a house of cards. And we feel as though we could comment on a serological aspect; we would support that, obviously. What we learned about trend reporting is really important and I thank you all for that.

And yet, we've got a lot of good people and no push and no motivation from the people that really matter at the end of the day. And so, for us, it feels like a house of cards. And that's why I chose that term, Dr. Jackson. Because I think we've got to -- if we're going to look at the big picture and we're going to change the policy, for us in the bleeding disorders community,

it's got to be lockstep with surveillance. Because surveillance tells us about the trends; it tells us what's happening. And we're happy to see it go to a year, if those are coupled. Uncoupled, there's difficulty.

And I think that -- one thing I might say is, in hemophilia, we paid a pretty big price the last time it went south. And we're ready to see the change because the change is important. The policy is not scientifically supportable. And yet, where are we going to get the money to do the surveillance and get the support of the secretary? Thank you.

CHAIRMAN JACKSON: Other general comments on the recommendations or the deferral period? Dr. Leitman?

DR. LEITMAN: We're not really discussing this, the recommendation made by the Advisory Committee on Blood Safety, but you asked for comments. So I'll just say this, because it's a comment. In 31 years of blood banking, since 1983, it's been -- it's been pounded into our heads that we are to mitigate risk --

MR. DUBIN: Yep.

DR. LEITMAN: -- for recipients.

MR. DUBIN: Yep.

DR. LEITMAN: Over and over again, use of a precautionary principle that sometimes makes no sense at all; that's clearly discriminatory. It's discriminatory against travelers who lived

in England for six months. Or people in the military who are on a base in Germany or other parts of Europe for six months during 1980 to 1996. So there's a lot of exclusions and some of them -- they're all driven by data and by science. But sometimes there's not a lot of data to suggest it's a reasonable risk/benefit outcome, but you use the precautionary principle.

This is the first time in 30 years that a step away from that mitigating risk has been taken. And I don't think any of the data I've seen today calms me in terms of not increasing risk to the transfusion recipient. It has to be the case, really, that more HIV-positive and other marker positive units are going to enter the quarantined inventory in the blood center or transfusion service. And if they do, there'll be an increased risk to staff of a percutaneous injury, which we know happens. And a very small risk of a quarantined release error, which we're going to talk about later. So this makes me uncomfortable.

If I look at the science, I would be very, very wary of a one-year deferral for MSM. And it really -- it sounds to me as if we're talking about politics and civil rights and what one of the public speakers just mentioned, rather than what our primary duty is. Which is transfusion safety for the recipient.

CHAIRMAN JACKSON: Well, I would agree with much of what you said in the sense that I think it's always been the mission of this committee, as long as we can have an adequate supply of

blood, that we should do whatever it takes to increase the safety of that blood supply. In this case, with the 12-month deferral -- you know, we've done very, very well, I think. If you look at the data and the number of transmissions, which look like they're probably about 10 a year that get through the window period of being NAT negative, which is really quite, quite good.

It's -- by changing this policy it's hard to see that there's -- from a scientific basis, in terms of improving on the transmissions, that that will likely happen. There's more downside risk than upside risk. But given that, you know, I think it's important that this committee really think about, within the context of the serological markers or a hemovigilance program, what can we do to make sure that this change in policy does not increase risk for blood transfusion recipients. And what are the markers and types of studies -- maybe not so much studies, but in this particular case, we're looking at various markers to see whether, in fact, risk is going up in terms of window period transmissions.

I think Dr. Stramer presented some very good data on the NAT yield data, and offered one of the suggestions about what might be a confidence interval and NAT and maybe could be done in conjunction with some of these recency antibody tests to help confirm or not. Obviously, there's a -- what we didn't see was

what is the association of these recency test results with NAT test yield. I mean, that's what we don't know. And so you could get an increase in recency tests, and maybe they're not due to false positives, but it's not clear that that necessarily means that we're actually having more window period transmissions or not. Whereas, my own opinion is the NAT yield is the most direct marker and would come closest to telling us whether we are having more window period transmissions or not.

I think there does seem to be a -- judging from the emails that probably many of us got, being on this committee, that the science -- you know, the testing is so good that the risk is minimal. But, in fact, you know, there is this window period of, you know, eight to 10 days or so, and there are to date transmissions occurring. So it's not a perfect test at this point. And I do think it is reasonable to have deferral periods.

I guess what we don't know -- I mean, it could be a good thing, changing the deferral period to 12 months. Because maybe compliance or noncompliance will actually go down and it makes the blood supply safer. On the other hand, it might get worse and it may make it worse. So I think we just don't know. But if we don't know, we should put something in place to make sure if there is a problem, we know it soon and reliably. So, Dr. Knowles.

MS. KNOWLES: So I think we're mixing apples and oranges a

little bit today on our -- with our question that we're being asked and the topic that we're talking about and the public were talking about. So we were talking a little bit about this. And it seems to me that if our question is based on the assays that we need to be really clear that -- what those assays can do for us is quite different, and in some ways not related to the immediate change that we're making in terms of safety, which you were asking about earlier -- in terms of making the blood supply safer immediately.

So by that I mean -- my understanding, and I'd like to be corrected by the experts who spoke if I am not right about this, is that -- since we're talking about such small numbers, we're looking at these assays as a way of increasing the time, the MDR, that we have to be able to get better estimates and better data. But that's not -- that's going to tell us about -- long-term about the implications of our policy change, should there be one, and about disease trends and population trends. And that really feeds into more information about the general background of blood safety.

But what it doesn't tell us is about individual units and it doesn't tell us about reasons for non-compliance of future donors. It doesn't give us any of that individualized data that we might want, that would then feed into a better risk portfolio that -- what we should be looking at in terms of putting policy

changes into place. The risk that a number of people talked about, and the way we do manage risk, generally, and lots of other scenarios in the government. So it doesn't give us those kind of individual -- capturing more cases or individual motivation.

So it's -- and it's also related to a very small subset of bloodborne pathogens. So it's -- and not the most prevalent one. It's all focused on HIV. It's -- so it seems to me to be a very, very small set of what would be a hemovigilance -- a true hemovigilance program. So I think we need to kind of unpack a little bit: one, the policy change; two, the testing that might come in additionally to give us post facto information about the effects of some policy change; and then this larger issue of hemovigilance, which seems to me to be a much larger level issue as well -- that's being requested to go hand-in-hand quite strongly, it seems to me, by the blood user committee -- community, I mean.

CHAIRMAN JACKSON: Dr. Simon.

DR. SIMON: Yeah. I'll just take this opportunity to summarize the industry position. And I think as you've heard and seen in some of the statements, the blood banking community has looked at the data and feels that they can scientifically and medically support the change to the 12-month deferral. And, as you've also heard, they strongly support the kind of

hemovigilance program that's been discussed and that the FDA is seeking to have fully funded. So I think we have a strong support there from the blood banking community.

