DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

FDA WORKSHOP ON BEHAVIOR-BASED DONOR DEFERRALS IN THE NAT ERA

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C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

DR. DAYTON: Welcome. Thank you all for getting up so early to join us. This is the FDA Workshop on Behavior-Based Donor Deferrals in the NAT Era. I don't think we need more of an introduction than that. Our CBER Center Director, Jesse Goodman, is going to open the workshop with some welcoming comments. Jesse?

Welcoming Remarks

DR. GOODMAN: Well, I would like to welcome everybody and also thank you for your participation and interest and input because this is really what this is about--discussion and input.

Just a few very brief comments, some of which will be echoed by Dr. Epstein, but I think that many of the people in the room here have a lot to feel very positive about. Whether you are a donor, a part of the government or part of the blood community, blood recipient community, there has been such a dramatic change and improvement in the safety of the blood supply, particularly from the viral pathogens we are all so aware of in the

last 20 years or so. I remember very palpably, having been involved in the care of HIV and hemophilia patients at UCLA when this was all happening, just the terrible toll of that situation, some of which still continues but it is because of a lot of people working together, despite really challenging issues and because of the application and development of new technology that we really are in such a better place.

So, I think we should start with that as a congratulatory note. In addition, some methods continue to improve. We refine our ways in which we screen donors and we improve testing. Now, I think, as I will get to in a second, that is not a reason for complacency. In fact, that is a reason to tell us what we can achieve and why we should try to continue to achieve that because we should not take safe blood supply for granted.

One of the reasons for this discussion is to consider how and whether improved testing may change any approaches practically to how we manage blood safety. Of course, one issue in recent years

that contributes to this openness to think about this issue is the general introduction of nucleic acid testing and screening which, as people know, has really tremendously improved the safety margin for viral pathogens, and also is a platform that allowed us to face new emerging pathogens--West Nile virus.

As I said, I think today for FDA we are here to be primarily in a listening mode but also to share our current information, models, some of the scientific basis for where we have been. I want to emphasize that this is not a decisional meeting or process at this time. It is also not intended to be a debate. We can say quite openly that we don't have a preferred or predetermined outcome. I want to say that personally I know many of us and we have spent a lot of time dealing with blood availability challenges as well as having blood and plasma products available to benefit people. You know, personally I am a donor, except that I am currently excluded because of travel. I have to talk to our staff about that.

But we do appreciate the desire to donate. I think this is a very important and socially valuable thing in a society where we really need to value those kinds of contributions highly, and we appreciate the interest in making sound policy.

Sometimes there can be some emotional issues in this but, you know, I want to assure everybody that our policies and our considerations of this are based on the science, the protection of the recipient and also feasibility, what can be done. So, we have to look at all of those things.

We do particularly have a primary responsibility to the safety of the blood supply and to the health of recipients. I was thinking about this actually, you know, coming over here and I realize that that, in fact, is a common goal. It is not that readily apparent but why does somebody want to donate? Well, their desire is to give life, to make a recipient healthy. So, we really have to keep in mind the ways in which the donor community, the recipient community and the blood community have common goals.

It is also important to keep in mind that we have a complex system. It has managed to make these accomplishments in safety from contributions from a lot of people, and that starts with the donor, goes to the recipient and includes the healthcare provider and includes the blood community, whether blood banks and systems or transfusion, and it certainly includes the contributions of technology, diagnostic testing, etc. It includes the contributions of our surveillance system and our colleagues at CDC. So, as we look at information we want to hear from all these groups, and as we look at possible approaches we always want to hear from all these groups.

The final thing I wanted to say is, as I started with, there will always be new and emerging threats to the blood supply. You know, one that is mentioned and is on the program because it relates to one particular behavioral deferral, potentially to geographic deferrals, is the HHV-8 issue. In that case there are science gaps, etc., to be discussed. But, you know, we are obviously all

facing a great concern about things like TSE and other future threats to the blood supply.

So, I think we should also be very forward looking and focused not just on the issue of the moment but what are the tools in the long-run that will help protect us against future threats. This is sort of consistent with FDA's scientific initiative, the Critical Path initiative, which is to have, for example on a policy and guidance end, our practices be as robust as possible to face not just the issues of today but the issues of the future.

But also there are probably scientific opportunities there and, again, some of these opportunities in the blood area are not always the focus of huge, large-scale investments. I think we should identify and prioritize what are some of the things we can accomplish scientifically and work with our colleagues in industry, NIH and CDC to get there. Examples there are better testing, abilities to move pathogens in and out of our testing systems, ability to detect multiple

pathogens, processes to inactivate and assure the safety of the products themselves. There has been a lot of work on these but it is all in very early stages; then, finally, improvements in the products themselves, you know, the move towards recombinant products in certain areas, exploration of synthetic products, etc.

So, I try to keep the big picture in mind even though I focus here today on where are we with donor deferrals? How does the testing and changes in testing affect that? And, you know, what are your creative ideas and what is your input?

So, with that in mind, I just again thank you. We are really going to listen to this input. We will try to identify if there are scientific needs, what those are and we will try to move forward in that kind of collaborative spirit. So, I thank you very much. I apologize in advance for having to head off to a flu meeting in Canada, but I will be very engaged in hearing what comes out of this meeting. So, thanks very much, everybody.

[Applause]

DR. DAYTON: Thanks very much, Jesse. Now let me introduce Jay Epstein who is going to give the introduction to the workshop. Jay?

Introduction to the Workshop on Behavior-Based Donor Deferrals in the NAT Era

DR. EPSTEIN: Good morning and welcome. It is my pleasure and privilege to provide a little bit of background and then a quick overview of the program for this meeting.

The FDA general strategy for assuring safety of the blood supply is based on five overlapping layers of safeguards. Our concept over the decades has been to optimize each safety layer as if independent.

What are these safety layers? Well, first, as you know, we engage in screening and deferral based on risk factors. These can be geographical, behavioral and medical. We go about this through a process of donor education, which is followed by self deferral, and then we have a health historian perform an interview and if these factors are elicited then, likewise, there is

deferral.

The second tier, of course we focus on a great deal, which is the laboratory testing. We test, as you know, for HIV-1 and 2, hepatitis B, hepatitis C, HTLV-I and II, West Nile virus and syphilis variably under regulations and in compliance with guidance.

Additionally, we utilize deferral registries so that deferred donors are identified and use of their blood is prevented, should it be inadvertently collected.

Additionally, and we are going to focus a lot on this in the present workshop, we have as part of the current good manufacturing process quarantine controls which are intended to prevent the release of a unit pending the complete verification of donor suitability, including behavioral and medical screening as well as testing.

Lastly, a little appreciated layer is, again under CGMP, the requirement to investigate and correct any deviations that could affect the

quality of the product.

Now, these strategies have been very highly successful at reducing the major transfusion-transmitted disease risks over the last one and a half to two decades. I think the point, which I will illuminate further in the next slide, is that these advancements which are on a log scale represent a combination of effects, both from behavioral exclusion and also testing, although it is without a doubt that testing plays a very dramatic role.

In fact, our current risks are now so low that they cannot be measured directly and, hence, we rely on models to estimate the current residual risk, that is to say the risk after all the safeguards have been followed. That becomes important because in today's workshop you are going to hear a lot about model building in order to estimate risk and this is how we need to go about it.

Those are numbers from the current literature and risk per million donations, ranging

from 1 in 2 million for HIV/HCV; a little bit higher, 1.5 per million for HTLV; and then the highest residual risk of a major transmissible disease is still from hepatitis B and if you assume 14 million collections and about 1.7 units per collection yielding 23 million components, you can estimate that this is the number of contaminated components that may be entering the blood system each year. Now, this is not adjusted for rate of transmissibility or the disease attack rate, it is just the potential rate of exposures to potentially contaminated units.

But looking a little bit more closely at the role that has been played by behavioral exclusion, this is just an example for viral hepatitis. In the 1970s there was concomitant introduction of labeling of paid versus volunteer donation for blood for transfusion, which was at the same time as the first generation of the test for HBsAg, and the combined effect was a very dramatic, approximately 90 percent, reduction. We have never completely teased out how much of this

was due solely to the change in labeling which eliminated paid donation, but we do know from the antecedent literature that paid donation was highly associated with transmission of hepatitis.

These are percents here, this is as high as 30 percent in the 1960s, per transfusion episode which might have involved multiple units of exposure per episode. Again, another example here was when we introduced the high risk exclusions for HIV based on certain categories of risk, we had a further reduction in the hepatitis B risk and it was because of the convergent epidemiology of HIV and HBV. So, the point here is that these two strategies have at various times worked well in tandem.

What I am going to describe next is the general paradigm of the way the oversight system responds to an emerging threat. What happens when an emerging pathogen threatens the safety of the blood supply? Well, generally the first step is that we introduce deferral criteria which are based on epidemiologically determined risk factors and

those can be medical, geographic or behavior-related exposures. Where feasible, tests are then developed but we generally maintain the deferrals as an overlapping safeguard. The reasons for that will become clear later because risk is a result not only of screening out detectable positives but also avoiding the collection in the first place because they are then a threat for inadvertent release from the quarantine inventory.

Of course, there is also the benefit of reducing the number of window period cases if you can eliminate persons with recent infection through screening. Then over time test sensitivity and specificity generally improve. This is because of competition in the marketplace, as well as the upward vector of science and technology. But, again, risk-based deferrals are usually retained as an overlapping safeguard, especially when data are lacking on the relative safety contribution of risk-based versus test-based deferrals. This is an area where we generally are weak. It is the unusual case where information is brought forward

that can actually tell us over time what the relative contributions are of the risk-based deferrals and testing.

Over time the expansion of risk-based and test-based deferrals has certainly added to blood safety, and we showed that in earlier slides. But we also recognize that it has added considerably to complexity. As the number of risk-based deferral criteria has increased, it has been asked whether the blood questionnaire is as effective as it should be and whether simplification would enhance its value. Additionally, the question has arisen whether testing has become so effective that some risk-based deferrals no longer provide a significant added safety value. We do understand the argument that, whereas we measure testing as an added benefit to risk deferral initially, we ought to be flexible enough intellectually to look at it the other way later and say, well, what does behavioral exclusion add to testing were the sequence reversed. So, we understand that.

Now, at the same time these very same

safety strategies have sometimes raised social issues, particularly focusing on donor selection. FDA is aware that some current donor selection criteria have been perceived by some individuals as possibly based on prejudice or on past needs rather than on current science. It is our hope that this forum will clarify the rationale for current deferrals and also provide an opportunity for scientific input and discussion into current donor policies.

We further recognize that the blood system depends on the trust, generosity and good will of donors, and we very much appreciate the altruism and the intended social contribution of all who seek to donate. I think that Dr. Goodman stated this very well in opening the workshop. However, while we consider the donor's perspective very carefully and seriously and, indeed, this is part of the reason for the workshop today, FDA's primary responsibility is to the safety of the blood supply and those who will receive blood and blood products.

So, we come then to the structure of the workshop. It is important to state that we are not here to make policy today. We are here to listen. We are here to gather information and, hopefully, to have a critical review of the current science which underlies our present policies.

That said, the public discussion of the scientific basis for the use of behavior-based donor deferral criteria to prevent transfusion-transmitted infectious diseases is our primary charge, and to consider whether the blood safety advancements from introduction of nucleic acid based tests, NAT, or other methods would permit changes to these deferrals without compromise to blood safety. So, that is our charge and I hope everyone will keep it in mind as the day goes on.

I don't think I turned up the lights and the slide is still a little bit dim. Maybe that is a signal! Okay, let me quickly then review the structure of the workshop. It is organized in your agenda in three segments. In the first segment we

will have a review of the current behavior-based deferrals. We will review FDA's policies for blood and also touch on our policies for cell and tissue product donations. We will review the effectiveness of donor screening procedures. We will get some international balance by hearing about the deferral policies in Europe. We will discuss the social dimensions of the issue and we will have a discussion, disease agent by disease agent, on the association of transfusion/transmissible disease risks with specific behaviors that we call high risk behaviors. We will then have a panel, and the panel will include the presenters but also that will be an opportunity for participation by all of those assembled, and the focus will be on the question what behaviors are associated with risks of transfusion-transmitted disease--of course, infectious disease is what we are talking about--and how do these risks compare amongst cohort groups with these behaviors?

In the second segment of the agenda we

will assess the risk of the transfusion transmissible infectious diseases. We will hear presentations on current estimates of risk for these infections; on inventory errors as a source of the residual risk; risk estimates for certain candidate modified deferrals; and a critique of the value of donor questionnaires. Again we will have a panel of the discussants and the audience on the question how do behavior-based deferrals contribute to blood safety when donors additionally are tested by nucleic acid tests?

Then, in the final segment of the agenda we will have a discussion on potential alternatives for blood donor screening and testing, and we will critically review two things, first, an overview of alternatives that might be considered as well as a framework for thinking about them, and then a specific focus on how these behavioral risk factors ought to be considered in relation to emerging infectious diseases. Once again, we will convene a panel. The panels keep getting bigger and bigger, incidentally. This panel will focus on considering

the implications of the quantitative risk models which will have been presented earlier, and then try to draw attention to the need for additional scientific data where it would help us to resolve whatever may appear to be the most critical questions.

In closing, let me just say that I am very pleased with today's turnout. I am glad that this subject has drawn in so many participants, and just to reiterate, FDA values everyone's contribution to this workshop and we look forward to a lively and enlightening day of presentations and discussions. Thank you very much.

[Applause]

DR. DAYTON: Thank you, Jay. I will introduce Eve Lackritz who is going to moderate the next session.

I. Behavioral Risks for Transfusion-Transmitted Diseases and HCT/P

Current Policy and Social Dimension,

Eve Lackritz, M.D., CDC, Moderator

DR. LACKRITZ: Good morning, everybody.

This is a very optimistic schedule that we have to keep time on. We are going to have a number of presentations that are all timed differently so I will have to ask each presenter to keep track of the time. We will have questions. We might have time for maybe one burning question but otherwise questions will be left for the open discussion.

Our first speaker is going to be Dr. Alan Williams who is going to present on the design and efficiency of current FDA recommendations for blood donor deferral.

Design and Efficiency of Current FDA Recommendations for Blood Donor Deferral

DR. WILLIAMS: Thank you, Eve, and good morning, everyone. What I am going to do is build somewhat on the introduction that Dr. Epstein presented and give a few more characteristics about the donor eligibility policy development process; present some of the behavioral deferrals that are the subject of discussion today; and then, in kind of a combination of things, introduce some of the studies that help assess what the efficacy is of

the current deferrals, and at the same time introduce some of the modes of survey data collection that gave rise to some of those data and how they all provide data that contribute to the understanding of the process, but don't necessarily mean that you can take data from one mode of study and compare it directly with a different mode of study. You need to keep in mind that sometimes you get different answers.

Clearly, one of the most important reasons for providing accurate donor qualification is related to the layer of safety that is involved with determining donor eligibility before the testing process. Obviously, it is critical to maximize blood safety, particularly in relation to known agents where there is a laboratory screen in place because of considerations related to testing window periods that may be present, albeit a very small opportunity for testing errors, release errors and staff protection.

Similarly, it is important to provide mechanisms to ensure safety against known or

unknown agents for which no laboratory screen currently exists. In some instances donor screening by epidemiologic criteria may be the sole protection in place. There may be a threat that is recognized and only partially characterized scientifically, and vCJD would be an example in this category. But there also might be a threat that is completely unrecognized but the contribution to safety may be possible through eligibility or ineligibility of individuals whose behavior has heightened exposure to a certain type of agent or certain agent that is transmitted in a parenteral manner. So, deferral for instance of individuals who might have a high rate of parenteral exposure may provide a measure of safety even though an agent may be unknown. I would use here as an example injecting drug users who have a high rate of needle sharing with other individuals who had a high rate of needle sharing and that provides an amplification effect leading to high rates of exposure of parenteral agents.

It is important to have accurate donor

qualification to minimize donor loss. In other words, the questions need to be as sensitive and specific as possible so that donors who truly are eligible remain eligible. It is important to minimize negative operational impact because a question that doesn't obtain its desired goal may result in something like donation information transmission which then could result in recall of products or other operational impacts.

I think one that doesn't get a lot of attention but I think is important to stress is that frequently component preparation and other production aspects of the collected blood unit take place before the testing results are fully available. So, the safer the blood is coming in the door and through the processing process, it helps to minimize staff exposures to infectious donations even though universal precautions are in place certainly in the blood collection centers.

There are various stages of donor qualification. One of the oldest ones is the exclusion of defined risk populations or provisions

for labeling. For instance, donors, in fact, can be paid for blood donations; it is just that the label needs to reflect that fact. Prisoners are excluded because of high risk particularly of injecting drug use. There is self-deferral prior to the appearance for donation. I put this bolded because, in fact, this appears to be the major source of self-deferral. The donors who recognize they are not eligible through educational materials or conversations with staff at the time they make an appointment just don't appear at the blood center, appropriately, and this is really the place where most of the deferral takes place. Donors can defer on site if they see educational materials prior to their interview. They can be deferred by staff during an interview. It could be a self-administered interview followed up by staff contact or a face to face interview. In reality, for some of the major risk factors that we are speaking about today, deferral at that point of the screening process is really fairly rare. Most of it takes place before that time.

You will hear of some data today about post-donation information which comes after the donor has donated a unit of blood. This can come from a donor calling back to say they really didn't feel that healthy that day or they are ill now. It can come from third-party information and it can come from subsequent donation history in which a donor reveals a factor that makes them ineligible that they should have admitted earlier.

I put together five principles for consideration of regulatory aspects of donor eligibility. The first is to ensure consistency and a risk/benefit balance to any potential policies, including the determination or modeling, if necessary, of sensitivity, specificity and predictive value wherever possible. It is important to consider that safety really is context dependent. As all of you are aware, it includes the continued availability of medically necessary products. So, eligibility criteria that had a major impact on availability of critical products would certainly not be appropriate.

The second principle is to strive for science-driven policy but recognize the need to act in the interest of public health when scientific answers are not fully available. That is, to take prudent measures if appropriate. This would be equated to the institution of deferrals for travel to countries with high levels of BSE that were put in place in fact before there was recognition of transfusion transmissibility of the agent.

A third principle that I think is an important one to keep in mind for today's discussion is to ensure that any changes in existing regulatory policy can be shown, within reason, to result in improved or at least equivalent safety of the blood supply for the recipients.

The fourth principle is vetting and public airing of proposed policy within FDA, within HHS, within the public and involved blood collection community, and other industry and provide opportunity for public comment.

Finally, to help provide liaison support

to organized industry efforts to define voluntary standards because not all of the standards, obviously, are regulatory and we do liaison actively with AABB, PPTA and other standard-setting organizations.

To move to some of the wording associated with some of the current deferrals, and all of these except the last one are based in guidance issued by FDA in April of 1992, entitled Revised Recommendations for the Prevention of Human Immunodeficiency Virus Transfusion in Blood and Blood Products. The wording cited here is the wording that was put together by a task force responsible for development of a donor history questionnaire on behalf of the blood community, and this questionnaire is available on the AABB web site and is now in widespread use throughout the country for standardized donor screening.

Criteria organized by time frame in the past 12 months--has the donor had sexual contact with anyone who has HIV AIDS or has had a positive test for the HIV AIDS virus; had sexual contact

with a prostitute or anyone else who takes money or drugs or payment for sex; had sexual contact with anyone who ever used needles to take drugs, and parenthetically, or steroids or anything not prescribed by their doctor? Steroids in this instance is actually an industry standard incorporated into the same question.

In the past 12 months, has the donor had sexual contact with anyone who has hemophilia or has used clotting factor concentrates? For females, has the donor had sexual contact with a male who has ever had sexual contact with another male in the past 12 months?

Since 1977, which was the first AIDS clinical case recognition in the U.S., from 1977 to the present, has the donor received money, drugs or other payment for sex from 1977 to the present? Have you--referring to males, had sexual contact with another male even once?

The so-called indefinite deferrals--has the donor ever used needles to take drugs, steroids or anything not prescribed by a doctor? Has the

donor had sexual contact with anyone who was born in or lived in Africa? The last question is due to potential exposure to group O HIV, and stems from a 1996 interim recommendation related to HIV group O infections, published in December, 1996.

Now I would like to move a little bit to some thoughts about assessing the efficacy of donor deferrals. I wanted to introduce, first of all, what are some of the sources of data. Actually, the blood collection environment and donors in particular are really rich sources of epidemiologic information. There have been many, many observations and publications related to donor prevalence and incidence in the donor population. There is information related to rates of deferral, rates of post-donation information reported back to blood centers, and other operational measures.

Related to efficacy, for at least 15 years now there have been active programs to interview donors found to be positive for infectious disease markers, particularly hepatitis and HIV, to determine what their risks were that resulted in

that infection. Then, starting in the early to mid '90s, there were some anonymous mail surveys which actually got at risks in donors who did not have infection to determine sort of what the risk burden was in the current donor pool, the rich sources of information in the donor pool.

The general population--there are certainly data available, but the data available to actually compare with the donor population is somewhat limited. There are marker prevalence studies. Many of these are in defined subgroups or risk subgroups. There are limited behavioral risk surveys. Some of them are AIDS-related risk factors like condom use. But if you try to find a general population to look at something like sexual contact of a woman with an IV drug user or male sex with another male, it is really very difficult to come by any general population information.

I just wanted to note here that there is a special category which is donors who appear to a blood center for the first time. They are a very crude representation of the general population but

they do represent the incoming general population which has been exposed to the educational materials from the blood center, has been screened one time at the blood center and not, for the most part, tested by the test results. So, it is a unique source of comparison with the general population and the impact of the donor screening.

So, these are all different modes of data collection. There can be comparisons made between data from different sources. They may not be rigorous and often aren't, but it does make use of the only available data, and I think you are going to see a fair amount of those comparisons today so perhaps keep that in mind.

So, just an example of data reflecting reduction of infectious disease marker prevalence in accepted donors, donors compared with the general population. There were studies from CDC which showed that there were 0.47 percent confirmed HIV-positive in the donor aged general population around the 1994 time frame, '93, '94 time frame. At that same time frame there was the RED survey

data around 1995 showing 0.03 percent confirmed HIV-positive in first time donors.

So, reflecting back to what I mentioned about first time donors, one can estimate roughly about a 93.6 percent reduction in HIV seroprevalence that is, for the most part, related to the donor eligibility education and screening.

There can also be determinations made related to infectious disease marker prevalence over time. This is now I think a classic diagram from Mike Busch, published in 1992, showing from a combination of observations, including HIV look-back studies in donors in the San Francisco area, a 90 percent reduction of post-transfusion HIV-1 transmission in that area prior to the implementation of specific testing. One can see in estimated exposure recipients up to the '80s, again the first AIDS case and then, at the peak of the curve, recognition of high risk groups, initiation of donor deferral, progressive impact of different at risk individuals and then, by 1985 when HIV screening was implemented, a large portion of the

risk of blood supply had, in fact, been removed by behavioral screening.

An additional thought on where there is no test data involved is comparing risks in accepted donors. Studies out of University of Chicago in 1994 showed a 4.1 percent prevalence of MSM in the past 5 years in the male general population. We had a similar risk from the RED study. The anonymous male survey showed a 0.6 percent risk in accepted male donors so, again, a crude correlation but about an 86 percent reduction related to risk as opposed to markers.

Then, similarly, for injecting drug use 3.9 percent since 1978 in the general population--this was from the pilot Dallas household survey--versus about 0.5 percent IDU ever among accepted donors, again about an 86 percent or 87 percent reduction.

So, some of those are the positive aspects of efficacy of deferral but I think there still are some developmental research areas. The first would be observations about false-negative behavioral

screening. The first point is that interviews of accepted seropositive donors frequently identified behavioral risk that should have prevented donation. These studies are important to monitor the risk exposures that resulted in the donor's infection and also to rule out unusual modes of infection transmission, and CDC supported quite a few studies in the '90s to help look at these factors.

These are data showing comparison between data from interview studies. These are in-person interviews of donors found to be HIV seropositive. A study was in place for at least a decade, and I think a little bit longer, showing in males in the late 1980s the risks for male contact with other males, heterosexual contact with a known at risk partner and a fairly sizeable component of no reported risk, and a smaller component of injecting drug use. That proportion changed a little bit by 1997 so that males who have sexual contact with other males was down to about 40 percent, and I think some later data, up through year 2000 shows

that MSM constitutes--without separating by gender--about 23 percent of the total risk associated with HIV seropositive in interviewed donors.

Similarly, for females, as you might expect, the largest category of exposure is heterosexual contact with an unknown at risk individual and a large component of no reported risk.

Similarly, again looking at risk rather than markers, surveys of accepted unselected donors also identify behavioral risks and identify the behavioral risk burden in the donor pool. This donor pool potentially contributes to incident infection, which is important because it includes potential for window period cases.

This is the first anonymous male survey done by the RED study, published in 1997. I won't go through all of these, they are in your handouts, but it documented in the overall donors who responded to the survey risk factors that, in fact, should have resulted in deferral prior to donation.

Since 1977 MSM deferral criteria was defined as 0.6 percent; IDU ever 0.5 percent; and overall cumulatively 1.9 percent of donors who reported one or more risks known as deferrable risks that should have prevented the donation, about 242,000 donors a year at that time.

REDS did a similar study methodologically in 1998, and there was a recent publication in Transfusion that provides some of these data. Although there are a couple of potential explanations, interestingly, the male respondents who reported MSM since 1997 had just about doubled. Now, whether this is measurement error whether it is a true increase in that donor population, or whether it is due to the fact that there is five years additional time to develop that group of donors needs to be worked out. The observation is that the reports increased two-fold, from 0.6 to 1.2 percent.

One of the real values of surveys like this is not quite as much the estimate of overall prevalence because, you know, there is a certain

lack of validation of those data, but that the survey method itself is reproducible over time and I think one of its real values is the ability to stratify against other factors.

Some factors found in correlation with these donors were other deferrable risks, including injecting drug use, receiving money or drugs for sex, self-reported HIV test seeking--not a deferral but an interesting observation. These were higher in all subgroups reporting MSM contact since 1977.

There was some distinction made between MSM who had had activity within the last five years versus those who had abstained from MSM activity for the last five years. Reactive screening tests were correlated with the group with recent activity but not with the group that had abstained for five years.

Another observation related to this paper is that 92 males out of the 25,000 respondents reported MSM activity in the past year. That is 0.36 percent. This subgroup of male donors was higher for all other transfusion-transmitted

behavioral risks for HIV test seeking, for other test markers and for numbers of lifetime sex partners compared to other males who responded to the survey.

The HIV window period is known to be considerably less than one year so what this translates to is that there are approximately 16,000 individuals, extrapolating from the survey data, with MSM activity in the past year. These donors may have a variety of reasons for proceeding with blood donation, but I think one can't argue the fact that this is a source of incident HIV entering the blood supply and, in fact, when these donors were interviewed, you know, the MSM risk came out. So, this is the risk pool; this is the risk burden for a certain proportion of HIV. So, I think it is important that improved behavioral science continue to identify and interdict blood donation by overtly high risk donors, and this really should be treated as a priority.

I am going to end with a few thoughts about some behavioral science perspectives and some

of the research things that are going on which I think are really quite interesting and progressive. Information about personal behaviors is inherently difficult to collect, and there are a number of reasons for this. There is the phenomenon of social acceptability of the information. If you are sitting across from an interviewer you may be hesitant to give them your full life story in terms of your risk history. Right response rates in surveys tend to be low and there is frequently missing data in certain data elements and inconsistencies frequently occur.

I would point out that regulated blood establishments are a special case because of the training involved. Often I think, you know, there is much better quality medical history in the blood center than in some other settings, including research, but still it is the nature of the behavioral data collection that it is not entirely reproducible. People tend to avoid careful reading. This is a known phenomenon so that, you know, often the educational materia was there but

the donors just don't read to the end and get the full message.

It is known that there is improvement in quality with serial data collections or serial donations. Many of the donors are repeat and you actually see evidence of improved education in deferral as donors repeat more frequently.

Donors frequently form their own basis for risk assessment. This can be related to denial of a certain risk or lack of respect for the policy that is in place. There can also be external factors which prevent appropriate self-deferral. This can be some sort of perceived or actual secondary gain from donation--peer pressure and environment, including privacy; comprehension of the question; and the fact that some of the questions themselves, trying to meet scientific criteria, actually end up being quite complex for the lay individual to understand.

There are some very useful areas of applied research that have taken place and continue. The AABD uniform donor history task

force has been working close to a decade now on improving a streamlined donor questionnaire, which includes the use of capture and interval questions, improved educational materials and, importantly, cognitive validation to the extent possible to see how well people understand the questions that are actually being administered to the donors.

Also, following on some of the behavioral work related to the AIDS epidemic, the use of computer assisted self-interview, particularly when there is an audio component through head phones, has scientifically been shown to produce a better interview process because it is private. You don't need literacy. It is standardized. It can have multiple languages. It can have visual aids and the respondent often can control the speed of the interview. This is now making its way into blood establishments. Several centers are now using this process and finding that the donors like it; the staff like it; and I think the evidence points to a better interview process.

So, in conclusion, FDA considerations of

donor deferral are grounded on several well-defined principles that are science-based but also consider the context of risk and the inevitable scientific uncertainties.

Second, based upon limited data from donor screening situations, we estimate that there is about 85-99 percent sensitivity of current blood donor screening procedures in their ability to determine donor eligibility.

Finally, further behavioral research in this area remains critical, in particular methods that will support the identification and interdiction of donation of overtly high risk donors who fail to self-defer. Thank you very much.

[Applause]

DR. LACKRITZ: Could the projectionist come down now to correct the projector? Alan, do you want to stay there and answer questions while we are getting that fixed--if we get that fixed?

[No response]

For our next speaker we have a

replacement. It is going to be Melissa Greenwald who will be presenting on FDA's current recommendations on behavior-based HCT/P donor deferrals.

FDA's Current Recommendations on
Behavior-Based HCT/P Donor Deferrals

DR. GREENWALD: Good morning. Dr. Solomon sends her apologies. She is very sorry she couldn't make it today but I will be here to talk to you about FDA's current recommendations for behavior-based HCT/P donor deferrals.

Why are we discussing these today? HCT/Ps are human cells, tissues or cellular or tissue-based products and you see why we call them HCT/Ps. We have two different donor types. We have cadaveric donors, what we call cadaveric donors who are not heart-beating donors and, obviously, we can't do testing and follow-up on those donors. We also have living donors. If the donor is available we do have the opportunity to do testing and follow-up so we are interested in looking at various options such as testing the

donor, quarantining products, re-testing and release.

Obviously though, any changes to blood donor suitability policies may well affect HCT/P donor policies, and there are some differences between the blood donor and HCT/P donor deferral policies based on behavioral risks.

I will go through a brief history of the regulation of human tissue for transplantation. Back in 1985 CDC made some recommendations to test for HIV-1 in organ, tissue and semen donors. Then there was really a sentinel publication in 1992 where there was a report in the New England Journal of Medicine of transfusions of HIV-1. That transmission came from a serum-negative organ in a tissue donor. Of course, we all know that testing was a bit different back then. There were four organ recipients and three fresh-frozen bone recipients who ended up developing HIV from transplantation.

As a result of this, the Public Health Service formed a working group which was comprised

of individuals from both the Public Health Service as well as external consultants. The result of this working group was that there were CDC guidelines for preventing transmission of HIV through transplantation of human tissues and organs that was published in MMWR in 1994.

So, I will take a little bit of a look at those 1994 CDC guidelines. They directly apply to donation and transplantation of human organs and solid tissues, but also serve as a general guide for human breast milk and semen. The publication itself listed some factors that were considered in developing those guidelines. There are differences between organ donors and tissue donors, heart-beating versus non-heart-beating donors. There are differences in time constraints and variability. Organs must be transplanted much sooner than corneas, which must be transplanted much sooner than bone, for instance. Bone can be stored in freezers for years before being used.

There are differences in risk transmission. Vascularized organs are much better

vectors for transmission of infectious agents than avascular tissues. This limited availability of organs and the risk/benefit ratio at transplantation to the recipient is different. We call organ transplantations generally a life-saving procedure, whereas tissue transplantation is generally considered to be life-enhancing. Despite the fact that these factors were recognized, it really was too complex to stratify the behavioral exclusionary criteria.

We will go through what those precise exclusion criteria were: Men who have had sex with men in the preceding five years; persons who report non-medical intravenous, intramuscular or subcutaneous injection of drugs in the preceding five years; persons with hemophilia or related clotting disorders who have received human-derived clotting factor concentrates; men and women who have engaged in sex in exchange for money or drugs in the preceding five years.

Persons who have had sex in the preceding 12 months with any person described in the previous

slide or with any person known or suspected to have HIV infection; persons who have been exposed in the preceding 12 months to known or suspected HIV-infected blood through percutaneous inoculation or through contact with an open wound, non-intact skin, or mucous membrane; inmates of correctional facilities; and children 18 months or younger born to mothers who either have or are at risk for HIV or who breast fed in the previous 12 months.

Finally, we move on to the FDA regulation of HCT/Ps. As a result of the transmission, FDA published an interim rule in 1993. This was really just the beginning of trying to get a standardized regulation to approach screening and testing of donors, HCT/P donors.

The interim rule had similar requirements to screen and test donors for HIV-1 and 2, hepatitis B and hepatitis C, and also had a few requirements for written procedures, records and inspections. That interim rule was finalized in 1997, and there was a guidance that was published along with that rule. That guidance describes the

behavioral deferrals for HIV, hepatitis B and hepatitis C, and those were based on the 1994 CDC guidelines criteria. It also described clinical evidence of HIV, hepatitis B and hepatitis C, as well as physical evidence of HIV and viral hepatitis.

Then, in 1997 we also published a proposed approach to regulation of human cellular- and tissue-based products. So, this was FDA's sort of announcement to the world that we were going to be taking a broader scope to the regulation. In 2001 the final rule was finalized and 2004 was a busy year for us. The donor eligibility final rule was finalized. That has requirements for screening and testing for HIV-1 and 2, hepatitis B and hepatitis C, syphilis, and also some other infectious agents for specific tissue types. It also has requirements for screening for TSEs, including CJD and variant CJD.

Along with that donor eligibility rule came the donor eligibility draft guidance which is in the process of being finalized. In that

guidance FDA announced its intention to add West Nile virus, SARS, vaccinia and sepsis to the list of relevant communicable disease agents or diseases. At that time we gave recommendations on how to screen for those agents. The current good tissue practice rule was also finalized in 2004, which provides for manufacturing controls to try to improve the safety of cells and tissues as well.

In the process of writing and revising the rules, there was consultation amongst the Public Health Service in June of 2000. The purpose of that consultation was to look at whether or not the 1994 CDC guidelines should be revised. In other words, should the behavioral deferrals be changed. This meeting was a closed meeting that involved members of the Public Health Service as well as invited members of the public. There was a review of the incidence and prevalence data that was available at that time in high risk groups.

Looking at that data, they tried to make a determination of how much benefit might be gained by having an increased donor pool versus how much

additional risk you might be taking on to release an infectious product if the deferral criteria were changed. The conclusion of that consultation was that more studies are needed and the current data really did not support the identification of safe subsets of groups that were at risk.

Our draft donor eligibility guidance that was published in 2004 basically really retained the 1997 deferrals which, of course, was based on the 1994 CDC guidelines. There were some changes from the 1997 guidance, and these are just some of the changes. We didn't want to bore you with too many of them: Sex or other close contact in the preceding 12 months with any person having clinically active hepatitis. Really, that used to be any person having hepatitis at all, viral hepatitis. Persons who have had a past diagnosis of clinical, symptomatic viral hepatitis after age 11, unless the evidence from time of illness documents that hepatitis was identified as hepatitis A virus. Previously, that last part of the sentence about hepatitis A was not included.

Also, it included exclusions for CJD, variant CJD, West Nile virus, SARS, vaccinia, sepsis and xenotransplantation. It is our current thinking that the final guidance will clarify for everyone that we consider HIV-1 group O to be part of HIV-1 and that, just as is done in the blood industry, donors should either be screened or tested for group O.