In the plasma community, it's a little bit different. I think we're willing to support the 12-month deferral and to support the hemovigilance, just as the blood bankers do. But as to what we will actually do will depend on whether the European regulators follow the U.S. regulators. So if the U.S. makes a change to a 12-month deferral, source plasma donations cannot change in those centers that are also EU-qualified, unless the European regulators also change. And we've not been able to get a reading on that. So in terms of whether there would be a change or not, it remains to be seen. And just a little reminder, there are actually more source plasma donations in the U.S. each year than there are blood donations. So that's a big part of what it's regulated.

We do have an internal program to monitor viral markers that's required within industry. And because our donors frequently donate frequently, we actually pick up those incident cases. In other words, a donor could be negative within a few weeks and then appear NAT-positive. With our 60-day hold, all those units would be removed. So I think if we did make the change and we saw a safe -- could see a safety signal fairly quickly and revert back if necessary. So that's just a little

aspect.

I do want to amplify Dr. Leitman's comment about the political issue and the right to donate. And I think it is important that this not be -- we try to keep this in the scientific, medical realm and not as a political issue. And we're seeing some evidence of this around the country where, you know, it's seen as a civil rights issue, public accommodation issue. And that we do have to be focused on the recipients' safety first and foremost. And there isn't a right to donate, but a right for our patients to have the safest and most efficacious product we can provide.

CHAIRMAN JACKSON: Dr. Nelson.

DR. NELSON: Yeah, I fully support your last statement. I think that that's quite true. That there is -- this isn't a civil right. I mean, I can't donate because I -- often because I travel to Asia and Africa frequently and have been to places where malaria -- where -- was common. And I don't feel like I'm a pariah just because of that reason.

But one of the concerns I have is that if we change -- if we make changes, and I'm -- I more or less support the change. But if we make changes, will it be misinterpreted by a segment of the community that is at high risk? We know that a segment of the MSM community does have high prevalence and incidence. And we've seen from the data that Dr. Custer presented at the other

meeting, and was summarized by Alan Williams, that there are donors who ignore the current prescriptions from donating, and many of these donors come from the MSM community. And is -- if we make a change, will it be interpreted by some, maybe minority of the minority community, that now it's okay to donate irrespective of behavior.

And it's hard to measure, but I would think that maybe in addition to hemovigilance we should do -- if we make changes, we should try to do some behavioral research to go along with -- such as the behavioral research that was reported and summarized by Dr. Williams -- to see if the change in donor qualifications is properly interpreted by the community that may be at the highest risk.

So I -- and because I agree with Dr. Stramer that even if this leads to one or two transfusions of HIV, that's not acceptable. And it's going to be hard to measure that because there's natural fluctuation and the rates are already low, and they probably will continue to be low. But we really need to know how -- if we make a change, how is it interpreted? And is there a change in interpretation of the donor exclusion criteria by the community that might be at highest risk?

CHAIRMAN JACKSON: Mr. Skinner.

MR. SKINNER: Thank you and thanks for the invitation to expand beyond just the question that was being posed to the

committee today. I'm fearful that we're at risk of leaving a lot of people, both on the committee, as well as in the audience, and those listening, unsatisfied if we don't have this expanded discussion. Because what we were expected to discuss today, or at least what I thought I was being invited to join the committee to discuss, is not the question that was presented, nor does it really reflect what was in the federal register.

So I think we have made some leaps of faith. And to avoid this dissatisfaction, I think we need to figure out the path forward which is equally unclear to me, in terms of how the administration is sequencing or going to deal with these issues. We've already heard, and I have deep respect for Dr. Epstein, but funding is uncertain. We don't know what's going to happen. And Mr. Berger's comment this morning to my question about the secretary's response -- I recognize the secretary has changed -- but the recommendation for a hemovigilance system has been sitting in the secretary's office for over a year. And I think the secretary's support for this is clearly undetermined. So we're facing today, dissatisfaction, uncertainty, undetermination, and unclarity in terms of the path forward. And that's troubling to me. And we're not being asked the sort of -- the ultimate question or even the penultimate questions that lead towards that.

As a consumer and a recipient of blood products and someone

who acquired HIV and the hepatitises in the 1980s, I have a deep sensitivity and, obviously, a great personal connection to blood and plasma and safety. So my own personal evolution is really hard to separate from sort of the scientific judgments that we're being asked to make here today.

But as we've discussed it, as Corey and my colleagues in the plasma users community, and joined by the thalassemia, and back in 2010 in the sickle cell community -- we have all said that we want a science-based decision. And for the integrity of what we called for, we feel obliged and feel grateful that the administration has moved forward with a series of studies. All of the data wasn't presented here today. Some of it was summarized and many of us had the chance to read or see the previous testimony. But we did reach the conclusion and are comfortable with a one-year deferral not being an increased risk for the populations that we represent. Our goal is not chasing zero, in terms of zero risk. Our goal is looking at a balancing of risk.

And we recognize that there are fundamental inequities in the system. And I completely empathize with my friends in the -- in I guess what I'll characterize as the gay rights community, but also the gay health community. I think they raise very legitimate issues. And while discrimination can be appropriate, we have an -- to protect public health -- we have an obligation

to reduce it where possible. And we believe the one-year is certainly that appropriate balance.

I think we have the issues a little bit out of order. And I would like to see this committee on record firmly for a hemovigilance system before we discuss an add-on or discussing the recency. It seems to me discussing that without a firm basis on which that builds is a little bit lacking. We need certainty and confidence as end-users of the blood supply. And if we leave that uncertainty, I think we only risk muddling the debate even farther than it already is, and perhaps, increasing the politics around the issue. And our goal should really be to really keep it focused on science. So I would like to see us -- if it's not possible to take a vote, to get a sense of the committee that a strong hemovigilance system is a prerequisite before any discussion of recency as the test forward.

One of the pieces of data on which we reach the conclusion that there is not -- that one-year is appropriate is the data -- Brian Custer and the Blood DROPS data, which indicated a likelihood that there would be an increased compliance rate with a shorter deferral period. And I believe, as Dr. Alter summarized at the ACBTSA, that assuming that compliance rate was going to improve, there was minimal difference between one-year and five years. Our friends to the north, in Canada, picked one-year to provide that buffer of confidence. And if we rely on the

evidence that was presented at ACBTSA, one-year should provide us that same level of confidence.

But that all sort of evaporates if the hemovigilance system is not there to track that and to test that over the course of time. So our acquiescence, acceptance, support, whatever you want to frame it, of one-year is strongly preconditioned on that hemovigilance system. We need to know that the small study of Blood DROPS is in fact indicative of the whole population. And I think a hemovigilance system will also leave others more satisfied that the government is taking seriously their concerns and going to have the data to continue to evaluate. We may find that we need to pull back or we may find that we -- actually the data supports going farther.

But without that system in place, everybody's going to be uncomfortable. The patients that are the end-users are going to be uncomfortable that we don't have the data to support the conclusion. Those that are feeling discriminated are going to be uncomfortable because they don't feel like the government has a commitment to collect the evidence and go the next step to go farther. So I would ask, as chair, that you consider putting before the committee a question or a statement or allow us to make a strong statement on hemovigilance before we really move into the discussion of recency. Because I only see that as an add-on that's built on a foundation.

CHAIRMAN JACKSON: Well, I think those are all excellent points. I can ask Dr. Epstein. I know we are not going to vote on any particular issue today, but I know that comments regarding these issues are certainly welcome and the FDA is very interested --

DR. EPSTEIN: Yeah.

MR. EMERY: -- in hearing that.

DR. EPSTEIN: I think, coming back to the remarks by Ms. Knowles, it's important to share with you the concept that is in the mind of FDA and the NHLBI with regard to donor marker monitoring as part of blood safety surveillance. First of all, we do understand that HIV monitoring, and more specifically HIV recency monitoring, is a small piece of a larger whole. It would be our intent to support a monitoring system that includes other infectious disease markers. Additionally, you made the point that following those rates in the aggregate doesn't tell us what's going on with the individuals and doesn't tell us where the risks are coming from. This was understood when the REDS-II study, that you heard summarized by Dr. Glynn, was undertaken. And it was the reason that that study had two components. One was about the marker rates and, of course, computation of prevalence and incidence. But the other was to look at risk factors by interviewing the positive donors and controls.

We share that concept. It would be our expectation that as

a monitoring system is developed and progresses that it would incorporate the risk factor analysis, although it may not be able to do that immediately in so-called phase one. But as we developed a system, we understand that that's an essential element to understand whether there are changes or there are not changes and the sources of risk.

With that, I think we hear, loudly and clearly, that there's a need to further study the interpretation of the deferral policy to figure out why there may be noncompliance. So it isn't good enough to figure out that perhaps an attributable portion of risk is coming from a certain population; we also need to understand why that's happening. So we get that too.

And then lastly, we do understand the need for a system that is capable of addressing emerging infectious disease. We're going to hear about Ebola. I think right now it's not a significant threat to the U.S. blood system, but it is a concern. You know, Chikungunya, dengue virus, hepatitis E, the list goes on. We know that we're going to continue to face challenges.

So I just want to be perfectly clear that we do understand the need that the monitoring system should be comprehensive. That it is not a question simply of HIV. And that -- although it will have the capability to assess whether risk has changed subsequent to any policy change on MSM, that's not its principle

driving force.

In fact, the principle driving force is to recognize the need for an ongoing surveillance system based on donor marker data which enables us in a continuous fashion to assess the risk to recipients from transfusion-transmissible infections. And that the decision to implement such a system was made prior to this meeting, but, obviously, prior to any final decision about a policy change on the MSM deferral. And that's exactly for the reason that's been articulated by several committee members. Namely, that we need it in general. That we need to be able to monitor the safety of blood supply. This is the most efficient way to do it; and there has been a commitment of funds by FDA and the NHLBI.

Now I appreciate the disquiet that's been articulated. You know, how long does that go on? You know, is there commitment in the department? And so forth. But what I can tell you is that the agencies do understand the need; we do appreciate that it needs to be comprehensive. We also do appreciate that it needs to be long-standing and we have put forward financial commitments. That's as far as we can go today. But I would like to believe that that position of the agency is reassuring.

CHAIRMAN JACKSON: Dr. Allen.

DR. ALLEN: Thank you. Let me briefly just reiterate my strong support for comprehensive hemovigilance, the type of

studies that Dr. Epstein talked about, and certainly the type of studies typified by now REDS-III that is well into its initial lifespan. The importance of a study such as REDS, supported by National Heart Lung and Blood Institute, is obviously that it changes over time. It has moved and grown as the information has warranted that. And rather than just a static surveillance system, I think it's important to have one that is capable of responding to our -- to new information that might be there.

I personally support a move to a one-year deferral. I recognize that there can be some unexpected issues that come up with that. The primary one is how can we get everyone, all potential donors, to comply with the deferral criteria that are there? And if we change it, we don't want, you know, more people coming in who are not compliant with the system. We want to increase the compliance with the system.

So that speaks to me to the need for behavioral studies to understand how we better communicate with potential blood donors about risks. How we get them to hear the need to answer the questions honestly. And we haven't done enough in that over the years. And I think this is a whole area about educating donors and getting the questions asked that need to be asked with regard to behavioral risks and getting people to understand the important of self-deferring if they have any of the risk criteria.

So I think there's a lot of things that need to be done. We'll move on at some point this afternoon to discuss the actual question that's before BPAC or the discussion item. But I think that this is an important point for us to make, that -- yes, it is time to move on. There have been changes throughout. The blood supply today is much, much safer than it was 15 years ago. And we can do even better than we've done.

CHAIRMAN JACKSON: Thank you Dr. Allen. Dr. Rhee.

DR. RHEE: You know, I just wanted to say that I'm a little frustrated by this process, actually. Because there's a lot of mixed things going on here. Then there's -- there's politics and then there's science. And we're an advisory committee, we're supposed to be a lot more about science than politics and policy, which we really don't do a lot of policy. We answer specific questions as the one that's been posed here. But there's a lot of implications and interpretations as can be done as a result of this.

So this a commentary time period, so I'm just going to make a couple of comments because there's a -- [unintelligible] that everything is based on really good data and that these policy changes are based on abundance of data. And I don't think that I've heard that data. So I know that MSM is one of the highest risk populations. And if we allow that into the pool, our blood product is not going to be as good as it used to be. Our -- we

have one of the best products out there in the world, and our safety record is one of the best, and it's because our policy is probably one of the best.

So as we lax on that policy, it's going to probably put us at some risk. And it's going to be a small risk. And it was mentioned, it's probably going to be a balanced risk. So there's science that lets us make some good decisions, but there's also estimates and there are going to be guesses. So I think as we go to this deferral period, that's more of a guess as to what's going to happen and is going to take time before we get the data that proves to us whether that was a good decision or not.

But, you know, some of the simple questions are not been answered, which is going to help people make that policy decision. For example, one of the big political issue here is about, you know, men who have sex with men. And I agree that, you know, just a blanket policy like that, that was done decades ago, is not a good one. It makes sense to try to quantitate people more in risk than just saying, you know, a blanket statement. But then -- if we're going to do that, then I need to be able to have some numbers for comparison.