Now, the donor eligibility rule does allow limited uses of HCT/Ps from ineligible donors. If donors are ineligible based on behavioral risks, clinical or physical evidence or even reactive test results, under some circumstances those donors may still be able to donate. Those would be allogeneic use in first-degree or second-degree blood relatives; directed donors of reproductive cells or tissues; documented urgent medical need, which is when there is no comparable cell or tissue available to the recipient and that recipient would be likely to suffer death or serious morbidity. Really, that is mostly related to HLA-matched hematopoietic stem cells. It does require special

labeling and physician notification if otherwise ineligible donors are used as donors.

So, there was a study that was published in August of 2004 in the New England Journal of Medicine, which has been really the only large study that has been published, looking at the incidence and prevalence of HIV, hepatitis B, hepatitis C and HTLV among U.S. tissue donors. The study involved a little over 11,000 donors, between 2000 and 2002, involving five tissue banks. They looked at confirmed positive test results and determined the marker prevalence rate. They used that information then to estimate the incidence rate and the probability of viremia for HIV, hepatitis B, hepatitis C and HTLV among those tissue donors. Of course, these are deceased tissue donors. The conclusion was that the prevalence and incidence rates are lower among tissue donors than in the general population but, in fact, higher than in first-time blood donors.

This data chart is from that study. Really it is just so you can look at it and see

where the tissue donors kind of fall out between first-time blood donors and the general population.

I am going to end with just a little bit of background about the rationale behind the HCT/P behavioral deferrals. One would expect more reliable answers to the donor history questionnaire if questions pertain to the recent past, such as the past five years, as opposed to all the way back to 1977. This is especially important because many times with tissue donors we are talking to the next of kin; we are not really talking to the donors themselves.

There is limited availability of certain cells and tissues. HLA-matched cells are needed, and there are size restrictions for pediatric tissues like heart valves. Finally, there are differences in risks of viral transmission due to more extensive processing of some types of tissues. Some examples of processing include removal of blood and viable cells by extensive washing, use of alcohol, hydrogen peroxide and irradiation, and other proprietary methods for viral clearance.

So, if you would like some additional information, Ruth's e-mail address is on there but, actually, it is pretty easy to find because if you substitute my name, melissa.greenwald into the same e-mail address you will find me as well. Thank you very much, and have a great day.

[Applause]

DR. LACKRITZ: Thank you. Our next speaker is going to be Dr. Cees van der Poel who will be speaking on behavioral risk exclusions in other countries outside the United States.

Behavioral Risk Exclusions in Other Countries

DR. VAN DER POEL: Ladies and gentlemen, thank you very much for inviting me here today. I am going to present the discussions we had in Europe about behavioral risk exclusion, and the main focus of those discussions at the moment were related to MSM behavior. Now, we are, and I am aware of the fact that, of course, there are more risk behaviors than MSM but the problem was that we had to address this issue first because it was put on the agenda in Europe. We will proceed

afterwards to go to the other risk behaviors in more detail this coming year, I hope.

Now, I am not completely speaking on my own behalf; I am speaking on behalf of the European Blood Alliance which is an alliance of blood establishments, of blood operators, if you like, from non-profit institutions in Europe. Since the board of that blood alliance asked me to come up with advice, we got scientists from different countries in a small working group together and tried to assess the issues.

Now, the background was to report strictly on MSM deferral and provide background information to the EBA board, the board of directors of the blood establishments in Europe. The questions from the MSM interest groups were actually raised to political levels that were different in different countries. It was raised, for instance, in The Netherlands to our parliament where the parliament asked questions of the minister and the minister answered those questions. In Belgium the minister just had discussions with the blood establishments,

and in Italy the minister went out in the open by saying that blood bankers were nuts.

[Laughter]

So, the tendency and the atmosphere was completely different in different countries. One of the main issues that politicians have to face in being responsible for public health and being responsible for blood safety is the discriminatory effects of the measures. So, that is why we addressed that aspect as well. Also, we tried to assess whether a change from permanent deferral to temporary deferral, for instance for 12 months, would be fruitful.

We thought we would have to take into account the residual risk of HIV transmission to recipients of blood and we had to take into account the present practice and regulations in Europe. We looked at the task from different aspects. First we were going to survey the epidemiological data from public health surveys where we would be looking at the prevalence and incidence of HIV in MSM and other infections that would be prevalent or

incident in MSM like hepatitis B, syphilis or recently lymphogranuloma venereum. Then we would look at the epidemiological data from the blood establishments and what is the relative contribution of MSM to donors who are positive for HIV and other infections; the positions taken by governmental authorities; the European regulations which are laid down in a directive in 2004/33/EC; and to address some compliance and public address issues.

Now, first the epidemiological data from France, as reported by G. Follea, in France MSM is about 27 percent of the new HIV infections in 2003-2004, whereas only 4 percent of the general population has a history of MSM. The 4 percent, by the way, is quite similar to what I just heard from the FDA as a background figure in the general population of MSM behavior. And, 51 percent of HIV in MSM is recent, within 6 months; 78 percent of MSM have multiple partners during the last 6 months; and in MSM stable relations, 63 percent have other partners.

If we look in the past, from 1997-2004 there was an increase in unprotected anal intercourse by about 70 percent; syphilis by about 20 percent; gonorrhea by about 35 percent--increase, that is. Cases of hepatitis C have occurred, which is usually not sexually transmitted, by anal intercourse among MSM.

So, that is a trend that you will see in different countries in Europe where the impression is that the fairly effective treatment of AIDS in the last years has generated more freedom to experiment with new partners, and there is more promiscuity at the moment than there was in the past. Of course, this needs to be further studied in detail.

Now, the epidemiological data from Germany, as reported by Kurt Roth [?] and the data that were provided to him by the German authorities, in Germany MSM is 40 percent of new HIV since 2001 and MSM as a relative proportion of HIV-positive cases, new HIV-positive cases, went up from 37 percent to 46 percent from 2001 to 2004.

MSM went from 30 percent to 40-50 percent in new HIV cases and since 2001 there is about a 30 percent increase in new HIV cases among MSM in 6 metropolitan areas. MSM at present is 70 percent of the new syphilis cases in Germany and there have been small outbreaks of lymphogranuloma venereum in 2003 and 2004.

In The Netherlands the picture is not very different. MSM here consists of about 49 percent of new HIV cases in 2003-2004. Whereas about 37 percent of new HIV is heterosexual, increase of MSM as a main risk factor has occurred between 2003 and 2004. In anonymous screening programs in STD clinics the HIV prevalence in MSM is increasing. It used to be about 10-11 percent and it is now up to 20-30 percent, and it is predominantly in the older age groups which is a fact that we do not understand completely, but it seems that in The Netherlands at least the incidence in older MSMs is higher than in young MSMs.

HIV prevalence in the general population is comparable to the data you have just seen from

the FDA. It is about 0.06 in rural areas to 0.2 percent in the cities. Cohort studies of HIV incidence in new cases per annum in MSM increased from 1-2 percent to 3-6 percent between 1991 and 2002. The entry criteria of the cohorts did not change but, of course, a cohort is a cohort and may not be totally representative of the whole population or the whole group that you are trying to address. But we have a long-standing tradition of large cohort studies with MSMs in Amsterdam, for instance, and that is an ongoing program.

The non-Dutch HIV is becoming more important but it is presently decreasing and I will show you the slides later on. It is about 17 percent of the HIV cases in The Netherlands. In recently HIV-infected MSM, 70 percent had sexually transmitted disease also, and sexually transmitted disease in MSM increased by 16 percent during 2004 and we had primarily in the Rotterdam lymphogranuloma outbreaks in HIV-positive MSMs, but it is now in other parts of the country as well.

Here is a slide which shows you from our

public health department new HIV diagnoses by year, gender and here you see the blue line, which is the absolute numbers of HIV diagnosis and you see that there is a dip. This was the encouraging period where we thought that the public address and safe sex propaganda would decrease the incidence, but here it is up again.

Here are the heterosexual males and the heterosexual females. So, it is about 1,000 new cases in 2004, half of which are from MSM, and if you add these two heterosexuals up you have about half of them. But, interestingly, the female heterosexual, apart from the intravenous drug use, is predominantly import from countries south of the Sahara, in Africa, and there is a decrease here.

Here are the figures so you see that MSM is about 49 percent--this is in 2004--49 percent of the total new HIV diagnoses. Heterosexual contact is about 40 percent, evenly spread between male and female. Then, here you see that intravenous drug use is low, and that is low because of our preventative measures, we hope, on needle exchange

programs. Blood products--those are partners of hemophilia patients and incidental cases. Mother to child transmission, needle stick injury and not known but, of course, this is usually a percentage of 10 that you don't know.

Infectious syphilis from 2000-2004 by sex and sexual preference, you can see that there is an increase of syphilis cases in MSMs. The red bars is women and the blue bars are heterosexual men.

The risk factors in acute hepatitis B--this is another program. Hepatitis B is a notifiable disease in The Netherlands, and you see that in 2001, the blue proportion, is the proportion acquired by MSM and here it is getting larger. This is the heterosexual transmission of hepatitis B, and this is the unknown. The yellow bars are sexually unknown and the very slight green bar here is intravenous drug users.

Now, the epidemiological data from public health in U.K.--this picture is slightly different from The Netherlands and Germany and France. MSM is only 32 percent of new HIV cases in 2004,

whereas 64 percent of the new HIV cases are heterosexual. We have no denominator for the extent of MSM behavior in the general population in the U.K. but we estimate that maybe it will be the same as in France, The Netherlands and America.

From 1996-2003 there is a 16 percent increase of HIV in MSM, mainly acquired in the U.K., but the incidence in MSM is about 4.5 percent in London, 2.5 percent outside London after a dip in 1999. So, it is the same profile that we have. The incidence is increasing and we are talking about an incidence of about 1/100 or 2/100.

In 2003, 22 percent of gonorrhea and 56 percent of syphilis was in MSM and between 200-2004 there was an increase of unprotected anal intercourse by 40-50 percent. They had outbreaks of lymphogranuloma in MSM also in the U.K., but there is a 400 percent, 4-fold, increase of HIV by heterosexual contact in Africa south of the Sahara. So, this will be a new project for the working party of EBA to look at how we are going to address this.

The Health Protection agency, which is the public health agency in the U.K., looked at all these figures as well and declared, from a governmental point of view, that there is considerable HIV import by heterosexual contact in Africa, but the group most at risk in the U.K. is still the MSM.

Data from Belgium--in Belgium there were syphilis outbreaks in Antwerp from MSM. There was an 86 percent increase in active syphilis in the last quarter of 2003, about 80 percent of which is in MSM, and co-infection of HIV with syphilis is at 51 percent, of which 58 percent is MSM.

So, now we come to the effects of those public health data on the blood donors. In France, the HIV incidence in the donors is about 3.0 to 1.0 per 105 donor-years so it is about 1-3 per 100,000 donor-years, which is more or less stable over the period of '98 to 2004. From 1992-2004 there is an increase of HIV-positive male donors as a proportion among the HIV-positive donors. So, in 2004 41 percent of HIV-positive donors is MSM, and

the proportion of recent infections within 6 months rose from 10 percent to 44 percent.

Germany and The Netherlands--in Germany they had about 100 HIV cases in the donors and about 30 percent of them had an interview for risk factors. Of those who answered the interviews or who were interviewed, 40 percent were MSMs.

In The Netherlands we have an ongoing program which started in 1995 voluntarily and had about 77 percent compliance, but it is now mandatory that every donor who is counseled for a confirmed positive infection is extensively interviewed with a five-page questionnaire, and it turns out that the donors are very much in favor of that because they want to know themselves. This program is now ongoing with ongoing epidemiological monitoring. We found that HIV in new donors, 20 percent of those is MSM, but in repeat donors, and that is our main concern because of seroconversions with potential infection to the recipient, about 30 percent is MSM. Hepatitis B in new donors is only 3 percent in MSM, but in repeat donors it is about

14 percent.

If you look at the prevalence of HIV, for instance, in The Netherlands in new donors it is about 1-2 per 100,000. It has been higher in the past, as you see, and we estimate that the prevalence in the general population is about one log higher. So, the data that were shown previously from the FDA--the impression that your donor selection up front reduces the risk that you get an infected donor in the house as a new donor is about a one log reduction. You see that over the last years this was pretty stable.

What is worrying though is the incidence. The incidence is quite low. We were fairly happy here at the end of the '90s where we had about 0.2 per 100,000 donor-years but then, in 2002, we had a national discussion on whether MSMs could donate again and it went up and we have to see what happens next.

HIV in blood donors in the U.K., period 1995-2004, HIV in new donors, 21 percent was in MSMs and in 42 percent was acquired heterosexually

in Africa. So, that is really a problem and that is reflecting what goes on in the general population but it is in new donors. Whereas, in repeat donors HIV cases, 45 percent of those were from MSMs and only 29 percent were heterosexually acquired abroad. So, probably in our deferral or our communication method there is something that has to be looked at.

HIV in donors with an applicable deferral criterium is 64 percent in MSM; 8 percent in intravenous drug users; and 26 percent heterosexual in Africa. So, the problem in the U.K. is the reason that the European Blood Alliance is going to look at this in the coming year. HIV in repeat donors seroconversion has been stable with a similar figure as you see in the other countries.

Now we come to the modeling studies. As Jay very clearly said and is true, the safety of blood is so high at the moment and the incidences are so low that we cannot measure easily the differences in safety and we have to make model studies. Fortunately, we have one of the authors

of the models, Kate Soldan, on our panel se we critically looked at all these models and I think that not only for this infection but also for other infections the modeling studies are becoming more and more important and this is a trade that we will have to learn as the blood banking community in the future.

In the Soldan study there was a suggestion to deselect--they call it deselect; that means to unselect the present permanent deferral for MSMs for the last 12 months versus all. So, if they would go from permanent deferral to 12-month deferral, the risk to recipients would increase by 60 percent in that paper. If they would not select at all for MSM behavior they would have 500 percent increase. But there is new unpublished data from Kate which says that the unsafety, if you like, of increasing risk is less than previously published.

But there is a problem. There are two uncertainties in the model, the uncertainty of compliance that is not measured so that was an estimate, and the discussion was if we would not be

so strict for homosexual men, then maybe they would comply better with our questionnaire. But the problem in this model is that compliance with the questionnaire is already assumed at 97 percent. So, statistically, if you would hoist it up to 100 percent it doesn't matter in the outcome of the model, and it is also not likely also.

Uncertainty of HIV incidence in MSM who do not practice for 12 months which, actually we felt in the working party, was the most crucial point where we have no data, and I can come to that later. There is no data to base the estimates or the assumptions on to say, okay, if people say they had MSM behavior but not for the last 12 months, what is the safety of that in terms of HIV or other infections?

The German model is going to be addressed later on at this meeting so I will be short about it. The risk incremental is on the same order of magnitude as the present risk, but current MSM deferral is five times more effective than the deferral of female contact with contact to MSM.

The limitation of that study is that it was in one center, and there is also uncertainty on the data that you use for non-recent MSM behavior.

The Sanchez study, which is very well known here in the United States, is an anonymous study and they suggested that the cutoff would be five years rather than 12 months. So, we will have to continue those discussions I think.

Now we come to the regulatory part. There is a recent new directive in the European Union, and that directive is under a treaty and the treaty says that all laws in the European Community, the 25 countries, will have to comply with that. So, if something is in the directive in the European Commission, then it means that all the laws of these member states will have to be changed in order to comply with that.

Article 2.1 says that persons whose sexual behavior puts them at high risk of acquiring severe infectious disease that can be transmitted by blood is permanent deferral. There are also statements on other sorts of risks but there was no discussion

within EBA that MSM behavior is to be considered as sexual behavior with a high risk of acquiring HIV which, by the way, is a severe infectious disease. So, based on these three criteria, the directive has to apply and we have to permanently defer.

Now we look at governmental political positions. France is not likely to change. They have this in their guidelines from the EFS. Germany has the Richtlinien and Bundesartztekamme, the guideline from the medical profession. They are not likely to change. The Netherlands has discussed this on the parliamentary level and the minister of health has said to the parliament that he is not going to change in light of the European directive. In the U.K. there is a national committee and they have an annual review, and although it is quite thoroughly discussed there is no change in policy yet. In Belgium, where it was discussed between the minister and the establishment, there is no change after discussions.

Now, the public address issue, we feel

that the present safety is based on self-deferral for at least a big part because you can see that in the difference of prevalence in new donors versus prevalence in the general population, and that goes up for one log and you see that figure coming back in many studies. Apparently, that is because we communicate quite massively that some people should not donate. So, those communications are apparently effective to a certain extent but there is room for improvement. We have to inform the donors anyway. That is also in the European regulations. So, maybe we could look at how we inform donors on this issue if we would want to change or whether we would not want to change.

Uncertainty of safety, if deferral would change in modeling studies, it is our conclusion that they indicate some loss of safety but that the extent of the loss of safety is uncertain. But we feel in Europe that the equality in deferral where you would argue you are permanently deferring a group of people, X, while you are temporarily deferring a group of people, Y, would seem unfair.

That discussion, we feel, is not fruitful because we feel that there is no right to donate. So, we would only go based on the analysis of the safety and supply, for that matter, for the recipient. We would not go on a sort of equality and right to donate.

The committee on equal rights in The Netherlands translated the European requirements on equal treatment in Dutch law, and I can give you that paper because it is translated in English, if you want. It firstly discussed in 1998 several cases of discrimination of the blood banking community against MSMs but also against people from Africa, etc. The point here is that in the European laws direct and indirect discrimination is forbidden, and indirect discrimination is when you discriminate in practice when you do not intend to discriminate but the effect of your act is discriminatory. So, the concept of indirect discrimination is in conformity with the definition of the EC directive on equal treatment on the grounds of race or ethnic origin.

This committee looked at that and I think it took one and a half years to come out with a verdict. There were actually four cases which were discussed, four cases of MSMs against four blood banks. They claim that the Equal Treatment Act forbids discrimination on sexual orientation, age and ethnicity in offering goods or services, and MSM behavior is a manifestation of sexual orientation and, therefore, the blood banks are discriminatory.

The verdict of that committee which is, by the way, much longer and much more nuanced, is that in the case where there is no direct discrimination the purpose of the donor selection was not to discriminate but to prevent transmission of HIV and other infections. Homosexual men are disproportionately affected by the selection. That is true. But there is an indirect discriminatory distinction, however objectively justified and not disproportional, in the interest of the recipient's blood. That is the bottom line, the interest of the recipients of blood.

In summary, the public health surveys show MSM is at high risk of HIV and a considerable proportion of MSM is in positive donors where we have to look carefully at seroconversions rate and outcome. This is still a big proportion.

Risk of MSM--no practice for 12 months is not established but should be established. Recipient risk increases, however the extent is unknown. And, MSM is at increased risk of sexually transmitted diseases and emerging known and unknown infections. HIV incidence in repeat donors is directly linked to blood safety, but is presently low and stable despite increasing frequencies in the public health data. Any HIV transmission in The Netherlands and in Europe is to be reported to the European competent authorities, as is every seroconversion with a look-back.

So, the conclusion of the European Blood Alliance was to not change the present policy of permanent deferral. The reason for this deferral, such as summarized in this report, should be publicly communicated, preferably in collaboration

with MSM representative groups. That is now done in Belgium and we are going to do that in Holland.

G. Follea looked at the questionnaire and what the practice is at the moment, and 15 of 15 country questionnaires have the same policy at the moment. And, further studies could be envisioned to assess the safety of multiple infections of a low risk group. So, this is the the formal position of the EBA. I could elaborate a little bit more as a person and as a scientist.

My question, or the question in Holland is would the gay community really be helped by deferral of 12 months? I have discussed this many times with their representation groups and we discussed this often in recent times again. They feel that it is highly disputable whether that would help them. That would mean that they would have to communicate that you would not have sex for a year, which in Amsterdam terms is quite a laughable position.

[Laughter]

And it is reflected on the negative side

in Australia where they are merging all the blood banks in Australia into one Red Cross system. There was no uniformity about this deferral so they made it uniform for 12 months deferral, temporary deferral. But now they are sued in Australia for being discriminatory, and that is what the gay people told me, they said, well, not being able to donate if you have sex for one year we feel is discriminatory, but what we feel is that we have now gained acceptance in Holland and many other countries to be able to marry, and we have a stable relationship, and so why could you not focus on a totally different point of view as a subset of safe MSM donors, the monogamous donors? So, from their point of view, the discussion is not so much on temporary versus permanent but more the appreciation of their relationship, if you like.

Now, we have in Amsterdam cohort studies. That is a separate foundation which does very large studies not only on MSM but also anybody with a risk who wants to enter these studies is entered, and we have discussed this with the scientists from

this group whom you may know, and there is a subset in the cohort with a safer profile. The problem is that we don't yet know what that profile is but we feel that it could be elaborated. So, we think that we should extend this cohort, not to draw these people to the blood banks but to the municipal health services and get a cohort where we would say that there are people with a safe risk profile but MSM monogamous behavior for instance or no MSM during the last year.

So, we would not only test them for HIV but anonymously test them for anything that is sexually transmitted, anything. Why? That is because if we only measured HIV we probably would not have the power to do this study in reasonable terms. We will do the same set of tests, extra tests on a cohort of new donors, a representative cohort of new donors entering the donor population in Holland.

We are just doing the arithmetic on the power and duration of the study. The problem is, of course, if we would get enough people

participating and, problem number two, is the duration. But we feel that even if it would take us three years to solve this, the gay people are in favor of that because we have had the problem now for 25 years so two years or three years extra to make a good solution is acceptable.

Why I come to that conclusion is that there is a subset, for instance if you look at the hepatitis B, acute hepatitis B, in MSMs there were 6 cases in 2004 in people with a steady partner and 82 in people with a casual partner. So, we will have to look at that subset of people who are less at risk.

Also, what we are going to do with the EBA, as I announced earlier, is to look at the import of HIV from countries with high prevalence. I shared with you the differences in epidemiology of HIV in Europe and you see that this part of Europe is especially of concern but that is introduced by intravenous drug use and prostitution for intravenous drug use, whereas in Belgium, here and in England there is import of HIV from

sub-Saharan Africa and here you see that this, in yellow, is all the same with about the same prevalence. Thank you.

[Applause]

DR. LACKRITZ: Our last speaker of our first session will be Dr. Ronald Bayer, from Columbia University, speaking on social dimensions of current deferral policies.

Social Dimensions of Current Deferral Policies

DR. BAYER: I guess it is time for a different perspective. By way of background, I have been dealing with this issue since 1982, since before the HIV test was discovered when the New York Blood Center was trying to develop deferral policies. I have come back to it periodically and I find my own perspective on this issue shifting, in part because of my understanding of the shifting science.

It is 23 years since the U.S. Public Health Service first addressed the threat to the blood supply posed by the then emergent AIDS epidemic. Almost a year before the identification

of HIV, which was in 1984, then called HTLV-III or LAV, and two years before the licensure of the antibody test, the pressure largely from the hemophilia-related community began to mount to exclude high risk donors from the list of eligible donors. Among those thought of as posing a risk, of course, at that point in the epidemic were gay men. From the vantage point of just a few years, resistance to such exclusionary measures would seem utterly misguided.

Gay organizations, first beginning to struggle with the implications of the new threat to the survival of gay men, were concerned that an explicit bar to donation by men who had sex with men would only serve to bolster stigmatization and homophobia. Banning men who had sex with men from the donor pool would exclude them from one of the great acts of altruism in contemporary society so carefully mapped by Richard Titmus.

Recall also that discussion of such restrictions and bans occurred at a time when half the states in the United States still criminalized

sex between men, consenting adults, and that in 1985 the Supreme Court of the United States in Bowers versus Hardwick would uphold Georgia's sodomy statute, dismissing claims that gay adult men had a right to have sex as vacuous.

Typical of the resistance to exclusions were comments like these, "a ban on gay donors would be a return to the bad old days when a recurrently scapegoated minority could be sweepingly stigmatized for the taint of bad blood. A ban will pit victim against victim and serve only to divert attention from the vital medical and ethical concerns that lie at the heart of this health crisis."

But gay men and those who spoke on their behalf were not the only opponents of the imposing donor restrictions. Some of the most knowledgeable and experienced blood bankers, concerned about the adequacy of the blood supply, also expressed doubts about what they felt would precipitate action in the face of inadequate data. The director of Yale,s Blood Center, Joseph Bove, was joined by

Aaron Kelber of the New York Blood Center in issuing warnings. "We are," said Bove, "contemplating all those wide-ranging measures because one baby got AIDS through transfusion."

Against such voices of restraint were those who saw an emerging crisis that asserted and required immediate action. The remarks of CDC's Donald Francis, memorialized in the book "And the Ban Played On," reflected the sense of alarm. "How many cases will it take?" he demanded of those who were reluctant to take precautionary steps. And Jim Curran at the CDC warned, "the thing is people are dying. The medical problem is more important than the civil rights issue." Curran's expression of concern was echoed by some physicians within the gay community. "We must," said one doctor, "spread the word among gay men to avoid blood and plasma donation until more is known. Gay men cannot, even with the best of intentions, add to morbidity and mortality."

It was in this context of this dispute which captured in some way claims and concerns that

would animate and punctuate debates over the next decades that the Public Health Service issued its first formal recommendations on March 4, 1983: Sexually active homosexual and bisexual men with multiple partners should refrain from blood donation. These were, of course, exclusions that were modest in comparison to those that would later be imposed excluding any man who had sex with any man since 1977.

Much, of course, has changed since the imposition of restrictions based on interviews or questionnaires about risk behavior. Increasingly sophisticated specific and sensitive blood tests have been relied upon. The first antibody test, employed in mid 1985 with its problematic window period, has been replaced by subsequent tests and now NAT. Such tests all but closed the so-called window of undetectable infection. With such tests in place, debate resurfaced repeatedly over the role and necessity of restricting men who have sex with men even once from donating blood.

At the heart of that debate are a series

of empirical questions, but they are empirical questions with profound moral significance. More than three decades ago the National Research Council made a clear conceptual distinction between the process of risk assessment, which it asserted entailed an essentially empirical analysis and risk management which involved political judgments about the acceptability of risk. But strikingly, according to the NRC, even risk assessment involved irreducible elements of value judgment given the uncertainties involved. How conservative was one to be at each step of the assessment was in part a policy choice, not a choice dictated by science in and of itself. Hence, to portray the response to risk in public policy as a matter of science alone was to mask the matters at stake. The question of acceptable risk was, and has remained, essentially a moral question.

When the federal government began to address the issue of protecting the rights of those with disabilities, the Supreme Court in the landmark case, called Arline versus Nassau County,

determined that discriminating against those with infectious disease, in this case tuberculosis, could only be justified if such individuals posed a significant risk. To do otherwise, stated the court, would be to yield to society's accumulative myths and fears, and the court articulated a four-part test including the duration of risk, the severity of risk and the probability that a transmissible agent would be communicated. Ultimately, that four-part test was incorporated into the Americans with Disabilities Act.

At bottom, the Supreme Court's and congressional determination was an embrace of the proposition that in facing the question of acceptable and unacceptable risk the accumulated prejudice of society should not serve as a foundation for public policy.

Let me suggest to you that this whole discussion around HIV was reflected in a quite bitter dispute about whether or not people with HIV infection--clinicians--should be allowed to continue to practice medicine. Remarkably, in that

context those who said people with HIV should not be allowed to practice medicine said no risk at all is tolerable. The risk they were talking about was a theoretical risk or the risk that came from one dental practice in Florida where five patients had been infected by one dentist, the only documented case in the United States of transmission from a healthcare worker to patients, and that was the only evidence. There was a theoretical risk certainly, but it was a theoretical risk not substantiated by any demonstrable evidence.

It should be clear now where I am trying to take you. There is no right, as we have heard over and over again today, to donate blood if, in so doing, one places potential recipients at risk. No principle of equity or respect for persons could justify the imposition of such burdens on those in need of blood. That much is obvious, but how much risk is tolerable in blood donation? What price should one be willing to pay for achieving greater levels of security? Are there some risks that are so vanishingly remote, maybe detectable in models,

that the imposition of costs in dollar terms or in terms of discrimination that they would require would be either an irrational expenditure or an unfair burden?

In 1989, Harvey Feinberg, then dean of the Harvard School of Public Health but now president of the Institute of Medicine and an expert on risk analysis, said to a conference on the nation's blood supply that, quote, a simple-minded focus on safety is no longer an appropriate approach for those concerned with sensible uses of the blood supply. With very high levels of security already achieved incremental improvements would come at very high costs and would produce only marginal benefits. Today, said Feinberg, the harder kind of question is how can we define and attain a desirable balance among the goals of safety and adequate blood supply and our ethical responsibility to society, to the patient and to the donor?

It was those issues that surfaced when just more than five years ago the FDA addressed the

issue of its ban on blood donation from men who had sex with men within the prior 23 years. An advisory committee upheld the restriction, but just barely by a 7-6 vote. It was not surprising that gay spokesmen would state HIV is a disease that affects the African American community disproportionately. More telling was the fact that the American Association of Blood Banks, which opposed the extant policy, said by way of explanation, that the longest window we know to detect virus is a year. The science is there.

It is that issue that we now address today. There are two questions we need to confront: Are the risks associated with permitting donation from men who have had sex with men ever at any point during the last 29 years or, for that matter, in the last five years, greater than we are willing to tolerate in blood donation generally?

Secondly, is the risk aversion policy we embrace applied in a way that entails an invidious discrimination? Does it reflect our accumulated prejudices whether conscious or unconscious?

In preparing for today's talk, I looked at the current exclusionary policies with regard to behavior and was troubled more than I was comforted. Current restrictions based on sexual or other risk behaviors include, as Alan Williams pointed out earlier, anyone who has had a tattoo in the last 12 months, unless applied by a state-regulated entity with sterile needle and non-reused ink;

Anyone who has had an ear or body piercing in the last 12 months, quote, unless the ear or body piercing has been done using single dose equipment;

Anyone who in the past 12 months has had sexual contact with a person with hepatitis;

Anyone who in the past 12 months has had or been tested for syphilis or gonorrhea;

Anyone who has had sex with a prostitute or anyone who takes money for drugs or payment for sex;

Anyone who in the past 12 months has had sexual contact with anyone who has ever used

needles to take drugs or steroids, or anything not prescribed by their doctor;

Any female donor who in the past 12 months has had sex with a man who has had sex with another man;

Anyone, man or woman, who in the past 12 months has had sexual contact with a member of the opposite sex who has AIDS or has tested positive for HIV;

Then, men who have had sex with men since 1977, no matter how monogamous their relationship is classed, such men are linked with prostitutes, sex workers and drug users. Given the current testing technology, there is clearly a public health rationale for jettisoning the 29-year exclusion for men who have had sex with men. But why stop at five years? Why not three years or two years? The logic of shifting from a 29-year exclusion, since 1977, to a five-year exclusion is hard to uncover. Why not three years or two years? Indeed, it is hard to understand, given the goal of safety and the commitment to precaution that is

embedded in public health practice, why anything more than a one-year exclusion is justified.

Officials may believe that to make such a radical move would be political suicide, but to claim that the evidence or the ethical premises of medicine and public health require an exclusion more exacting than that which prevails for women who have had sex with a man with AIDS is difficult to understand, and I am afraid it may confuse the dictates of convention with the requirements of science or ethics. What we cannot do as a result of this discussion is take refuge in science when, in fact, what we are responding to is political pressure. Thank you.

[Applause]

DR. LACKRITZ: Thank you. We will now take a 15-minute coffee break so we will see you back here at 10:20.

[Brief recess]

DR. DAYTON: Let me bring the second half of the session to order. I have to warn everyone that there is no food and drink allowed in the

auditorium--not anyone in particular, mind you and, as we said, the penalty is permanent deferral!

The second part of this over-arching session is on the prevalence and incidence of known and potential transfusion-transmissible infections in relation to behavioral risks. Mat McKenna is not only going to moderate this session but he is going to give the first talt in it on the transmission of HIV by blood transfusion.

Prevalence and Incidence of Known and Potential Transmission-Transmissible Infections in Relation to Behavioral Risks,

Matthew McKenna M.D., M.P.H., CDC Moderator

Transfusion of HIV by Blood Transfusion

DR. MCKENNA: Thanks, Andy. Good morning. I think just as a quick orientation, this session is really going to be devoted very much to presenting the overall epidemiology of the various pathogens and viruses that are of interest to protection in blood transfusion processes, not so much focused on transmission of these particular viruses. The talk I am going to be giving in

expressing that epidemiology is focused on the incidence and prevalence of HIV by behavioral risk factors in the United States or the current status and, of course, that has implications, as we all know for transfusion risk.

The topics I will be covering are listed above. For most of the presentation I will just be presenting population-based case surveillance data collected by state and local health departments that is forwarded to CDC according to existing public health reporting laws. I will refer briefly to a few cross-sectional cohort studies that have looked at the prevalence and incidence of HIV in certain specific populations. Of course, these are studies where individuals have generally consented to participate or are in selected populations where there may be anonymous testing so their generalizability is not quite the same as the surveillance data.

I will also discuss some information on the population distribution of behavioral risk factors in the U.S. and focus somewhat on the

implications for understanding HIV infection incidence. Another piece embedded in this is presenting data on population-based information regarding trends and testing for HIV and the CDC estimates for overall levels of diagnosed versus undiagnosed infection in the country.

All the data I will be presenting will be from published sources, or sources that have been presented in public or scientific meetings, or data that is imminently to be published.

The challenge we face--it hasn't been discussed very much but the challenge we face in sort of talking about the incidence of infection, of course, is that our case surveillance system in the U.S. focuses on diagnosed cases, sort of the right-hand side of the events that we actually measure in depiction of the spectrum of HIV infection. However, with population-based information and certain assumptions and a lot of background information about the natural history of HIV infection, it is pretty reasonable to be able to infer back to the issues of most interest, which

are the behavioral risks for HIV infection and the undiagnosed population in the U.S.

To further clarify the assumptions behind such estimation procedures, I think it is useful to think metaphorically about the progression of HIV and how the surveillance data can be used to provide a complete picture of the epidemic. All the numbers here, by the way, are broad estimates for prevalence and incidence of HIV infection as well as the clinical events.

But overall, if we think of the health status of persons infected with HIV as pots in a sense; they sit in the different health states in pots and transitions from one health state to the other are spigots that represent the flow from one to the other, then the flow through each of the spigots represents a rate determined by two things: the incidence and, in the case of flowing from the highest pot to the second pot, the level of testing. In a sense, testing opens and closes the valve on the spigot and the incidence rate increases or decreases the pressure on that

particular spigot. We then can directly measure most of what is depicted here and infer the actual incidence rate as long as we assume that there are no major changes in how open the valve is.

The most important determinant, of course as I have alluded to, is the HIV testing trends, particularly in the most recent past. However, in terms of overall population testing in the U.S., this data source is the most comprehensive, which is from the national health interview survey and shows that really throughout the latter part of the 1990s both the overall prevalence of lifetime history of being tested for HIV as well as being tested for HIV in the most recent year has remained fairly stable in the general population.

Now, this, of course, doesn't tell us very much about testing in very high risk populations. Indeed, if we were to be successful, as CDC's most recent initiative in advancing HIV prevention really tries to augment testing in high risk populations, we could see very small, if any, risk or change in HIV testing in the general population

and, yet, see an increase in the number of new diagnoses. But generally the evidence that such a change has occurred is pretty limited.

Just to also give people some background in terms of the national data I will be presenting, it is from the national HIV reporting system but currently only 33 states have quality data that can be used to analyze trends in that system, and those states are depicted above in yellow for the data.

The two lines here depict the trends in the number, which is the top line, the yellow line, and the rates of HIV diagnoses occurring in the 33 areas during the period 2001-2004. Just parenthetically here, we saw a map earlier from Europe showing the highest rates to the lower rates with gradation and groupings. The U.S. rate, which has generally been a little bit above 20 per 100,000 would equate to above 200 per million in the slide we showed before from Europe, which is among the highest rates in the European arena. EAPC here stands for the estimated annual percent change, which is just an expression of the percent

change per year of each of these parameters. Just to easily think about it, it is pretty much what your mutual fund company quotes to you about increases or decreases on an annual basis for your investments; it is the same sort of idea.

Generally the basic message is that there has been very little change. Neither one of these estimated annual percent changes are statistically significant when compared to zero. So, for us with a mission of prevention, the stability here is very disconcerting.