And I don't have that number for comparison, because the odds ratio is kind of here for me. And it tells me that when you do tattoos or exchanging money for drugs or sex, your odds ratio goes from 2 to about 5. And if you go into a group of people who

are MSM, then your odds ratio goes to 62. And then if you have HIV -- you have sex with someone who is HIV, that odds ratio is 131. It's huge.

But if we're going to take some of the comments that were made by the public, then I think we need to ask that question. For example, if you are MSM who is monogamous and you have -- are HIV-negative and your partner is HIV-negative, I'd like to see what your odds ratio of HIV is. And then we can make a good decision that's to say -- you know what, we should probably not be so blanketing with our policy, make some alterations and that. But I just want to state that that type of data, it was not presented to us. But a whole bunch of other information was presented to us. And then on top of all of that, there's a policy and -- that policy's probably going to go through. But yet, at the same time, we're asked a very specific question about the serological test.

And then, from the committee perspective. You know, we're mostly all here -- we're mostly all very science-grounded and based. So, of course, we're all going to, you know, vote for and ask for hemovigilance. But it is going to come at a cost.

CHAIRMAN JACKSON: Dr. Stowell.

DR. STOWELL: Actually, we've talked about several things today which potentially could have an impact on donor safety. And one is changing the MSM deferral, and one can speculate that

that could make it safer because fewer noncompliant people show up. Or maybe it'll make it less safe because more people who are -- at risk for HIV show up to donate. We've talked about the hemovigilance -- enhanced hemovigilance system along the lines of the REDS study and using MDR as a tool for that. We talked a little bit also about recipient hemovigilance, if you will, or improved reporting of A.E.s.

But with all of -- and we've seen a fair amount of data about all of these things. None of the data, though, that we are looking at are perfect. And after we have MDR and all the rest of it, those data aren't going to be perfect. They're never going to be complete. And we can ask for data for decades. [laughs] I think one of the points that Sue Stramer made was these are very, very, very low-frequency events. Accumulating data on them is extremely difficult, as we have seen. So we're going to have to make some decisions and make some leaps of faith, because we're never going to have perfect data.

CHAIRMAN JACKSON: Okay. One last and then we'll address the question. Mr. Dubin.

MR. DUBIN: Thank you Mr. Chairman. I want to respond to Dr. Rhee. I think that we would all agree on hemovigilance. The problem is -- FDA supports it, we know that. And we appreciate that and we believe the agency does. But that hemovigilance will not be delivered without the support of the administration and

the secretary.

And I think that's almost a scientific question, because if -- for us as end-users or people with an arm in the game, as we like to say, that surveillance is critical to any forward movement in policy change. It's the science you speak of that underwrites the policy that -- I think we agree that's the job of this committee. To look at the science and say, "We have enough science to say yes to this" or "No." And I think that that's what this discussion had to happen, because a lot of us were troubled -- you can look around this table and know, probably, everyone sitting here supports hemovigilance. That's clear. How we get there -- and for us to say, "This is okay", given who we are, there has to be that sense that beyond FDA, up above, there is real support. And we don't see that. And I agree with what -- Dr. Miller?

DR. STOWELL: Stowell.

MR. DUBIN: Stowell, sorry. I agree that it's -- and what Sue Stramer was saying, that they're low -- low-level events, to use radio analogy, kind of low-frequency -- because I'm in radio -- kind of like a 60 cycle hum. But at the same time, what you said, Dr. Jackson, is true. There will be a risk change. And what does that mean? Well, the only way to find out is good science.

CHAIRMAN JACKSON: Okay. Let's move on to the question for

the committee, which is, "Please comment whether serological tests for recency of HIV infection and HIV antibody positive donors are sufficiently accurate to be useful for blood safety monitoring." So we heard the presentations, and we've had some comments on those. But people want to comment on whether they think they're sufficiently accurate at this point? Yes, Dr. Basavaraju.

DR. BASAVARAJU: So I think for me to comment on this I would probably need some clarity from the FDA on what you mean by "useful for blood safety monitoring". So do you intend for the recency assays to be used to calculate residual risk of transmission? Or do you intend for those to be used to get a general idea of how recent the infections are among antibody positive people? And what exactly do you mean by "useful"? What would you do with the results?

DR. EPSTEIN: Well, I mean, ultimately, what we want to be able to measure is the residual risk. In other words, what is the risk of a marker negative donation? We recognize that recency test results don't directly give you incidence related to window period negative collections. Right? Because they're not measuring the NAT window. And I think what we heard is that you can mathematically deduce the NAT window from the recency window, but that the uncertainty would go up.

So the bottom line here is that if we have better

numerators from recency testing compared with NAT only testing, we can get an earlier answer whether something is changing. We won't be able, immediately, to go from there in the short term to knowing whether residual risk has changed. But it would be a clue to us that something has changed, and then that can lead to investigation. So this is all about surrogates that would be helpful towards monitoring change in the system and, ultimately, safety.

Now, if the question you're raising is, "Well, what would be a trigger for making a further policy change?" We're going to have to have that discussion at some subsequent forum. Because first we have to figure out what our metrics are, and then we're going to have to figure out how do we use them. But, clearly, the idea would be triggers that would alert us. And then the question is, at what point do we have to reconsider policy? So that's what we mean by "useful".

DR. BASAVARAJU: So would you -- would the FDA consider individual NAT?

DR. EPSTEIN: I'm sorry. Could you repeat that? I couldn't hear you.

DR. BASAVARAJU: I said, would the FDA consider individual NAT, if you're going to make this policy change?

DR. EPSTEIN: Well, you know, I think that that's a legitimate question, first of all. We understand that the window

period from individual sample NAT is about half as large as the window period for mini-pool NAT as it's currently practiced with, you know, various pool sizes. There would be a lot of risk and benefit discussion that needs to take place because the impact on the industry of moving to individual sample NAT would be very large. And can that change be absorbed by the industry? So I'm not going to pre-judge that question. I think it's a fair point.

We do know that in some countries, like South Africa, when they made changes in their donor selection criteria, they offset any candidate or potential increased risk by risk reduction moving from mini-pool to individual NAT. So I do think it's a fair question, but I do think that it has very, very large operational implications which would need to be discussed.

Now, we dealt with this, as you know, for West Nile. And we settled on a triggering strategy so that we don't do ID-NAT for West Nile year-round. And that's been tolerated, I would say, by the industry and with benefit to blood safety -- but not easily. And it would be on a much larger scale if we now do it for all of the markers. It would be done with multiplex testing; it wouldn't be isolated to HIV. That means that much more resolution testing and -- also, ID-NAT has higher false positive rates. I'm sure you're aware of that. So perhaps, I guess, with your permission, Mr. Chairman, perhaps someone from the industry

would like to comment. It's not as if no one has thought about this.

CHAIRMAN JACKSON: Dr. Stramer, Dr. Dodd [spelled phonetically], would you want to comment on that or not?

[laughter]

DR. STRAMER: I think -- Sue Stramer, Red Cross -- I think Dr. Epstein did summarize the issues quite accurately. We do West Nile triggering during the summer when the risk is highest. We adjust what we do to compensate for that increased risk. We do so and we do see increased false positive rates. The difference in specificity between -- or should I say the false positive rate in an ID versus a pooled NAT is about tenfold, so we would increase the number of false positives we see. We use pools in this country of 6 to 16, so that would increase the volume of testing by 6- to 16-fold.

We're not supposed to address financial issues at this committee meeting. But if we're talking about funding of a national hemovigilance system, probably the cost that would -- it would take to drive individual unit testing would maybe be better used in driving a hemovigilance system. Because the cost would be astronomical and the benefit may be very, very small.

CHAIRMAN JACKSON: Dr. Nelson?

DR. NELSON: I think that the -- that these recency test could be very useful. And we don't know what we'd find. But --

as an example, I was involved with investigating a harm reduction program in Taiwan after there was a major outbreak in injection drug users. And during that -- and it was very effective. But one of the tools that we used in addition to screening drug users, and surveillance, et cetera, was a recency assay -- was a BED assay. And we found that of the positives, most of them were not recent after the harm reduction program was in place.

If we found a population, or an area of the country, or something like that where there were an increase in recent -- evidence of infections within the last six months or whatever the window period -- you know, the period was for a recency assay, we'd have a better chance of doing that than we probably would pick up window -- you know, NAT positive, antibody-negative. The numbers would be larger. So I think the chance that we might find something -- so I think it's a useful -- I would think it'd be a useful surveillance tool if it -- you know, if it was affordable. And I would support use -- implementing it as a surveillance tool.

CHAIRMAN JACKSON: Let's see, Dr. Knowles.

MS. KNOWLES: Yeah. I just think it's probably important for us to be clear that -- to drill down again to what it's actually useful for. So I think it's important to understand why we're coupling this with the other topic of MSM. So I think it's -- I

want to highlight the fact that -- my understanding is -- it's really for background blood safety information; and that one of the things that may be happening may be a change in the MSM policy.

But if we're going to answer this question specifically, it seems to me that we can answer, from what we've seen, that it -- the issue of sufficiency, I think, would be good for us to address -- whether it's sufficiently accurate from what we've seen. It's clearly not accurate with -- one of the tests is clearly not accurate with some of the HIV strains that we don't see in the United States. And it doesn't just say "in the United States", but is assuming that's what it means. But also we might -- it might be useful to see population trends. It might be useful to see -- to what Dr. Epstein was talking about -- if we see change. That change might be a change in donor populations, in age of donors, in impacts of intravenous drug use, legal changes.

So I don't think -- I think we need to understand that we're not just going to necessarily be looking at this to try and pick up changes that derive from the MSM changes that are coming or not coming. But that we'd be looking at this more broadly to see general trends and changes in blood safety that might have nothing to do with the MSM policy changes whatsoever. And I think in that larger frame it makes sense to look at this.

Would you agree with that, Dr. Epstein?

DR. EPSTEIN: Yes.

[laughter]

MS. KNOWLES: Thank you.

CHAIRMAN JACKSON: Dr. Simon.

DR. SIMON: I must say, you know, in my simplistic way of looking at this, I assumed that the interest in the recency is - - if you changed the question to 12-months and somebody comes in to donate who says he hasn't had MSM in 12 months but the -- and he's positive and the recency shows that it was something -- was it something a long time ago or was it something in the 12 months? It kind of informs how well the question is doing.

But I think in a general sense, I had a little difficulty understanding the detuned assay when it came out back a few years ago. And I think we heard a lot of very interesting data. But my sense would be that this would be a useful tool and it would be -- as part of -- could be considered part of the research effort in this area. I don't think one would rely on it exclusively. But certainly I'd be supportive of including it, and I think it would be helpful in the hemovigilance effort to the FDA. So I guess my answer -- I'm not sure it's sufficiently accurate to be useful, but I think it would be useful to employ it in -- as part of the research [unintelligible].

CHAIRMAN JACKSON: Mr. Dubin.

MR. DUBIN: I think from our perspective, it becomes more a question of the tool box, if you will, or arrows in the quiver, that help us to understand something. I think the reason is it's important in an MSM-context, from a scientific standpoint, is if it does -- and I agree with you, it may not be accurate enough. We don't know yet. But if the trend in population changes that Ms. Owen and Mr. -- I'm sorry, I -- Brambilla?

FEMALE SPEAKER: [inaudible] --

MR. DUBIN: Yeah. And I know your name.

[laughter]

MR. DUBIN: And if it's that kind of added tool that allows us to see trends potentially in changing demographics in your donor population or what's -- I think Dr. Rhee or somebody or Toby, you said about injection drug users -- one of you. I think those are trends -- from an end-user or recipient who's got an arm in the game, so to speak -- those are trends we must be able to see. And so we might add tools in the tool box that we're not sure yet are absolutely on point, but add to our general scientific-based tools to get some sense of trends that could be trouble. And trouble's something we know about.

And -- so for us, it becomes important to MSM because we don't believe you're going to do one without the other. And so it kind of -- you're right -- crosses into just a bit of policy. But in order to understand why the science might be important,

we have to understand the bit of the policy. And I think, as Mark said, we don't see zero risk. Although people think we do. We understand there's a risk landscape and we would go back -- everybody got the IOM summary, Recommendation 12 that talks about physicians and patients and discussions and that. That's still ongoing, Recommendation 12.

And so I think all these tools in the tool box helps us to learn. But I agree with you totally, we need to stay on the science. That's our route, that's our charge as a committee.

CHAIRMAN JACKSON: Dr. Allen.

DR. ALLEN: After reviewing the background papers that were provided to us and listening to the discussions today, which have been very helpful, I think the answer to my question is -- absolutely. They're sufficiently accurate. We've in fact been using them in the RED studies and in many other types of studies over the years. And they've developed over that period of time; we're in a very good point in the development now. Are they the same ones we're going to be using in five years? No, we'll have much better tools at that point. So you're absolutely right, Mr. Dubin, in terms of these are part of the tool box.

So I think we need to move forward. And as much as the question of the sufficient accuracy of the tests is the design of the study. And we need to -- not we the committee, but the groups that are responsible for putting this together, need to

spend a lot of time carefully designing what the studies are that will use this in order to help with the safety monitoring and improving the overall safety of the blood supply.

CHAIRMAN JACKSON: Dr. Kuehnert.

DR. KUEHNERT: Yeah. I would -- well, first of all, I want to say as far as this issue about coupling with policy, I think if everyone's agreed that hemovigilance is important, that it should just be done now. And then we don't have to worry about coupling because it's ongoing. And then whatever happens after that is fine. So, you know, I think it sounds like everyone's agreeable to state that we've needed it for a long time. So there's no better time than now.