When the number of cases per year diagnosed in the U.S. is looked at by behavioral risk we get a slightly different picture. Except for trends amongst men who have sex with men, the trends for all other risk groups have been statistically significant in a downward direction. Some of these, particularly the pink line which is high risk heterosexuals and the yellow line, men who have sex with men in the injection drug using population, are a bit more modest and we think could be due to artifacts in the HIV reporting

system in the U.S. However, the rates in the green line, the decreases among injection drug users, is almost 10 percent per year and has been part of a longer-term trend we see in a variety of other data sources that we are convinced is really quite reflective of decreasing incidence in that population.

However, as I have talked about, are there data to support the assumption that trends in incidence of HIV diagnoses is an indicator of incidence of HIV infection? Sort of during the '90s when we didn't have as high quality and as comprehensive HIV diagnosis reporting, we were having to thrash around quite a bit. This is data from a meta-analysis that was done by Quan at CDC where he took 74 studies either from cohort information or from studies that were using the serological testing algorithm for recent HIV seroconversion, which is utilization of an assay which allows us to estimate incidence on a cross-sectional basis--he took those 74 studies and meta-analyzed them in a sense.

What you see is these two black lines from about 1982 to 1998. This line, here, represents trends among men who have sex with men and this is the line for injection drug users. In an earlier period of time from the data I was showing you, it very much reflects what we see now, decreases and then stabilization, decreases in the late 1980s and incidence rates of HIV in these two risk groups, and then stabilization among men who have sex with men throughout the 1990s and continuing decreases in injection drug users.

It is also worthwhile noting the absolute rates here. Amongst men who have sex with men the general infection rates were about 3 percent per year, and in injection drug users it was getting below 1 percent per year into the 0.5 percent per year range.

We have more recent data from anonymous counseling and testing centers in Louisiana and Texas, where we use the serological testing algorithm assay to estimate incidence in persons who were getting tested for HIV for other reasons,

shows amongst men who have sex with men--despite this blip that we think is just part of the inherent variability in these sorts of studies--a stable rate between 2-3 percent per year amongst men who have sex with men and rates in the 0.5 percent per year range in other persons, both females and males.

This number is almost quite disconcerting to me when we go to national meetings and we see poster after poster and presentation after presentation of these sorts of data from clinic-bases surveys. These are high risk populations, of course. These are people who are being tested for HIV or attending clinics that have counseling and testing services, and these rates are probably a bit high but the number is almost always the same, between 2.5 to 3 percent, no matter what populations are looked at. There are some in San Francisco and others who are seeing somewhat slower rates in their STD clinics but for the most part this is what is seen around the country--very consistent with what Quan found in

his meta-analysis.

In terms of prevalence, these are data that got quite a bit of publicity and I thought they were worth reviewing, not so much for their representativeness but just to clarify where they came from and what they mean. They were published in the MMWR back in June of the past year, and they represent data from the national HIV behavioral surveillance program in five cities where HIV testing was done, in addition to surveys of men who have sex with men who were attending venues frequented by persons who engage in that behavior.

The most notable piece that was highly publicized, very highly publicized out of this was, of course, that there were a little over 1,700 men that were surveyed at these venues and 25 percent of them were HIV-infected and almost half, 48 percent, of them were not aware that they were infected. One of the strongest predictors, of course, of awareness was the age. The older they were, there was decreasing unawareness of their infection.

But the issue about the data I just showed you is to please understand that these are very high risk populations. It is not population-based; it is not a household survey. These are persons attending venues where we know individuals are going to be at very high risk. But in terms of understanding prevalence of undiagnosed in the population, we return again to the case surveillance information. I just want to go once again through some of the assumptions and methods used to see what is really a diagnosed population, though very population-based; whether it is truly representative of all those being diagnosed and how we infer these other pieces of information.

That calculation method for estimating overall HIV incidence has been around since the 1990s, and is mostly used for AIDS cases to estimate that. Today, with more comprehensive HIV, we can use HIV detection, differentiating between persons diagnosed with HIV/not AIDS and AIDS, as well as well as the CD4 distribution, to understand the trajectory of CD4s over the length of an HIV

infection to make some estimate among those diagnosed inferring back to the incidence rate in the past. That gives us very good information about cumulative historical incidence and allows us to come up with reasonable prevalence rates, and really is still highly precise for more recent periods of time in terms of calculating incidence.

But this sort of methodology is the data from which I will be presenting where the data over the next few slides was derived and has been presented in a national meeting by Glynn and Rhodes.

Overall, we estimate that for total HIV prevalence in the U.S. the number of persons infected by the end of 2003 was about 1,039,000 to 1,185,000. Amongst those, 42 percent were HIV without AIDS, 34 percent with AIDS and about 24-27 percent with undiagnosed infection.

When looked at by risk group in the terminology we are currently using, transmission category, about half or 45 percent of those infections were in men who have sex with men; 27

percent in persons identified as having high risk heterosexual contact; and 22 percent in injection drug users.

Now, though we know among those infected about 25 percent are undiagnosed, is there much difference amongst these various risk groups in that proportion? Our estimates are that there is not very much difference. This is looking at a slightly different sort of number but, luckily, with algebra we can get to the other one. This is what was actually presented at the meeting but it is the distribution amongst the diagnosed and diagnosed by risk factor.

What it really shows is that amongst men who have sex with men we estimate that the proportion with undiagnosed infections is about the same as it is in the rest. The injection drug users actually have a lower rate among the infected and heterosexuals have a slightly higher rate. But in general there is not much variability, between 23-28 percent we estimate amongst all the risk groups are all the infections--the individual

infected who is unaware of the infection.

Now, in terms of distributions of risk behaviors, we have heard from our European colleagues about their estimates of the size of the MSM population. Data we just released in September of this year from the National Center for Health Statistics from a national survey of family growth--the national survey of family growth is a long-standing survey, population-based household survey that traditionally has interviewed 15-44 year-old women in the United States. In this most recent cycle going through 2002, they also interviewed men in what is right now the most detailed sexual history we have. From that, 6 percent of the men ages 15-44 reported a lifetime history of sex with another man, and about half of those reported such activity in the last 12 months.

Another study by Catania, which is a fairly population-based phone survey amongst men from zip codes enriched and known to have high levels of men who have sex with men residing there, found that 90 percent of urban MSM reported that

they had engaged in MSM behavior in the previous 5 years. So, when we are talking about some of these deferrals and what the opportunities are for opening up and making available more donorship, figures about this are about the best we have in terms of what the volume is or how many persons would be donating on a population basis.

In terms of estimating the IDU population, Friedman has recently estimated, in a '96 large MSA, the rate and prevalence of injection drug use between 19-173 per 10,000 persons. If you extrapolated that across all of them, it would be about 1.6 million persons. However, they also estimate that lifetime injection drug use--because those were just for the last 12 months--is about 2.5 times that size, which would give you somewhere in the neighborhood of about 4 million persons who have some lifetime history of injection drug use.

The estimation of the high risk heterosexual and coming up with what that looks like is probably, we almost think, methodologically impossible at CDC. In terms of the surveillance

data I have been showing, it is just impossible in terms of behaviors. At CDC we do require that for a person to be classified into that category in the surveillance data as a diagnosed individual, they have to report or someone needs to record or document that men have had sex with men or sex with an IUD drug user or persons from other high risk groups, persons with hemophilia or persons who are HIV-infected.

Also, in a very interesting study, a cohort study out of Baltimore, where Strathdee looked at risk of new HIV infection in injection drug users and found that for men it was mostly related to their injection drug use behavior, whether they shared needles recently, did not take precautions in harm reduction, but amongst females, actually their sexual practices and whether they had sex with men who had sex with men or other unprotected sexual activities was a stronger determinant of their risk.

What this has left our national HIV behavioral surveillance system with in trying to

identify high risk heterosexual populations is not really being able to default to any information from the individual about their own heterosexual practices. In fact, from the NSFG, the median lifetime partners for males was 5.6 partners per man and 3.3 lifetime partners in that age group I was talking about earlier, which in some of the surveys and some of the classification systems would put half of the population into the high risk heterosexual category.

For our behavioral surveillance program, what we have defaulted to is basically anyone who engages in heterosexual sex who is either residing in or reports to us contact with a social network in a geographic area where there is a very high HIV infection or diagnosis rate. They need to have HIV present in a prior assessment of exposure to HIV, or engage in behaviors with a population with very high risk of HIV needs to be there. Behavior itself in terms of heterosexual practices is very difficult and doesn't seem to be a very accurate differentiator for high risk heterosexual sex.

So, limitations of the data, as I have talked about in terms of using the case data, it is modeled from national surveys. The models are assumption laden and imprecise, especially for very detailed subgroup analyses, which I know people here would like us to talk about. Also, at CDC we really are now focused much more on what are the next steps we need to take to decrease the rates of transmission in the general population. Therefore, we tend to focus on defining, identifying and understanding high risk groups and do very little study or investigation into low risk populations.

As has been discussed, it is very resource intensive to collect enough--particularly numerator information--numbers of infections in low risk populations, to make that efficient from a resource and expenditure standpoint. As I said, the public efforts focus on high risk populations.

Then, just some thoughts about risk among the donating population, and people with more experience in this have talked a little bit about it. What is the association of risk in the

donating population, both in terms of self-deferral but also in knowing their own infections? I have already indicated that older age persons who are at risk, if they are infected, are more likely to know that.

Then, again performance of the classification methods--you know, in the research setting where we do up to a year of formative research and working with populations to develop instruments, how different is that than working in a blood donation center and implementing questionnaires?

So, in summary, the best estimate we have is that approximately half a million men who have sex with men are infected in the United States and about 25 percent of them are unaware of their infection. About equal numbers, perhaps a little bit more of persons who have been heterosexually exposed to injection drug use are in the 250,000 to 300,000 range. Three-quarters of these infected persons are diagnosed in both of those groups. The incidence overall amongst men who have sex with men

is about 2-3 percent per year. In these high risk populations though there does seem to be some evidence in some areas that in low risk it is about 1 percent per year. But these numbers have been disconcertingly stable since the early 1990s at least. The incidence in injection drug users has been decreasing and has now gotten down to below the 1 percent per year rate, and it continues to decline from all the evidence we have.

Just as an overall point--it may be obvious but it bears repeating, coming from an agency with a mission to decrease the overall population risk, when we are coming up with all these conditional probabilities about what might be the event that ends with a transfusion of an infected unit, what it starts with is what the overall marginal probability of the infection is in the overall population, and the more we can all work together to decrease the rates of infection in everyone, the more we all will benefit and can be more efficient in the goal that we are discussing in this meeting.

I have some references that you can look at for some of the things I discussed in my talk. With that, we can move on to the next presentation.

[Applause]

The next scheduled presentation is from Dr. Ian Williams, a CDC colleague who is with the Division of Hepatitis.

Transmission of HBV and HCV by Blood Transfusion

DR. WILLIAMS: Thank you and good morning. As Dr. McKenna said, I am going to be focusing sort of on what is the epidemiology of hepatitis C and hepatitis B virus infection in the United States, really focusing on what has been going on in the last couple of years because, as we will see through this presentation, there have been some dramatic changes in the incidence of both hepatitis B and C over the last 20 years or so although the risk groups haven't changed very much. Then I am going to close with focusing on some estimates about prevalence of hepatitis B and C virus infection in selected populations.

Just so we are all on the same page here,

and I am sure this is all very familiar to all of you, we are really talking about two separate viruses here. We are talking about hepatitis B and C virus. One is an RNA virus, one is a DNA virus. They cause a common clinical presentation, inflammation of the liver--hepatitis. The incubation periods for both of these tend to be relatively long, typically 6-7 weeks for HCV and longer than that, 8-12 weeks for hepatitis B. That has profound implications for studying the epidemiology of both hepatitis B and hepatitis C because you are asking about people who have had exposures oftentimes 2, 3, 4, 5 or 6 months in the past.

Another challenge from an epidemiologic perspective is that most people with hepatitis C are not symptomatic. Only 20-30 percent actually have clinical signs and symptoms. And, among people with hepatitis B it is only a third to a half. So, most of the people who get infected actually don't have the signs and symptoms so don't come to clinical care and can't get included in

epidemiologic studies.

Most people with hepatitis C go on to develop chronic hepatitis C and are persistently infected. However, for hepatitis B, among adults less than 5 percent or so actually become chronically infected so they become infected but very, very few of them actually have chronic infection as adults. However, if they are infected during childhood most of them, or 30-90 percent, can become chronically infected.

So, what is the chronic disease burden for hepatitis B and C in the United States? Well, in the U.S. population 4.9 percent of people have ever been infected with hepatitis B and 1.6 percent have ever been infected with hepatitis C virus. In terms of chronic infections, about 1.2 million people are chronically infected with hepatitis B virus infection, about 3.2 million with hepatitis C infection.

In terms of the number of new infections, we are going to focus on both of these a little bit later as hepatitis B is a little bit of a moving

target in a good way in that the incidence has declined quite dramatically over the last 20 years, and in 2004 it is estimated that there are about 60,000 new infections every year in the United States. For hepatitis C the incidence has been relatively stable for the past decade or so and there are still about 30,000 new infections every year in the United States.

In terms of deaths, there are about 5,000 from hepatitis B and for hepatitis C it is in the neighborhood of 10,000, and there have been a number of studies that have suggested that maybe this number is actually going to increase in the coming decade or two due to the impact of past HCV infections.

Many of you have seen this slide before. This shows the relative distribution of acute viral hepatitis in the United States. However, this slide focuses on what has gone on in the last four years. The reason this is a little different is that hepatitis A historically has been the bigger part of the pie, however, in the last couple of

years the incidence of hepatitis A has dropped quite dramatically in the United States and now we are actually seeing more hepatitis B cases than we are hepatitis A cases. So, about 56 percent of all the acute cases of viral hepatitis are actually hepatitis B and about 9 percent are hepatitis C. So, we are seeing more B than A.

When you talk about transmission of both hepatitis B and C, it is important to remember that these are blood-borne viral infections, just like HIV, and they are spread through all the same sort of methods that any blood-borne pathogen is, that is, through percutaneous or permucosal exposures. For percutaneous exposures, these can either be apparent or inapparent. By apparent exposures, I mean injection drug use or needle stick injury if you are a healthcare worker. Inapparent exposures can include blood and serous body fluid exposures. Permucosal exposures are things such as sex with an infected partner or a child born to a mother who is infected.

So, what separates these blood-borne

pathogens? Well, what really separates hepatitis B, C and HIV is the relative efficiency of transmission. If you look at hepatitis B, it is extremely easily spread through injection drug use, sex with an infected partner, perinatally, as well as in the occupational setting because it is extremely environmentally stable. If you look at hepatitis C, it is extremely easily spread through injection drug use, but not easily spread either through sexual contact or from mother to child. HIV sort of hits moderately on all of these sort of parameters so it is somewhere between hepatitis B and HCV.

So, let's focus a little bit on what the epidemiology of acute hepatitis B in the United States has been in the last couple of years. I mentioned earlier that the incidence has declined quite dramatically and this slide shows that. You can see a decline from about a peak of near 300,000 new infections every year back in the mid to late 1980s and now we are down to about 60,000 infections.

I put two important landmarks on the slide because they are germane to later discussion. The first is the licensure of the vaccine back in 1982 and consequent recommendations to vaccinate people in high risk groups. Unfortunately, we didn't really do a great job of vaccinating high risk groups other than healthcare workers, and even that was a challenge. But in 1991 there was a broader recommendation to immunize infants. Since that time point we have really seen dramatic declines in viral hepatitis infections in the United States.

If you look at the reported risk factors in the last couple of years, what you actually see is what we have sort of seen historically, that the major risks for infections are people having heterosexual contact with an infected partner, men who have sex with men, and injecting drug users. Altogether, these account for about two-thirds of the infections that we see. About a quarter of the people have no identified risk. No identified risk basically means they didn't admit to a risk factor. When you look at these people and actually look at

other factors, probably a number of these people actually belong in these other risk groups so they actually don't admit to risk factors or they just don't remember because, again, the incubation period is relatively long.

Since we are talking about blood transfusions, I wanted to point out that blood transfusions here fall under this other category and in this time period there have been exactly two people who were diagnosed with acute hepatitis who said they had a transfusion during the incubation period. However, both of those cases were followed up and neither one could actually be linked to a transfusion. One of the challenges in doing epidemiologic studies on some of these rare events is trying to actually pin down was the transfusion associated specifically with transmission, and in both of these instances we basically never found an infected unit of blood, which could suggest that either the person was lying to us about their risk factors or they acquired it through other means, potentially mucosomally during their hepatitis for

the transfusion.

I want to also mention a little bit that we have done some looking at transfusion-associated cases reported to CDC. We actually did a validation study in 2003 to look at how many cases are actually reported to CDC every year of acute hepatitis B who said they had a transfusion to sort of see does this make sense what we know in terms of how rare this event should be.

Basically, what we did is we followed up everybody who had a case of acute hepatitis B and said they had a transfusion. In 2003 there were slightly more than 7,500 reported cases, acute symptomatic cases, and 49 were reported with transfusion as a risk factor. However, on the follow-up the box was checked in error in the majority of these. On further follow-up of these people, only one was found to have an infected donor who was in the window period of infection--so, again, a fairly rare outcome.

I also wanted to mention some other data that may be germane to the discussion this morning.

We have been recently involved in some case reports of HBV infection following transfusion. There were actually two specific case reports, one from New York and one from Texas. I would just like to briefly review these for you and maybe draw some conclusions.

The first one happened in New York in 2004. This involved a 60 year-old woman who developed acute hepatitis B in September of 2004 and then died. She had no traditional risk factors for infections. She received four units of packed red blood cells in May of 2004. They went back and traced all four donors. One donor was found to have become infected with HBV since donation. He admitted to multiple male sex partners in the 3 months prior to donation which was not disclosed at the time of donation. Unfortunately, there was no archived specimen for testing, but the implication here was likely that the donor was in the early incubation period of HBV infection that that is what led to the transmission.

The second case report, also in 2004, sort

of looks at the other end. This was a repeat blood donor who was found to be surface antigen positive on a repeat donation. He was found to be positive in August, 2004. He had donated previously in June, 2004 and at that time his donation was hepatitis B surface antigen and anti-HVC negative. When they traced that donation forward, it had basically gone to a single recipient and, as they were tracing the recipient, the recipient essentially developed acute hepatitis B in September as we were locating her. They went back and looked more closely at the donor and re-interviewed the donor. The donor did not disclose any risk factors at the time of donation either in June or August, during the donation or on re-interview. While it is not exactly clear whether this was an early incubation period transmission, it seems likely that maybe that is, indeed, what happened in this situation.

So, what are the implications of these couple of recent investigations and was the surveillance data taken as a whole? Well, one

thing is that clearly transfusion-transmitted HBV infection is a rare event. The surveillance data sort of bears out what we have seen from mathematical modeling and from other data from other sources.

Overall, the risk of collecting HBV infectious blood in the window period is about 1/200,000 donations. When we have observed transmission, it basically has been due to window period donations and not due to testing errors, and that may become germane to some of the discussions later today. So, it really looks like window period donations, when we have seen them--that is how these have occurred.

I also want to remind people, as has been mentioned several times earlier, that donor deferrals based on geographic, medical and behavioral factors are really just the first line of defense here. I mean, it really all depends on donor honesty to make behavioral exclusions work.

I want to mention briefly hepatitis B immunization because it really has a profound

impact on the epidemiology of hepatitis B virus infection in the United States. The current strategy to eliminate HBV infection in the U.S. is really sort of a multi-pronged approach. Really, the most important and one of the key things is universal vaccination of all infants beginning at birth, and this was recommended in 1991.

We are also focusing on preventing perinatal HBV infection through routine screening of women for hepatitis B surface antigen, as well as prophylaxis of children born to hepatitis B surface antigen positive women or women with unknown status.

We also have done some catch-up hepatitis B vaccination in older children and adolescents who were born after 1991, and in the last couple of years really focusing on vaccination of previously unvaccinated adults at increased risk of infection.

So, how have we been doing in terms of vaccination? Well, the good news is that after the recommendation, vaccination coverage went up quite dramatically and currently around 90-92 percent of

2 and 3 year-olds have completed a 3-dose series of hepatitis B vaccine. So, vaccination coverage rates are currently very high among young children.

Actually, if you look among older adolescents and adults, vaccination coverage is still relatively high. This is data from the national health interview survey. They basically found vaccination coverage of 19 and 20 year-olds to be between 50-60 percent. So, vaccination rates are actually pretty high among older adolescents.

However, as you look among older and older adults you can see that the rates of vaccination go down quite dramatically. If you actually look a little bit at vaccination coverage in specific adult populations, you find quite a bit of variability.

If you look at dialysis patients, about 60 percent have been vaccinated against hepatitis B. If you look at healthcare workers, only about 75 percent have been vaccinated against hepatitis B. Among men who have sex with men, it is about 32 percent. This is actually data from the young

men's survey. It focuses on men 22-29 years of age. There is very little data among older men. There is essentially no data among older men but the reduction rates are actually likely to be even lower than seen among young men. It is the same thing among young injecting drug users with vaccination rates of about 40 percent. It is likely that among older injection drug users the rates are even lower. In one study done in San Diego among STD clinic patients vaccination coverage rate was only about 10 percent.

So, we are doing a very good job of vaccinating children and not such a great job of vaccinating adults. Data has shown that actually a number of people at risk for hepatitis B have actually been in venues where you could vaccinate if vaccine was available. So, one of our challenges moving forward is actually figuring out how to vaccinate people at risk for hepatitis B.

I want to turn now to epidemiology of hepatitis C in the United States currently. If you look from a historical perspective, hepatitis C

virus is a bit different than HIV in the sense that this is not a newly emerging infection; this is a virus that has been around for long, long periods of time. By doing some modeling, it looks like the virus has been around in a relatively low prevalence in the population at least 50 years or so.

However, through the 1960s and into the 1980s there was a tremendous increase in the number of new cases. Again, this is the incidence number of new infections, and a lot of this is due to an epidemic of injection drug use in the United States as well as transmission that was fueled through transfusion-associated hepatitis C virus infection. But the incidence actually peaked in sort of the late 1980s, early 1990s, and peaked on the order of about 270,000 new infections every year in the United States but since 1990 there has been a tremendous decline in the number of cases. Currently, we are down now to around 30,000 infections. Actually, if you look at the data the incidence of hepatitis C virus infection in the

United States has been relatively stable for about the past decade or so.

So, what are risk factors for infection? This is focusing on people in the last four years. I want to make one point here, right in front, hepatitis C virus infection is relatively rare now in the population. This is data from the Sentinel Counties study, which is a 6-county study that has been going on for 20 or so years and focuses on about 5 million people in these 6 counties. This 4-year period actually represents 100 cases of acute hepatitis C. So, the estimates are a little unstable and it is what it is, but this is the best data that is available.

So, if you look at what are the risk factors for acute hepatitis C, basically injection drug use is the number one risk factor. This was reported by 40 percent of people so they admitted to injecting drugs during the incubation period.

If you look at the other predominant risk factors, the next big one is people who basically didn't have any identified risk. Probably when you

look at people who had no identified risk, they actually report a number of other behaviors that would make you think they actually belong in another risk group, predominantly sex with an infected partner; they have ever injected drugs; they have ever been in prison; they have ever had an STD; they have ever snorted drugs. So, 18 percent of this whole chunk here probably belong some place else in the pie here so you have to take the data with a grain of salt.

I am going to talk more specifically about sexual transmission, but sexual transmission does occur with hepatitis C although it is relatively unusual, again, because transfusions here is 2 percent. Again, these are people who reported transfusions and did not report any other risk factors and, again, this is 140 people so it represents 2 people here.

On follow-up of these two people, yes, they had received a transfusion but, upon follow-up of the donors we couldn't actually test all of the donors so we don't know whether they actually got

it from a transfusion or not.

In the study mentioned earlier, this validation study done in 2003, we actually followed up all the hepatitis C reports who actually had transfusions as well. We found basically a similar sort of thing. There were 891 reported case of acute hepatitis C, 16 were reported with transfusion as a risk factor and on follow-up basically only one person had acute hepatitis C and was transfused during the incubation period. So, basically the other 15 were in error.

In follow-up of this case, he had received blood and blood products from six donors, Four of those six were tested and found to be uninfected so it is unclear whether this person actually got it from one of the other two donors that weren't tested or basically was a window period donation or what another explanation is. This is very similar to what we see in the Sentinel Counties study where we followed up people if they had a transfusion. Did they get it from transfusion? I don't know because we can't test all of the donors.

Let's talk a little bit specifically about post-transfusion hepatitis. Actually, this is a wonderful slide from Harvey Alter that basically looks from a historical perspective. I think we are all very well aware that transfusion was a very important risk for hepatitis C historically. Somewhere around a third of all donors prior to 1970 basically got hepatitis C following a transfusion.

You can see that a number of safety nets were implemented and you can see that the incidence of both hepatitis B and C virus infection post-transfusions dropped dramatically and now we are down pretty close to this zero risk where we are doing a mathematical model to actually look at what the risk of transfusion is.

It is important to say that a significant proportion of acute infections were due to transfusion historically, and one of the reasons why we have recommendations for anybody who received a blood transfusion prior to July of 1992--when the second generation tests became

available--to get screened for hepatitis C, even though the risk was probably very low, especially in the late 1980s.

So, the number one risk group for HCV infection in the United States is injection drug use. I think you all may have heard historically that the prevalence among injection drug users is incredibly high. However, that is maybe not the whole story because it does look like the overall prevalence is relatively high, but it looks like there have been changes in the incidence of infection over time.

On the top is actually one of the landmark studies from Baltimore, done by Rich Garfein back in the mid 1980s, that basically looked at what is the prevalence of hepatitis B and C virus infection by the duration of injection. Basically, he found that 60-80 percent of injectors were infected within the first 12-24 months from the time they started injecting. In terms of hepatitis B, we are talking about 50-60 percent that became infected within the first year.

However, there is more recent data in the last couple of years that have looked at similar population of young injectors and they basically found much, much lower incidence rates. Here you see incidence rates of 10-15 percent per year for hepatitis C and maybe in the ballpark of 8-10 percent for hepatitis B. So, the incidence is still incredibly high among injecting drug users, but it probably is not what it was actually back in the mid 1980s.

I wanted to just briefly mention sexual transmission of HCV, specifically talking about two recent reports of clusters of acute HCV infection of heterosexual men in Europe, as I thought it might be a little germane to the discussion today in terms of what the implications of these are.

So, just briefly about sexual transmission, sexual transmission of HCV occurs but the overall efficiency is low. What does that mean? Well, it is a little bit of a complicated issue but it basically means that it is rare among long-term steady partners. How rare is a bit of a

debate but it seems to be extremely rare among long-term steady partners. When you look at men who have sex with men, they appear to really be at no higher risk than sexually active heterosexuals.

The one thing that is not clear about sexual transfusion of hepatitis C is that we really don't understand or know the factors that facilitate transfusion between partners, things such as viral titer, other STDs, being in acute phase of infection, sex during menstruation, certain sexual practices. We don't understand if any of these actually facilitate transmission and may actually increase risk. These studies are incredibly, incredibly difficult to do and none have really been done that adequately address these questions.

So, with that in mind, I want to mention these two case reports, one from France and one from The Netherlands. The first basically involves five HIV-infected men who had sex with men who had acute HCV infection identified at a single clinic during a 13-month period. These men all denied

injection drug use or other parenteral risk factors for infection and all reported unprotected anal intercourse and had a concomitant STD, syphilis.

The second case report from The Netherlands involved seven men who had sex with men with HCV infection who were basically identified through contact tracing. This involved 16 sexual contacts of one of the acute cases here. These seven men denied injection drug use or other parenteral risk factors. All reported unprotected anal intercourse and had sexual practices that included fisting. Six of the seven cases had concomitant LGV. Six of the seven cases were also HIV-infected.

So, what are the implications of these two case reports? Well, the first thing is that no such cases or clusters have been identified in the United States. Well, what does this mean? Is this a rare event or is this going on and we don't know about it? I think it may actually be a little bit of both. This is an extremely difficult thing to study. Sexual transmission as a whole is very

difficult to study. Really, one of the complicating factors is the role of unreported injection drug users. Hepatitis C is so easily spread through injection drug use and injection drug use is a socially stigmatized activity and people are loathe to report it. So, the question that is always hard to tease out is what is due to sex, what is due to other things versus unreported IDU. But, clearly, I think this is an area that needs further study. It is something that is worthy to try to sort out what is going on.

I want to close with looking at estimates of past HBV and HCV infection in selected populations in the United States. Before I show these estimates I want to sort of do a couple of caveats. First, I want to mention that incidence does not equate with prevalence. There are a couple of epidemiologic principles that apply here. These are age, cohort and period effects. These are particularly true given how the incidence has changed in the last couple of years in the United States. That is, changes in disease rates

according to age, year of birth and point and calendar time are very important with hepatitis B.

On top of this, there are in-migration and out-migration populations. This is very important for hepatitis B specifically since geographic distributions around the world of HBV infection--a lot of people in southeast Asia are chronically infected with B and in-migration in the United States may actually change prevalence estimates. There are also geographic differences in prevalence. That is, prevalence estimates can vary from city to city, from urban to rural areas. So, what is going on in San Francisco may not be the same in Detroit or Atlanta or Orlando. Individuals may also have multiple risk factors for infection. They can belong to several population risk groups and, given how important injection drug use is in driving the HCV epidemic, unreporting injection drug use is very important to try tease out when making prevalence estimates.

Finally, as was mentioned earlier, is this whole issue of external validity and how do these

prevalence estimates actually apply to populations of interest. So, when we talk about prevalence estimates in gay men, are these gay men who are likely to donate blood? It is also important when making these estimates to think about where some of these studies recruited their subjects. Did they come from STD clinics? Did they come from street recruiting of injection drug users? How did these do in terms of making general estimates towards the larger population?

Finally, I want to basically say that prevalence of past infection, which is what I am going to present here, is different than the prevalence of chronic infection. Only about 10 percent of people in the U.S. with past infection have chronic infection. In the general use population this is about 4.9 percent of people who have past infection but only about 0.4 percent are chronically infected, so about 10 percent of those people.

For hepatitis C, as I mentioned earlier, about 75 percent of people with past infection are

chronically infected. So, 1.6 percent of the U.S. population has past infection and 1.3 percent are chronically infected.

Here are the estimates of past infection. I am not going to read them off to you, but for a number of these groups I put a range up here, such as young IDU use between 10-20 percent because there are not really good point estimates for all of these. I put these in relation to both the general population and blood donors. Blood donors, whether they are first time or repeat blood donors, tend to be 10 to 1,000 times lower risk than the general populations in terms of prevalence.

So, you can see there is quite a bit of variability. Also, there tends to be a strong age effect so young IDU use tend to have a much lower prevalence than older IDU use. Young MSM tend to have a lower prevalence than higher MSM. For hepatitis C, just to put it on here, you can see that in the general population the prevalence of past infection is lower. It is actually higher among young injecting drug users; 20-50 percent of

young IDU are infected with HCV; 50-90 percent of older IDU. However, as hepatitis C is not efficiently spread through sex, young MSM are really in the ballpark of 2-4 percent, slightly higher among older MSM. Among STD clinic patients you only see typically between 5-10 percent infected. Among prisoners, again, injection drug use drives a lot of this. You see that between 15-50 percent are infected.

In summary, the incidence of acute hepatitis B and C infection has declined in the past two decades. Primary risk factors remain unchanged, and when you think about the changes in incidence, hepatitis B vaccination has been a very important component of this.

Transfusion historically was an important risk factor, especially for HCV infection, but currently is extremely rare. When we have seen transmissions due to transfusion, they have basically been due to window period donations. Because the incidence has declined so much, prevalent infections are much more common than

incident infections. Finally, prevalence is lower in younger age groups than older age groups.

With that, I will close. Thank you very much.

[Applause]

DR. MCKENNA: Moving along, the next speaker, Dr. Edward Murphy from UCSF, will be presenting on HTLV-I and II. Dr. Murphy?

Transmission of HTLV-I and II

DR. MURPHY: Thank you very much for inviting me to speak about HTLV. Particularly for me, it is sort of nostalgic because I was a medical staff fellow here at NIH from 1985 through '88 when I first began my work on HTLV. So, it is really great to be back on the campus!

Also, it is important I think to recognize that I am glad HTLV was included because often I feel that in the blood bank community it is under-emphasized, but I think that that is more perhaps due to a lack of good testing, as I will touch upon, rather than a lack of appreciation of the seriousness of the infection.

Finally, just to say by way of introduction that I will use mainly published sources. It was a nice opportunity to go back and to review some of the older literature, but I will try to supplement that with more recent data although, I must say, there is not a lot of really very recent data on this subject.

What I will touch upon today then by way of outline, I will give some background because I think, again, it is a more obscure virus and I do want to just, you know, bring everyone up to speed on that. I will touch a little bit on the disease outcomes and why we should be concerned about HTLV in the blood donor population; review the two or three studies that really have documented transfusion transmission. Then I will go into prevalence and risk groups, and a little bit of data on the incidence, which is pretty minimal, and then try to touch upon some conclusions and recommendations.

This is a classic electron micrograph, showing HTLV-I on the top, HTLV-II in the middle,

and then what was then known, for those of you who can read that fine print there, the virus HTLV-III. This is just a historical artifact, of course. That is really HIV on the bottom and you can see the different morphology with the bar-shaped core as opposed to the circular core in HTLVs.

HTLV is a deltaretrovirus. It is related to bovine leukemia virus, only remotely related to HIV. It is a primary example of simian origin, an emerging virus that has, however, been emerging for more than 15,000 years--

[Laughter]

--and it is a chronic infection. I think that is important to emphasize. So, the infection is mostly in terms of integrated provirus and lymphocytes; little free virus production; and infection is thought to be mainly by cell-to-cell transmission.

There is worldwide but somewhat spotty distribution, which I will illustrate here. The blue figures are cases of introduced HTLV and the red ones are more endemic areas. As you can see,

the primary endemic areas are certainly Africa, southern Japan and parts of the Caribbean and northern South America. However, we do have prevalent HTLV in the United States, in Europe and in India where, I guess, one can argue whether it is prevalent or introduced.

When we introduced testing in 1988 for HTLV in the United States, HTLV-II had not yet really been recognized. In fact, it was picked up by cross-reactivity with HTLV-I. But subsequently the epidemiology of this virus has been much more worked out. In fact, there are two endemic populations for HTLV-II. In central Africa there are particularly pygmy tribes but also other tribes that have HTLV-II infection and these give the subtypes of the virus as well. Native Americans throughout the south, central and United States are endemically infected with HTLV-II, which I think is not widely recognized. Again, the populations here, in blue, are those where the virus has been introduced and these are predominantly places with substantial injection drug user populations--United

States and Europe.

As you can see, the subtypes are a little bit different according to geography and risk groups, which I will touch upon in a second. This is just a quick introduction to show you the phylogeny of all of the HTLVs and STLVs put on a single page and, of course, you can't really read this. Interspersed among these human isolates are a number of monkey viruses. So, there are, in fact, closer monkey viruses related to various HTLV subtypes than there are human cousins so clearly, evidence for multiple episodes of simian to human transmission.

Focusing in on HTLV-II, I think this is an interesting picture and I bring this up only because I believe the test kits only include mainly subtype B, which is one of the predominant strains in drug users in the United States and in Europe. But, in fact, subtype A is a predominant strain in North America. Subtype C is in Brazil and may be under-recognized by some of our current test kits, and particularly HTLV-II subtype D is quite a rare

isolate in Africa. But there is a number of subtypes which differ by a fair amount.

Proviral load also differs by HTLV-I versus II. This is data from my cohort study showing that HTLV-I proviral load, on the left, is significantly higher, by about a log, than HTLV-II proviral load. So, that may have some implication for testing for the viruses, with sensitivity probably lower for HTLV-II. Even within subtypes of HTLV-II there are differences in proviral loads, with the subtype A being a higher viral load.

HTLV diseases--for HTLV-I these are well recognized and include T-cell leukemia which, of course, is one of the original reasons why testing and screening was introduced. Actually more common though is HTLV-associated myelopathy, which is a paralytic disease resembling multiple sclerosis with a 2 percent attack rate. Uveitis is proven but rare, and arthritis and other autoimmune diseases are reported.