Concerning the question, there -- I think we've heard -- and hopefully, I got this right. Dr. Owen can correct me if I'm wrong. That this recency test is somewhat -- it's dichotomous in terms of the answer that you get. So really the key is at what time point that you're looking at for, you know, the test that you're using. So it really does -- it's very important to understand the question that's being asked in terms of monitoring. If we're talking about it, 12 months or six months or a sooner time frame.

And the other issues really are related to, you know, what was presented in terms of variability when there's sparse data. The false positive rate, so false recency, and then -- and then

the confidence interval, which again relates to, you know, your numerator. So I think all those things have to be taken into consideration when the question is about sufficient accuracy. So, you know, echo the thoughts Dr. Allen had, that it really has to do with how the study is structured as to whether it's sufficient or not -- but certainly useful.

CHAIRMAN JACKSON: Dr. Stowell.

DR. STOWELL: Yeah. So also put in a good word for the recency assay and its use. It's intended to be used as an exploratory tool, as a research tool. And so I -- some of the criteria that we'd look for -- do screening tests or to tests that we use to managing specific donors are different. The presentation by -- and I forgot her first name, Owen, I believe -- and she talked about specificity and sensitivity of one of the assays being somewhere in the 85 percent range. But for screening tests [unintelligible], that's horrible. But this isn't a screening test; and so, I think it -- the considerations are really very different. And so I think it can't help but be useful. If there's -- 15 percent of the time, it doesn't give an answer, well, that's what Western blot did too.

CHAIRMAN JACKSON: I guess, I think it is a potential tool in a tool box, although I think I'm more skeptical than probably many on this committee. Having been in this field and have seen, you know, over the years, there's clearly been a selection bias

in publication when it works. And then as soon as somebody tries to duplicate it with a different population it falls apart. And we see this over and over again. And that's why I was asking about -- did they fit the algorithms -- which algorithm fit that data. And so before you spend a ton of money and design all these studies, I would certainly want to do a simple duplication of a population that may be similar, just to see whether you really can get the sensitivity and specificity that you need here.

Again, it's another tool. I don't think it's as good a tool as a NAT yield test. And I'm surprised that, you know, we can't always get this data, as Dr. Stramer was saying. The Red Cross does it because they agreed to do this as a project. But many blood centers across the country do not confirm these NAT yield tests. And I would think it would be fairly simple for the FDA -- maybe I'm wrong, Jay, in terms of guidance -- to say we're only talking 10 a year of 14 a year, we saw up there -- to make sure that if they have one that they send it somewhere or contract it to actually confirm, so we get a much more or at least a better idea of what the real NAT yield is. Because I think that is the best marker of window period infections, figuring it's probably double whatever that is.

And I thought Dr. Stramer's, you know, suggestion of that confidence interval, if it goes over 20 you start getting

worried. Obviously, it would be nice to have some other data that might support that, but it may not. I mean, you just -- we didn't see data that correlated the recency tests with actual window period or NAT yield type tests. So I'm not sure what -- in theory, there should be a relationship, but not necessarily, because you could think of all sorts of reasons, population-wise, why that might reflect -- be discordant in that.

So I certainly wouldn't want this to be the only test for monitoring blood safety; and would really suggest that NAT yield be bolstered with sort of mandatory reporting of that and confirmation. And so -- yes, Mr. Dubin.

MR. DUBIN: I forgot -- excuse me, I'm just having some cramps from one of the ARV drugs. It gets a little rough on the muscles. I apologize. Oh, I know what I wanted to say.

There's a 900 pound gorilla in the room, and that's called recipient surveillance. It's something that the committee's raised for many, many years. And not that we've fallen on deaf ears, because I think Dr. Epstein has always responded and listened and discussed with us. As has his team at FDA, Dr. Weinstein, Robin, all of you have heard us.

And yet, we still feel we have to raise it, put it on the table, and say, "We understand the focus on donors for the blood bankers; that's your bread and butter game." But there needs to potentially be a reevaluation from a scientific standpoint by

this committee and maybe by Dr. -- Mr. Berger's committee of policy -- of recipient surveillance. The only one we understand doing recipient surveillance is the Centers for Disease Control under these two gentlemen. Thank you.

CHAIRMAN JACKSON: Point. Yes, Susan -- Dr. Leitman.

DR. LEITMAN: So maybe this is simplistic or too direct, but what you're talking about in a recency test is confirming that you donor educational and training tools worked; particularly, if you change eligibility criteria for MSM, which is what we're talking about the 12 months. You want to make sure the message of a risk activity that's very well-defined in the 12 months prior to donation is understood and abided by the donor. That's what a recency test will get us. So it's very pertinent to this discussion we're having today.

But if you really want to best validation that your screening materials are working, it's to speak to the donor. And it's a very small number of donors. There's 343 on the last page of Sue Stramer's Red Cross handout. That's about half what you'd see in the U.S. as a whole -- so maybe 350, 700 total. Plus those are NAT positive, serologic positive. Then you add -- 12 times 2 -- 24 NAT yield. You're talking about a minuscule number of donors to call. And that was one of my roles in -- at the NIH, to call the donors. They'd come in. They universally came in. They came in within hours of a phone call that the blood

bank director wanted to speak to them.

And one-on-one -- there's a universal honesty, especially, if it's presented by a counselor who's had experience in this. So if you want to know when the exposure was, talking to the donor by an experienced counselor is the way to do it. And it's got to be much more accurate --

[laughter]

DR. LEITMAN: -- than an 85 percent sensitivity and specificity for an assay. So that's what, across the entire United States, should be done. And it wouldn't be difficult.

CHAIRMAN JACKSON: Excellent points. Any other comments? So -- yes, Dr. Allen.

DR. ALLEN: Just -- this actually goes back briefly to the other earlier discussion. And that is they were talking about the need for -- in discussing hemovigilance approval -- for support from the secretary's office and the administration. I would also like to remind everybody here, especially those who have access to large groups of members, that funding of the studies comes from Congress. And getting to the members of Congress, especially educating the new members -- education to the members of Congress in advocacy is extremely important in terms of getting funding. Actually, far more important than getting the secretary to support it.

CHAIRMAN JACKSON: Okay. I think -- in terms of this

discussion, I think several points were brought up. One I thought I heard a lot of support for, the hemovigilance program and funding for that program. It sounded like the number of people on this committee were supportive of the recency test as a potential tool in the tool box for -- as a supplemental test, as part of our other tests -- of being able to monitor blood safety or looking at the risk of what we're seeing in the donor population and its correlation with this. But at the same time, you know, having more direct markers for blood safety, such as NAT yield or asking donors specifically their -- who are positive -- their risk factors or motivation for donation could be much more direct and certainly cheaper and easier and probably more accurate than some of these -- this test. Although it can be used for different things, especially more epidemiology-type data for the population as a whole.