With HTLV-II, in our cohort we have definitely associated HTLV-II with HAM/TSP, albeit

with a somewhat lower attack rate apparently than for HTLV-I. We also see higher rates of pneumonitis and bronchitis, as well as arthritis in the HTLV-II population, and have recently published an increased mortality associated with HTLV-II. So, I think, you know, neither virus is benign. HTLV-II is perhaps a little less pathogenic, in particular not being associated with leukemia.

Now to go back again historically and talk about the studies that spurred testing for HTLV, clearly it is transmitted by blood transfusion. The sort of seminal study by Okoche [?] in Japan showed that fully 60 percent of recipients who got cellular products seroconverted; FFP, zero out of 14 and not receiving negative units. There have been case reports by other authors of both ATL and myelopathy following transmission-acquired HTLV-I.

Angela Manns, my colleague and I in Jamaica did a similar study which was a retrospective design, and observed again a high rate of transmission of HTLV-I with cellular components, again no transmissions but a rather

small N with liquid products. One thing to note is that storage time appeared to diminish the risk of transfusion of HTLV-I with no transmissions occurring at greater than 15 days in this study.

Similarly, Donegan, reporting from the transfusion safety study in the United States, found a transmission rate overall for type I and type II of about 35 percent; again, no cases with FFP or cryo. So, that means that out of the total of these three studies, there were about zero out of 50 cases of transmission of FFP or cryo. One can, of course, calculate a confidence interval on that as less reassuring. HTLV-I is perhaps a little more transmissible. Storage time again was found to be important, with no cases in blood stored over 10 days.

Now I am going to switch gears and talk about current blood screening for HTLV, which is done by means of a screening EIA. Current assays include antigen from both HTLV-I and HTLV-II. The strategy of alternate EIA testing is used to diminish the number of samples requiring

supplemental testing because, embarrassingly in my opinion, there is no licensed supplemental test for HTLV and this has been problematic for donor counseling for quite a while. Recently a number of blood systems in the United States--Red Cross and others--have sent their samples to the California Department of Health Services lab which does supplemental testing and use that for their donor counseling.

This is a slide courtesy of Sue Stramer from some recent data, which I believe is soon to appear in Transfusion, showing some experience over about a two and a half-year period from the American Red Cross system. This shows that out of 17 million donations tested there were 21,000 which were repeat reactive on the initial EIA. About a quarter of those repeated on the alternate EIA and, of those, about a fifth confirmed positive on supplemental testing done by the California State laboratory. So, this works out to a prevalence of a little less than 1/10,000 or 5 percent of the initially reactive specimens.

However, I think there is still some concern in my mind, particularly for HTLV-II, about the sensitivity of the current EIAs. These are a couple of papers, one from my lab, the first one, and then another from Bernie Poliesz' lab who was the discoverer of HTLV. The sensitivity may not be optimal. These are sort of post-marketing tests that were done on research specimens. We took about 600 specimens that were from a predominantly drug user population in San Francisco. We just went down to the emergency room at San Francisco General and were able to get a huge number of positive samples. The test performed really quite well but not really up to the standards that one expects in operational screening. With the best test, which is equivalent to the current assays, including both type I and type II antigens, showing about 99.5 percent sensitivity.

Bernie Poliesz' data was a lot more worrisome. However, the caveat there is that this was heavily a South American Indian population. So, it may not be entirely relevant to the U.S.

situation.

Be that as may be, we will still present the prevalence data now and I will present prevalence both in blood donors and in various risk groups. The first population is a study of mine just to show the age prevalence determinants of HTLV. You can see that in a study of Jamaican food handlers there was 4 percent prevalence, and this is kind of a general population survey in Jamaica. Prevalence rises definitely with age and is higher in women than in men, presumably due to sexual transmission.

In U.S. blood donors you see much the same pattern of age and sex dependence but the obvious magnitude of the infection is a lot lower, with the overall rate of HTLV-I being about 1/10,000 in U.S. donors. This was data from the early 1990s from the RED study published in JID. But you can see, you know, almost the same pattern that you saw in the Jamaican data.

From studies from Brazil, the Kayapo Indians are one of these endemic tribes in South

America which has a 25 percent prevalence, and shows a similar kind of age and sex dependence with excess among women but reaching extremely high rates of infection.

In U.S. donors though we see a different pattern, with an age maximum in the middle age groups and again an excess in females. This resembles hepatitis C prevalence and is, in fact, due probably I think to the epidemic of injection drug use in the 1960s and '70s. So, HTLV-II in some ways resembles HCV but with the addition of sexual transmission.

So, what are the risk groups? In our country we don't have really endemic populations, with the exception perhaps of native Americans for HTLV-II. We have people of ethnicities, Japanese, Caribbean or central African ethnicity. We don't have great data but it is probably a tenth of a percent to one percent. Prostitutes--and this probably is a combination of type II and type I--have a seven percent prevalence. STD clinics--a big study back in the early '90s--about half a

percent. For injection drug users with HTLV-II the prevalence can be as high as 18 percent, depending on the city, with most of it concentrated on the West Coast as we see also with hepatitis C. Sex partners of IDU--again, we don't have good data on general population, but by extrapolating what the odds ratios are our estimate is that it may be about 0.5 percent. Then, native Americans, 2-3 percent, again based on rather scanty data in clinic-based populations.

This is a study published by our RED studies in which we looked at a case control study of HTLV-I and HTLV-II positive blood donors. There we see sort of the standard distribution. The donors of lower socioeconomic status and of minority race had a 5-10 times higher prevalence, or rather, their risk of being HTLV positive was 5-10 times higher. History of blood transfusion was a definite risk factor, having more than 7 lifetime sexual partners or having an endemic sex partner or HTLV-I.

For HTLV-II the picture is somewhat

different, with most of the risk concentrated in these two groups. Clearly, IDU themselves are more likely to be deferred from blood donation. So, our biggest numerically sized population are women who are sex partners of IDU, with a 20-fold odds ratio; and then, again, lower socioeconomic, minority race and promiscuity factors for HTLV.

To just finish up now I am going to talk a little bit about what is known about incidence of HTLV. This is pretty much limited to studies in blood donors. The original study from REDS, Schreiber et al., 1996, New England Journal, over about a 2-year period found 9 seroconversions out of 800,000 person-years for an incidence of about 1 per 105, and residual risk of about 1.5 per million. This really is the last time that residual risk has been formally calculated.

Glynn reported a follow-up study on this from the RED study with a slightly bigger time period, and again found an incidence which was about the same, if anything, maybe a little bit higher per 105 person-years. The residual risk was

not calculated but would be, you know, equivalent or slightly higher than this number.

Finally, recent data from the Red Cross system found 38 seroconverting donors and an incidence somewhat lower, about a quarter per 105 person-years. I am not sure of the difference between this data and the REDS data, whether it is simply a time period effect or if there is some difference in the testing that contributes to this as well.

Again just to begin to conclude here, residual risk, as I said, has not really been estimated formally. It is still probably in the range of 1-2 per million units, as was mentioned in the introduction today. Storage time and leukoreduction probably reduce the risk since it is a cell-associated virus. The storage time data is definitely, I think, real but it has not really formally been tested recently and there is really only indirect data, no direct data I know of for leukoreduction in reducing the risk. But, nonetheless, both of those would seem to be in the

positive direction for reducing risk.

So, in conclusion, I have shown that prevalent HTLV-I and II are concentrated in sex partners of IDU, and in sexually active, low education and minority populations. Of some concern I think for future research, and I have tried to give some suggestions here, is that current EIAs may lack sensitivity for HTLV-II, and the other big problem is that there is still no licensed supplemental assay. I think this remains an issue for donor counseling. So, the current residual risk is unclear. It may be higher than for HIV or hepatitis C. There is no NAT currently for HTLV, nor is one under discussion. And, the effects of cold storage and leukoreduction could bear some research.

So, you know, I hesitate to give recommendations, but just some suggestions I guess for this. I think clearly maintaining lifetime deferral for IDU would be a good idea. One might consider, if one believes that prevalent infections matter, that sex with an IDU might be of concern.

Obviously, this is not so much an issue for window period infections.

I should mention while we are talking about risk factors that men who have sex with men are not a risk group for HTLV. For whatever reason, the virus has not entered that population and their prevalence rates are equivalent, more or less, to the general population.

I think more research on current EIA sensitivity may be a good idea; licensure of a supplemental assay and, should I venture to say this, whenever I talk to people running NAT labs about HTLV-I and II NAT, but I think once cellular sample prep would become available that would be a logical solution both to improve screening and also to solve the supplemental test problem.

So, with that, I think I will finish up and thank you very much.

[Applause]

DR. MCKENNA: Our next presentation, and the last presentation of this series, is by Dr. Sheila Dollard, another colleague from CDC, talking

about HHV-8.

Transmission of HHV-8 by Blood Transfusion

DR. DOLLARD: Thank you for inviting me to talk. I am speaking about human herpesvirus-8, which many people may not be familiar with. The clinical impact of HHV-8 in the United States is quite different from that in Africa but I am going to be focusing on the United States today.

It is the etiologic agent for Kaposi's sarcoma, which is the number one malignancy associated with AIDS. It is also the number one malignancy following organ transplantation, although that is not a common complication of organ transplantation.

It was discovered in 1986. It has probably been around for a long time. but it was shortly after HIV was discovered. It is also the etiologic agent for other illnesses that are mainly associated with AIDS--primary effusion lymphoma and multicentric Castleman's disease. There are a few other disease associations that are under study but they are a little tentative at this time.

Evidence for blood-borne transmission of HHV-8 has been around indirectly for a while. People who receive blood transfusions and acquired HIV are in organ transplantations--HIV from organ transplantations. A small portion of them also developed Kaposi's sarcoma. A rather landmark study in 2001 showed that acquisition of HHV-8 was very strongly associated with the frequency of injection drug use. Possible transmission of HHV-8 by blood transfusion was shown in U.S. cardiac surgery patients who received numerous blood transfusions that were not leukoreduced. That distinction of being not leukoreduced is important because HHV-8 is primarily cell associated. As you know, most blood components in the U.S. are now leukoreduced. Whether or not that eliminates the risk is not known but it is under study.

To address directly whether or not HHV-8 is transmitted by blood transfusion, we designed a study in Uganda where the seroprevalence of HHV-8 is about 10 times higher than in the United States. I have seroprevalence slides later for the U.S. It

is 35-40 percent and in the U.S. it is around 3.5 percent.

HHV-8 is a herpesvirus so people with antibodies don't necessarily have circulating virus. The question we wanted to ask was how many people who are seropositive may be transmitting the virus in blood transfusions. In Uganda the storage time for donated blood is very short because of the high demand, which would increase the odds of an infectious agent being transmitted, and there is no leukoreduction performed. In out study all the recipients of blood transfusions had linkages to donors and donor sera were available.

The results of the study were as follows: We enrolled 1,811 transfusion recipients and they were followed up to 6 months. The mean follow-up time was 4.8 months. And, 991 of the 1,811 were eligible for seroconversion analysis, meaning that they were HHV-8 seronegative prior to transfusion and they completed at least 2 months of follow-up. Of the 991, 41 patients became infected with HHV-8 although several of them were among patients who

didn't receive HHV-8 positive blood because this is an endemic area and we were seeing a lot of community infections in the background of possible transfusion infections. So, out of the 41 patients that seroconverted, 24 received HHV-8 positive blood and 17 received HHV-8 negative blood. Forty percent of all the recipients received positive blood. Remember, the seroprevalence was 35-40 percent so a disproportionate number of people who received positive blood became infected, but it was only slightly disproportionate. The risk ratio was 1.9. It was significant. But we wanted to try to stratify the data to try to cut away some of the community infections.

I hope you can see this slide. The 41 seroconverters were stratified according to the week during follow-up in which the specific IgG appeared. So, when people become infected with HHV-8 or other herpesviruses or other viruses in general or most viruses, IgG will appear 3-10 weeks following primary infection. So, our reasoning here was that the people whose IgG appeared 1-2

weeks after transfusion, that is too soon; that couldn't have stemmed from infection at transfusion. Those people became infected before the transfusion.

If you will notice, the red bars represent people who received HHV-8 positive blood and the yellow bars are people who received HHV-8 negative blood. From 3-6 weeks and 6-10 weeks a huge proportion of people who became infected received positive blood. Then, again, these later infections, some of them might have been through transfusion. If people are really immunosuppressed, it could take them longer than 3-10 weeks to develop IgG but it is our guess that most of these very late infections were community infections.

This is a summary of the risks of different categories of seroconverters. Along the top are all the recipients. Those are the values I presented a few slides ago. For the whole group of seroconverters the relative risk was 1.9 and it was statistically significant. We also stratified the

seroconverters by age because we saw the largest number of community infections, infections in people who received only negative blood, among very young transfusion recipients, and this is exactly what we see with several other herpesviruses, HHV-6, HHV-7, CMV and EBV. The most rapid period of acquisition is in infancy when maternal antibody wanes. So, it is really interesting that we saw the same pattern with HHV-8. When we only considered transfusion recipients that are over 2 years old the risk increases to 2.95 and the p value drops.

Another really interesting observation is when we stratify seroconverters by how many days their blood was stored. People whose blood was stored less than 4 days had a higher risk than people whose blood was stored more than 4 days. Then, down here are the risks for the 3-10 week period that I showed in the last slide. It has the highest risk and had the lowest p value. So, when you combine these two, the risk really skyrockets to 9.8, with a very large range because we are now

getting down to really small numbers.

The conclusions from the transfusion study were that 2.3 percent of the seropositive blood units actually led to an infection. However, this estimate is certainly low. The study was large and we had the luxury of cutting away a lot of the ambiguity and focusing on the numbers of seroconverters that we were absolutely sure about. So, our definition of seropositive and seroconverter was very stringent and this is likely an under-estimate.

Here are seroprevalence data from several publications, including many publications from our group at the CDC listing seroprevalence of HHV-8 in various U.S. populations, starting with the lowest risk up to the highest risk. In blood donors it is 2-4 percent. HHV-8 is different from other herpesviruses. This is one of the interesting things about it. As you know, most herpesviruses have extremely high seroprevalence rates worldwide and it is not really known why HHV-8 is different but it is. General population--now, these are

convenience samples that a lot of studies use for their controls, hospital patients, general clinic patients and pregnant women. The seroprevalence is a little bit higher.

Injection drug use, heterosexual and HIV negative, 6-11 percent, and for HIV positive the risk goes up. Among men who have sex with men, HIV negative, the seroprevalence is 12-16 percent. So, the biggest risk, as I said earlier, is the number one malignancy in AIDS patients, but most of the HHV-8 in the U.S. is among men who have sex with men. Acquiring HIV increases seroprevalence enormously, 40-50 percent. Of course, for people with Kaposi's sarcoma it is almost 100 percent.

There are very few incidence studies. I really can't say much today about incidence, unfortunately. How many of the people who have antibody have circulating virus? This slide addresses that. There is a study in our laboratory that we are just publishing now, following 50 men who have sex with men, HIV-positive men who have sex with men. Patients had an average of 6

follow-up visits 3-6 months apart, and 32 percent of patients had detectable HHV-8 DNA in their blood for 2 or more visits. So, the amount of patients with detectable virus in their blood was fairly high. But, again, this is not a particularly healthy population. The average viral load was 1,720 copies per ml. In natural infection the viral load for this virus is quite low. We know from some limited studies on healthy blood donors that virus is much lower, much, much lower and the prevalence of circulating DNA is quite low in healthy people. It is a herpesvirus. It goes latent.

Diagnostics for HHV-8--the most sensitive test, the best test out there really is not a particularly convenient test, probably not suitable for high volume screening if that were ever warranted. It is an immunofluorescence assay. My lab uses this test and most labs that use it grow their own cells. It is based on a naturally infected cell, body cavity base lymphoma cell line. We grow our own cells and make our own slides; do

all of our own quality control. It is not fast.

The other two assays that my lab uses, that other labs use too, were developed by the CDC. They are peptide ELISAs. What is common of peptide ELISAs is that they are highly specific but they are just not that sensitive and they wouldn't be suitable to be used by themselves.

Future studies on HHV-8 and blood safety--we are near the end of approval for a study at the CDC with Matt Kuehnert and Eve Lackritz where we are collecting blood from naturally infected people and taking a sample, leukoreducing the blood and then taking another sample and measuring HHV viral load. We do a lot of PCR testing for HHV-8 at the CDC--another thing I wanted to mention is that a NAT test wouldn't be practical because viral loads are so low--and possibly develop higher throughput serology assay for HHV-8, though I wouldn't predict at this time that that would be fast. That is all. Thank you.

[Applause]

Open Discussion

DR. MCKENNA: We are running a little late but we do want to take about 20 minutes or so and have the presenters from this morning come and assume positions at the table behind your name plate, those that are still here, and give an opportunity for the audience to ask questions and get some feedback from you all and to amplify any particular concerns or questions that you have from this morning's presentations.

DR. LACKRITZ: I think we are open to all sorts of questions. It looks like the mission to address is what behaviors are associated with risk of transfusion-transmitted disease and how does the risk compare among various cohort groups with these behaviors. We have had multiple speakers. There may be questions and comments regarding particular presentations. If you could help us, as moderators, direct your question that would be useful to open this up. I see two microphones at the back of the room.

DR. DAYTON: Can I also, for the transcriptionist, ask the speakers to introduce

themselves?

DR. WILLIAMS: Alan Williams, FDA. I wanted to just comment on one observation combining some data that I included in my talk with some subsequent data from Mat McKenna. If you recall, I mentioned some of the measures of efficacy across comparing studies between donors with risk factors in the current blood donor population versus some of the general population studies, and most of those appear to be in a range between 85-99 percent. Interestingly, in looking at the 0.36 percent measurement from active donors from the second REDS anonymous male survey, combining that with the 2.9 percent figure from Dr. McKenna related to MSM activity that took place in the past year, in fact, you get an 86 percent reduction which is right in the same range as the other risks that were looked at. It says to me that there is really no undue influence from one direction or another, and it appears to be the message as a whole that this sort of consistent proportion of donors are failing to self-defer but you can't

really single it out in relationship to one risk factor or another.

DR. HOLMBERG: Jerry Holmberg, Health and Human Services. Dr. Greenwald, just to start the questions off with you, what is the rationale for your Division using the five-year deferral?

DR. GREENWALD: I can't really give a specific rationale, other than what I have discussed in my talk about some consideration going into the fact that the donors themselves are not being questioned. You are asking next of kin and trying to get accurate responses as well as differences in availability of tissues as compared to other products.

DR. EPSTEIN: Jay Epstein, FDA. A question for Dr. van der Poel, in your talk you mentioned the possible value of adding tests for STDs as another approach to dealing with certain current lifetime deferral. In the U.S. we already have serological tests for syphilis and we use, as a one-year deferral, the history of diagnosis of syphilis or gonorrhea. So, what tests or deferrals

are under consideration in Europe as additional safeguards?

DR. VAN DER POEL: First, those tests I suggested at the end of my talk, additional tests, were not intended to be introduced as an additional safeguard. They were intended to enhance the power of a comparative study with low risk MSMs, if you like, a cohort of low risk MSMs as compared to new donors. In principle, anything that you can test which is sexually transmitted is then applicable. Of course, there are sexually transmitted diseases which are more prevalent in other populations than MSM. But it was just a means of making the power of the study more efficient than only looking at HIV. It was not a safety measure. So, we could include HHV-8 but not as a safety measure.

DR. BAYER: I actually want to make an observation about the morning session. I am Ron Bayer. I know from my own reading that within the blood banking community there is a huge diversity of opinion about the utility of the lifelong deferral of all MSM. I am troubled by the fact

that, other than my sort of ethics, non-data presentation, none of the evidence or perspective of the blood banking community which has kind of expressed concern has been articulated as a way of framing our discussion for the rest of the day. So, what we have gotten--and I am not criticizing those who have presented--what we have gotten is a steamroller, as it were, that shows that current practice is unproblematical. And I don't think it is a very useful way to frame the discussion for the day when the question before us--the FDA's own question is should we move to a five-year deferral.

So, I guess it is a question to the organizers. You can say that perhaps I am getting it wrong and that only people who don't know anything about blood and about the risk of transmission would even think of moving beyond the deferral that exists now. In fact, that is the message we got from Europe, that it would be a disaster to do that. I think there are many American blood bankers who have a different position and I don't know why we haven't heard from

them.

DR. VAN DER POEL: I think they are on a little later in the program.

DR. BAYER: I know, but the end of the day isn't always the end of the day.

DR. KATZ: Lou Katz, Mississippi Valley Regional Blood Center. I don't like to defend the FDA necessarily, but the data we heard this morning is the data, and I don't think there are many in the blood banking community, including those of us who very strongly support a change in the deferral criteria, who argue with the data. I think that Dr. Bianco and Dr. Dodd later on in the day are going to discuss that. To us, the real issue isn't so much is the prevalence higher in this group or that group; is the incidence higher in this group or that group per se. It is how much risk are we willing to tolerate and how much risk are we not measuring that is related to things like "our computer doesn't work" and "let's release a unit that should stay in quarantine."

So, I think the data that I heard today so

far is exactly what I would have expected to hear. Most of it is published, and it is a pretty good way to frame the issue, and I still think we should change.

DR. HOLMBERG: Jerry Holmberg. Dr. Bayer, in your discussion you commented about the risk and you just now brought it up again, but what would you envision to be an acceptable risk? And, at what period of time? You know, one thing that I was sort of disappointed with in both the European data and from the United States is seeing some sort of stratification along the years, and maybe we will get some of that this afternoon. But how much risk is acceptable?

DR. BAYER: That is the ultimate question which I don't think is a scientific question at all. In the language of national research that is a risk management question. It is not a risk assessment issue. In some way, I would wish that we could spend a bit more time trying to think about what acceptable risk means. You know, every engineering equation has built into it a safety

factor. It is a convention. You figure out what the risk is of a gust of wind blowing over a bridge and then you multiply by a certain number in order to give yourself a margin of safety. I think the same thing has to operate in thinking about blood safety, but it can't be that the only acceptable risk is that which is technically achievable because that would mean we could spend vast sums on preventing one in a billion cases, when we could be using those sums to do something much more socially valuable in the context of blood safety.

So, that is the first question, how much are we willing to spend? The second question, it seems to me, is the distinctions we now create, do they entail, wittingly or unwittingly, invidious discriminations? So, I simply can't understand how the risk of someone who has had sex--it could be repeatedly--with someone with AIDS until a year ago is less grave than the risk of someone who has had sex with another man in a monogamous relationship. I don't understand it, and no one has been able to explain it to me. If you say that people kind of

aren't completely forthcoming, well, that cuts through the whole question of the utility of deferral mechanisms that are not biologically based. People typically, when they are given an option of deferring without humiliating themselves--I don't think many people lie. That was the experience of what happened at the New York Blood Center when you gave people an opportunity to indicate why they were deferring without indicating which of the various deferral factors were involved, or they could indicate that the blood unit was for research purposes only, which was a code for don't transfuse this.

So, I think the question is, you know, what the social statement is for kind of global deferrals, and I raised the issue of race because it is crucial. In New York City today 20 percent of African American men of a certain age group are positive. Would anyone dare to propose that we bar all black men in New York City from donating blood? The risk of a woman who is black being infected is about 20 times higher than the risk of a white

woman being infected. Would anyone say that all black women should be deferred or rejected from the donor pool? I don't think so. Why not? Because somehow moving down that path in terms of human cost in terms of blood safety, that would be unacceptable. And I wonder why we don't have the same standards for gay men.

DR. LACKRITZ: To summarize the issue, I think there are lot of inconsistencies within the deferral questioning among blacks, among other risk groups and certainly among women as well who have contact with persons at risk. Yes?

DR. KESSLER: And the truth is we are making more of an outreach into more diverse communities so we can get blood for chronically transfused patients, and we know that we may be picking up more markers in that community but we do it because we have a patient population in need.

I wanted to address the point about the people who don't tell the truth about their risks. Alan, maybe you want to respond to this. Even if we change it to one-year deferral for men who have

sex with men, what are your thoughts that any more people will start lying at that point or possibly fewer people will lie because it is seems to them to be a more reasonable question now?

DR. WILLIAMS: It is a good question. I have the same one going on in my mind. I think the truth is I don't know and it is a little unsettling to not know. We don't really understand completely the dynamics of self-deferral. We know that there is this core group of 10-15 percent of donors who, for whatever reasons and the limited data seem to indicate that it is a variety of reasons, persist with donation. But how that dynamic will change by permitting, you know, part of the cohort, for whatever risk factor, to engage in donation and be eligible and whether the affected community will suddenly say, well, finally everybody woke up to the science and, you know, we are going to start deferring appropriately. I just don't know and I think it is an area where probably it would be prudent to get some data and some further insight into the question.

DR. VAN DER POEL: I think the point that you raise in terms of the compliance with the questionnaire and the problem that Kate Soldan had when she made her model which was published, as you remember, was that she had to assume compliance of 97 percent which was based on the discompliance, if you like, from the REDS studies. Right? So, the overall discompliance would be about 2.4, let's say 3 percent. They have 97 percent compliance. If you changed that in her model up to 100 percent it doesn't make much of a difference in the outcome.

So, the discussion, in Europe at least, is saying if you make your questionnaire more reasonable, like if you had sex with another man more than 12 months ago, the compliance would go higher. That was the debate. But it turns out that in that model where we estimate risk it doesn't really mean much. So, that was one thing.

The other thing about risk management which I want to address is that if you think about risk management and acceptable risk, then you have to think in terms of a public health approach. The

problem we have in Europe is that we moved from a public health approach towards a production environment, if you like, where the responsibility for the safety of the product is held by the producer. Interestingly, last year when the European Commission was addressing many issues and some of these, they were recognizing that many states in Europe consider blood transfusion as a service and not so much as a product. You could manage the production of the product as a pharmaceutical service but for the transfusion itself--the whole thing is a chain--it may be more applicable to have a public health model.

But we have to discuss this with management because we asked for anti-core testing in Holland as a blood establishment and government said no because they were confused by the cost effectiveness. The cost effectiveness was great, by the way, but the total costs were high. So, what are governments then considering if they consider acceptable risk? Are they thinking about the public health mechanism where blood is embedded

in this public health issue or clinical care, if you like? And, are they thinking about cost effectiveness? Or, are they thinking about total cost? If you look at the data from hepatitis B vaccination, I get the impression that they don't look at cost effectiveness but they look at total cost. So, there is lots of discussion.

DR. KESSLER: Can I have a follow-up question on what you are talking about in the Soldan study if you assume 100 percent compliance and it doesn't make much difference, you mean in terms of capturing back more donors. But you can't just look--

DR. VAN DER POEL: It didn't mean much in terms of the change in safety.

DR. KESSLER: Right. Good. Because you might be capturing back more donors than you would just by looking at men who have had sex with men in the past. You would capture back drives that you have lost because they object to the policy. So, it might make a difference in numbers of collections.

DR. VAN DER POEL: Well, that needs to be studied I think. In my country it is less than half a percent so it would not be a great advantage to the supply, if you like.

DR. ALTER: Harvey Alter, from NIH. Just to support Debra and Dr. Bayer, I think the whole issue is veracity. If you reframed the question and you said that every donor told the truth about their risk behavior and we had current tests in place, then I think we would agree that if every donor told the truth our tests, whether one-year or five-year deferral, would pick up virtually every case or would prevent virtually every case. We would have the same small breakthrough that we have now.

So, the question is are the donors telling the truth? But if the donors are lying it doesn't matter if it is a one-year deferral or five-year deferral or a lifetime deferral, the same donors may lie about their risks. So, there is a built in, inherent untruth but that shouldn't affect the deferral. So, you can get the same effect, I

think. Let's take your five-year deferral. I think you would have the same risk with a five-year deferral as a lifetime deferral and our tests are very, very good, and there will be some slippage because an occasional patient will lie but that happens now. So, I don't see the rationale for the lifetime deferral.

DR. EPSTEIN: Epstein, FDA. Well, there are a couple of points that I would like to comment on. Dr. Bayer, you have framed the lifetime deferrals for male sex with males, commercial sex workers and injection drug users as outlier policy compared to a more general policy of one-year deferrals. But I think it needs to be understood that the origin of using lifetime deferrals was based on scientific data that correlated certain risk factors with extremely high prevalence and incidence relative to other cohorts as defined in other ways. So, there is an underlying rationale.

The debate really hinges on whether we can control the risks related to prevalence as well as we can control the risks related to incidence. We

haven't yet had that discussion at this workshop. The problem with accepting cohort groups that may have very high prevalence is that the burden on the blood system to eliminate risk from those units is greater. You have to interdict them better at the history screening level, the testing level and the quarantine control level. We are going to have a discussion in the next section of the agenda on where the risks are coming from. So, that is the first point.

The second point that I would make is that the policies have been reexamined many times and they are not driven solely by looking at the population-based epidemiology, that is to say, prevalence and incidence. They are also based on looking at where is the risk coming from in the donor pool. I think that you heard both Dr. Williams and Dr. van der Poel explain that when you look at donors found positive certain risk factors are very highly associated with being found positive as a donor. That is another driver that causes us to focus on those risk factors.

So, those were comments. My question to you is what is your reaction to what you heard from Dr. van der Poel about the specific review in the EU of the question of whether there was an indirect discrimination that was in some sense wrongful? The answer that we thought we heard was, yes, there is an indirect discrimination in that there is an unequal impact on certain population groups but that it was not unreasonable in the context of the relative risks that one is addressing. So, I just wondered if you could focus on that last point.

DR. BAYER: I don't want to minimize the importance of what the Europeans did, and in nations that in many ways have a much better human rights record than the United States I take their judgments very, very seriously, especially coming from a country like Holland. I don't know enough about the review process. I don't know how it was constituted. I know it was part of the blood community but I don't know if it went beyond. You know, the blood community in some way has been seared by the experience of the early years of the

epidemic and the years whe hemophilia transmission and kind of the disasters occurred. In some ways, I think one has to understand that as a way of a background factor in shaping how potential risks are judged and viewed.

Harvey Feinberg isn't a rabbi actually, but I will cite him once more. Harvey Feinberg's most interesting work took place in his analysis of the swine flu epidemic that never was. His book was called "The Epidemic that Never Was." And, he had two warnings, that we will be so burned by the experience of having tried to prevent a flu epidemic that never occurred and have created the Epstein-Barr disease that we will not act when we ought to. In other words, we will be once burned, twice shy, or something or that we will do the opposite.

The question for people involved in public health is to try to kind of follow a path that kind of acknowledges that the values of public health are not the same as the values of managing a business and not the same as the values of even

clinical medicine, but that certain precautionary values are central to doing public health. I acknowledge that. The question is, you know, even in the exclusions that we now have, are there patterns of exclusion that represent kind of an inexplicable distinction among groups, and what does that say? I use the example of the risk of black women or black men who are now so hugely burdened by HIV in comparison to their white counterparts, and I ask would we want to go down the path of racial exclusion policy and if not, why not? And, what does that tell us about the way we think about this issue?

Again, I would like an answer. I understand that there aren't as many women who have sex with men with AIDS, or their numbers are small, but those few women, relatively few women, represent an extremely high risk group for AIDS and for transmitting HIV if they are blood donors. Why do we exclude them only for a year?

DR. LACKRITZ: I hate to disrupt the dialogue of brilliant articular people, but we did

have two other questions in the back. So, for issues of equity I am going to take an extra five minutes. Is that all right? We are over time. Yes, at the microphone in the back?

DR. ALLEN: Jim Allen, Blood Products Advisory Committee. Thank you, all, to all the presenters for a wonderful series of updates. What is missing obviously, however, is a very good translation between the science-based data and the behavioral risk data and how one assesses that. The conundrum that we face in the blood donor room is not only what the policies are, but how do you ascertain the information easily and reliably. I am not going to suggest that donors may or may not tell the truth. I think they sometimes don't understand the truth and don't know how to reply. So, there are a lot of issues here, regardless of what policies are developed and how one implements the policies.

Dr. Williams, in his presentation, clearly pointed out that the first step is to get the information out to your donor communities so that

people at risk don't ever come in. That is clearly a stage that needs a lot more investigation and application. I think Dr. Bayer has raised some very good questions.

Let me just throw out a question and I am not sure who might respond, but, you know, in the early '90s we did face an issue where there was a tradeoff. If you remember, coming out of the 1980s we did exclude all people of Haitian origin as donors. Then, as we made a tradeoff decision about implementing some questions about heterosexual transmission we dropped that Haitian exclusion. I don't know whether anybody has any information about what the impact of that was overall. But perhaps for our models for what we need to do I think, clearly, this workshop is very important because we must examine these issues and continue to look at the policies dispassionately in light of how best to collect the information that is necessary to ensure a safe and adequate blood supply.

DR. LUCEY: Charles Lucey, FDA. I wanted

to ask the panel if it was the conclusion of the panel that HTLV risk does require lifetime deferral for anybody who has had an IDU experience, and whether that is reflected also in the cell tissue area as further guidance. That is what I gathered from the HTLV presentation, that a strong recommendation was being made for continuing lifetime deferral for that risk factor.

DR. MURPHY: Yes, I think for two reasons. One is the issue that there is not a NAT assay to capture window period infections for HTLV, and as we are told we are still to hear about the errors in releasing prevalent infections, errors in quarantine, etc. So, I think certainly lifetime deferral for injection drug use is still strongly supported for HTLV, if not for other viruses. I don't know if you want to comment about the relevance to tissue versus blood exclusion. I also raised the possibility of sex with IDU lifetime deferral. That might be more debatable. I kind of raised that to stimulate discussion.

DR. DAYTON: Andy Dayton, FDA. I wanted

to address one of the apparent inconsistencies pointed out by Dr. Bayer in the donor history questionnaire. This question asked a lot. If a woman had sex with an MSM even once, she is only deferred for 12 months. If a man had sex once with an MSM, he is essentially a lifetime deferral. This, of course, prima facia seems absurd but then when you look at the correction you would have to do to alleviate that inconsistency, you can see the problems you would get into.

The answer wouldn't be to say, okay, well, if you are a man and you have had sex with another man was it only once or was it twice or was it three times? Then you are stuck with having to stratify MSM behavior in the context of the questionnaire and, (a) it is very hard to do that accurately and, (b) there is not good data which says, well, if one man has sex with another man once or twice or three times what are his prevalence rates of HIV. There is just not very good data on that. So, to correct the apparent inconsistencies like that puts us in a difficult

position.

DR. DODD: Thank you. Roger Dodd, Red Cross. I think, from Dr. Dayton's perspective, if you look at that in today's situation he is absolutely right. But if you go back and think why was the original MSM question asked, it was asked at a time when we really didn't understand what was going on with HIV, and when we had a clear perspective that this was a strange disease that entered our country round about '77 we retained that through thick and thin, and the issue is really what is the delta that is going to occur if we change it to be more compatible with other things.

I think as the day goes on we will find that we are really not talking about risk associated with incidence; we are really talking about risk associated with prevalence. But I think that we have to be very careful in understanding where our questions came from and how the rationale might well have changed since 1984 or 1983 or 1985 even when we learned what the cause was and really

how to deal with it.

DR. LACKRITZ: Would it be okay if I take one more question? I have a feeling it is going to be a lively lunch and the rest of the day.

DR. DAYTON: We could also bring some of these questions back up in later sessions. There is a 2:45 panel discussion which is somewhat longer than this one due to the vagaries of extra speaker times. So, we can revisit some of these questions then and at the end of the workshop there is another wrap-up open discussion section and we will welcome all of these questions throughout all of these discussions.

MR. CAVENAUGH: I am Dave Cavenaugh, with the Committee of Ten Thousand. I will be very brief. I am not sure how many other blood consumer organizations there are here today but it is a topic that we are quite concerned about and are watching very closely. I can't wait to get to the discussions about donor questionnaire assessments and inventory controls. Thank you.

DR. LACKRITZ: Thank you.

DR. DAYTON: Why don't we aim for about 55 minutes for lunch and that will catch us up a little bit? Come back at 1:10, 1:15; make it 1:15.

[Whereupon, the workshop was recessed for lunch, to reconvene at 1:15 p.m.]

A F T E R N O O N P R O C E E D I N G S

II. Assessing the Risks from Transfusion,

Indira Hewlett, Ph.D., OBRR/CBER, Moderator

DR. HEWLETT: I am Indira Hewlett. I will be moderating the next session which actually will be focusing on assessing the risks from transfusion. Our first speaker is Dr. Michael Busch, from Blood Systems, and he will be talking about residual risk of disease transmission by transfusion: causes and components.