And then, I guess, another point being made that any sort of hemovigilance program shouldn't just be focused on this, but, of course, the other markers and bloodborne pathogens that we all worry about. Because changing this -- changing this policy, this is not just potentially increasing the risk for HIV. I mean, the MSM population has much higher prevalence and incidence of things like hepatitis B, or syphilis, or HHV-8, things like that. So it's not just HIV we're talking about here, so.

So any other comments at this point? Dr. Epstein, is there anything else you want this committee to address before we take a break and then hear the Ebola presentation?

DR. EPSTEIN: I just want to thank the committee for the discussion. I think this is very useful to the FDA and we've obtained the inputs we were hoping for.

CHAIRMAN JACKSON: Okay, thank you. All right. We're going to take a quick 10 minute -- 15 minute break and then have an update on Ebola.

EBOLA VIRUS AND POTENTIAL IMPLICATIONS FOR BLOOD SAFETY

CHAIRMAN JACKSON: So the next topic will be an update for the committee on Ebola virus, which I'm sure generates a lot of interest these days, and its potential implications for blood safety. And I think to give us an update is Dr. Gerardo Kaplan from OBRR, FDA. And I think there are slides in your packet, as well, on this.

DR. KAPLAN: Thank you Mr. Chairman for the introduction. My name is Gerardo Kaplan. I am a principal investigator at the Office of Blood Research and Review, CBER, FDA. And what I will talk today is about an update of the activities that the Food and Drug Administration is doing on the area of blood in response to the Ebola virus outbreak in West Africa.

So, basically, I will talk about two main areas. One is related to the issues that we are dealing with blood safety itself. The other set of issues is the use of convalescent blood, convalescent plasma, and immunoglobulin preparations as a therapeutic intervention for Ebola virus disease patients. I will go fast through my introductory slides because we -- everybody is very knowledgeable with this issue. We are constantly being bombarded by the news agencies; and so, the level of understanding of the virus is pretty high at this level. And I will emphasize some things that I think that are important for the blood safety.

So Ebola virus is enveloped virus belonging to the Filoviridae. It's negative-sense RNA, has about 19 kb. It's -- the form -- filamentous particles with different shapes. The virus is [unintelligible]]. The Ebola glycoprotein is one of the main -- is the main component of the envelope. And antibodies against this glycoprotein induce immunity. And most of the vaccines that are currently being used are based on immunization with a glycoprotein. This is a zoonotic virus. It's a Category A agent and it has to be dealt under [unintelligible] conditions.

So Ebola virus causes Ebola virus disease and is highly pathogenic in humans and primates. Incubation period is about four to 21 days, usually more four to 10 days. At the onset of the disease, it is characterized by fever, severe headache, muscle pain, weakness, followed by diarrhea, vomiting, abdominal pain, and sometimes, diffuse hemorrhage. It can induce multi-organ failure, and in some cases -- lead to severe hemorrhagic fever. It has a very high level of morbidity and very high levels of mortality rates.

So the natural reservoir is presumed to be fruit bat. But other animals are also infected, for instance, monkeys, duikers, pigs. And there's reports of the transmission, animal-to-humans. And it's probably the way that the disease started. There's also human-to-human transmission, and this is done by direct contact with body fluids of symptomatic individuals.

Blood and blood products from symptomatic individuals can transmit Ebola virus through -- but it's unlikely that these donations will be even taken because people will be symptomatic and would not be able to donate. However, and this is -- I think, it's a very important issue, there's a potential viremia prior to symptoms and this pose a risk for blood safety. The groups at risk are the healthcare providers caring for Ebola virus patients, and family, friends, and other close contacts with Ebola virus patients.

There are no treatment. There are no vaccines. The standard care is intravenous fluids and electrolytes, treatment of secondary infections and pain control. And convalescent whole blood, plasma, and immunoglobulin preparations have been used empirically as investigational treatment.

There -- some compelling blood safety issues in the U.S., for instance, the potential transmissions from Ebola virus disease from donations of asymptomatic individuals, including travelers from the endemic areas, and potentially secondary and tertiary transmissions. And we have such cases in the U.S. So, a person that presents with no symptoms, but is infected, then develop the disease. There's -- and this is quite important -- there's no proven effective therapy right now for EVD. And the efficacy of convalescent plasma, monoclonal antibodies, and small molecules have not been proven. And another issue is the

use of convalescent plasma and blood products for expatriates or local cases in the U.S.

And CBER has developed a group of initiatives in dealing with the Ebola epidemic. And the first one is the draft of a guidance. FDA is also serving as a WHO consultant on empirical use in control studies of convalescent blood in West Africa. FDA is also participating in U.S. government/blood industry working groups to allow the availability of plasma and immunoglobulin preparations for U.S. patients. FDA is granting INDs and IDEs to allow plasma collection and treatment of patients. And lastly, we have -- FDA has developed assays that can be used to check for antigens and antibodies. And these assays could be used for diagnostics and also to qualify donors that have high antibody titers.

So the draft guidance is expected to address donor suitability, donor deferral recommendations, and blood product management. This draft guidance will be issued for comment. I would like to point out that the industry has already developed recommendations and -- for instance, PPTA has recommended a 60-day deferral, where it's possible exposure. And AABB has recommended a 28-day deferral for travel or contact.

On the area of WHO consultations, FDA has contributed to the development of the Blood Regulators Network, BRN, position paper on convalescent whole blood and plasma as treatment for

EVD, Ebola virus disease. This paper gives the general consensus of why this treatment could be useful and just also outlines some of the implications of the use.

FDA has also contributed in the development of WHO guidance on the use of convalescent whole blood or plasma collected from patients for transfusion as an empirical treatment during outbreaks. And in this guidance, WHO has described in more detail donor suitability, transfusion of blood, et cetera -- more detailed guidance. And we are -- FDA is also currently participating in WHO working groups for convalescent blood and plasma for use as empirical treatment, in clinical trial design, and in development of reference materials for Ebola assay standardization.

As I mentioned before, FDA is also participating in U.S. government and blood industry groups. For instance, Ebola Convalescent Plasma Working Group has been formed. And several agencies and associations are participating, for instance, FDA, CDC, HRSA, ARC, ABC, USAMRIID, AABB, ASPR, and DOD. The idea is to coordinate the effort and facilitate the use of convalescent plasma for the treatment of Ebola virus disease in the U.S.

FDA is also participating in meetings of the Randomized Control Trial Protocol Working Group organized by NIAID. And these are investigators from the three clinical sites where convalescent plasma is used as empirical treatment, mainly NIH,

Nebraska, and Emory. And so, these groups discussed with U.S. government agencies the implementation of randomized control trial protocol to test safety and efficacy of therapeutic interventions also including convalescent plasma. It's interesting -- this group -- the moral issues and the issues here for the implementation of the randomized control trials are very significant. And it's very clear that we will need such randomized control trials to really understand the efficacy of not only convalescent plasma, but also many other treatments.