Residual Risk of Disease Transmission by Transfusion: Causes and Components

DR. BUSCH: Thanks, Indira. I appreciate the invitation to be here today. As you see, I have a lot of slides there; I did remove some of them, fortunately, but I put a couple more in--

[Laughter]

--so, that is the way it is! Actually, a couple of the slides at the beginning were shown earlier. For example, I wanted to just emphasize how the early evidence, particularly in San Francisco, of donor deferral before we knew about

HIV and on the heels of that first baby dying, was quite effective but Alan showed that. But I wanted to just show a couple of the other slides that are relevant, more historical. This is actually a profile of the risk factors, the rate of HIV-positive donations, and risk factor distributions in those very early years, starting with the TSS repository in '84 where, you know, 0.24 percent of donations were positive and almost all of these were MSM.

But then as we started to screen the blood supply and improve the deferrals, you know, really it dropped the rate of infected donations dramatically and now we only have one or two HIV positive donations per year in the San Francisco Blood Center, and most of those are heterosexually acquired infections.

This is the latest data that Alan showed, the pre-latest data from the CDC HIV donor study but in the final period that was published, and actually the paper focused on subtype distributions. There were 312 donors whose risk

factors, identified from '97 to 2000, were determined and, as Alan indicated, at that point 23 percent of these HIV-positive donors who were brought back in and subjected to a full CDC interview acknowledged MSM behaviors. So, it dropped profoundly after these rates, these overall positive donations dropped.

One other point I just added is that we have had some breakthrough transmissions in the last four or five years. Since that screening was introduced in '99, there have been four really proven HIV transfusion transmissions missed by mini-pool NAT. We heard earlier about the hepatitis C and hepatitis B cases of reported post-transfusion events, and almost all of those end up sorting out to non-transfusion cases although there are occasional cases.

But with respect to HIV, there have been four really unequivocal recipient infections. These were all found through look-backs. So, for three donors who seroconverted look-back was done to prior donations and these four infected

recipients were found. I just wanted to point out that none of these were MSM, or acknowledged MSM. Two of them were women with heterosexual infection and one was a male who, on follow-up extensive interview, denied MSM activity. So, what is getting through now is not related to MSM.

In terms of risk, I think we all historically recognize four possible breakthrough sources. One is predominantly the window period issues. The second is viral variance. The third is what we call chronic carriers who were missed by serologic tests historically, infectious non-seroconverters, if you will, and then testing errors. I am going to focus most of my time on window period but then touch on each of these others as well and give a little bit of data on the errors from some recent work.

In terms of window period risk, we understand now that we have to think in terms of an exposure date followed by a period where viruses are replicating strictly in the tissue itself and there is not a viremic phase. We call this the

eclipse period. That is followed by development of infectious viremia, and then it takes time for that viremia to achieve levels that can be detected in a small sample of blood by NAT and even more time, of course, for the serologic response.

A lot of the work has been to better understand these windows. The challenge is that, you know, ideally we could infect someone and sample them every day and ascertain when markers become positive, transfuse these samples into some other animal of test vehicle to define the development of infectivity and then progressive appearance of markers. The reality is, you know, we can do that in animal models, and I will touch on that, but those animal models often are not perfect in terms of the events, the infectivity, etc.

Instead, what we are relying on are sort of populations of opportunity to sort these window periods out. One of the areas is patients presenting with disease, clinic patients. Unfortunately, these people tend to present during

the viremic early immune response phase so there is really a bias towards symptomatic cases, and the first samples available in the studies that are done are during the acute symptomatic high viremic phase. So, this is a biased population although, once these people are found, they can be serially studied to determine downstream events. Our blood donors are really donating so infrequently, random blood donors, that although you can do the look-back studies and figure out--as I will show--when did the infectivity develop, there are wide confidence intervals because the sampling or the rate of donations is quite low.

As I will show, the plasma donor population that are giving twice a week and are determined to be infected and, fortunately, for which there are stored frozen quarantine units that allow us to study the viral parameters and even transfuse these units into relevant animal models, it has really become the major source for better understanding of window periods.

One important study that Lyle Peterson led

a number of years ago looked at recipients of donors who seroconverted, somewhat similar to those three cases I summarized earlier from the NAT screening period, but this was work that was done really based on seroconverting donors in the late '80s. Overall, of 179 recipients who got blood from pre-seroconversion donations, 36 or 20 percent of these recipients had seroconverted and become infected from these units in the '85 to '90 time period.

Glenn Satton, at CDC, modeled this and derived an estimate for the infectious window period based on the relationship between the donation interval, between the seropositive unit and the prior seronegative unit, and the probability that these recipients were infected. You can see that there was a good fit between the theoretical model and the observed data, and it derived an estimate of 56 days for the window period overall but it showed that once we went from that first generation to the second generation test, in I think about '87, that window actually

dropped to 42 days.

Progressive improvements in the antibody tests have further reduced that window. This is obviously a very busy slide. This is a study from individuals who presented with an acute syndrome of HIV and were found to be infected. They were followed downstream to when different antibody tests seroconverted, when Western Blot seroconverted, and you can see very consistent evolution of development of antibody. All of these individuals, when they presented and were found to have HIV, were already in the viremic antigenemic stage of infections. So, this is that bias with respect to clinical case ascertainment.

This is one paper though that did have important data that we all wish we had better numbers on. Of this total of 38 cases of acute HIV, 15 of these people had very discrete exposure dates. In 13 of those 15 cases--I can't even read this myself, but in almost all those cases the average time from the exposure to when they presented with acute syndrome was about 15 days,

about 2 weeks. That is quite consistent with earlier but, unfortunately still unpublished data from CDC from needle stick accidents for the average time from the needle stick accident to seroconversion cases, back in the '80s. So, at that point it was about 2 weeks. There was an outlier that didn't seroconvert till close to 6 months. But those, again, were early tests; early data. But the time from exposure to acute syndrome or to seroconversion is, unfortunately, still not well defined but is probably about 2 weeks on average.

So, this is actually Sue Stramer's slide but it just illustrates these plasma donor panels where we have these individuals who were giving plasma twice a week and, unfortunately, you know, at certain rates these people proved to be infected based on the tests in place at the time. Fortunately, the plasma units are in quarantine preventing introduction into pools but, importantly for us, making them available to study and to characterize the rate of increase of viremia and

development of serologic markers.

In extensive studies of these kinds of panels, we have been able to define stages of progressive viremia and seroconversion, the lengths of these periods so, for example, in this work there was a 5-day estimated period of antigenemia preceding first antibody seroconversion--I am sorry, this is RNA pre-antigen and antigen positive, and then evolution of antibodies. Through analyses we have been able to estimate the lengths of these stages with confidence intervals and characterize the viral load distributions as these plasma donors evolve to seroconvert.

We have also been able to characterize the rate of increase of viremia over time. As you will see, we do this for all the viruses, and that allows us to derive a doubling time estimate or rate of increase in viral load that, in turn, lets us map when different nucleic acid tests would detect the infection in the window periods between detectability by individual or mini-pool NAT, as well as to back-extrapolate when infectivity would

begin in terms of theoretical lowest viremia detectable in blood.

Another finding though from these plasma donor panels has been detection before the unequivocal ramp-up viremia. So, if you look at the viral load here, it is non-quantifiable and then we enter what we call ramp-up where the viral load increases profoundly, antibody conversion kicks in and viral load drops. So, this is classic early HIV ramp-up and seroconversion. But what we have discovered, as we studied these stored plasma units in the freezer in the weeks preceding that ramp-up phase, is a phenomenon we term blip viremia which, in HIV, we pretty consistently see about 10 days prior to first ramp-up and is evidenced only by doing high input replicate analysis.

In the studies that we have published this is seen in about almost half of the viremic, or about a third of the plasma donor panels that demonstrate low level, transient blip viremia, consistent with an early infection viremia. That is followed by this eclipse phase where the virus

is strictly replicating in tissues and then the explosive ramp-up phase proceeds.

As an aside, this is of great interest now in the Chavi [?] program now studying the early viremia that is present in these cases, to compare that with the virus that grows out in the early immune responses that play out. These blip cases are actually turning out to be very important for vaccine development studies.

I mention this now because I think we should sort of throw it all out. There are some concerns, both from the plasma donor panels and from other studies, that there may exist transient infections in various high risk populations. One study from an excellent group at the University of Washington really studied large numbers of high risk seronegative individuals, mostly gay men, and by doing very high sensitivity PCR on cells they find low-level viremia that was genetically homogeneous over time in a small proportion of high risk seronegative individuals.

In the SIV model, if they inoculate

intravaginally low doses they see transient blips of viremia in the absence of subsequent infection, progressive infection. Finally, there is lots of work in Nairobi prostitutes, etc., where high risk seronegatives have immune response, suggesting that they were transiently infected but managed to resolve the infection. So, there are these phenomena that we have to at least consider.

This is a paper by Harvey Alter and Chris Murphy to try to look at the infectivity questions by inoculating animals and then sampling those animals over time, and then secondarily transfusing the blood from the animals in the window period into secondary animals. This study was interpreted as very reassuring in that although these animals were inoculated and going through a prolonged eclipse phase, secondary transmission was not apparent until the animal became detectable by NAT assays so it suggested that there is no infectivity during this eclipse period. But I think concerns have been raised about the relevance of the chimp model to this kind of secondary transmission

question. It is a model that is not very susceptible to HIV-1 and the replication dynamics that are seen in the chimp are very different from what we see in humans.

We are now launching studies in the SIV system, the same model I alluded to a minute ago, with mucosal infection, and then sampling these animals during the blip or the eclipse and then transfusing pooled blood from animals into secondary animals. So, we are trying to address this question again in the SIV model.

So, this is a summary of HIV exposure. A transient blip of viremia seems to occur in the immediate post-exposure period then ramp up and we can quantify at what point and the lengths of window periods between NAT detectability, antigen and progressive antibody with the first, second and third generation tests, really closing the window dramatically. So, we now have about a 22-day antibody window, preceded by about 5 days of antigen detectability and about another 5 days or so of viremia.

With hepatitis C, fortunately, there are much larger studies of post-transfusion infection from the old non-A, non-B data that has subsequently been worked up to define time from an infectious inoculum, i.e., a blood transfusion, to detectable viremia to ALT elevation to antibody conversion. These indicate that individuals become viremic within days of an infectious blood transfusion and then seroconvert consistently, with about a 70-day time from transfusion to seroconversion, about a 60-day viremic antibody window period.

We also have the plasma donor panels and extensive studies of those panels have allowed us to characterize the rate of ramp-up viremia, the length of the plateau phase and the viral loads during the plateau phase. Similarly to the HIV situation, we have these pre-ramp-up blips that I will talk about a little bit more. But, basically, from multiple studies of plasma donor panels, including extensive work from Europe as well, we have very consistent data of about a 50-day to

60-day viremic pre-seroconversion phase. So, very consistent data from all over the world.

As with HIV, the blips are a little bit disturbing in that if we test these plasma units that were collected prior to quantifiable RNA, so prior to the ramp-up phase, in multiple replicates we find transient viremia, what we call blips, and often valleys between the blips where we don't detect virus. This is the proportion of replicate TMA assays that are reactive, and we see this sort of intermittent viremia that has been observed not only in our studies but studies from folks in Germany on these panels.

This is a busy slide but it is just a series of these plasma donors. Basically, these black dots for each case represent periods when we could detect blip viremia. In almost all the cases there are intermittent periods with no viremia. So, exactly what is going on here is an important question that we are studying and, most important for us, the studies are nearing completion with Harvey Alter where we have taken samples from both

cases that were clean, no blips and simply went through an eclipse into a ramp-up, and also now cases from the valleys and the blips of animals or humans--these are plasma donors--where we have, in the freezers, large volumes. We use 50 ml per sample, per donor, and we then transfuse into chimps 50 ml per donor from multiple donors into challenged chimps and ask do these units transmit during the pre-ramp-up eclipse phase or from the valleys and blips in what we call the complex cases.

Once the animals do become infected, then Harvey kicks in with extensive studies to characterize the molecular immunologic features of acute infection. But, importantly, what we have discovered in these studies so far is that there is no question that very low-level viremia from the earliest ramp-up phase is infectious. In the work that has been fully done in looking at the clean cases and defining when does infectivity develop relative to the ramp-up phase, we have documented transmission by one donor who had as few as what we

estimate to be about one genome equivalent per 6 ml of infused plasma.

So, when we tested back in transfused units, 50 ml volumes from donors into chimps, we did document transmission from a unit that tested negative. When we went back though and tested that with multiple replicates, we could detect RNA in 2/24 replicates. So, this is telling us that although NAT has narrowed the window, it has not completely eliminated it and unless we are willing to, you know, do 25 replicates on every unit of NAT we couldn't anticipate interdicting infectivity completely.

But the ongoing studies with the blips and valleys are quite reassuring in the sense that there has been no transmission. All the valleys are negative and we are almost finished infusing those blips and they are not transmitting either. So, whatever that stuff is in the very low-level viremia in that pre-ramp-up phase doesn't appear to be infectious.

So, with HCV we have the blips but then

those don't appear to be transmitting. Then we go into ramp-up that is detectable by NAT with very brief intervals with ID and mini-pool detectability in the plateau phase, and then seroconversion with the current antibody tests, about 70- day window period and really just a very brief period of blip viremia. There has only been one confirmed HCV--and even that case isn't well documented--HCV breakthrough case in the U.S. that was missed by mini-pool NAT to date with the 6 years-plus of NAT screening.

With HBV we have the work that was done with FDA, Robin Biswas and collaborators, where we characterized panels and the doubling time, the same as HIV and HCV. Then we have modeled in where different antigen tests can detect HBV and the window periods for pooled and single sample NAT. So, similar to the other viruses, we can derive these window period estimates.

One recent advance, if you will, is to use these doubling time data to back-extrapolate a theoretical infectious window period, being very

conservative and basically saying that infectivity could commence at the point where there could be as few as one viral particle in an infused volume of plasma. So, we have done this for each virus and we have developed window period modeling that allows us now to begin with the point of theoretical infectivity at one copy per 20 ml, and then derive point estimates and standard errors around the length of time from that one copy to detectability by ID NAT, to mini-pool NAT antigen, to serologic tests. We can then use these window periods for HIV, HCV and here is the similar window period for HBV with infectivity developing at one copy and then the time to various markers becoming positive.

We can use these window periods in an approach we call the new strategy which uses the relative length of window periods and the fact that we are now screening with NAT or antigen, and we can pick donors up in these window periods to estimate residual risk. Where I want to take this is what is the current risk?

Again, we have two approaches. We can use the classic incidence window period model and now we can use what we call the new strategy which takes advantage of the fact that we have NAT yield or antigen yield for these various agents, and we can then measure the rate at which we are picking up donations in that transient viremic, seronegative window. We can use this as a tool, a direct measure, if you will, for monitoring the rate of newly infected donors, and that tool can then be used to extrapolate the residual risk based on the length of the NAT yield window compared to the pre-seroconversion viremic window.

We have done that now for the viruses. This is just a summary of the NAT yield data over the last years for each virus. The HBV piece of this is really quite limited because this is based on the clinical trials. But for each virus essentially we measure the rate at which we are picking up donations in the viremic pre-seroconversion window period. Then, we use that rate for picking those cases up with quite

simple formulas--this is the wrong slide, sorry--to use that to estimate residual risk for each virus. I am sorry, I deleted that slide somehow.

But, basically, the numbers are the numbers that Jay presented at the very beginning of today and the bottom line is that the rate of risk estimated using this new strategy driven from the NAT yield cases and window period ratios is identical to the risk that we have measured in the recent data that Roger reported of risk based on incidence window period modeling. So, it is quite reassuring I think that multiple approaches to derive residual risk estimates are consistent.

Now I am going to change course here because one of the big issues I think is this concern over errors. So, we are aware of error related contribution to risk. A few years ago FDA convened an error workshop and an analysis was begun at that point, with Jay's suggestion and discussion, particularly with Sue Stramer, Steve Clime and Sally Caglioti. What we realized was that by having NAT and serology screening in place

in parallel, we have at our hands a tool to actually detect errors because if we get cases that are discordant, that for example appear to be NAT yield cases, viremic seronegative, but then we retest them and we find out that, in fact, those units were actually antibody positive, that is a serology error case. Vice versa, if we get antibody positive donations that are mini-pool negative and investigate them and find that actually those should have been detected by NAT--they had high viral load but were missed, those represent mini-pool NAT error cases.

So, we embarked on an analysis that quantified the rate at which these errors are actually seen in the massive screening setting. By quantifying those rates, we could then understand the sources of those risks and actually apply those rates to derive the risk due to errors.

What we did was to take the data from I guess the first two or three years of NAT screening. For example, with HCV in about 17 or 18 million donations we had 84 yield cases. When

those cases were retested by antibody, 4 of them turned out to be antibody reactive. So, those represent presumptive NAT yield cases that actually were serology false-negative results.

Then, we can take the overall rate of antibody positive units that were seen during that period, and that is the denominator, and we can calculate a false-negative error rate. Importantly, these errors actually were all seen in the first couple of years of NAT screening and not subsequently. So, these are probably worst case estimates.

In Sue's analysis of several of these cases, she was actually able to track bases for these errors down to some of the manual components of the system that we are currently using and, for that reason, we think as we move to more automated screening platforms these serology errors will further diminish. No errors were seen with HIV.

The other side of the coin here is that we detect cases that are seropositive but mini-pool NAT negative. For example, here we had 534

donations that were confirmed antibody positive but were negative by mini-pool NAT. Now, that is not a big surprise because we know that individuals clear HCV, but when we retested these samples by ID NAT we found 18 samples that had viremia. Now, 17 of these 18 had very low-level viremia and it was understandable that they were missed by mini-pool NAT. But one case had very high-level viremia and was highly positive at a 1:16 dilution. So, we interpreted this as a presumptive error in NAT. We could then derive the denominator relevant to that error and derive a frequency that we were actually having a false-negative NAT result in the context of the large-scale, real-time screening.

So, if we sum up all these serology errors and NAT errors for both viruses, we actually derive error rates that run around 0.03 percent of confirmed positive units that should be detected by routine testing are missed by those routine tests. The issue then was to apply that error rate to the relevant risk of those units entering the donor screening setting.

For example, one scenario is that you could have a NAT screening error on a window period unit. To derive the consequence of that happening you have to take the rate of window period donations that we are projecting to occur and multiply that times the probability that this error in NAT screening would happen on a window period unit. So, the frequency that an error on NAT would occur on a window period unit is in the range of one in a billion donations, so extremely remote.

Similarly, an error could occur if you had a viremic seropositive unit. You would need to have two errors. You would need to have both tests fail. You would need to have a false-negative antibody error as well as a NAT error simultaneously on a prevalent infection that we are screening by both systems. When you multiply the prevalence rate of infected donations times each of these errors, you are down in the 0.06 per billion rate that you would have dual errors on prevalent units. Finally, you would have an isolated NAT error on a low-level viremic unit and, again, that

error is in the one in a billion range.

You could then sum all these error relationships up and you are down in the range of 3 per billion for HCV and 0.1 per billion for HIV. So, the probability that errors in routine screening will result in release of a unit in our analysis is so remote as to be inconsequential. As summarized here, you know, we are dealing with errors in the 0.3 percent and these risks are about 4 per billion, which is less than 1 percent of the risk of window period units getting through themselves. So, from our analysis we believe that errors are really minimally contributing to risk, and that they should be further reduced through enhancements of automated platforms that the companies are putting through FDA.

Just a couple of other comments about these other sources of risk, in terms of genetic variants we have done studies. This was work done with CDC to track the rate of genetic variants of HIV and hepatitis. In this HIV work we see rates of about 3 percent in the most recent period of

variants in U.S. blood donors. Now, the tests have always been enhanced as we discovered these variants to detect these, but just to point out that we are tracking them. We don't think this is a significant source of risk. Both the NAT and the serology assays are constantly improved to assure that they detect variants.

This is data from Sue looking, importantly, at the NAT yield donors from the first 5 or 6 years, 200 NAT yield donors for hepatitis C genotypes--again, we are just emphasizing that we are keeping our eye on the distribution of different subtypes in the donor population. In fact, the new REDS-II program is, hopefully, going to finalize in the next week approval of an ongoing study that will monitor the distribution of genetic variants, particularly focusing on the incident infections in the donor pool for at least the next 3 years. I don't have time to go into this but it will include ARC, Blood Systems, the REDS centers and the New York Blood Center, representing about 70 percent of the blood supply or 8 million

donations a year. The HIV, HCV and HBV-infected donors will be tracked, particularly the recently infected donors, and characterized with respect to viral diversity.

The final source of risk is this concept of immunosilent carriers. This is the idea that you can have people who are infected for prolonged periods but never seroconvert. Indeed, with introduction of NAT screening, there were 3 such infected donors identified. All were picked up in the first year of screening by the Red Cross. This is actually some data that was in the New England Journal paper that Sue led. These cases of immunosilent infection were easily detectable by NAT screening. They had very high viral loads. Two of them have remained seronegative throughout follow-up. One of them did subsequently seroconvert. Actually when treated for HCV they transiently seroconverted.

These cases have been studied genetically and, interestingly, they are composed of quasi species with highly defective viruses that have

large deletions within the quasi species. How that relates to the immunosilent nature we don't understand, but the bottom line here is that these were picked up as soon as we introduced NAT testing and we have not seen any since. All of the subsequent donors who have been picked up by NAT and followed have seroconverted.

The last thing I am forced to present--

[Laughter]

--is the MSM analysis from the REDS group. This was an analysis that we did based on the survey work. Unfortunately, George Schreiber and Simone Glynn are not here to present this. I was a co-author. This is an analysis that used the REDS survey system to ask the question of risk profiles among donors on anonymous subsequent survey but a survey that did link back to the test results, but this survey inquired as to whether these donors who went through the system had MSM acknowledged risk on history, and we understood from the analysis what the time period and frequency of MSM activity was so could do a pretty rigorous analysis of the

relationship of this MSM activity to other risk behavior.

As an initial emphasis, these individuals didn't acknowledge their MSM activity at the time of donation so essentially they lied when giving blood with respect to MSM activity and then were determined to have that based on a recall survey. So, this was a probability sample and we were able then to look at the responses relative to the demographics, the first time repeat status and screening test reactivity. And, 92,500 donors responded and were sampled with a 52,000 response, including 25,000 male donors which were the focus of this analysis.

Among these male donors there was a total of 569, or 2.3 percent, that acknowledged having had MSM at some point. This included a group of about 1.2 percent that had MSM since 1977. So, this is the group that should have self-deferred. There was an additional 1.2 percent who indicated that they were males who had had sex with another male but prior to '77. So, these were eligible

MSMs, if you will. This is the group that should have deferred but didn't. You can see that they were fairly evenly distributed as to whether the MSM activity had occurred within 12 months of the donation versus 12 months to 5 years or greater than 5 years.

This is looking at the distribution among these donors who either did not report MSM or the groups that did report MSM, the distribution of first time repeat status of non-MSM donors. You can see the typical 80 percent repeat. Among those who admitted to MSM, you actually have over-representation of first time donors, which suggests that there is some test seeking going on here, people coming in for the very first time, giving blood and then on survey acknowledging MSM.

It also shows the rate of confidential unit exclusion or call-back by these donors, and you can see that there was a significantly higher rate of call-back by the donors indicating MSM compared to the background 0.3 percent. So, these people are, after the fact, at a higher rate but

still quite a low rate, calling back and saying "don't use my blood."

This is the proportion of these MSM groups or no MSM background comparison groups that indicate that they did, in fact, give blood to get tested. You can see that compared to, you know, a fraction of a percent of background non-MSM donors who indicated they came to get tested, you have significantly higher rates of MSM activity of test seeking for HIV specifically or for all infectious disease test seeking among these denied MSM donors, if you will, with higher rates in particular among the donors who had the MSM activity of test seeking in the last year or less.

Then you can look at the rate of sex partners among these individuals who were giving blood and misrepresenting their MSM activity. Again, I am not going to go into detail but particularly among the group that had recent MSM activity, there is quite a high rate of multiple sexual partners, many even having greater than 11 sexual partners, with substantially higher rates

when you benchmark the recently infected against the this MSM group.

We also looked at unreported risk other than MSM. We sort of asked is the MSM activity also, if you will, a surrogate for other risk behavior. So, we looked at whether these individuals who indicated that they had engaged in MSM activity had also injected in the past or taken money for sex or given money for sex.

What we found here, kind of across the board but in certain situations statistically significant, was that compared to the donors who did not report MSM, those who did report MSM had higher rates of these other deferrable risks. This resulted in a conclusion that these individuals do fail to not only represent their MSM activity but also fail to represent other deferrable risk criteria.

When this was analyzed in a multivariate adjusted model, you can see that particularly for the group from 12 to 5 years, even more so than those less than 12 months since the last MSM, there

were significantly increased rates of undenied other reportable risks.

Finally, in terms of other screening test results, the individuals who had MSM risk had increased rates relative to no MSM of various screening reactivities for hepatitis anti core, etc. I think that was the major driver in this analysis. But important from the conclusions of this paper was that the rates were as high, and even slightly higher in those who were in the one-year to five-year group compared to the less than one-year group.

So, this study though, importantly, has some limitations. These donors who responded, who reported MSM may be more likely to disclose other risks so this association with other undisclosed risks may be, if you will, a reflection that these donors were divulging their MSM and were perhaps more likely to divulge other risk behaviors than the individuals who didn't disclose MSM.

But perhaps most important, I think the question is are these the liars and should we be

extrapolating the findings from the people who misrepresented their MSM history to individuals who would come to give blood if we changed the criteria? I think this is really the very important caveat to prevent over-interpreting this data.

In conclusion again, the study concluded that the findings did support increased reactive screening tests for other infectious agents among donors reporting MSM, both in the group in the less than five years and in the group with one year, and that infection appears to occur in this population not only through potentially unsafe sexual practices but also through other deferrable risk reasons. Thank you very much.

[Applause]

DR. HEWLETT: Thank you, Dr. Busch, for that very comprehensive presentation. I think we are going to hold questions till the end so we will move on to the next talk, which is inventory management efforts in whole blood release, and this talk is going to be given by Sharon O'Callaghan

from the Office of Compliance at CBER.

Inventory Management Errors in Whole Blood Release

MS. O'CALLAGHAN: Good afternoon. I will be discussing inventory management errors in whole blood release, this afternoon. Now, through the biological product deviation reports that FDA receives we are able to monitor the erroneous release of products due to inventory management errors. So, that is really what we wanted to focus on for this presentation this afternoon.

The biological product deviation reporting system is a mandatory reporting system required by 21 CFR 606.171. It is a passive reporting system, which means we have to wait for the reports to come to us; we are not actively going out seeking these reports. We do evaluate compliance through the FDA inspections, and what we have found is that, for the most part, the industry is complying with the regulation for reporting so we feel that we are getting most of what we should be getting through the BPD reporting system.

Now, I want to make sure that you

remember, and I think most of you do know this, but these reports are limited to events associated with distributed products so we are not able to identify inventory management problems that occur with products that are actually caught before they are actually distributed. We are limited to what we get, only products that are distributed.

Now, the facilities that are required to report are the licensed manufacturers of blood and blood components, including source plasma, unlicensed registered blood establishments and transfusion services.

The requirement for reporting says that you must report any event associated with manufacturing of a licensed or unlicensed blood or blood component that either represents a deviation from current good manufacturing practices, regulations, standards or specifications, or represents an unexpected or unforeseeable event that may affect the safety, purity or potency, and occurs in your facility or a facility under contract to you, and involves a distributed

biological product.

Just to give you an overview of the number of reports that we received and the time frame that we were looking at for these reports, we looked at the last three years, fiscal years 2003, 2004 and 2005, and we have received roughly almost 40,000 a year, broken down by the facility that we just described that is required to report.

Now, when we were looking at quarantine release errors we wanted to look at the BPD reports, look at the total number of reports we received, and look at the reports by the type of manufacturer. We focused only on the blood centers and hospitals. The data we were able to use for this analysis we received from the American Red Cross so we extrapolated some of that data so we focused only on blood centers and hospitals and didn't include the plasma centers and transfusion services.

We wanted to focus specifically on the reports in which a positive unit was inadvertently released. Now, a positive unit would be either a

repeat reactive or a confirmed positive and that is what we were looking for. We specifically targeted viral markers and the testing for the following markers, HIV, HBV, HCV, syphilis, HTLV and core.

So, when we look at the BPD reports, and this covers all the blood establishments, we wanted to focus on what we captured as QC and distribution deviations. This is something that you will be familiar seeing and this is the way we presented the data in the annual summary report. So, we wanted to take a look at the QC and distribution errors, this group of reports right here. That was about 7,800 reports that we wanted to look at.

Within that group of quality control and distribution deviations, what we wanted to focus on was the ones involved with a product being released in which required testing was incomplete, repeat reactive or confirmed positive which represented about 269 reports. Of those 269 reports, it includes the incomplete testing so that would be that testing was not done and the unit was released but when it was done it was negative. We didn't

include those reports. We also didn't include testing associated with the typical routine testing, ABL or H antigen testing, antibody testing, compatibility testing, which is also included in that group. So, out of those 269 reports, we focused on the repeat reactives for HIV, HCV, surface antigen, core, HTLV and syphilis.

Now, the chart on the left represents the number of repeat reactives during that 3-year period, 2003 to 2005. We received data from the American Red Cross for their repeat reactives, the number of repeat reactives they saw during that 3-year time frame, and extrapolated that information to include the whole blood industry. We wanted to get a nationwide assessment of the number of repeat reactives so that is where those numbers come from.

On this side is the number of BPD reports. There were 25 reports in which a repeat reactive unit was distributed. They are split pretty much evenly between the blood centers and the hospitals.

For the number of confirmed positives here

the data was extrapolated the same way as the repeat reactives from the Red Cross data to get a nationwide number of confirmed positives. Out of the 25 repeat reactives that we saw, there were only 2, 1 HCV and 1 syphilis, that was actually confirmed positive.

The HCV report involved a unit that actually tested confirmed positive, was not identified to be quarantined appropriately and was put into the available inventory. At the time of shipment there is a procedure in place to check the testing results. That wasn't done so the unit was actually shipped and it was confirmed positive.

The syphilis case was a case of an initial reactive. It was apparently a negative unit that was released. Upon further evaluation, when the firm received the confirmation result of positive, they realized that the testing had been done incorrectly and it wasn't identified so that unit had been released that was a confirmed positive for syphilis.

What we wanted to do is take this

information and try to come up with an erroneous release rate. We had 12 reports from the blood centers. This is for the repeat reactive and this is combination of all the markers. So, we had 12 reports. We had 290,400 repeat reactives. This took into account that blood centers collect 94 percent of the blood supply and hospitals collect 6 percent of the blood supply so we factored that into these numbers, here, for the number of repeat reactives. So, we came up with a rate of 0.4 per 10,000 repeat reactive units. For the hospitals there were 13 reports, with a repeat reactive number of 18,536 for a rate of 7 per 10,000 repeat reactive units.

We did the same thing for the confirmed positives. Again, we didn't include the hospitals. They didn't have any confirmed positives. It was just the blood centers. So, we had 2 reports of confirmed positives from the blood centers. The number of confirmed positives was 37,323 for an error rate of 0.5 per 10,000 confirmed positive units.

This basically just gives you the idea of the data that we were able to collect from the BPD report. This shows the rate of quarantine release errors for repeat reactives and confirmed positives that we were able to determine. So, we had 0.5 per 10,000 confirmed positive units for blood centers; 0.4 per 10,000 repeat reactives for blood centers; and 7 per 10,000 repeat reactives for hospitals. I wanted to make a correction. There is a "CP" in your handout. That shouldn't be there.

So, these were the rates. Basically, like with this one, we are saying that for every 20,000 confirmed positive units one unit will be released due to a quarantine release error. This data will be further explained in the next presentation by Dr. Dayton. Thank you.

[Applause]

DR. HEWLETT: Thank you, Sharon. Actually moving on, the next two talks are going to address quantitative models for transfusion risks associated with selected behavioral categories. The first speaker is Andrew Dayton from OBRR and he

will abe talking about point estimates of transfusion risks from quantitative models of deferral policy changes.

Quantitative Models for Transfusion Risks Associated with Selected Behavioral Categories

Point Estimates of Transfusion Risks from Quantitative Modelsof Deferral Policy Changes

DR. DAYTON: Thank you, Indira. I will point out that the point estimate of transfusion risk from quantitative models--the risk is not from the models, in spite of what may have been said earlier; it is really from the predicted unit that is let through.

To give you a brief history, even since the late '80s after good tests for HIV became available, the question came up should we continue to rely on deferral policies for interdicting HIV-positive units, and this issue has been revisited several times in the past. I came into it in 1998 and first introduced the use of quantitative models that I am going to show you later on today to address that question, revisited

again in 2000.

These quantitative models are very helpful. We also know that the are problematic. They are certainly not stand-alone devices. We always keep in mind the general approaches for identifying a behavioral category and then comparing prevalence and incidence of that donor category to things like prevalence and incidence in the general population or in current blood donors.

I want to point out that in the model that I am doing I am looking at changes in risk with respect to changes in policy as opposed to trying to calculate total risk. The reason I am doing this is because we are in the here and now and we want to know how things are going to change if we change policy. On a mathematical level it also works out that seven inconvenient terms are dropped out of the analysis and make the calculations a lot easier.

It is really fairly straightforward. The model centers around the blood bank refrigerator or quarantine inventory, how bad things get into it

and how bad things get out. If you end up with an infected unit in here awaiting testing, it can get out either by being a window period unit which is, by definition, undetectable, or it can also get out due to a quarantine release error. In other words, it may actually be detectable when the tests come back or if they come back correctly but somebody will grab the wrong unit and release it. Notice that window period and quarantine release errors can only be interdicted by deferral. That is the only way you have for stopping them.

We are going to spend a fair amount of time analyzing this central category here of false negative. False negative in terms of the model has a somewhat different meaning than has been used for developing tests for licensing tests and also in earlier talks here. Obviously, false-negative errors are such as the kind that Mike Busch talked about in which there is an execution error in the testing of some sort. I am going to introduce an additional category of false negative for this model called the biology.

I should point out that these models were originally designed to quantify HIV and they were actually fairly advanced with respect to the HIV models. We are going to extend that in this talk to HBV and HCV and HTLV, and there are some difficulties in doing that. One of the problems, certainly for HBV and HCV, is that the levels of virus in many cases come back down after you get into the infection for a while and the test virus loses some of the overlap protection that Mike was talking about.

The false negative way of getting out of here incorrectly basically involves a prevalent unit, one that should be detectable by the test, getting out by a test error of some sort.

The way we approach this, as I said, is change in risk as a function of change in the size of the donor pool with the specific characteristics being modeled. First we want to determine the change in the size of the potential donor pool. Actually, this quarantine inventory term refers to the next step. We look at the potential donors and

the ones who will show up to donate and we use prevalence and incidence terms to figure out how many of bad units get into the blood bank refrigerator. Then we use the false-negative rate, the quarantine release error rate and the window period term to figure out how many of those get out.

It is really a very simple equation. If we change the policy we will have a change in the window period units that get out of quarantine release. We will get a change in the false negatives that get out of quarantine release; and we will have a change in the quarantine release error units that get out to give you total errors.

As an illustrative example, we are going to start off with considering changing donor suitability criteria to defer for MSM behavior within the last five years prior to donation or within the last one year and also, in parallel, develop some other information for other models.

Using data from the Census Bureau and the National Center for Health Statistics and the REDS

data, we have been able to calculate that with the 5-year abstention model we would have about 1.7 million new donors. We would have a potential of about 85,000 new MSM donors--this is the MSM part of the analysis. From REDS data we can calculate that about 16 percent of these are already donating so with the 5-year abstention model we would end up with about 71,400 potential donations. This number, here, has also been reduced by the yearly donation. We assume that 5 percent of the new donor pool will actually donate. That is how we got this number.

For 1-year abstention, the new eligible donor pool is 3.3 million roughly, which would give you 165,000 potential new donations, except that about 16 percent of those are giving so we would end up with 139,000 new MSM donations.

I will talk about injection drug use. Using a similar analysis, we can calculate that for a 1-year abstention policy for injection drug use we would end up with about 92,500 new potential IDU donors. I couldn't do a 5-year analysis because I

couldn't find data for 5-year abstention.

The next step is to figure out what prevalence to use--there seems to be a slide deleted here but I will just go ahead. What is the prevalence of HIV in the MSM population? We figure the average prevalence is about 8 percent. But to give you an idea of how that compares to the general population, if we take the general population and back out the MSM HIVs, the general population non-MSM only has a prevalence rate of about 0.14 percent. So, the ratio of average MSM prevalence to the non-MSM population is about 60-fold, which is a problematic number, a worrisome number.

We know that about 75 percent of HIV-infected MSM know their serostatus and it is likely that these people will self-defer so we assume that the effective prevalence of likely MSM donors is approximately 2 percent. To give you some idea of how that compares, we compared that to the HIV prevalence in current donors. For first time donors it is 1 in 10,000. For repeat donors

it is 0.1 in 10,000. This is data supplied by the Red Cross. This leaves the effective MSM prevalence ratio of 2 percent, which is 200 times that of first time donors and 2,000 times that of repeat donors.

Of course, this is assuming that the prevalence of HIV is invariant with respect to abstinence history. You heard very interesting data from Mike Busch earlier that there is a reasonable suggestion that amongst MSM who have abstained for five years or more the prevalence is not as great as the general MSM population. In fact, it may be similar to non-deferrable categories of behavior, in which case these ratios would be misleading. Also, that being said, there is no data to support that the 1-year deferral prevalence is not as great as this 2 percent number.

If we multiply that 2 percent number with its caveats, new donations, MSM donations for a 5-year deferral, we would calculate that we would get about 1,430 HIV-infected units in the blood

supply in the first year of a new policy. For a 1-year deferral that is about double, about 2,780. These are non-window period of infection sources for blood supply contamination.

I am going to skip some things here. I will say that in our previous analysis and in 2000 we were very worried about delayed seroconversion but in the NAT era that worry has essentially disappeared. So, for HIV, HCV, HBV and HTLV window periods greater than a year are extremely rare and the deferral policies that we are considering here all involved switching to a deferral time of one year. So, the window period term of the equation essentially drops to zero and you are left with the total errors from the false negatives and the quarantine release errors.

How do you determine false negatives? Well, Mike showed you some data earlier this afternoon, and one way is to measure it by retesting, essentially retesting discordance. There is other information you can apply. You can get data from the package inserts, which is

generally pretty optimistic. Also, there is data from the clinical course of infection. Again, this is what I refer to as biology false negatives. This refers to the direct antigen test, either NAT or HBsAg, not being able to pick up violative units of late infection. Many people have their virus levels drop way down.

Again, this is from Mike's data which he generously shared with us based on the retesting. For HCV he was getting numbers like the ELISA had a false-negative testing error rate of about 3 in 10,000 and the nucleic acid maybe 5 in 10,000 and the actual data is down here.

For HIV--I took some liberties here but it will be okay, they turn out to very small numbers. We are saying that the actual data was that he found zero out of the denominator of 580 for the HIV. So, we assumed for our calculations that it was less than the 1 out of 580 which comes out to 17 per 10,000. That is the worst case scenario and I am sure it is nowhere near that. But it doesn't really matter because you get overlap protection.

Again, we are not looking at window period units; we are not looking at incidence infections. We are looking at prevalent long-term infections over a year.

We are asking the question, well, if it is through a test error of some sort, what is the chance that the NAT will pick it up, and vice versa, and we calculate the chance of a simultaneous error in both tests as the product, and they are separate false-negative rates.

If you assume that very high number for the HIV of less than 17 out 10,000 you still end up with a very small error rate of about 3 per million when you test, and that is a number that we can live with and it is surely considerably lower than that. So, if you have 3 per million for 5-year or 1-year deferral, these are very small numbers of infectious donations that would be newly entering the blood supply with a 5- or 1-year deferral.

With the HCV it is a little bit more complicated. Mike did directly measure test error and came up with 3 per 10,000 for the ELISA. But

now with the NAT test we figure approximately 20 percent would bring their NAT levels down to undetectable or very low. So, there is a high false-negative rate in 2 out of 10 samples. If you miss it on this test in 2 out of 10, you will miss it on this too. So, the simultaneous error rate for detecting violative units--violative is ever infected and we will do a correction for infectiousness later--the simultaneous error rate would come out to about 0.6 per 10,000.

HBV is a similar problem. We don't have direct data on the anti-core failure rate so we assumed, for purposes of discussion, that it is equivalent to the one that Mike measured for HCV ELISA. We assigned it a 3 per 10,000 false-negative rate. But with the HBsAg tests we assume that about 95 percent of people resolve their infections and come back down to undetectability so there is almost no backup. If this one misses, this is really not providing much backup for detecting violative units. Again, we will factor that back to infectiousness later on.

So, for HBV we are assuming an overall simultaneous error rate of approximately 3 per 10,000. We realize that some of these models are further along, as I said, than others.

For HTLV, for determining what number to use for false negative was a tough one because it is all over the map. Bernie Poliesz suggested a reasonable number was 5 per 100 but, as you heard Ed Murphy discuss earlier, there is a range of 5 per 1,000 to even 2 out of 10. But that 5 per 1,000 is actually a very significant number and you will see that we get very large numbers when we throw this into the calculation, but even when you throw this into the calculation there are still fairly large numbers.

Now quarantine release errors--in 2000 when we last analyzed this, we came up at the time with the suggestion that quarantine release errors may be the biggest source of risk for us. We based that on some unpublished data, which was generously supplied by Jeanne Linden, covering New York State in the mid '90s. I can tell you that the answer is

going to give the higher estimate for quarantine release errors. It was all we had at the time to go on. Basically, out of 700,000 donations that they followed in New York State, they had hospitals releasing 1 HCV-plus, HCV ELISA positive; 1 HBV anti-core positive; and blood centers released 1 anti-core positive.

We compared these to expected prevalence rates in the quarantine based on data supplied by Red Cross and came up with these quarantine release error rates at the time, which were disturbingly high. This is 130 out of 10,000 in the hospitals, in that neighborhood. The blood centers were better than that with 3.5 per 10,000.

If you plug those numbers into the equation for HIV and MSM, we figured that hospitals, which now collect about 6 percent of the blood supply, they would have in the quarantine inventory this many MSM HIV-infected units. Blood centers in that first year would have this number. And, if you multiply them times the expected error rates, you would get this number of released

components, and components are about 1.7 components per donation so you have to multiply these error rates times this number and you get this. It would give you a total of 5.3 components in the first year erroneously released HIV-infected components.

I am not going to go through this data again. This is exactly what Sharon O'Callaghan just showed you when we actually looked at blood product deviation reports for 3 years. The reports came for the entire whole blood industry. Then the Red Cross provided us with prevalence data that they experienced during most of that time in quarantine inventory. We used that to extrapolate to the whole blood supply.

The last slide was the data for the confirmed positive analysis. This is the data for the repeat reactive analysis. This is the key slide. Whether we looked at confirmed positives or repeat reactives, blood centers were getting about 0.4 per 10,000 release errors. The hospitals were doing about 17.5 times worse than that, with about 7 per 10,000. It is not surprising. Hospitals

collect about 6 percent of the blood supply, yet they account for about half of the deviation reports. So, in 2000 when we last analyzed this, the quarantine release errors were a significant problem but the hospitals contributed a disproportionate amount of the risk.

Here is how you add them all together for the 1-year and 5-year MSM abstention results. The numbers here and here, the big numbers come from the New York State quarantine release errors data. The numbers here and here come from the blood product deviation report errors. You have to decide which you want to take. Granted, the New York State data was generated at a time of transition to more modernized inventory management systems but, you know, we don't know which is necessarily the right one.

So, if we put it all together for MSM 5-year and 1-year modeled with HIV and HBV for MSM, we did HIV, HBV, HCV and HTLV for injection drug use, and here is a table. I am not going to go into this in detail. You do have it in your

handout so I will spend more time on the summary slide which compares it to current residual risk. But this is the contribution from the false-negative term. This is the contribution from the quarantine release errors, and the quarantine release errors--generally, if there is good redundant testing the false-negative term predominates and when there is poor false-negative testing, as there is for HTLV, the false-negative term tends to predominate. I have expressed it as total components over here. I should say that this is based entirely on the blood product deviation reports. If you want to look at the New York State data you would basically take the quarantine release number and multiply it by a factor of 10.

So, where does this takes us? Well, in the last column of the last slide, these are the total errors you would get with the blood product deviation report analysis. These are the errors you would get if you based the quarantine release errors on New York data. But these are in violative units. This is current residual risk

that was presented earlier but these are infectious window period units. So, we have to convert these to infectious units to be able to compare them for that and we basically just back multiply them by the correction factors we used in the false negative.

So, for HBV infections only about 5 percent are going to be violative so we multiple the HBV numbers times 5 percent and we are able to compare them. For the HCV infections about 80 percent of the violative units are going to be infectious. So, the grand summary here is if you use the blood product deviation report or the New York data, this is expressed as a percent of current residual risk. I think this is the easiest one to look at.

Let me remind you of some of the caveats. We assumed for 5-year that the prevalence is invariant with respect to abstinence and that may or may not be correct. We have good data for HIV effective prevalence being lower than the real prevalence based on self-knowledge of serostatus in

MSMs. It is not clear whether that also pertains to injection drug use. We don't have similar data for HBV, HCV or HTLV. So, only the MSM HIVs have been reduced by the self-knowledge of serostatus over here, in this data.

Now, if there is a conclusion to this talk, it is these last two points here. The New York data which we were working from in 2000 certainly suggests caution with either of the MSM extension policies. The 5-year would result in possibly a 25 percent increase in the current residual risk, and the 1-year would be 40 percent. Of course, if you go to blood product deviation reports, all of these numbers are really not so bad. They are in the rough neighborhood of the 1 percent or so that you would increase the donor population by.

The second big take-home here is that by almost any analysis the IDU just doesn't fly. This is the percent increase you would see. We used the 5 out of 100 false-negative rate to make these calculations, but even if we used the bottom one,

the 5 out of 1,000, these would still only go down by a factor of 10 or so, so you would have a tremendous increase in the current residual risk.

Finally, what do we need for future research to do these models? Well, we really need better data on prevalence and identifiable behavioral categories, particularly prevalence with respect to abstention. Mike's data is exactly the kinds of step in the right direction we are looking for.

We would like to know more about self-knowledge and serostatus. We would like to get much better data on false-negative rates, particularly for HBV and HTLV. Those have been hard to pin down, and particularly in hospitals where we know there is almost a 20-fold worse quarantine release error rate. Finally, we need more data on quarantine release errors. We think we have some interesting stuff with the blood product deviation reports, but we would like to get corroboratory evidence if possible.

I think with that, I will wind up. The

next speaker is going to give you error limits or uncertainty limits on what we have just been analyzing.

[Applause]

DR. HEWLETT: Our next speaker is Dr. Steve Anderson from the Office of Biostatistics and Epidemiology at CBER. He will be talking about probabilistic modeling of uncertainties associated with transfusion risks.

Probabilistic Modeling of Uncertainties Associated with Transfusion Risk

DR. ANDERSON: I am going to talk, as Indira indicated, about probabilistic modeling and the uncertainties associated with some of these transfusion risks. I should start basically by saying that the work I am going to present really is an extension of Dr. Dayton's model. So, what I am going to be showing you is some of the confidence intervals and uncertainty limits that we tried to put on some of the input data. Because the input data for a lot of these parameters is really highly uncertain, with this sort of modeling

effort we are trying to figure out what the impact of those uncertainties is on our final risk estimates.

With that, I am going to say our goal is to use a probabilistic model to evaluate potential risk and benefit and then, again, also to sort of get at some of the underlying uncertainties of allowing donations from particular populations.

As in Dr. Dayton's model, what we are doing is looking at three populations in this model. Those are MSM abstention for five years; MSM abstention for one year; and then injection drug users abstention for one year as well. Again, as I said, our work is an extension of the model that Dr. Dayton developed. I think our approach really is, rather than using the single numbers or point estimates that he used in his model, we are employing statistical distributions for the input parameters. Then, what we are getting back out are statistical distributions for the outputs. So, this represents and captures some of the underlying uncertainty of that data that is going into the

model for the inputs.

In addition, another element that we have is we use a Monte Carlo method to work this model. Basically, it chooses a value from each distribution as a single number for one iteration of the model, and then generates the output as distributions. But what happens is that the model actually has run thousands, or we could run it millions of iterations, and what we generate from those thousands or millions of iterations is a single aggregate output distribution for each of the outputs throughout the model, and then for our final predictions from the model. Again, I am just going to be sort of harping on this, that we are representing the uncertainty and variability of some of these input data.

Let me just talk a little bit about uncertainty. Uncertainty arises from the lack of or limited data for an input parameter. Some other uncertainties arise if we use assumptions in the model. For instance we assume in the model that the prevalence for HIV is constant for all MSM

populations, that is adding uncertainty to our model because we don't know what it is for the MSM 5-year population or the MSM 1-year population but we are making that assumption.

I think what is important is that there is a significant lack of high quality data for estimating the size of the MSM population and other factors like HIV prevalence, the error rates, etc., as Dr. Dayton discussed. Again, we are representing the uncertainty with our confidence intervals and mean estimated outcomes.

This is an overview of the model, as Dr. Dayton discussed. What we are interested in first and begin with in the model is the size of the new donor pools that we are evaluating. Then we are interested in the prevalence of infectious disease among those donor groups, and what we specifically want in this component is to get out the number of contaminated units that occur as our output. Again, in component III, once we have those contaminated units, what is the likelihood that they would be released and potentially transfused

into individuals? So, we are interested in quarantine inventory, the quarantine release rates and then the false-negative rates that would cause these contaminated units to be released undetected. Finally, what are we doing? We are trying to estimate the number of additional potentially infectious units that enter the blood supply and could potentially be transfused.

You have seen this data already. This is the input data that we use. It is essentially the same input data that Dr. Dayton generated for his model. I just wanted to point out again that 8 million donors is the total annual number of blood donors. Again, from these numbers what we are doing is applying the donation rate to the MSM populations and the IDU populations, and then we generated these numbers that you previously saw in Dr. Dayton's model.

I also wanted to just remind people that the MSM 5-year and 1-year estimates were corrected and include only new donors. So, we have adjusted, and it does not include those donors already

donating blood.

Moving on, estimating the infection prevalence of these potential new MSM donor groups specifically for HIV prevalence, what we have done we have sort of kept the prevalence at 2 percent for both of these populations. What we have done as part of our sort of statistical analysis is assigned boundaries to this prevalence estimate. For instance, the 95 percent confidence interval that we have got is 1 percent to 3 percent. Then, the wider range, the minimum value of that distribution would be 0.55 percent. The maximum would be 3.5 percent.

I just wanted to say something about what is a 95 percent confidence interval. If you are trying to remember back to your basic statistics course, that means that prevalence rates for this population have a 95 percent chance of falling within this range. So, that is just a little primer there. For hepatitis B, 18 percent for our mean estimate. Again, we bounded that with the minimum of 2 percent and a maximum of 39 percent,

and I am not going to sort of talk through each number on the slide but what I will do is try to point out some of the highlights of the slide.

For estimation of the infection prevalence for the IDU population greater than 1 year, again, the input data for prevalence, again, HIV of 5.9 percent. I am going to point out that the maximum in this distribution was 28 percent that we generated. For hepatitis B we didn't use the fixed point like Dr. Dayton's model. We allowed it to go up to as high as 60 percent, which is numbers that we have seen in the literature. For hepatitis C 58 percent was the mean but that could go up as high as 70 percent and as low as 44 percent. Then, for HTLV, again, Dr. Dayton used 10 percent and we allowed it to go up as high as 21 percent based on literature.

So, now we have our prevalence and now we are going to estimate the number of infectious units that could potentially enter quarantine from these populations. So, with the MSM populations what Dr. Dayton did and what we are doing here is

taking these numbers and multiplying by the prevalence to get these estimates. But what we have done is, now we have our prevalence that has statistical confidence intervals and minimums and maximums, and using that statistical distribution we generate the statistical distribution for the mean number of HIV infectious units from these populations. For instance, for the MSM 5 years, 1,441 are predicted. It could be as low at the 5 percent boundary as 726 or 2,153. So, that is the level of uncertainty in these estimates already. For hepatitis B, 13,820; it could be as high as 21,000. For the MSM 1 year population, 26,000; it could be as high as 41,000.

I wanted to sort of focus on this for a moment and show you some of the output from these models. We got an estimate of 2,788 as a mean estimate from the model--this is actual output in the model so we got a prediction of 2,788 donors; a 5 percent boundary of 1,400 and 95 of 4,185. This is the distribution that we got. So, here is 5 percent at 1,400, the 95 percent at 4,185, and we

are somewhere around here with a mean of 2,788.

I just wanted to say that what is happening for each iteration of that model is that the computer program is taking one slice, picking a number, inputting that in prevalence and doing that all down the line throughout the model, and doing that thousands of times. So, with that, I just wanted to point out two minimums and maximums. Of course, this is the maximum; this is the minimum. So, it lies outside, obviously, of the 95 percent confidence interval.

The number of infectious units entering quarantine inventory for the IDU population--I am sorry, this is the prevalence. I am sorry, the number of infectious units entering quarantine inventory for the IDU 1-year population based on 92,500 donations multiplying by prevalence, except we have a range here, these are the numbers we would expect to see predicted from the model. So, this is actual model output once again. We generated distributions for all these things but I am not going to show those just because of brevity

here.

Again, I just wanted to point out some highlights, 10,363--again, some of these higher estimates, it could go as high as 16,347, etc. So, those are the outputs for the IDU greater than 1 year population.

So, now we have our estimate of the potential infectious units that could come from these populations. The next thing of interest that we want to know is what is the probability or the likelihood that those units could be released through error into the quarantine inventory and then be transfused into an individual. Again, you have sort of seen this slide previously in Dr. Dayton's talk. The total error rate is what we are interested in. This is the sum of errors arising from the window period infection rate plus the false-negative rate and the quarantine release error rate. That is represented by this equation. This should be a sum sign of the errors and each error is added together for each unit.

What we are doing is we are assuming the

rate of window period donations as zero. Therefore, our actual equation that we are using in this model is just a function of the error rate of false negatives for each unit, and then the error rate of quarantine releases for each unit.

Let's talk about the false-negative rates. You have previously seen this slide from Dr. Dayton's presentation so these are the error rates that we have generated from the data. From those, we generated a few uncertainty distributions for hepatitis B and HTLV. For HIV we just used a single point estimate because basically the confidence interval is so narrow at this point that it is really not necessary essentially to use that confidence interval, and the same down here for hepatitis C.

So, those error rates are considered and then, finally, estimation of the quarantine error rates. There are two sources of the quarantine release errors. Those re the BPDR, blood product deviation reports or biologic product deviation reports that Sharon O'Callaghan spoke of. Then,

there is the New York State data from Jeanne Linden that Dr. Dayton spoke of.

So, the New York State data basically is giving you the most likely estimates and then we put the 95 percent confidence intervals about those. Then, we have the BPDR data, the quarantine release error date both for hospitals and blood centers, and then the confidence interval around those as well.

I think one thing you should note is just the distinct difference between these numbers. Basically, the New York State data is anywhere from 10 times to 20 times or more higher than the BPDR rates. So, I think that is a very important thing when we look at our final outcomes generated by the model.

Like Dr. Dayton, what I did was actually just generate the estimated number of additional potentially infectious units that could potentially enter the blood supply. Again, those are listed up here. The MSM 5 years for HIV, a total of 0.2 donations; 8; and then here are the confidence

intervals for each of those. You get down here to the MSM 1 population, hepatitis B, again, 15 donations released; it could be as high as 28.

I also applied the total average number of components. So, for our average, if we had 15 donations we might expect on average 24 components to be generated. So, if you are looking at a number like this, this is about 1.7-fold, you are looking at something in the range of as high as 50 components that could potentially be generated for this MSM 1 hepatitis B population.

Then the numbers start to get scary as we go up the ladder. For the IDU population hepatitis C, 10, but it gets pretty stark up here for HTLV where the false-negative release rate is quite high. Again, it could be even as high as 5,100. This actually should be 3,500; this is an error. Then, if you top that off, that could be as high as 7,500--I am sorry, it probably could be as high as 9,000. Again, we are just showing you with these estimates what the range of possibilities is and the uncertainty in these data and outputs.

Again, I am not going to walk through this particular data too much. This is a comparison between the New York data and the BPDR data that I just presented. What I really wanted to show--you have this information in your handout--was really sort of the graphic representation of what those data mean.

Let me just walk you through. This is a representation where we are comparing the quarantine error rate using the New York State data from Jeanne Linden and then the quarantine error rate for the BPDR data, and then comparing it to the current residual risk. If you look at the MSM 5 population--again, this information is in the table as well--for the New York data it is an estimate of 2.4 units. This should be 0.2 units I believe, and 12. So, you see for that this population we are fairly well below what is the current--this line should be up and this should be representing the current. For hepatitis B it edges up a little bit. I didn't imply infectiousness to this so these numbers for hepatitis B could be

potentially 20 times lower actually; and then the current of 85.

So, what this is sort of showing you is not only the error bars, which we couldn't put on that previous table, but also as the restrictions become less tight for the MSM 1 population. You can see that there is sort of a shift upward in the risks so we have more units potentially entering. Instead of 2.4, we have 5.2, etc. Again, our standard here is 12 for the current risk and then 85 up here.

I also wanted to say just for comparison, just to remind people that we couldn't really represent it in the chart here but remember that these populations for MSM 1 and MSM 5 really represent about 1-3 percent of the total donor population of 8 million. So, this is 85 out of 8 million and this is 2.4 out of less than 150,000. So, that is something to consider when you are comparing risk/benefits here for these populations.

Again, as Dr. Dayton, looking at the injection drug user population greater than 1 year,

for HIV actually our standard here is 12. This line actually keeps shifting because this is an intense graphic to handle, and you can see if we look at the BPDR data it is estimated at 1 and it could be as high as 19 with the New York data, and our current risk is 12. Again, for hepatitis B this is corrected for infectiousness so this could be 20 times lower. I will just remind people of that. Hepatitis C gets a little bit scarier with the New York data. It could exceed the 12 current residual risk considerably, or if you consider the BPDR data it could be right around that 12 level now with the smaller population. For HTLV, currently the estimates go off the map compared to the current risk. So, we have an estimate of 36 for the current residual risk. The model predicts 2,134 using the New York data and for the BPDR data it is 2,117.

Again, kind of a quick look at the data with the error bars, this should read potential HIV infectious donations. That got dropped out of the slide. But what we are doing is comparing our

results from the FDA model to published models, and we are looking specifically at MSM risk for the less than one year population. For the U.S. model, our range was 0.01 to 0.2. This would, of course, be the BPDR data; this would be the Jeanne Linden data. For the United Kingdom with Kate Soldan's paper, she predicted if we adjust that as 0.27 potential infectious donations per million donations. Then, the Germain model from Canada predicts approximately 0.07. So, I think these models are in fairly close agreement as to the outcomes.

I wanted to talk a little bit about the key uncertainties and how we started to address that. What we do with modeling is we do sensitivity analyses which rank the importance of parameters by their influence on the final risk estimate. I have to say that doing this for three populations for two to four different types of infectious agents the sensitivity analysis ends up being a mixed bag because basically you have different things for different models being more

important than the other. But, essentially, from the sensitivity analysis it suggests really that a number of parameters are important and influence the outcomes for each pathogen and population and the outcomes from those models.

Again, prevalence really ends up being important most of the time. The false-negative rate ends up being a big-time driver, especially for HBV predictions and the HTLV predictions. The quarantine rate ends up being a big driver of risk too for HIV and hepatitis C especially. Overall, there is considerable uncertainty for many of the model input parameters. Again, many of these inputs have very similar ranges of uncertainty. I should say that as well.

So conclusions, just talking about the comparison of model results for the FDA model for MSM greater than one year, it is similar to U.K. and Canada models, and all use somewhat similar input parameters with some qualifications. The U.K. model didn't really consider error rates in its estimates for release errors. Each model

suggests that there is some HIV risk associated with the MSM 1 population. Again, the FDA model suggests risks for the IDU population greater than one year, and that is proportionately higher than for the general donor population.

Again, additional research is needed to reduce the model uncertainties. Additional information will allow us to get better and improved estimates from the model. These are things that I think Andy touched on in his earlier talk. I just wanted to thank Hong Yang who really did a lot of this modeling and a lot of the yeoman's work in developing this model. She is in my group in the Office of Biostatistics and Epidemiology. Lou Gallagher, who was a fellow from New Zealand that worked on this, this summer and then, of course, Dr. Dayton and the Office of Blood as well at CBER. Thank you.

[Applause]

DR. HEWLETT: Thank you, Steve. We will move on to the last talk by Dr. Kristen Miller from the CDC, who will talk about the promise and

challenge in behavioral questionnaire design.

Promise and Challenge in Behavioral Questionnaire Design

DR. MILLER: I guess we are going to be making a serious shift in the program and talk about questionnaire design. I wanted to begin my talk by starting with a little background. My position is within the Office of Research and Methodology at the National Center for Health Statistics which, as you all know, is one of the Centers for Disease Control, and one of the main things that we do is surveys to monitor the nation's health. The main work that I do is in the questionnaire design research lab. What we do is work on the questions prior to fielding, designing them and testing them to ensure that they provide good and accurate data; that they actually make sense to all the potential respondents on these nationwide surveys; that respondents can easily answer them; and that they are interpreted the same way across all the groups; and that, indeed, the way the people actually do interpret them is how

the researchers intend for them to be interpreted--which is kind of a challenge.

I was actually asked to give this presentation here because over the past few years our staff has conducted a number of projects that have evaluated the blood donor screening questionnaire. I am actually giving this talk for my co-worker, Paul Badey [?], who would be here, however, he just became a father for the second time so I am here in his place. If you have any more detailed questions then, of course, I will direct you to him.

As is obvious from the title of my talk, the purpose of me being here is to describe the benefits of behavioral self-report questionnaires, specifically the blood donor questionnaire and, very briefly, the kinds of information that we actually can gather from these behavioral self-report questions.

For the meat of my presentation I will describe the limitations to the self-report questions that were found when we were actually

doing our work, but in order to do this I want to first outline the basic elements of question design and the methods that we use to examine the questions. This will give you a much better framework to understand what we know, and what we don't know, and what is actually kind of conjecture about the quality of information that we collect, that we can collect in a blood donor questionnaire.

The advantage to the self-report behavioral questionnaires, like the blood donor screening questionnaire is, you know, somewhat obvious. This is a very straightforward way of getting relatively consistent information from many, many, many people. All potential donors are presented the same questions that have been determined well in advance. All the important behaviors and related information has been determined. The questions themselves have been written, scrutinized, tested, reworded and then retested so the questions can be easily administered to endless numbers of donors in a consistent fashion.

Because it is self-administered no interviewer is required so a fair amount of questions can be asked at essentially no cost. Also, because there is no interviewer and the donor or the respondent is actually filling out the questionnaire it is more private or discrete and we can probably assume that people are more likely to answer potentially embarrassing questions more accurately than in an interview where people are being asked the questions face to face although, of course, the nurse or the technician will then look at their answers.

Along this line, for the vast majority of cases the information that is collected by these kinds of questionnaires is accurate. I mean, the fact of the matter is that our health surveys, like the national health interview survey, are collected this way. This is where we get our basic health-related information, through self-reports.

So, those are the clear benefits why the initial screener is useful in the screening process. But there are limitations, limitations

that impede accuracy. By and large, those limitations stem from the fact that the information that is collected is dependent on the respondent, on the person. Unlike all the data that you have been looking at in the previous presentations, this is dealing with human beings and with human beings it is a much more messy situation, as I will describe as I go on. Of course, it is also dependent on good question design.

Of course, donors are the people who are filling out the questionnaire and this is where you get the information. You are asking them to reference their own life. So, of course, they are going to interpret the questions with their own understanding based on their own personal experience. They are not necessarily aware of why you are asking the question or what you want from the question, and they are likely to interpret abstract and familiar concepts differently, in many different ways. This is kind of where we are getting at with thinking about lying, if people are lying, and I hope that I can shed some insight into

that.

So, good question design, whether or not it is for a survey or for a blood donor questionnaire, the blood donor screener takes this into account. Of course, there has to be a scientific purpose behind the question but it also must account for the fact that respondents have different perspectives and they must be able to perform the various cognitive processes that the question requires.

So, very briefly, there are a variety of methods or strategies that we use to evaluate questions and I have listed cognitive interviews, vignettes and focus groups. By far, cognitive interviews are used more frequently because they are seen as gaining the most useful insight into the processes that respondents actually use--the cognitive processes that respondents actually use and go through as they answer questions. So, for the blood donor screening questionnaire we have conducted numerous rounds of cognitive interviews, but we have also used vignettes and I believe also

some focus groups have been conducted. But my presentation here comes from findings from the cognitive interviews.

Very, very quickly, cognitive interviews are used to identify the potential response errors related to question design. They are intended to understand why errors might occur, such as different interpretations, memory recall problems, problems that respondents might have in actually calculating an error, for example, counting how many times they have had sex in the last year, or other types of problems with providing a response. Cognitive interviews also can be used to identify socio-cultural factors such as respondents level of education that might impact the question response process.

I have brought along a clip of a cognitive interview so that you can kind of get a general idea as to the method that we used to examine questions by seeing how respondents actually understand or interpret the question. The question here that is being tested is about smoking. I

would have loved to have brought you some clips from the blood donor screener but, because of the nature of those questions our human subjects review board would't let me bring those clips. But this is a really good example that I am going to show you of how a very seemingly straightforward question can be taken different ways--not lying, just taken in a different way because of interpretations. Also, the main reason why I am showing you this too is so you can understand the method that we use. It is an in-depth interview that we collect and then we qualitatively analyze:

"At the present time do you smoke cigarettes daily, occasionally or not at all?"

"It's getting very occasionally. My wife's weaning me off of them, along with the doctor. Only occasionally."

[Laughter]

"So, let me ask that question again. At the present time do you smoke cigarettes daily, occasionally or not at all?"

"Occasionally."

"Occasionally. And what does occasionally mean to you?"

"Well, weaning myself off cigarettes, about every two hours."

"So, I'm wondering why--the question is do you smoke cigarettes daily, occasionally or not at all--that you said occasionally--"

"That could go both ways." You can answer that twice, occasionally and daily."

[Laughter]

"Okay, you are quitting."

"Right, I'm going occasionally."

"Okay, I see."

[Laughter]

Do you see what I am saying? So, for the blood donor questionnaire this was the type of cognitive interview that we conducted, basically getting from respondents how they were interpreting specific phrases. For example, in this question, in the past 12 months, have you had sexual contact with a person who has hepatitis? you know, we asked respondents what they thought sexual contact meant;

also, whether they have heard of hepatitis; if they know of anybody with hepatitis; and, of course, you know, what kind of contact they have had with them. Also, respondents were asked to get at the specific time frame that they were thinking of. Were they really thinking of this 12-month period or were they really only thinking since the beginning of the calendar year? Again, the tapes were transcribed and then we did qualitative analysis.

Now I am going to get to the specifics, the factors that were found to impact the accuracy of information collected. There are a few questions, as we all know, about sexual conduct. For some donors these questions may be very sensitive or potentially stigmatizing. Let me just put this right up front, however, because of the way we recruited our respondents we had to tell them what we were going to be asking them about. So, you know, we really didn't run into any problems with the people that we spoke with. I mean, nobody tried to outright lie to our face because they thought that they were embarrassed or

didn't want to step up to the plate and admit that they would lie about this. Of course, this is probably because of the way we ended up to do the recruiting.

However, we do know that for these kinds of questions, when they are asked in surveys like large-scale national surveys, the estimates are much lower when--I don't know whether it is much lower but the estimates are lower when it is an interviewer-administered survey as opposed to paper and pencil. But I do think that more work needs to be done on this. So, we need to acknowledge this is a problem though we really don't know how much information there is about this.

Another factor that we really are unable to examine but must consider when thinking about the accuracy is the issue of motivation. Unlike a respondent to a survey, the blood donor respondents have shown up to give blood. This is why they are there. So, if a prospective donor holds the perception that a particular answer may prevent him or herself from being able to donate they may be

swayed to rethink their answer, making it in a different way. Also, the screener questionnaire is dependent on the fact that donors can read and that they can read well relatively speaking.

So, in our work we have found that accuracy is also related to respondent burden. Ideally, what you want is for respondents to really look at the questions and take the time to consider each one, not just to give you some quick answer. Willingness to give proper attention decreases if the questionnaire seems daunting or is perceived to be too long by respondents. Sometimes what researchers will do in the interest of shortening questionnaires, they will, like, cram two questions together and often that really doesn't reduce the burden; it actually adds to the burden. So, what we have done is we have recommended striking kind of a balance between thoroughness and simplicity.

We also found a few problems related to time frame and recall difficulty. I believe that the primary problem was due to some formatting problems because respondents weren't really clear

which time frame to use, but that has pretty much been solved.

The primary source of error that we identified, however, is really associated with this last category that I am going to talk about, and that is about respondents' or donors' knowledge and what they bring to the question response process, and I have three points that I want to quickly go through about this.

First, there are a few questions that ask respondents questions that they really don't know the answer to. These are the questions that are not about themselves really but are about other folks that they have had sex with. So, what is happening is that respondents can really only answer to the best of their knowledge, which pretty much means that if they answer yes to these questions you can pretty much assume that, yes, they have been definitely exposed. But if they answer no, that pretty much means that they don't think so unless, of course, they haven't had sexual contact within the past 12 months, or whatever

sexual contact means to them.

That then takes me to my second point about the respondents' knowledge. We have found that respondents' interpretations of these seemingly straightforward words differs substantially. For example, the phrase sexual contact or payment for sex can really vary even though definitions of what to include and what not to include were provided up front and to us seemed very obvious. So, when we talk about sexual contact, respondents say, well, do you mean anal intercourse? Do you mean oral sex? Do you mean mutual masturbation? French kissing? What kinds of things are we really talking about?

In another unrelated project that we did for the NHANES, we found that what gay men thought would have included as having sex differed dramatically from what straight men and what straight women and certainly what lesbians would have counted for what to include and what not to include as having sex. This was, I should say, that the questionnaire was very clear in saying,

you know, include this, this and this.

So, in the end what we know is that respondents use the definition of what makes the most sense to them. Of course, this can change depending on the context of the question and what they think the question is actually asking and the purpose of the question.

This leads me to my last point. Respondents have different perceptions of risk and why a question is important. This is what their answer is based on, not so much on the literal response to a literal question but, rather, more pragmatically whether or not they see their actions as being at risk.

For example, if a donor does not see how 20 years ago, when he was drunk at a bachelor party and gave a stripper $50 for oral sex--if he doesn't see that as making him a risky candidate for giving blood, then very likely or potentially he would not see that as having sex. If he doesn't see that as being a problem, you know, he is going to start questioning, well, does the blood bank really care

about that? I mean, that must not be what they actually mean by having sex. Of course, there is a lot of grey area here.

Of course, this is the same with the same sex behavior. Are we talking about oral sex? I mean, when you say have sex with another man if somebody had some kind of sexual contact with another 20 years ago, I mean, is he really going to think of that as having sex? And, if he thinks that that is kind of a ridiculous idea, then he is not going to be really seeing that as having sex. Do you see what I mean? So, bottom line, the accuracy is dependent on the accuracy of the donor's perception of risk because there is so much grey area, there is so much wiggle room for defining what is "had sex."

Of course, it is impossible to tell for sure, but I believe this is more likely what is happening in these cases rather than just outright lying. You can see it totally in an interview that I had with a man about his smoking. I mean, he sees himself as an occasional smoker because to

him, you know, every two hours is occasionally.

[Laughter]

Then to conclude, the screener is valuable for all the obvious reasons that I stated up front, and improvements to question design which accounts for the ways in which respondents conceptualize key terms improves accuracy. I think perhaps more importantly because accuracy is based on a perception of risk, it is essential that donors correctly understand why certain behaviors and the time frames for those behaviors are risky, and why those behaviors are represented in the questionnaire.