In terms of the review work that the OBRR is conducting, it's mainly done by the Divisions of Hematology, in terms of the consultation with the treatment centers in the form of pre-INDs and IDEs to discuss possible treatment with different centers. Also, it's the review and approval of emergency INDs for single use patients, and also consultations with blood establishments and manufacturers for blood collection and product development and the review and approval of INDs and IDEs for specific products.

Finally, I would like to mention the assays that we are developing at the Food and Drug to test for antibodies and antigens. And we have developed a Sandwich ELISA to measure soluble Ebola virus glycoprotein. And this assay could be used as a confirmatory for PCR. I know so far they've developed for - - as a stand-alone and probably a rapid diagnostic test to be

implemented in Africa or in treatment centers here in the U.S. as well. We have developed ELISA to measure antibodies against Ebola, specifically against the glycoprotein. And these are two kinds: it's a capture ELISA with the recombinant protein as a fusion protein; and also, virus particle ELISA based on several variants that have the Ebola virus glycoprotein that expose Ebola virus glycoprotein. And this is, as I said, very important for the qualification of donors that have high titers for the Ebola glycoprotein. And this is very important for qualification of these donations.

We have also developed neutralization assays. And here, I'm talking about the last version of a neutralization assay, which is a fluorescent reduction test. We'll call it FRNTs. And this is a pseudovirus [spelled phonetically] that has the Ebola virus glycoprotein and also a green fluorescent protein. So when the virus cells are infected, the cells become green. If you want to check for neutralizing antibodies, [unintelligible] neutralizing antibodies that will neutralize this. So the virus -- the level of green fluorescence will come down and you can have a good reading of neutralization levels.

There are many challenges that remain. And perhaps the most compelling challenge is to prove that whole blood convalescent plasma and immunoglobulin preparations that according to empirical use, they're really effective. And this will require

the development of and understanding of clinical trials, randomized control trials, to figure out whether these treatments are effective or not. And this is probably one of the main challenges remaining. However, these trials should also provide us some clues about the criteria for the effective use of plasma: where to give it, which patients benefit more, doses, et cetera.

And finally, there's a compelling need to understand whether immunoglobulin preparations from convalescent plasma are effective for now, as well. And this could be done by using the monkey challenge model, which will provide us very direct information of the efficacy of these tests.

So to sum up what I've told you, is that the FDA has taken steps to enhance blood safety in the U.S. in response to the current Ebola virus epidemic in West Africa. FDA has facilitated the use of convalescent plasma as investigational treatment for Ebola virus disease. FDA is contributing to the worldwide efforts to contain the current Ebola virus epidemic by providing expertise to different groups. And finally, FDA has developed these antigen and antibody tests and that may contribute to international public health efforts. And I will be happy to answer any questions.

CHAIRMAN JACKSON: Okay, thank you very much, Dr. Kaplan. Just to remind the committee, the FDA is not seeking advice or

recommendations from the committee on this topic, but the committee members may ask questions of the FDA or Dr. Kaplan on this topic. But the FDA is not seeking advice or recommendations on this topic.

MR. DUBIN: Dr. Kaplan, are you aware of the work of Dr. Ciambrone [spelled phonetically], who was the first to fractionate for Highland Labs in the 60s, and then developed the Ciambrone Foundation? He was working in conjunction with UCI, University of California, Irvine Medical Center, on the antimicrobial and antibacterial qualities of whole plasma. And that work continues. He patented a number of things or they're in the process. But he had some interesting results. And I assume that some of the secondary issues with Ebola are bacteria-driven. Correct?

DR. KAPLAN: Correct. And this is a very important issue because we really do not know at this point whether convalescent plasma -- what is the active ingredient in convalescent plasma.

MR. DUBIN: Right.

DR. KAPLAN: Whether there's the immune part or just the nonimmune part --

MR. DUBIN: He did some work on that, is why I raise his name.

DR. KAPLAN: So these clinical trials -- control clinical trials are very important to figure out whether non-convalescent

plasma has a therapeutic effect. And we know that, you know, it's more valuable to use less restrictions. So it would be very important to determine whether non-convalescent plasma, non-immune plasma, has therapeutic efficacy.

MR. DUBIN: And there's a guy at UT -- his name slips my mind -- UT Houston, who's doing it with the military in mass [spelled phonetically] units -- actually pouring it into wounds and promotes healing. So there's a lot out there we're hearing about.

DR. KAPLAN: Yeah. And --

MR. DUBIN: I thought it might be helpful.

DR. KAPLAN: Yeah. And hopefully randomized control trials will give us the right answer.

MR. DUBIN: Yes. Thank you.

DR. KAPLAN: It's very important. Sure.

CHAIRMAN JACKSON: Dr. Kaplan, you mentioned the concern about a person may be viremic before they are symptomatic. With the tests that you're working on, or the PCR test that is being used now typically for monitoring, has there been any data to -- in people -- they've actually shown viremia before they actually became symptomatic or not?

DR. KAPLAN: No. There's very little information about that. I can tell you a couple of things. One, that the PCRs that are currently approved or in EUA, emergency use authorization,

they're notorious because they're highly insensitive. They're -- 10 to the 5, 10 to the 6 genome equivalent level [spelled phonetically]. So these tests are mainly to confirm that someone is infected. But it's nothing like we have for blood screening. And so, they will be useless. We are trying to develop more antigen tests that are very, very sensitive. You know, reaching the picogram level of sensitivity that could be used not only here, but also as a rapid test in Africa. So that's also a very important issue, how to control the disease, and how -- if it becomes more widespread in the U.S., how to use tests currently, [unintelligible] tests to control it.

CHAIRMAN JACKSON: Questions for Dr. Kaplan? Okay. Well, thank you very much.

DR. KAPLAN: Thank you.

CHAIRMAN JACKSON: And good luck. All right. So this is the last agenda item today, so we will adjourn.

ADJOURNMENT

CHAIRMAN JACKSON: We will reconvene tomorrow. I believe it's at -- no -- is it -- sure it's not 9:00 a.m.? I have 9:00 a.m. on here.

MALE SPEAKER: 8:30 a.m.

MR. EMERY: I've 8:30 a.m. right here.

CHAIRMAN JACKSON: I've got 9:00 a.m. right here. [laughs]

[unintelligible commentary]

CHAIRMAN JACKSON: Okay. So 8:30 a.m. we'll reconvene. And those staying at the hotel, I believe, will have the shuttle again at 7:15 a.m. Okay?

(Whereupon, at 3:29 p.m., the meeting was adjourned.)