[Applause]

DR. HEWLETT: Thank you, Dr. Miller. I think we need all the speakers to join us up here and we will get started with the panel discussion.

Open Discussion

DR. DAYTON: Well, let me just start with a couple of comments that I think have been actually well covered. I think this time around compared to 2000, one of the things we have going

for us is that a lot of the NAT tests not only interdict the window periods they were designed to detect, but they also serve a redundance function in the later course of the disease. I think that was well portrayed.

I did also want to make a comment about the five-year MSM abstention policy, comparing it to the one-year. Most of us come into this and we think, well, one year maybe, maybe not, but five years is certainly going to be safe. That may actually be the case but the sort of gut level thinking that goes into that is really incidence thinking or window period length because there is no particular reason for HIV that somebody who has abstained for five years wouldn't have the disease. I mean, it is not as if it goes away after three years. So, that five-year abstention data of Mike's I thought was very interesting suggesting lower prevalence in five-year abstention. The five-year abstention is probably acting as a surrogate marker for some other behavioral characteristic. We don't know what it is, and

knowing that doesn't really change the equation but it might change what we look for.

So, I would sort of like to start out by asking Mike again if there are any other caveats that you didn't get time to discuss about that five-year abstention data. Because in 2000 when we brought it before BPAC, that was one of the things they charged us with, getting more data on things like safe subsets, and here you have come along with some data that really does address that issue and we are hoping that we will see other data from elsewhere. But are there any other comments you want to make on that?

DR. BUSCH: No.

[Laughter]

I mean, within the study group there was a lot of controversy over interpreting that data and over the context of that paper within both the authorship and other REDS group members. You know, the major caveat is that these are individuals who initially misrepresented that they were not MSM and then indicated so on a follow-up survey, and

extrapolating from that group to the potential new donors who would come in.

DR. DAYTON: If we were to go after the same kind of information from an entirely different direction though, what are the options?

DR. BUSCH: Well, you know, the REDS group has considered in REDS-II, the new version of the study, trying to do studies of general population at donor centers, where people were recruited in the workplace or somewhere where the people who were not giving, to try to understand the denied risk behavior, the risk behavior in those settings. There have been several studies considered of deferred MSM and going to high risk community settings, like gay communities, and setting up, you know, pseudo mobile drives where we would ask individuals who felt they were safe to go through a mock interview process. All these studies are problematic in terms of power considerations and the decision at this point, pending the outcome of this meeting, is that we really can't effectively conduct those studies. So, it is very difficult to

design studies to address further the question you are asking.

DR. DAYTON: I want to make one more point before I open it up entirely to questions. There was considerable discussion here about the difference in the quarantine release errors between the New York State data from the mid to late '90s and the biological product deviation reports estimate that we made here for the first time. So, I would love somebody from the blood establishment to give us some insight into what has changed. What have been the changes in inventory management between the mid '90s and now, and could that account for the differences in the estimates? Celso?

DR. BIANCO: Celso Bianco, America's Blood Centers. I have spent most of my life in New York State so I am claiming the territory. The studies of Dr. Lindoen--before I make the actual comments, I am sorry that she is not here; we know she is not here for health reasons--have been extremely important in terms of error and changed our minds

from safety is in the product to safety is in the process and, actually, the product itself is extremely safe and has been for a good while, but not the process.

New York changed in the late '80s the requirements for reporting. They have a pretty rigorous assessment of risks of transfusion. There is a committee. There is a council, that reports directly to the governor, and it is made actually of blood bankers and they write the regulations. I think that this is very unusual, and this is not considered conflict of interest. So, we have blood bankers in the committee.

However, at that time all the studies that were done--there were between 250 and 275 hospitals that collected blood, and none of them had a computer system. The blood centers had so-so computer systems. The first computer system for laboratories in New York that they introduced was in 1991, and it was pretty superficial comparing to what we had after that. Initially we were just able to manage to collect all the data for all the

instruments. Now all the computer systems really are connected to the release process. The release process involves scanning of the unit and checking on a table that has set all the requirements for the release of the unit. So, I would almost say release error today is something that is so unusual, and so many rare circumstances have to come together for a unit to be inappropriately released. In that table, not only the test results are there, but that table will also have consulted the deferral file to check for prior events that might prevent the release of that unit. That is why Sharon and her work now is to deal with post-donation information instead of errors of this kind.

So, I feel very confident that the release errors today for blood centers--I am emphasizing they have 510(k) cleared computer systems--are close to zero. I don't think that this is the same for hospitals. They still collect blood and still send their tubes somewhere to do the testing, the clinical lab, but most often today to one of the

large blood centers and get results by fax, and will go check their pieces of paper to release a unit of blood.

DR. DAYTON: Why don't we open it up now for anyone anywhere who wants to say anything?

DR. STRAMER: My first question is to Sharon and it is just a clarification for the two quarantine release errors that you presented, one on hepatitis C and one on syphilis, because these two do represent confirmed positives. Could you tell us again a little bit more about what was in the BPD, or at least repeat what you stated in your presentation?

MS. O'CALLAGHAN: With the HCV report the unit actually tested confirmed positive and should have been quarantined. The documentation wasn't done properly to identify the unit to be quarantined. It was put into available inventory and then, at the time another tech. was preparing a shipment, the unit was pulled from the inventory and not scanned in the computer which would have caught the fact that it was a confirmed positive.

That wasn't done so the unit was actually released. That was actually a recovered plasma unit so it wasn't a transfusable product.

In the case of the syphilis confirmed positive, actually in this case the testing was done by an outside facility. They had received results back saying that it was negative. They went ahead and released it but then they got confirmed positive results back and they realized there was a discordant result here and didn't understand what happened. Then they found out that it was because the testing was done incorrectly to begin with and it had already been released. That was recovered plasma and packed red cell. There was no information on the report that the red cell was transfused.

DR. STRAMER: Just to complement what Celso said, in our system we wouldn't be able to print a label for units to be released unless all the testing came back negative. I mean, that certainly wouldn't address the syphilis case--

MS. O'CALLAGHAN: Right, I was not

surprised. When I pulled the data for these types of events I was not surprised at all at the low number of reports that came out because viral marker testing errors we don't see, and quarantine release errors, at least in the blood center, we rarely see.

DR. HEWLETT: Dr. Bayer?

DR. BAYER: I guess the question is what "rare" means. As I have understood from what I have learned today that the issue of the window has been eliminated. That is not an issue anymore. The issue of false negatives is virtually gone in the era of NAT. The issue is the release of positive units that shouldn't be released, and we see a huge distinction now between blood banks and hospitals. So, the question is to you, Andy, really if your data had not simply looked at the difference between New York State and the FDA but it only looked at blood banks, what would the risk of release of an infected unit look like? And, the question is whether the lingering risk is irreducible or whether technical changes can even

improve upon that.

DR. DAYTON: Well, I know I am not going to remember all those questions so I am going to ask you to repeat a couple at a time. Let me start off by saying that I didn't mean to say that the window period is no longer important. The window period was brought up only because of the mathematics of the calculations in the one-year deferral. Window period is still a very big issue, no question about it.

Now, in terms of false-negative testing going away and not being important, I wouldn't say that is true at all. It depends on the particular agent and whether there are backups for it. So, for HIV the HIV NAT is actually very good through the disease and you get good redundance there. HBV, of course, you know, you don't get that as much, and HCV you get it to a lesser extent. So, I think you have to be careful. I don't want to be misquoted in "The New York Times" saying that I think the window period is no longer important.

DR. BAYER: Let me just correct what I

asked and ask it again. If the issue were HIV, is it fair to say that the issue of false negatives and the window period is vanishingly small? I think the numbers were three in a billion, or something like that. Is that correct?

DR. DAYTON: That is putting an awful lot together. That is really a question about residual risk, which is still significant.

DR. BUSCH: No, he is trying to frame out the risk due to erroneous release.

DR. HEWLETT: False negatives.

DR. DAYTON: For HIV it is pretty darned small, and also testing errors for HIV are really quite small. So, have we answered your questions?

DR. BAYER: No, actually. Pretty darned small is what you are saying. The question from the point of view of public health is how small is pretty darned small?

DR. DAYTON: 0.004 and 0.008 donations per year for the 5 and 1 year MSM respectively for false negative HIV MSM. Dr. van der Poel?

DR. VAN DER POEL: Thank you very much. I

would like to elaborate a little bit on those risk assessments because we are going into a new era, if you like, and Mike will like this, and you have been in the meeting where risk assessment people came together. Now, what struck me in that modeling is that the probabilistic approach is getting pretty much consensus. If you put those mathematicians together of all these different research groups, they would have consensus within five minutes.

What we don't have is some consensus or some proper thinking through of the assumptions. We are now facing many of these risk assessments where the assumptions fly by in very complicated slides so we have no time to really assess what in philosophy we are really modeling. That is one thing.

Now my question, you model the window period risk to the delta window period for release 1 year or 5 years to be zero. I sincerely doubt that. I think there will be a difference in risk in the incidence because what you are asking donors

is the uncertainty that was addressed by this qualitative research. So, this uncertainty about the answer, if you ask the question have you had sex with a man for less than a year, is one remark. I don't believe that that risk is zero. I think it is higher than your mistake rates in testing but that is only assumptions.

DR. DAYTON: Let me answer that and I will certainly get to the second question. If there are going to be error window periods sneaking in because of changes in policy like that, I would predict that it would be something to do with changed interaction with the questionnaire, changed perception of fairness in the system. The reason it drops out is because we don't have any window periods that even approach a year. So, when you are looking at changes in policy, you know, we are still maintaining the one-year deferral. The dangerous assumption there come in that you are not going to change people's willingness to participate and that is an unknown; I mean, the model doesn't handle that.

DR. BUSCH: I want to address that. I completely disagree. I think if we move from the nebulous of '77 to a one-year deferral and can focus the donor's intention on the importance of acknowledging risk within that last year, we are going to reduce the rate of window period donations which sneak in. So, I think there would be a benefit on window period reduction by focusing on recent behavior.

DR. VAN DER POEL: Well, I don't think that is the case. I think that you get uncertainty. There is lack of compliance of about three percent so there is also lack of compliance about the incident cases. The discussion here is exactly reflecting what I was saying, that we now have modeling of assumptions, uncertainty if you like, which are not based on spread of data but are based on spread of expert opinions, and those experts need to sit down really and have a lot of time to discuss this philosophy.

The second question, I don't understand why you relate the mistake error or testing error

and the mistake error of release to prevalence. Because prevalent donors are screened out not once but many times. If they repeatedly donate they become succeedingly selected out. So, the risk error would be more related to incidence, in my view, than to prevalence.

DR. DAYTON: Well, we are looking at changes in the first year and we are looking at the new MSMs, for instance, who would be newly eligible to donate as donating once, and we assume that most of the time, if they are infected, they will be picked up and they won't be donating a second time. Of course, in the U.S. you have a large number of first time donors and that is how we are modeling it. Again, the incidence only drops out because we are assuming that the incidence doesn't drive on past a year.

I think the weakest parts of the assumptions--and I totally agree that we need to get this vetted from top to bottom, but I think the weakest parts of the assumptions are the behavior ones, particularly centering around the

questionnaire and how accurately you are getting data. Unfortunately, we just don't have any information on that.

DR. HEWLETT: In the interest of time, let's move on. We have a question at the back, one here and then, Steve, I think you have a comment. Yes?

DR. GOLDMAN: Hi. I have one comment. All the modeling is based on--

DR. DAYTON: Please identify yourself.

DR. GOLDMAN: Mindy Goldman, Canadian Blood Services. As pointed out, all the modeling is based on first time donors and, of course, after the first year most of your MSM donors will be prevalent donors. So, all your risks are sort of overstated, I think, or they only are true for maybe the first year and then they should increase as 80 percent of the donors with that risk are repeat donors, just like all our other donors.

My question is if you believe your numbers, you would have 1,000 or 2,000 HIV-positive donors a year, you would have a lot of positive HIV

NAT pools coming from a country where one a year would be an event. Mike, do you think that is a problem for the lab to handle? Do you think that would significantly delay inventory release? Or, do you think you would have a higher rate of false positives if every day, in a big lab like the American Red Cross lab, you had two or three true positive NAT pools?

DR. BUSCH: No. I mean, these labs are streamlined. I don't think that would be a problem at all in terms of the throughput of the labs. One, I don't think there is any way that you are going to see, you know, two to three additional HIV prevalent infections. First time donors with prevalent infections occur as a consequence of this change. But, were you to see that, that is trivial in terms of the lab's ability to identify and resolve that.

DR. HEWLETT: Thank you. Next question?

DR. KESSLER: Debra Kessler, New York Blood Center. I had a little bit of a struggle with the release in error when you were saying,

well, if one HCV was released in error and you have so many HCV in your freezer or your refrigerator what the increase could be. I think the denominator really should be overall units because many of those units are not fully tested in your error model and most of them are negative. So, the denominator of the positive units that you used to extrapolate I think is the wrong denominator.

DR. DAYTON: I am not sure I understand your point.

DR. KESSLER: You were talking about mistaken release, and you were saying that if you accidentally release an HCV or a core and then you increase the number of HCV or cores in your refrigerator, here is what you might wind up releasing in error. Your denominator is the total number of positive units, positive HCV or positive core sitting in your refrigerator--

DR. DAYTON: Are you talking about when we calculate quarantine release error rates--

DR. KESSLER: Three out of 10,000, you were saying--

DR. DAYTON: Were you talking about the part where we calculate the quarantine release error rates, or--

DR. KESSLER: Yes.

DR. DAYTON: --are you talking about when we apply those rates to what we calculate will be in the refrigerator?

DR. KESSLER: Both.

DR. DAYTON: Well, I believe both are correct.

DR. KESSLER: But I think that the denominator has to be everything in the refrigerator.

DR. DAYTON: Well, we could have done that, but then the question is it wasn't clear what to put in the numerator. In other words, you are looking at all erroneous releases so what we did is we took everything that was related to viral markers and syphilis and we just asked what is the chance that something that has an error with those will be released. If you wanted to increase the denominator for other erroneous releases you would

have to decide what to put in the numerator to go with them.

DR. KESSLER: Everything in your inventory.

DR. STRAMER: Debra is right because really you are doing reconciliation with everything in your refrigerator.

DR. DAYTON: i agree with you but you just have to decide what to add in the numerator. Then what you should do is you should look at every erroneous release and you would probably come out with the same thing. For instance, we got very similar data when we did confirmed positives and repeat reactives, and I think that speaks for the accuracy. I understand what you are saying, it is just it was a reasonable approach. The real question is to decide what to add to the numerator when you do that.

DR. LACKRITZ: I had a similar question. Maybe I got confused with Sharon's presentation. Because it is a pure probability, it is a probability of an error times the probability of a

positive unit. So, I think it would be more clear--because what you are talking about is increasing the potential positive units in the refrigerator so I think it would clarify it if it was just purely error times prevalence.

DR. DAYTON: Yes, we can discuss that. As I say, the question becomes what to put in the numerator when you do that.

DR. HEWLETT: I think Steve has a question and then I think Alan.

DR. KLEINMAN: Steve Kleinman from AABB. I just wanted to mention that we do tolerate a source of prevalent HIV infections today, and that is from HIV-positive autologous donors. We haven't mentioned autologous donors. We allow collections of HIV-infected people in most jurisdictions. I don't know how many units that contributes a year, but we haven't, as far as I know, had a release of an HIV-positive autologous unit. So, I think we need to take that into context. This kind of supports what Celso was saying about the computer systems. We can do some calculations but I note

from what Sharon said that the two units that were released, one was a recovered plasma so it wasn't a transfusable product, and the second error was really a testing error. It wasn't a release error. When it was released it was negative and then subsequently they found it was a test positive. So, harping on the prevalent infections and the release errors I think is still overdone in the model, actually.

DR. DAYTON: I will mention that we actually factored out autologous units because we did have some reports from them, and that is a very different system that we felt should be handled separately. Because usually what happens, there is confusion with how to handle it in the blood bank.

DR. HEWLETT: Alan?

DR. WILLIAMS: Alan Williams, FDA. This is for Kristen Miller. Thanks for your very nice presentation and thanks also for your group's work on the donor questionnaire. So, the question to you is you are familiar with the questionnaire and you have done cognitive work on it. Are there any

immediate next steps toward improving donors' understanding of the questionnaire, given that this has to be applied to a very broad demographic group with some very sensitive information? Is there some movement toward CASI [?] within the donor setting? Do you see any other obvious next steps?

DR. MILLER: Boy, do I wish my co-worker Paul was here because he has worked so much on this. In my conversations with him--I mean, I think what he sees that needs to happen is that there needs to be serious education of donors so they understand why it is that they are being asked these questions, and why the risks are--you know, why their behaviors are at risk. Just listening to this conversation, I mean, the scientists don't really quite have it wrapped up; how are you going to be able to communicate it to your average Joe on the street who is not going to understand anything about this? And, that is going to be the struggle.

DR. HEWLETT: Yes, Jay?

DR. EPSTEIN: I just want to make two comments. The first is about autologous blood.

Autologous units are managed in a separate quarantine, but there was an AABB survey in the 1980s about errors of release of autologous blood and, if anything, the numbers were worse. Now, it was hospital based and that may reinforce the earlier findings also of Dr. Linden, recent reports with those data. So, I think we still have a question mark about the role of release error contributing to residual risk, particularly in the hospital setting. If anything, the autologous data, at least the data available, would suggests things are even worse than we thought, not better.

The second comment that I would like to make is that if you take the worst case estimate from the statistical modeling of I think it was 0.2 per million--is that right, Steve?

DR. ANDERSON: Right.

DR. EPSTEIN: it was 0.2 per million, right?

DR. ANDERSON: Yes.

DR. EPSTEIN: So, that is the HIV. So, that is roughly 2 per annum in the U.S., and then

you compare that to the 12 per annum estimated current risk from window period cases. The important point here I think is that it is not a small percentage of the very low risk that has been achieved by spending hundreds of millions of dollars per annum. In that context, the way the question can be framed is in terms of costs and benefits. In other words, if a relaxation of policy would contribute a small added absolute risk which is, nevertheless, not a small percentage of the current risk but would contribute only a minuscule amount to the blood supply, then why is that a good policy change?

I think that that is the question that troubles the regulators. We are not really disputing that the models are yielding very low numbers of additive risk, but then we have to put it into the context of everything else that we are doing to keep these risks low. I think that that same point was made in the papers of Soldan and Germain, that it is the percent contribution to residual risk that is the troubling aspect of this

even though the numbers are very, very low, because it is a question of the tradeoff. I understand Dr. Bayer's point that maybe it is a good tradeoff in terms of social considerations but, you know, what we are trying to look at is whether it is a good tradeoff in terms of the relative safety and availability of blood supply.

DR. HEWLETT: Thank you, Jay. I think we have one last word from Dr. Holmberg.

DR. HOLMBERG: Thank you. Jerry Holmberg, HHS. I think that I would like to address this question to both Steve and Andy. In looking at your modeling and your calculations I see that there is increased prevalence with hepatitis B virus and also the HTLV. I would assume, if you had taken the logic backwards, the reason why the prevalence is so high is primarily because we do not have nucleic acid testing available. Would you be advocating nucleic acid testing in a change of policy?

DR. DAYTON: Well, I don't want to be up here recommending policy. I think you are

referring to the IDU data, which is where the HBV gets to be a problem and also, of course, the HTLV. Obviously, the big problem with HTLV is that even the ELISA sensitivity isn't all that reliable. Now, we don't know how well a NAT is going to work. We would have to see. But, yes, we would like to see better testing. Of course.

DR. HOLMBERG: But also I am referring to the 18 percent prevalence in both the one-year deferral for MSM and the five-year different on HBV.

DR. DAYTON: And the question is what?

DR. HOLMBERG: There are a lot more components being released. In other words, if you are saying that the number of components is less, that they are less because of the nucleic acid testing so, in other words, without nucleic acid testing for hepatitis B virus you would not get the same reduction.

DR. DAYTON: Well, it is not so sure that it would help because, you know, the big thing with HBV is that 95 percent or so come back down to no

virus anyway afterwards.

DR. BUSCH: Yes, I had a problem, Andy, with HBV, HCV where you are factoring down the persistent infection that people clear and then you are seemingly indicating that there is still residual infectivity risk of surface antigen negatives that might not score reactive on the anti-core. Those units have extraordinarily low infectivity. With HCV, you know, RNA negative, mini-pool negative antibody positive units do not transmit. There is good data out there--

DR. DAYTON: That is why we factored them out of the N. For the HBV we took five percent of the numbers--

DR. BUSCH: Okay, you took five percent--

DR. DAYTON: We reduced it by 20-fold and for HCV we reduced it--we picked up 80 percent.

DR. HEWLETT: I think we will end the panel discussion. Certainly, Jerry, you posed some issues that we should consider and we will obviously have to think about this but thank you.

DR. DAYTON: We would like to be back in

the room by 4:15. We have a hard deadline and we cannot go more than half an hour later overall so a brief coffee break would be appreciated.

[Brief recess]

III. Potential Alternatives for Donor Screening and Testing, Jay S. Epstein, M.D., OBRR/CBER, Moderator

DR. EPSTEIN: If I could ask people to please be seated quickly, we are very much behind time but we have an important concluding session, entitled, potential alternatives for donor screening and testing. But really it is two talks about opportunities and about threats. So, the first speaker in this closing session is Dr. Celso Bianco, America's Blood Centers, who is going to present a blueprint for decreased reliance on behavior-based donor deferrals.

A Blueprint for Decreased Reliance on Behavior-Based Donor Deferrals

DR. BIANCO: Thank you, Jay. While Andy deals with the computer, first, this has been a very stimulating day and it is wonderful to be here. The second thing that I wanted to say as a

matter of background is, yes, we are in our blood centers confronting major, major issues. Many of our centers are unable to collect blood, particularly in colleges and in other environments, because of a perception, and a real perception by many of the students, that we are being unfair about the issue that has been discussed all day today, that is, we have different criteria applied to different risk groups, and people don't understand the risk groups. These issues impact on our donations.

Not only that, we know that many individuals with deferrable risks continue to donate and we, and I personally think--and I say "we" because other people share this with me, that this fosters lying, or we shouldn't call it lying after the last presentation; we should call it misperception.

The other point that I want to make is that all the assumptions and all the surveys that serve as the basis to all the models that we discussed today, they take into account donors who

donated but did not reveal deferrable risk at the time of donation. We take into account the prevalence of MSM in the general population. We look at the proportion of MSM in STD clinics that do not know that they are HIV positive because those are the ones that would be unaware of their risk and would come and in good faith make a blood donation.

But we should be aware that HIV prevalence in successful donors is lower than that of the general population, and not only HIV, HCV, HBV, and actually Dr. Williams today pointed out that the prevalence of markers among first time donors is much lower than that of the general population. We don't know really why it is lower, if it is the pre-donation education or what is the effectiveness of medical history so that when we look at the prevalence of the people that donate it is different.

What I am trying to do here today is focus the discussion on deferral of the MSM. Second, I am sorry that I didn't hear Jim Allen the day I

start preparing this presentation. What he raised is this warning of tradeoffs. That is where I want to go. If I say here could we develop a list of measures that ensure the safety of the blood supply and allow decreased reliance on behavior-based deferrals, I am actually asking are there any tradeoffs? Are there things we could do that could allow us to change the deferral criteria--and the number that I use is from indefinite or permanent--to one-year deferral and take measures that ensure the safety of the blood supply?

I have to acknowledge the tremendous help of Marc Germain. They opened their model, their computers and their good will. Marc, thank you for your help but it was very cold in Montreal!

[Laughter]

The model--and I will not give details and you have available copies of the paper that they published in Transfusion, in 2003. Obviously, the risk calculations were based on Canadian data. They took into account all the issues that we discussed today in terms of modeling:

false-negative results; technical errors; and blood donor prevalence issues. I will also not go into the math, except for one number that I think is very important and that will define the prevalence in their model.

The prevalence of HIV or the proportion of unrecognized HIV in a cohort of gay men in Montreal in a study of follow-up of individuals that were negative over a period of time was 0.6 percent. Marc used that to estimate the additional MSM donors infected with HIV that would join the donor base and that would donate the first time. Their calculation at the end, what they call new one-year, is the additional number of HIV-contaminated units that would escape detection and become available for transfusion. They expressed it in years, that is, how many years would it take to see HIV-positive units. Since we, here, try to do it per million I added a translation of that. The numbers are there.

The other thing that I made a point of, and we discussed these very well, is that we have

had tremendous changes in technology in the last 10, 15 years. We have improved EIAs. You have just seen the example of HIV that came down from a 52-day window period to less than an 11-day theoretical window period, knowing that it is even less than that. We have licensed NAT implemented all over the country. Everything is computerized, and even the data transfer between a blood center that sends their tubes to be tested to central laboratories, be it in the American Red Cross system or be it among the ABC members, is all done electronically. There is nobody looking at faxes or getting a unit number on the telephone like we did 15 years ago.

So, I changed the assumptions that have been used by Marc and Gil in the January, 2003 paper. Their bottom line, if you look, is that they expected with the assumptions they made that by changing the criteria to one year we would in the United States, using their assumptions, add 1.1 units, HIV-positive units as a risk per year to our system, or 1 in 15 million. But when I looked at

the model and I changed the risks for the false-negative window period viral variance to numbers that everybody is more or less agreeing on here--and I still used the very high inappropriate release because I was afraid of challenging this audience but I see that we have got to much lower numbers--we would see a new HIV-positive unit once every 32 years.

This model is extremely conservative. The false-negative results, the technical errors overlap, and the likelihood that a unit is going to be released even when you consider that many of the tests overlap and, for instance, many units that are positive in one test will be positive in another test--that helps. And, Dr. Dayton took some of those into consideration. Viral variants are not an issue, and the risk of inappropriate release was based on old data.

The parameter that affects the risk estimate is the assumed prevalence of HIV in the donor population, and what if we reduced that prevalence? For instance, what was used in the

model in 2003 was 0.6 percent based on that cohort data from Montreal. If we reduced it to 0.3 percent or 0.06 percent we would have substantial changes in the prevalence or in the risk of release of a unit. If we took then the new assumptions that we added to the model, then the risk is really insignificant, on the order of many, many years to see the first HIV-positive unit.

Now, yes, we can theoretically feed these numbers and get different levels of risk but they are still models. That is where we come to the tradeoffs. Are there things that we could do? Are there additional measures that could facilitate the changes in deferral criteria?

We heard about one of them, and it is a change that we already feel that we are reaping the benefits of. That is the introduction of the uniform donor history questionnaire. The system was the product of a task force that involved many members of the blood community, involved FDA regulators, and got a lot of help from CDC in terms of evaluation of the donor history. It is still a

very complex history. There are still 40-some odd questions there and, certainly, I am of the belief also that reducing the number of those questions and focusing on the ones that truly represent high risk would even improve the sensitivity and the specificity of the donor history. Even if we take into account that we implement abbreviated donor history questionnaire, computer FCs to donor history that we know improve donor responses in terms of risk behavior, unfortunately, we cannot quantitate that into the model. There are no studies to date and those studies are impossible to do to see how much risk reduction we get because, as Dr. Busch explained a few minutes ago, those studies would require such a large population in order to have power because of the very low prevalence of all these markers.

There are other measures that we should have. For instance, Dr. Dodd is going to give us some sense of what is the risk that is imposed by emerging infections and what we could do, and which ones would be prevented by deferring gay men for

lifetime. There are other risks, as we heard, for HHV-8. If the link for transfusion becomes stronger, certainly a requirement for leukoreduction would address that risk. Or, there could be other methods like we have for Chagas, vCJF tests and filters, and many for the future. This would help ensure the safety.

The other thing that I believe is going to help ensure that safety is an issue that is going to be discussed at the Blood Products Advisory Committee in the next couple of days, the availability or potential availability of over-the-counter tests for HIV, or maybe if somebody comes up with another easy, low-cost alternative for confidential HIV test, what we would get from that is much less pressure for test seeking. Obviously, it is not approved yet by FDA. We do not know yet the public health impact, even if we may hear some studies at BPAC, and, again, the quantitative impact on the prospective donors is unknown. Also, we are aware that there are concerns by some people about the availability of

these over-the-counter tests.

There have been ideas that have been discussed, like what if in order to reduce the prevalence we, for instance, did a rapid test for all donors that revealed some risk behavior before they donated blood? That could look like a simple solution but it is certainly a very complex solution. Certainly, depending on the sensitivity and specificity of the test, it would reduce the predicted increase in prevalence of HIV because we would reduce the number of prevalent infections.

However, unless it is applied to every single donor the major issue that I see in terms of discrimination is the difference between certain types of behavior from other types of behavior, not so much on a rational basis for what we know today, not what was done 20 years ago. It would not address the perception of discrimination, so would not resolve the social, political issue associated with these deferrals.

The real problem with rapid tests is that they cannot be performed under CGMP and we are

controlled in our blood centers, all collecting facilities, by CGMP. Even if somebody at CBER tells us that we could do something, some inspector from our district will come and say, yes, they may something but you have to do it according to CGMP. The inspector will give you a warning letter and they can close you.

The other concern that we have about some rapid test is that it could certainly serve as an incredible magnet for individuals at risk. What a tempting thing to see that there is a blood drive down the corner, just to stop there and 20 minutes later I know if I am HIV positive or not! So, we have real concerns with that.

The other concern that we have is in confidentiality. That is fundamental to the blood donation process. That is how we believe that we have maintained the safety, that we have maintained the accuracy of donor history in what we do. And, a blood drive is not an easy environment to deal with in order to do donor notification and counseling. There have been historically many

attempts to develop rapid tests for high prevalence markers, like ALT when we used to do it or for core antibodies so that we would prevent donation by these donors but they never succeeded because of similar types of issues.

The other proposal that has been raised is a proposal to do what the source plasma industry does. The donor shows up. They collect a unit of plasma and put it in the freezer. In our case, we would collect a test tube, send it for testing and then accept the donor the next time but not collect the unit from a first time donor. Certainly, these would reduce the prevalence, however, our system could not deal with such a change. Our proportion of first time donors varies between 15-30 percent on regular blood drives but we do a lot blood drives with our new donors--those that are going to replace the people who are getting old and getting sick--those in high schools and colleges and those, in general, 80-100 percent are first time donors. So, for a very small risk reduction we would create serious problems of availability. We could not,

obviously apply it just to donors with risk behavior, again, because it would not address the perception of unfair discrimination.

So, I want to conclude by making some suggestions in terms of tradeoffs. First, if additional measures are implemented they must apply to all donors. Measures restricted to at risk donors would not resolve the issues.

Second, rapid tests cannot be applied to the volunteer blood donor sector without incredible disruption and where the benefits would be very, very limited. We know that substantial operational improvements have reduced the risks. Change in deferral to one year, at least with the numbers that I used, would increase the risk for one case every 32 years, and there are other measures that we could implement that could reduce the risk even further. And, further studies could reduce the actual risk.

What FDA could do as a tradeoff is establish a set of conditions that should be met prior to the implementation of modified criteria

for MSM deferral. Let's say we have a blood center that wants to change their criteria, they would have to apply and document that they have the uniform donor history questionnaire up and working and maybe the abbreviated--that is our dream to have it one of these days because I think that this will even improve compliance on the part of donors.

Implementation of qualified high sensitive screening tests--we still have some tests that we use for which the sensitivity is not optimal. And, implementation of validated, 510(k) cleared computer systems from donor to laboratory to inventory release. Thank you very much.

[Applause]

DR. EPSTEIN: Thank you, Celso. I think we will hold questions in the interest of hearing all the presentations and saving some time for the panel, which you will be on as well as Roger. So, it is my pleasure then to invite our last speaker, Roger Dodd, from the American Red Cross, who will speak on behavioral risks and emerging infections. Thank you.

Behavioral Risks and Emerging Infections:
Is there a Pattern?

DR. DODD: Thank you, Jay. The only thing that I can promise, Jay, is that my talk will be totally uncontaminated by data!

[Laughter]

This background statement was in the background materials that came with the handout. The FDA points out that deferrals are generally retained to provide additional protection, particularly for imperfect tests and imperfect inventory management. But what I have been asked to talk about is the extent to which the key behavioral risk questions that we have been discussing today may or may not have an impact on emerging infectious diseases that impact blood safety. In the past, I think it is true that transfusion transmissible infections tended to have very common epidemiologic pathogens. It was, therefore, thought that behavioral risk questions could have utility in reducing the risk of transfusion-related infection from new or

unrecognized infectious agents. I will cover that in a little bit more detail.

Conversely, another form in which the question was put to me is are there individuals with particular risk profiles who might be sentinels for transfusion transmissibility of outcoming emerging infectious diseases or, indeed, might be people that in the future you would want to defer on behavioral grounds.

I think a fairly good model to have in mind is that HIV, when it was first considered to be a transfusion transmissible agent, was presented as having properties in many ways very similar to HBV. So, what we are going to talk about is the degree to which this is extensible, if you like.

So, I want to talk a little bit about the basis for behavioral risk questions; remind you of the characteristics of traditional transfusion transmissible infections in the context of behavioral risk; then spend time on emerging infectious diseases from a number of different angles, with a real focus on saying do these

emerging infectious diseases that we currently now about demonstrate a common pattern with respect to transfusion transmission; and then to talk briefly about the sentinel or future risk populations.

I think as we look at this, this is something of a chicken and egg question, did the question come first or did the infection come first? To put it more in context, that is the way we have to think about the question about future infectious diseases.

The history of behavioral risk questions really was covered to some extent earlier this morning in the context of looking at paid donations, individuals in prison and injection drug users who clearly were very much more involved in other donors in the transmission of hepatitis before, indeed, we knew anything about hepatitis other than that it was an infectious disease or, as it turns out, a suite of infectious diseases.

Subsequently we started thinking about travel histories, which I guess is a behavior--it has become a behavior for me--and its relationship

to malaria and this concept, of course, has been greatly extended for a number of infections but mostly for BSE and vCJD, and that was also discussed earlier. When we knew more about hepatitis and hepatitis B, a variety of routes for blood exposure-- tattoos and, in fact, modified conditions for the use of hepatitis B immune globulin in cases of blood exposure generated other deferral questions for hepatitis B. MSM, and I use this advisedly, deferral, self-deferral, educational processes to try to discourage men who have had sex with men, along with some other groups, were introduced when AIDS was still AIDS and it wasn't known to be caused by an identified virus. As we started being able to test for the virus, other sexual contacts, sex for money and drugs and a whole litany of questions came into force, based partly I think on data that were developed, somewhat unusually, after the availability of tests but during a period when it was recognized that tests were not optimal.

So, by and large, I think behavioral risk

questions have been developed in reaction to disease states. So, when we started out the disease definitely came before the question or the egg before the chicken. In some cases, interestingly and I think this is why I have this talk to give, they appeared to be prescient, that is, as I already pointed out, questions that were designed to deal with, let's say, serum hepatitis also clearly served purposes with respect to reducing the risk of transmitting HIV, HTLV and even HCV.

Actually, once the data were available, these questions have usually been found to be justified at some level and were, as was the case with HIV, actually strengthened by test data once available. Data and information countering the use of questions has generally not been well available or has not been persuasive and that is really--I hate to use words like the core, but that is part of the issue that we are really discussing today.

But we have also talked about the problems of questioning. They are not specific. Clearly,

we know about that and probably the best example of non-specificity is questioning for travel with respect to malaria risk. But neither are they sensitive, but I would submit that we don't truly understand the limits of sensitivity of the questioning process. Often questions are confounded. We heard about this. Some of the risks associated with drug use actually turn out to be sexual so you don't actually know what you are getting or what you really want when you rely on questions.

And, they have generally been reactive and not proactive and, again, this is what I am asked to talk about. When you react to a situation with a question if, as was perhaps unusual in the case of HIV for us at least, you have to deal with a very long incubation period the question's efficacy is very much delayed because you are seeing disease long after many, many people have been infected. This is even true if the questions are developed before the transfusion transmission has been verified. This was the case for variant CJD. Of

course, there were societal and ethical issues and there were human errors both in terms of presenting the questions and responding to the questions. These are not reasons not to ask questions but all things that contribute to the difficulty of the discussion that we have been having.

Now, up to about 1999, and I chose this date advisedly, we really thought mostly about the big 5 transfusion transmitted infections, syphilis, HBV, non-A, non-B becoming HCV which of course it was by that time, HIV and HTLV. Although we were clearly knowledgeable and recognized issues relating to malaria, Chagas' disease, perhaps leishmania and certainly we recognized a threat, babesiosis, CMV and non-alphabetic hepatitis--

[Laughter]

--which, in fact, really didn't go anywhere. The characteristics really of the big 5 were that they were all chronic infections. They were all blood-borne. They all had significant asymptomatic periods and in some cases lifelong asymptomatic infection. They were transmitted

parenterally, including by sexual routes, and were strong behavioral correlates which, as I have said earlier, were generally overlapping--injection drug use, the number of sexual partners, whether they be homosexual or heterosexual, institutionalization, blood exposure and generally an inverse relationship to socio-economic status.

This I think led to what I am calling the millenial dogma. That was that blood safety is threatened by the next virus. By saying the next virus you have already generated a certain expectation that it will be a virus. The next virus will be chronic, blood-borne, emerging infection, probably an RNA virus because there is a lot more mutation in RNA viruses. It will threaten recipients of plasma derivatives and deferrable behavioral patterns will be associated with increased risk for the next virus. But, nevertheless, we should keep an eye on known parasitic diseases.

But the first large-scale new infection to impact transfusion safety in the U.S. was, I

submit, West Nile virus. Here it is. West Nile virus was essentially none of the above and that is pause for thought.

So, this leads me to talk a little bit about emerging infectious diseases, and this is the IOM definition and it is interesting because it actually talks about, in addition to diseases whose incidence has increased in the past two decades--not in the past 50,000 years--or threatens to increase in the near future, it also speaks to the fact that emergence may be due to the spread of a new agent or to the recognition of an infection that has been present but has gone undetected. By this account, things like HHV-8 and, indeed, HTLV could be regarded as an emerging infection.

Here are some. It is by no means a comprehensive list but some emerging infectious diseases that we can think about. I have put in red those that are transmissible by transfusion. Obviously, it is not all of them and obviously this is a very varied population of agents. For SARS we acted as though it was transfusion transmissible

but it was never demonstrated.

So, there are many, many emerging infectious diseases and they belong to all classes of agent, no matter how much or little nucleic acid they have. An interesting fact is that 70 percent of emerging infectious diseases that have been discussed to date are zoonoses. They have jumped from animals to humans. Most, if not all, transmission routes have been exhibited in the emerging infectious diseases portfolio and infections are acute and chronic, and many derive from human activities, changes in human activities--BSE, variant CJD from intensive farming; SARS traveled around the world by air transport; agriculture, irrigation changed the distribution of diseases. Global warming is changing the distribution of malaria. But emergence is unpredictable.

If we look at currently emerging potential transfusion transmissible infections, and I don't think this list is exhaustive but it covers most of the things we have thought about and talked about

lately, actually they have a tremendous variety of behavioral risk factors associated with them. West Nile virus, clearly, you get it outdoors. We did try to have a question for West Nile virus, fever and headache, and found it was not an effective question. Some represent travel, country of origin. Some, indeed, are associated with the risk factors that we have been discussing today, HHV-8, MSM and IDU. HAV, some outbreaks among men who have had sex with men. Papilloma virus, again sexual contact in MSM and some question as to whether this might be transfusion transmitted. But all the others on this list have no relation to the traditional factors that we have looked at. My favorite is anaplasma. Actually, I wish Jesse were here. This was one of his organisms which was found to occur much more frequently among bad male golfers than amongst others--

[Laughter]

--because they would hit their balls into the rough. Being men, they would go look for them and they would get bitten by ticks.

[Laughter]

Conversely, we can ask the question are there emerging infectious diseases that are appearing in these traditional risk groups that we have had to deal with? I did a literature search and what I looked for was the group and infections, and I eliminated HIV, HBV, HCV and HTLV and for MSM I think I got about 1,200 references back, and for IDUs about 800 references. What I found in the literature is that for MSM you are looking for papilloma virus, hepatitis A which we discussed, LGV, lymphogranuloma venereum, which is a chlamydial disease which was also discussed earlier today, HHV-8 and shigella and various mycobacteria. Not a lot of these currently are perceived as impacting transfusion safety.

Injection drug users, HCV-2, presumably compounded by sexual activity, HHV-8 again and, again, we heard about that today, HAV and staphs. and clostridia probably associated with injection practice. So, it is interesting but it doesn't say to me that all the new things that are popping up

in these groups are necessarily threats to transfusion safety.

In a very simplistic way, what I thought I would do is to take a bunch of them--it doesn't really matter that you can't read them--and plot them with respect to whether or not they had certain properties that I really laid out a little bit earlier: viral, persistent, transmitted by plasma, sexually transmitted, occur in MSM, occur in IDU. Up to this point we have the big 5. There was clearly great commonality. The one that is least common is syphilis and we haven't seen much transmission of that perhaps because we have so many measures dealing with it. HTLV has a couple, and plasma transmission and MSMs, as we heard from Ed earlier. But then the only one on the list that has a really significant number of attributes would be HHV-8 and potentially HBV.

So, looked at very simplistically, a lot of these emerging infections that are very likely to be transmissible by transfusion right now don't have the exact same patterns that we have

traditionally attributed to transfusion transmissible infections. A lot of them really aren't even very persistent. Look at West Nile.

What about the question of sentinel populations? Are there populations that would warn us about new transfusion transmissible infections? I think the conventional thinking might be that you would see these in clotting factors recipients, product transfused patients, injection drug users and let's just say a broad sexual risk population, STD clinic attendees. So, that is the thinking but today's thought, at least for me, is that, no, there really aren't clear sentinel populations that we should look to for the next threat or that we should try to eliminate prospectively because they might come up with the next transfusion transmissible EID.

If you think about clotting factor recipients these days, they are receiving inactivated products, admittedly something that is not going to deal with every emerging infection, but also recombinant products which step right

around the issue. Chronically transfused patients, yes, we have been trying to look at some of these ourselves but the results that you obtain may be too late to really do a good intervention. It is a complex population and it has limited numbers and availability.

IDUs are hard to work with and there is very little crossover, as I have tried to show you, with the current transfusion-transmitted EIDs and the ones that are popping up in addition to the big one. Similarly, I think you will find that with STD clinic attendees and MSMs as a subgroup.

It is interesting though to note that organ transplant recipients maybe, I should say, offer some promise in this direction. The following have been transmitted to transplant recipients recently, T. cruze and right now two more cases are being looked at, although we don't quite know the origin of these, rabies, lymphocytic choriomeningitis virus--another risk factor, hamsters in the house, HHV-8 and West Nile virus. In the absence and sometimes the presence of donor

testing, HBV, HCV and HIV have all been transmitted to organ recipients. But, again, recipients are at risk of many infections, including those due to reactivation so they are probably not a really good sentinel population but maybe we can look for warning signs, and there aren't an awful lot of them.

I will comment that as a group emerging infectious diseases do not have any common characteristics with respect to class of agent, transmission route of pathogenesis. So, I do not think that they can be considered as a homogeneous group, other than that they are increasing in prevalence or incidence in the population.

It is true that all transfusion-transmitted infections must necessarily have a blood-borne phase and this is a commonality of the emerging infections that are transmitted by this group. But it doesn't necessarily assure us that there will be transmissibility by sexual or other low volume, non-parenteral routes. You are going to have to think about something like

quintessentially transfusion transmissible like malaria to realize that that has a blood-borne phase; it is a chronic disease, but the inoculum will generally be relatively low and it just isn't transmitted by these routes. So, risk behaviors associated with such transmission routes are not going to be common to all transfusion-transmitted infections.

I think in a sense, and I don't vouch for the size or placement of these circles, but if you look at the field of infections we look at emerging infections; we look at those that are subject to the behavioral risk factors that we ask about; and we look at those that are transfusion transmissible, and there is relatively little mutual crossover. I could perhaps just have shown this made up chart and sat down and saved you a lot of time, but that is kind of how I see it. Perhaps one of the things we need to do is to put numbers or proportions into each of the parts of this ven diagram.

I will just again comment that the

questions have generally been developed to manage risk in the absence of a test. They have ben based on the epidemiologic characteristics of the infection in question. Current behavioral risk questions do not seem to be applicable to the majority of EIDs of concern. That is not to make a statement that there will be no EID that fits this pattern. I am sure there will be. When I was coming in Alan said I hope you are not going to say that there are going to be no parenterally transmitted emerging infectious diseases in the future. No, I am not saying that. I am saying there are going to be lots of emerging infectious diseases, some of which--only some of which will be transmissible by that route. So, we shouldn't necessary expect a new infection to fit an existing question. The future impact of retention or elimination of a question is actually not predictable.

I thought the other way of rounding out my talk was to say if you want to get a fish, don't get a chicken--

[Laughter]

--because that closes the circle. Thank you very much.

[Applause]

Open Discussion

DR. EPSTEIN: Thank you very much, Roger. That may have been data free but it certainly was not thought free and I appreciate it. So, now I would like to invite the discussants and our final panel to come up. They include the presenters that you just heard from Celso Bianco and Roger Dodd, to be supplemented by Andy Dayton, Mike Busch, Alan Williams, Mat McKenna and Mat Kuehnert, Cess van der Poel and Eve Lackritz. I understand there was a problem with a flight for a representative from HIV Medical Association but if there is a representative from HIV Medical Association, you are certainly welcome to introduce yourself and come forward.

The purpose of this concluding panel is to have some discussion on the improvement of the quantitative models that we heard about in the

previous session, and then to close with a discussion of what scientific information is needed to develop potential alternatives for donor screening and testing.

Let me just throw out a couple of things that I heard touched upon during the course of the day as far as ways forward. First of all, there was the simple direct suggestion, well, why don't we just move to either a five-year exclusion or one-year exclusion for history of male to male sex? And, we can have a debate about do the data support this or don't the data support this.

I think that Dr. Bianco made clear that in our current environment pre-testing is not such a practical option but maybe, Cees, if I could trouble you and if we are correct, I believe it is actually practiced in some countries such as Sweden where you have a pre-test and four weeks later you have a donation. The Netherlands too. So, you know, that is a question I think perhaps of social engineering.

I think that we heard a loud and clear

message that if part of the problem is weak quarantine controls and, indeed, maybe the lead problem for certain of the agents, that, well, there just ought to be strategies to improve quarantine management through computerized systems and automation.

We touched on the issues of pathogen reduction and filtration, which might work to different effectiveness for different agents but there is the tantalizing possibility that maybe that is the resolution for the HHV-8 problem, which I hope we will spend a little time talking about because it is a potential concern, at least with respect to any relaxation of the male sex with male deferral.

We didn't talk about quarantine and re-test strategies which are practiced at some centers for plasma for transfusion and is certainly not practical for platelets or red cells, unless we start freezing them all. So, there is probably nowhere to go with that.

There is the question of additional

testing. In other words, could we relax behavioral deferrals by some compensatory safeguard related to testing. Particularly HBV was mentioned and the need for better tests for HTLV. I think we would agree.

So, perhaps there are other alternatives that we might wish to talk about, but I think at this point we will throw it open for discussion. Now, we will have a solid 30-40 minutes. We do have to vacate this auditorium by 6:00 so wherever we are at 5:55 we are just going to stop.

So, who would like to perhaps start the discussion about the quantitative models and alternatives? Are there any thoughts about that from our panelists? Cees?

DR. VAN DER POEL: Well, I think I have said it before, but it may not be a bad idea to repeat it. There has been a meeting driven by Health Canada, a couple of meetings actually. The last meeting was I think in January or the beginning of February in Ottawa where risk models were discussed, and it came out that it is very,

very, very crucial how the data are put into the models, and we already had discussions, Mike and myself, that we did not agree on some assumptions. But that is nice; I mean, that is what we are trying to do, to not agree in academia.

But if it comes to outcomes of modeling then, it is most crucial that we discuss these models. I realize that if we present these models in our environment many of us go away because of the statistics, but we have to get rid of that very easily because we are going to say these data are put into a probabilistic model with marker modeling and whatever. The outcomes of that machinery are the same if you put in the same data. We can trust on that. What we cannot trust is what is put in up front.

There are two types of uncertainties. There are uncertainties of data. You have measured data which has a 95 percent confidence interval on the measurement. You have estimates which have another uncertainty, and we have extrapolations with even more uncertainties, and then we have a

tricky thing which is called expert opinion. That is the most uncertain thing to model. And the best we could to is model the different opinions. Right? There you also get an uncertainty which can be modeled mathematically and we can see where we come.

So, my plea would be that within our blood community scientific meetings we have sessions, repetitive sessions on these risk models which we are doing now for the TSE because that is a very big, important outcome that comes there. You know, we are modeling the risk of our plasma products. If you see what comes in up front, half of it is data but more than half of it is mere assumptions out of the blue. So, we have to be very careful how we handle these.

DR. EPSTEIN: Thank you, Cees. Other comments about how we react to the risk modeling? Of course, this was a major issue at the advisory committee which was very concerned about uncertainties and made a direct request to try to put error bounds, and that is why we came to this

meeting with a presentation by Dr. Anderson to try to put uncertainty boundaries on the analysis. Celso?

DR. BIANCO: Yes, that is correct and I agree with part of what Cees raised. But I think that if that is the point, and I am sorry that Dr. Bayer had to leave, but that is the point where we cross the line of science and we could get into the realm of moral judgment or politics or however we want to call it. It is more of a social decision.

I will give you an example of what just happened. Dr. Epstein, concerned about the prevalence issues, would be very happy if we could introduce a rapid test. You do pre-test in Holland. And, this was not enough for you to change your criteria. Actually, you are stuck with very rigorous criteria. So, how do we judge that? We go back to the issues of acceptable risk or tolerable risk.

DR. EPSTEIN: Did you want to respond directly, Cees?

DR. VAN DER POEL: Well, I think I fully

agree with you, Celso, because the decision in Holland to do pre-testing of new donors was merely historical. We had 22 blood banks and had to merge them into one system, and it turned out that three of the 22 did that already so we could not harmonize in the other direction. That was all. So, it was not an educated decision; it was just a decision.

[Laughter]

DR. EPSTEIN: Eve?

DR. LACKRITZ: I recognize the complexities of this but, on the other hand, if we sort of take the data that Mike presented, I thought Celso's presentation was very clear in outlining specific probabilities, if we look at release error, we have most of that data and actually if you vary the prevalence of infectious agents that probably will have minimal impact and we could probably very easily--which you did--plug in numbers and we will repeatedly get small estimates regardless of prevalence.

DR. EPSTEIN: Mike?

DR. BUSCH: Yes, I strongly endorse the position that we should have the people that do this stuff get together, both in terms of the model design and the assumptions, and just have some discussion. With Andy, I think we agree that there were some errors in the way that the estimates of prevalence would contribute.

I personally didn't think though--and, obviously, if after that fact we determine that prevalence is not a driver of risk forget what I am going to say, but I actually do think that the countries that have implemented required pre-screening of first time donors are on the right track. We are seeing that done in more countries. In South Africa that is a huge safety impact in a high prevalence setting. And, I do think that it is an opportunity to educate donors through the engineering of the donation process. I think it could be accomplished, that we could draw samples from prospective donors, encourage them through that process to definitely come back. We know from our NAT yield data that first time donors are two

to three times as risky with respect to incidence breakthrough transmissions. So, I do think that we should serious consider moving in that direction.

DR. BIANCO: I just want to make a brief comment. I agree with you entirely. In practice, we tried. If you recall, at one point we had the donor re-tested plasma and there was substantial difficulty with the intervals between the donations and the routine of how blood drives were run, and all that, to maintain inventories of the donor.

DR. BUSCH: That is a very different issue. I am not talking about trying to quarantine product. I am basically talking--and maybe this is something that obviously could be piloted with behavioral people involved, just looking at running some blood collection sites where prospective first time donors, particularly in places like high schools, etc., we would actually have a system to pre-test them before their first donations. I am not talking about an ongoing, you know, repeat donor quarantine.

DR. EPSTEIN: Mat?

DR. MCKENNA: What I was just going to suggest is that one thing that is missing out of the model that I haven't seen is that it sort of ends at how many units will be positive, and what you don't see is anything on recipient morbidity or mortality. I know most people think the model now is hopelessly complicated but why not just add something in addition that really gets to whatever one is trying to get at? You know, you are trying to save lives with transfusion. So, if you are looking at a true tradeoff, how many lives are you losing? And, I think that is important to look at. Of course, it is different for every pathogen but it is something that I think needs to be added in some way.

DR. EPSTEIN: Andy, go ahead.

DR. DAYTON: We totally agree with that. As I said, with different agents at different stages of modeling, we are actually quite far advanced with the HIV modeling. HBV and HCV are further behind. We definitely want to take it in that direction but this is the first step and we

decided to look at exposures. Mike and I had a very good discussion at the end of the last session and I think for the HBV and HCV we would probably reduce the false-negative errors significantly, but the quarantine release errors I think is going to hold up pretty effectively.

I think the biggest change from my perspective doing the models between now and 200, when we last investigated, was that we have I think a better handle on the quarantine release error term. Also, it is really quite small. For MSM for 5-year and 1-year for HBV and HCV you are dealing with numbers that are not that different from the one percent of so that the donor population would increase by if you changed these deferral policies. That still leaves pathogens like HHV-8 as a significant worry, but I agree with you anyway about where the models are and where they should go.

DR. EPSTEIN: I would just comment that we had a lot of discussion about that internally. We recognize that, you know, the real endpoint is

infection and morbidity and mortality. But the other point of view is that one wants to do for the sake of individual health is to minimize exposure to potentially contaminated units, almost regardless. Of course, from the population point of view it could be seen differently. Cees?

DR. VAN DER POEL: Well, I think first on your first question, we are presently modeling that and we came to the problem that we know very little about recipients in terms of a quantitative model. So, we are now doing a fast study with four economic centers, three clinical centers and ten peripheral centers, which are hospitals, which will be representative of the Dutch populations, and we are linking a lot of databases, what is called survival databases in governments, those sort of databases. It takes a long time. Don't do it; it is a lot of work. There are a lot of ethical issues but it is working now.

Strikingly, we came up with one thing. I was puzzled by the measurements that the Irish did. They could not do some of the measures because of

supply, but they did them for neonates only and this is not very fair, is it? I mean, young women about 24 years of age who have a transfusion are entitled to the same safety. But my mind started changing when we had a death after a bacterially contaminated product which was, by the way, after we implemented bacterial screening. The person did not die of this bacterial screening product, but my board was very, very much concerned about this death in a recipient of blood. So, I went through the data or this new database and it shows that 24 percent of the platelets do not leave the hospital alive. That means that 24 percent of the platelet transfusions are given to patients who die anyway. Right? So, in terms of tradeoffs I think you are right. We have to model into that the recipients network as well, if you like. That will bring into the discussion whether we are asking for the same level of safety for everybody, but that is a totally different question.

The second question was on pre-test of new donors. I will look back for you for what it

actually meant. We have had HIV and hepatitis C NAT testing for five or six years now and we found only one hepatitis C NAT, zero HIV. We got eight seroconverters for HIV, by the way, which meant that we had to look back and that kicked up a row anyway with or without transmission. The pre-tested new donors--I think there are two or three seroconversions that we did not have to do look-back on because the first donation was the first test without the donation. Right? So, maybe it is more effective than NAT testing in Holland.

DR. EPSTEIN: I think I would like to shift over to the issue of alternatives, but I would like to query the panelists specifically about HHV-8. Now, you know, we have discussed it in a workshop, not simply the male sex with male exclusion, I think we have tried to illuminate the underlying principles and the epidemiology for the different agents as they might apply to other risk factors, particularly illicit drug injection. But the male sex with male deferral has been the object of a greater social controversy and I think that we

have a particular problem. as Sheila Dollard informed us, there is, in fact, significant prevalence of HHV-8 positivity in males who have had sex with males. Additionally, there is convergence of evidence suggesting the likelihood of transfusion transmissibility of this infection associated with malignancy.

So, you know, what does this group think about this, and does it give us pause about the whole ID question? Roger certainly enlightened us that we can't expect future EIDs, let alone even the majority of them, to follow the classic paradigm. But it is certainly conversely true that some will. Some will be highly associated with intravenous drug use and/or sexually transmitted disease even if it is not the majority. So, how do we look at HHV-8, and is there a way out of the box?

DR. DODD: Well, I am probably not the person to answer this question, but as I was thinking about this, this seemed to me to be the most difficult case to manage. It sounds like a

retreat but I am not sure that we really know enough to be making a really good policy decision at this point, other than the sorts of things that are based on the use of the precautionary principle. We don't know how many individuals would actually be infected through transfusion in this country using the products that we use right now.

We don't know in general what the outcome of transfusion transmission of this agent would be, although we do know that organ transplant recipients have developed KSs, presumably as a result of organ transplant-transmitted, in fact almost definitively, HHV-8. We do know that there are tests but, as Sheila Dollard pointed out, the current method that is in use in CDC is not going to go down too well in the Red Cross testing lab, although, you know, I have seen mass use of IFA in transfusion environments.

The whole issue of what is a good test for HHV-8 is a very difficult one. I think in the past we have always tried to duck questions like this by

saying that we need more data, and I still think it is probably true in this case. But I think we are strongly warned that we have to think about it. I am not sure, even if the precautionary measures that we have were in place, that would be expected to deal with HHV-8 actually do. You know, the highest frequency was in MSMs who already have HIV. We don't know too much about the other groups. So, I think there are a lot of questions that need to be asked and answered, and I think we need to do them in a hurry.

DR. EPSTEIN: Celso?

DR. BIANCO: I want to add a little bit to Roger, but I think that for some reason there are certain approaches that could be taken. What makes it difficult is because the prevalence is high and the penetration is very low. I don't have the numbers but the incidence of HHV-8 seems to be quite low these days even among AIDS patients, for reasons that are not very clear. But because of the precautionary principle, when Europe rushed to leukoreduction of all products and Canada did the

same because of fear of variant CJD, I think that it would be easier to collect the elements to make such a decision in the case of HHV-8 and, in a certain way, preserve the fact that it can't be easily tested or dealt with and at least take a measure that should reduce substantially the transmission.

DR. EPSTEIN: I am just wondering whether there are members of the audience that want to speak to these two issues, the utility or reaction to the risk modeling and also the consideration of alternatives and additional scientific data that might be needed. Sue?

DR. STRAMER: Yes, I was kind of whispering with Sylvano Vende [?] earlier in the session and one comment, Andy, even though I spoke to considerable length about models, one thing that wasn't factored into the models was co-infection in the risk groups that we are looking at. For example, we introduced anti-core testing as a surrogate for HCV. We know that HIV positives also, in many cases, have anti-core reactivity.

So, when we talk about a dual layer for HIV and HCV just by the direct tests we do for them, we also have other cross-positivity or multiple positivity in these individuals that probably should be factored into the model.

DR. DAYTON: It all depends--to be perfectly correct, you are absolutely right and we didn't model those. My perception was that we weren't looking at co-infection rates of, you know, 50, 60, 70, 80, 90 percent because we have so many other uncertainties in the model. You know, co-infections weren't a huge percentage of the final thing. What are some of the co-infection numbers we are looking at here?

DR. STRAMER: Well, in most our HTLV positives, they are co-infected. I mean, core positives that are true core positives, again because of transmission routes, are the same for HTLV and hepatitis B in drug use, which we talked about today. I mean, those two run hand in hand. Syphilis also--

DR. DAYTON: They have very high

prevalences too. No, that is fair. We should do that.

DR. STRAMER: But, I mean, it is true when you are saying because HBV and HCV is transient and we are left with anti-core, if someone is truly infected from an MSM population with HBV, HBV won't be the only infection they carry.

DR. DAYTON: That is a fair point.

DR. EPSTEIN: Yes, Ed?

DR. MURPHY: Ed Murphy, San Francisco. Just a couple of comments. One is that I think that perhaps one thing that struck me was that perhaps the modeling could benefit, particularly the colleagues at CDC could contribute from science already taken place in the gay community. Obviously, you have the studies that are based more directly in the high risk populations to determine behaviors incidence rates, test seeking behavior that might, you know, inform our current modeling. In other words, instead of staying within the blood community, go outside to the folks that aren't donating, which might also yield I think

information socially on how broad is the demand for being able to donate blood. I mean, we are hearing from local representatives but, you know, colleagues in San Francisco feel that, in fact, this may not be as high on the agenda for social participation among the gay community as is felt elsewhere. So, that is just a comment.

Just to end, finally, I think one other place to look--I know we have representatives here, but both Brazil and Argentina, to name two, and maybe other countries have instituted a one-year MSM deferral and we could certainly benefit from their experience as they go forward.

DR. EPSTEIN: Ed, while we have you, one issue that has come up periodically at least from activists is why don't we just use the questionnaire to cull out the safe subsets amongst MSM. You know, the concept has been persons who assert mutual monogamy, for instance, or routine practice of safe sex. And, one of the frustrations to those of us within government who attempted to look at this is the extreme paucity of data. What

limited data were available mainly came out of the San Francisco gay men's cohort study and it was not encouraging that questionnaires could identify safer subsets. But I just wondered, based on your knowledge of studies in those populations, are we likely to get any answer to that question which is, again, one of the alternatives that has been proposed?

DR. MURPHY: Well, again, I couldn't answer the question in detail but a colleague of mine in the San Francisco public health department, Dr. Willie McFarland, has studied the issue in depth and he, himself, put together a talk on this issue of relaxing the deferral. His data, although limited, was somewhat anti, just based on concerns about test seeking and high incidence rates as measured by NAT testing in some of the alternative test sites.

DR. EPSTEIN: Thank you. Debbie?

DR. KESSLER: I just wanted to point out that the target isn't necessarily just to bring in men who have sex with men. The target is all of

the groups that have cancelled, especially colleges; we have had high schools jump in--cancelled blood drives because of this policy, and these are key blood donors for now because they are a large sector, at least of our donor population in New York, and donors of the future. This is the age group you are really trying to capture into becoming lifelong donors. So, if you turn them off to donating because of the policy at their school, they will carry that attitude with them maybe for the rest of their lives. So, I think that you have to remember that we are not just looking for the additional gay men but the public opinion on the subject.

DR. EPSTEIN: Mat?

DR. MCKENNA: Just to follow-up on that, I think that is an important point and I think something that was said earlier about education of the donors is very important. Most people don't even know why these questions are being asked. They are run through at lightening speed. They don't know what babesiosis is, and maybe it is not

worthwhile explaining completely what that is but I think some education would be useful.

But one thing I was going to comment on is on the importance of surveillance, and what we are talking about is looking for data in low risk subsets and low risk populations and that is not something that, you know, there is a general focus on, as you might imagine--you know, the group of people who have been abstinent for five years, I mean that is not a group that is going to be focused on. So, if that is going to be a priority there really needs to be a discussion amongst the community and government agencies to develop an agenda specifically focused on that, because that is the only way I think we are going to get at some of these data.

DR. LACKRITZ: Can I just get a clarification on what you are saying? Are you also suggesting if there were deferral to five years or one year, that really doesn't eliminate the problem that you are talking about? Right?

DR. KESSLER: Most of the donor groups

that I have gone and spoken to about this subject would be happy if it was the same as all other risks. They could buy that. I don't know how well they would buy the five-year. Some of them say, well, there should be none at all, and I am happy and I am comfortable answering that question about risk to the blood supply, but they would be satisfied if all risks were treated the same.

DR. EPSTEIN: Harvey?

DR. KLEIN: Harvey Klein, NIH. I want to get back to HHV-8. I think it is an agent worth keeping our eye on, but I think we also, particularly in terms of modeling, need to keep our eye on the ball here. We have transfused a lot of HHV-8. We certainly transfused a lot in the 1980s prior to leukoreduction, if that does anything, prior to screening for HIV, and we really haven't seen an epidemic of disease. In fact, the CDC did some studies in the plasma recipients, the hemophiliac population, and really found almost nothing. In fact, they found nothing.

So, I think we really need to remember

that this is not transmitted very easily, not transmitted easily by stored blood. Again, in your modeling you need to take that into account. It is probably removed effectively by leukoreduction. The population you are most worried about, the immunosuppressed recipient is even less likely to get out of the hospital and the patients that you looked at, they don't. And, I think that while it is worth considering that this is a risk, that high percentage of MSM people who would come back who are HHV-8 infected are also HIV infected, and I would say to you that it is probably a lot worse to get an HIV-positive unit. You won't even think about HHV-8 if that occurs.

DR. EPSTEIN: Steve?

DR. KLEINMAN: Just one follow-up comment on HHV-8, we actually thought this was an important agent to study within the REDS group and, as you know, we have this radar repository which allows us to link donors to recipients. We met with Sheila and some other HHV-8 testing experts to try to design a study and the fact of the matter was that

there weren't any reliable antibody assays that would allow us to triage the appropriate donor units. So, when we talk about getting more data, I think that we thought we had a resource that would allow us to study transfusion transmission of HHV-8 and, in fact, despite this wonderful resource we can't study it because of the technological, I guess, state-of-the-art, which isn't likely to get better in the near future because it is based on the low antibody titers and PCR on cell preparations is just too expensive to do. So, I don't think we are likely to get the definitive study on HHV-8 and I think, therefore, the epidemiological data that Harvey was just mentioning is what we need to keep in mind I think.

DR. EPSTEIN: Could I pick up the earlier point that was made about institution of one-year deferrals in Brazil and Argentina that Debbie mentioned?

DR. VENDE: Sylvano Vende, from Brazil. We have no data to present to you, but actually this is my own perception, that with the advent of

NAT in Brazil we are actually finding new cases that are detected by NAT, and probably it has some linkage with this reduction for MSM from at least ten years to one year. But this is not scientifically evidence-based.

DR. EPSTEIN: Mike?

DR. BUSCH: Just the fact that contracts have been signed, I believe, so that the REDS-II program is adding international sites and Brazil is one and China is the second. Both of those sites will be conducting extensive studies of positive donors, HIV and others, interviewing those donors, and this discussion is important because we can actually sort out what proportion of positives are MSM and are MSM who have remote risks. So, I think this is a good point to follow-up on.

DR. EPSTEIN: Harvey?

DR. ALTER: Harvey Alter, NIH. I come away with only two things that have really swayed me today. I mean, I think one is that my real only concern is not that any agent we currently test for is going to add increased risk if we change policy.

Roger's presentation has convinced me that the emerging infectious agents that we know about don't seem to be a particular risk from this population. So, the only real rationale for excluding or treating the gay population differently is this theoretical next AIDS agent that we fear might emerge. I don't think anything has emerged yet and the only rationale that I can think of for continuing this policy against logic, I think, is this fear that this population will be an incubator for the next AIDS agent and will get a little bit of a heads up.

The other side is that we usually come out of these conferences and say we need more studies; we need to remodel; we need to look at new populations, and this and that. I think anything that will happen on the remodeling will make it even more safe than the models show now so it is not going to get worse. So, I don't think we are going to come to any increased risk from remodeling. And, the studies that we talk about are so difficult to do that they are going to be,

at best, very long in coming and, at worst, won't give you an answer.

So, basically we are going to wind up at some point in the future where we are now, that this is not a scientific issue very much. This is a social issue and a recruitment issue and a fairness issue, and I think we can make that decision now, whichever way it goes, but I think we are going to have the data we have and it won't get better in the future.

DR. EPSTEIN: Yes?

DR. BENJAMIN: Richard Benjamin, American Red Cross. Having worked in the New England Red Cross for quite a while and spoken to many student groups on this matter, I just want to back up what Dr. Alter said and what Debbie said, that it would be very helpful if we could at least get this to a fairness equation where the students would see that the deferrals are equal for equal risk. I think that would help us on the donor recruitment side, especially on school and college campuses. So, that is my plea to this meeting.

DR. EPSTEIN: Thank you. Mike?

DR. BUSCH: Just a thought that we have kind of bantered about the REDS group. I mean, FDA seems to have recently been receptive to the idea of INDs and IND applications and post-market surveillance and, you know, I am very supportive of moving to a one-year deferral but if that were coupled by a commitment to investigate the HIV-positive donors--and, again, the REDS program, perhaps in conjunction with the major organizations, could institute a post-change careful surveillance, particularly HIV but potentially other agents as well, to make sure that we are not seeing some surprising influx of MSM that admit to recent behavioral change.

DR. EPSTEIN: Cees?

DR. VAN DER POEL: Just to play the advocate of the devil, I would like to do the same study without the recipients as the outcome model. What is the difference then?

DR. BUSCH: He is suggesting to actually change the policies and collect blood from these

individuals would be perhaps not appropriate. Rather, you could open the policy but not actually collect blood, just get the sample and do the testing, so pre-testing a population like this.

DR. EPSTEIN: Sylvano?

DR. VENDE: Well, this is only a comment. I understand this is an American meeting for an American problem--

[Laughter]

--so when you are talking about the REDS international study, please do not take any advantage from the Brazilian results that you are going to get in the future because Brazil is a completely different country so it has to be concentrated on this particular American country. That is my caution about this multinational study.

DR. VAN DER POEL: I think the same would go for Europe and especially Holland. So, can we forget about what you said?

[Laughter]

DR. EPSTEIN: Unfortunately, it was memorable! Debbie?

DR. KESSLER: I like Mike's idea about a post-implementation follow-up study, and part of that might even be asking donors about risk for MSM allowing them if they fit more than one criterion and that way we would be able to really hone in on the ones--you know, tell them that this is part of a study and we are loosening up because you want us to and we are going to look at it.

DR. BUSCH: I think we are getting into nuances of studies but I think you are going to have a hard time selling blood centers on taking units where the donors have acknowledged MSM criteria. I don't know, but my sense would be that a study that would track carefully the positives coming out of screening and make sure that we are not seeing an up tick and that that is attributable to this group to actually try to sort up front, I think.

DR. EPSTEIN: But, Mike, what about a scenario in which you tell a donor we are not able to accept you today under current standards; we would like to offer you a screening test and

interview you because these studies might help us change policy in the fairly near future? There might be a lot of cooperation and we might actually get some useful information that way. This harks back to a much more general principle which is that we don't do a lot of studies on the deferred donor and, yet, there is a lot of information in the deferred donors. Celso, hold for a moment because this gentleman is in line to speak.

DR. NOTARI: Ed Notari, American Red Cross. Pre-tested donors that you propose to collect from, they could be compensated. Is that true? I mean, you wouldn't be collecting a unit from them.

DR. EPSTEIN: They could be compensated because they are not giving a unit so you are not labeling the unit as paid, but that is a whole other issue. Celso?

DR. BIANCO: Just to that point of studies, as we started, let's just remind us that there are things that have been added or can be added that even ensure regardless of changing

criteria. I think that every blood center should have by requirement a good computer system that holds units and they are not inappropriately released. I think that everybody should adopt a uniform donor history questionnaire. And, I think that when we release the abbreviated questionnaire it will be even easier. And a Phase IV study of that type would be something quite acceptable. However, just a research study in a university environment, in a university like the ones that I have been to, talking to donors--Jay, I am sorry, but their reaction is so intense, they are so upset with what they think is very, very unfair that they would not participate in that. The argument that we use is that when you block a blood drive you are really preventing blood from being collected to help people with AIDS in the hospitals and they don't get it. They just feel so intensively about it that they don't respond even to that.

DR. EPSTEIN: Is there anyone who would like the last word? Harvey?

DR. ALTER: While I made sort of a plea

that we don't end this meeting by saying we need more studies without being specific, Mike's idea has tweaked my brain here and I think it would be worthwhile to see if we could come up with a study where I think it should be that we make the rule that these donors are okay and we have recipients and we follow recipients. I want to see if there is some way that that could be done. I think that kind of commitment would be worthwhile and could get by the FDA and the IRB.

Closing Remarks

DR. EPSTEIN: We will think about it. So, taking the prerogative, I just would like to first thank all of our speakers. I think that we enjoyed a quite excellent series of talks today, and I would just thank everyone for their participation. We have had some very informative discussions and I think it has been clear that FDA has been listening carefully and we will, of course, be revisiting these issues. As I said in my opening remarks, this is not a policy-making forum; it was an exercise in information gathering, scientific

information as well as opinion. So, I have enjoyed the day. I hope that each of you has as well and, again, my thanks to all the presenters and to the participants.

[Applause]

[Whereupon, at 5:56 p.m., the proceedings were adjourned.]

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